

Chlorhexidine Anaphylaxis Masquerading as Septic Shock

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Established Facts

- Chlorhexidine allergy is increasingly prevalent as a result of increasing use in the health-care setting
- Chlorhexidine anaphylactic shock is rare and has only been reported in healthy individuals

Novel Insights

- We report a case of superimposed clinical presentation of chlorhexidine anaphylactic shock in a patient with septic shock
- Perioperative anaphylactic shock from chlorhexidine is unusual (the usual suspects are muscle relaxants, antibiotics and latex)

Key Words

Chlorhexidine · Anaphylactic shock · Septic shock · Adverse drug reaction

Abstract

Chlorhexidine is a commonly used antiseptic and disinfectant in the health-care setting. Its usage has increased in recent years with intensive campaigns and infection control guidelines to combat hospital-acquired infections. As a result, patients and health-care workers (HCW) are exposed to increasing chlorhexidine usage. In recent years, adverse reactions to chlorhexidine ranging from allergic contact dermatitis, photosensitivity, fixed drug eruptions, urticaria and anaphylactic shock have been reported. Most have been isolated case reports on adverse reactions occurring in

healthy individuals or HCW. We report a case of anaphylactic shock caused by applying chlorhexidine cleansing solution and masquerading as septic shock from left-leg necrotising fasciitis.

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Introduction

Chlorhexidine is a commonly used antiseptic and disinfectant in the health-care setting. It is a cationic bis-guanide with wide-spectrum antimicrobial properties. Chlorhexidine is attracted to negatively charged bacterial cell walls, disrupting the integrity of cell membranes and leading to increased permeability and leakage of the intracellular components of organisms [1, 2]. It has good

activity against Gram-positive bacteria, somewhat less activity against Gram-negative bacteria and fungi and minimal activity against mycobacteria [1, 2]. Its usage has increased in recent years with intensive campaigns and infection control guidelines to combat hospital-acquired infections [3, 4]. The WHO guidelines on hand hygiene in health-care recommend the use of hand-rub in six clinical situations to prevent the spread of infection [5]. The UK guidelines recommend the use of 2% chlorhexidine gluconate in 70% isopropyl alcohol solution for skin antisepsis prior to central venous catheter insertion and for cleansing when dressings are changed [6]. As a result, patients and health-care workers (HCW) are increasingly being exposed to chlorhexidine [3–6].

In recent years, adverse reactions to chlorhexidine have been reported, ranging from allergic contact dermatitis, photosensitivity, fixed drug eruptions, urticaria and anaphylactic shock [1, 2, 7–14]. Most have been isolated case reports and the adverse reactions occurred in patients who presented for elective procedures. We report a case of anaphylactic shock, caused by applying chlorhexidine cleansing solution and masquerading as septic shock from left-leg necrotising fasciitis.

Case Report

Our patient was a 66-year-old male (with a weight of 72 kg and height of 164 cm) with a past medical history of hypertension, type 2 diabetes mellitus and ischaemic heart disease. He had had a coronary artery bypass surgery 20 years previously and was on life-long aspirin. The latest 2-dimensional echocardiogram performed in November 2009 showed an ejection fraction of 54%, mild mitral valve regurgitation and aortic valve sclerosis, a dilated left atrium with concentric left-ventricular remodelling and prolonged left-ventricular relaxation. There were regional wall motion abnormalities over the left ventricle region. He did not report any food or drug allergies. There was also no history of atopic disease.

He initially presented to the emergency department with pain, redness and swelling in his left leg that had lasted for 4 days. This was associated with fever and chills. There were no other systemic complaints. On physical examination, he was alert and conscious but febrile and sweaty. The left leg was swollen, erythematous and tender on palpation. The swelling was prominent at the level of the calf up to the distal thigh, but no blisters or skin lesions were noted. Left inguinal lymphadenopathy was also present. Physical examination of the heart and lungs was unremarkable.

The patient's blood pressure (BP) on arrival was 92/61 mm Hg (MAP: 71) with a heart rate (HR) of 82 beats/min and an oxygen saturation of 96% on room air. He became drowsy, his BP continued to drop to 85/50 mm Hg (MAP: 62), his HR to 70 beats/min and he was not responsive to fluid resuscitation. Intravenous (IV) dopamine of 10 µg/kg/min was started and the BP increased to 105/80 mm Hg. His white blood cell count was 21,000/µl, C-reactive protein level 400 mg/l, lactate 2.1 mmol/l, serum urea 13.1

mmol/l and creatinine 193 mmol/l. An urgent orthopaedic consultation was requested and the Laboratory Risk Indicator for Necrotising Fasciitis score [15] was 7, showing a likely diagnosis of necrotising fasciitis. The clinical impression was septic shock from necrotising fasciitis with resultant acute kidney injury. He was started on IV penicillin, clindamycin and vancomycin in the emergency department.

Following application of BP-monitoring devices, including an intra-arterial line and a non-chlorhexidine-impregnated central venous catheter, we induced anaesthesia with fentanyl (50 µg) and propofol (120 mg). He was intubated by means of rapid-sequence intubation with suxamethonium (100 mg) and atracurium (35 mg). Anaesthesia was maintained with desflurane in oxygen and air. The orthopaedic team performed an emergency left-leg fasciotomy and debridement, using 0.05% chlorhexidine acetate as the cleansing solution. The findings were large amounts of 'dishwater' fluid (classic murky dishwater-like fluid due to the lysis of polymorphs) from the medial and lateral leg compartments, with unhealthy fascia being noted but also that the muscles were contractile and viable. Intra-operatively, he required 0.2 µg/kg/min of IV noradrenaline to maintain his BP at 100–110/70–80 mm Hg. He was sent to the surgical intensive care unit postoperatively and remained ventilated overnight; it was noted that he required high ventilatory support (Pi: 24 mm Hg and PEEP: 10 mm Hg) with a left-lung collapse evident on chest X-ray. The decision to perform a bronchoscopy was made. The bronchoscopy revealed thick mucus plugging the upper and lower lobes of the left lung. Bronchoalveolar lavage was performed, and he showed improvement in ventilatory requirements after the bronchoscopy. He was successfully weaned off ventilation and then extubated the next day. Inotropic support was discontinued as well.

The patient was reviewed by the orthopedic team and a re-look debridement and change of dressings were planned. In the second operation, under general anaesthesia (GA), he developed hypotension and non-ST-elevation myocardial infarction (NSTEMI) about 20 min into the anaesthesia, right after the left-leg cleansing and draping were performed. ECG changes were noted with elevated troponin levels. He was given 300 µg adrenaline boluses and 10 ml 10% calcium gluconate and subsequent IV adrenaline and noradrenaline infusions. Arterial blood gas showed type 2 respiratory failure with a pCO₂ of 56.4 and pO₂ of 70.1 and bilateral wheezing on auscultation; 12 puffs of salbutamol were administered and IV magnesium sulphate (10 mmol) was started, with subsequent resolution of the bronchospasm. Intra-operatively, he was noted to have transient flushing of the chest and face. No urticaria or angioedema was noted. The surgeons performed a medial-thigh fasciotomy and some 'dishwater fluid' was drained. The medial and lateral leg fasciotomy wounds were lavaged and the dressings were changed. A bronchoscopy performed after the surgery again revealed thick mucus plugging the left lung; bronchoalveolar lavage was performed with good results. He was monitored in the surgical intensive care unit afterwards. The following day, he was well, was extubated uneventfully and his dressings were changed at the bedside by the orthopaedic team. A relook debridement for 4 days later to allow soft-tissue demarcation was planned. In the meantime, the tissue and fluid culture grew *Streptococcus dysgalactiae*. He was continued on IV penicillin. Inflammatory markers showed a downward trend with a white blood cell count of 14,400/µl and a C-reactive protein level of 88 mg/l.

In view of his previous reactions to GA, regional anaesthesia was chosen for the subsequent relook debridement. He underwent 2 more operations under spinal (lignocaine and bupivacaine) and femoral anaesthesia with a sciatic-nerve block (lignocaine and ropivacaine), respectively. Both times, surgery was complicated by hypotension and bronchospasm; the patient underwent emergency intubation to secure the airway and was treated with inotropic support (adrenaline and noradrenaline), salbutamol puffs, IV magnesium sulphate and calcium gluconate. These complications occurred about 20 min into the anaesthesia, right after the leg was cleaned with 0.05% chlorhexidine acetate solution. Despite improving inflammatory markers and a wound that was healing well, the patient continued to have recurrent episodes of hypotension, bronchospasm and transient facial and chest flushing during surgery. The initial diagnosis of septic shock no longer correlated with the clinical presentation. Case records were then reviewed and we noted that the patient had been exposed to chlorhexidine cleansing solution prior to each episode of hypotension, bronchospasm and transient skin flushing. The dressings used did not contain any chlorhexidine.

Common allergens such as latex, antibiotics and neuromuscular blocking agents are usually the culprits in anaphylaxis. This patient had 2 GAs for the initial left-leg fasciotomy, exploration and debridement when he was still in presumptive septic shock, followed by subsequent operations under regional anaesthesia (spinal and femoral with sciatic-nerve block). During this period, the initial regime of broad-spectrum antibiotics consisting of IV penicillin, clindamycin and vancomycin was continued without any reactions. After the intra-operative tissue and fluid culture grew *S. dysgalactiae*, only IV penicillin was continued, again without any reaction. Moreover, the anaphylaxis episodes only occurred during surgery, leading us to be able to limit the inciting agents to local anaesthetic drugs (lignocaine, ropivacaine and bupivacaine), a sedative (midazolam) or a cleaning agent, i.e. chlorhexidine. Upon analysis of the patient's initial presentation, clinical progress and each individual episode of shock, our team decided to put the drugs that were most under suspicion for initial testing via skin prick tests.

The serum tryptase level was measured after the 4th intra-operative event and was noted to be elevated at 16.7 µg/l. Following that, a skin prick test was performed by our hospital's allergist. Histamine was used as the positive control and normal saline as the negative control. Lignocaine, ropivacaine, bupivacaine and midazolam did not yield any results, but a positive reaction was seen with chlorhexidine (0.05% chlorhexidine acetate solution). The skin under the chlorhexidine solution had become red, surrounded by a raised wheal and was itchy. There was erythema measuring 18 × 10 mm and wheal of 8 × 7 mm.

These findings were conveyed to the patient and he was labelled as having an allergy to chlorhexidine. Subsequent reconstructive surgery for the left-leg fasciotomy wound involved using a non-chlorhexidine washing solution such as cetrimide and sterile normal saline. He underwent split-thickness skin grafting of the leg wounds successfully under spinal anaesthesia. Upon inspection of the wound, the graft had taken well, and he was discharged to a rehabilitation hospital for further ambulatory exercises and therapy. He was given strict instructions about avoiding chlorhexidine-containing products and an allergy card. At his latest follow-up 2 years later, his leg wounds have healed and he is able to ambulate without walking aid.

Discussion

There is an increasing trend of chlorhexidine usage in the health-care setting [3–6]. It is used most commonly for skin decontamination during hand-hygiene practice, shampooing or body/oral wash prior to surgery, skin antisepsis prior to venepuncture or insertion of vascular catheters, as a component of lubricant jelly or topical cream for local disinfectants and, occasionally, as a coating on vascular or urinary catheters [1, 2, 7–14, 16]. This increase in chlorhexidine exposure has led to potential allergic sensitization of a majority of our patients, causing a full spectrum of adverse reactions ranging from contact dermatitis and generalized urticaria to anaphylactic shock [16]. Although there have been several reports in recent years about these adverse reactions to chlorhexidine, the majority of these were isolated case reports on HCW or on patients admitted for elective procedures [1, 2, 7–14, 16]. To our knowledge, this is the first report on chlorhexidine anaphylactic shock masquerading as septic shock from necrotising fasciitis.

Anaphylactic shock due to chlorhexidine has been reported after exposure to chlorhexidine via several routes such as direct contact with the skin or mucous membranes from chlorhexidine gargle, skin antisepsis lotion, lubricants or chlorhexidine-coated vascular and urinary catheters [1, 2, 7–14, 16]. In 2008, Bae et al. [8] reported chlorhexidine anaphylaxis after digital rectal examination using chlorhexidine as a local rectal disinfectant; it was initially contributed to a latex allergy. In 2012, Noel et al. [9] reported that a patient with a known allergy to a chlorhexidine skin preparation developed anaphylactic shock from urinary catheterisation using a lubricant containing chlorhexidine (Instillagel®, Clinimed, High Wycombe, UK), and Guleri et al. [10] reported a case series of 3 patients who developed anaphylactic shock after insertion of central venous catheter impregnated with chlorhexidine. In 2013, Chopra et al. [1] reported on a patient who developed generalized urticaria from chlorhexidine oral mouthwash. In radio-isotope studies, chlorhexidine has been shown to penetrate unbroken skin, leading to both local and systemic symptoms [17]. It was also suggested that chlorhexidine may cause severe anaphylactic reaction by the mucosal route at a much lower concentration (0.05%) than by other routes [13]. Our patient presented initially with septic shock and a left-leg necrotising fasciitis, for which fasciotomy and wound debridement were performed. Chlorhexidine cleansing solution was used in each operation on his exposed leg wounds, and rendering a plausible immediate

inoculation intravascularly that resulted in both local and systemic reactions.

It was easy to attribute the patient's initial clinical state to septic shock secondary to necrotising fasciitis. There was also evidence of an acute myocardial event in the early stage of his illness. As such, a cardiogenic component to the septic shock could also account for his haemodynamic state. Moreover, transient flushing of the chest and bronchospasm occasionally occurs as a result of histamine release from muscle relaxants and opioids during GA. This resulted in a delay in suspecting the etiology of the shock to be due to anaphylaxis. However, the consistent clinical manifestation of intra-operative hypotension with cardiovascular collapse, bronchospasm and the cutaneous feature of flushing while the patient was improving clinically from his necrotising fasciitis raised the possibility of anaphylaxis as a differential diagnosis.

This case was interesting for two reasons. Firstly, the clinical presentation masqueraded as the patient's presenting pathology of necrotising fasciitis. The second point of interest was the unusual trigger, chlorhexidine, a cleansing solution.

The classic approach to differential diagnoses of a state of shock is to classify possible causes according to the main categories hypovolemic, cardiogenic, obstructive and distributive; however, it is not usual for patients to have >1 contributing factor. Typically, haemodynamic parameters such as HR, central venous pressure, pulmonary capillary wedge pressure and the systemic vascular resistance index may be utilized to help differentiate the various types of shock. However, the presenting clinical picture usually guides the clinician's diagnostic and management strategies. This case illustrates the importance of being vigilant for other clinical features suggestive of a particular shock type. For example, while it was easy to attribute the cutaneous flushing and bronchospasm to histamine release from common anaesthetic agents (i.e. muscle relaxants and opioids), these features were, in retrospect, classic for anaphylaxis. It is also prudent to mentally run through all the possible causes of shock even when the diagnosis appears obvious. A meticulous review of previous anaesthetic events may also assist an earlier diagnosis. In this event, even in the presence of sepsis, the state of shock may be related to other etiologies such as cardiogenic and/or anaphylaxis. One possible etiology to be considered would be Kounis syndrome [18, 19]. Kounis and Zavras [18] first described the concurrence of acute coronary events and acute allergic reactions as a syndrome of allergic angina and allergic myocardial infarction in 1991. This is characterized by the degranula-

tion of mast cells in the setting of an allergic reaction, followed by the release of copious inflammatory mediators such as histamine, leukotrienes, proteases and a host of cytokines. These vasoactive mediators can lead to coronary artery vasospasm and atheromatous plaque rupture and result in acute coronary events [18, 19].

The second point of interest is the identification of the trigger agent. Even after suspicions were raised with regard to the possibility of anaphylaxis, we initially directed our attention to anaesthetic drugs. As mentioned, the usual suspects are muscle relaxants, antibiotics and latex. As such, initial efforts were directed at keeping the drug exposure to a minimum and regional anaesthesia techniques were used for the patient. It became clear that the incriminating agent was not one of the usual suspects, and with the expert help of the allergist, we were able to identify the trigger as the cleansing solution, chlorhexidine.

We were limited by the availability of specific IgE and the index serum tryptase level as the initial clinical presentation was attributed to septic shock. Nonetheless, we did manage to measure the serum tryptase level after the 4th intra-operative event and it was noted to be high.

Conclusion

Chlorhexidine anaphylactic shock is rare. Previous isolated case reports have presented adverse reactions on HCW or patients admitted for elective procedures. We describe a case of chlorhexidine anaphylactic shock masquerading as septic shock from necrotizing fasciitis. We hope that this case report will remind clinicians to be vigilant of other etiologies of shock even when the cause seems apparent.

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