

## Case Report

# Life-threatening anaphylactic shock due to chlorhexidine on the central venous catheter: a case series

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**Abstract:** In this article, we report two life-threatening anaphylactic shocks by an antiseptic coated central venous catheter (CVC) within a 6-month period in our cancer center. Anaphylactic shock was preceded immediately after insertion of a central venous catheter (CVC) coated with silver sulphadiazine and chlorhexidine acetate (Blue FlexTip® ARROWg<sup>+</sup>ard Blue®, 14Ga, Arrow International, Inc. USA). Though antiseptic coated CVC anaphylaxis has been reported in Japan, Europe and America, to our knowledge, this is first reported in China. We present these rare cases to remind clinicians about hypersensitivity to chlorhexidine that could potentially be life-threatening.

**Keywords:** Chlorhexidine, anaphylactic shock, central venous catheter

### Introduction

Chlorhexidine is widely used as skin disinfectant, dental hygiene and personal hygiene commodities. It also present in potentially hidden forms, such as a bactericidal coating for CVC or as a component of urethral lubricants, but clinicians may not be fully aware of it. The use of chlorhexidine in healthcare setting has increased extensively following the universal drive to reduce the incidence of hospital-acquired infections. Anaphylactic reactions to chlorhexidine once were regarded as rare, but recent literature seems to challenge this [1]. Our two cases happened in quick succession, the incidence may be more common than we thought. The anaphylactic reactions of our patients should alert clinicians of the potential danger of this hidden allergen which could lead to severe, life-threatening systemic hypersensitivity.

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#### Case 1

A healthy 48-year-old man had general anaesthesia for elective esophageal carcinoma

resection. No premedication was administered before the anesthesia. Entiodine (a solution containing 0.2% iodine, 0.45% chlorhexidine, 65% ethanol) was used for skin preparation. An epidural catheter was placed in the T7-8 thoracic vertebra interspace under local anesthesia. Prior to induction of general anesthesia, a CVC (Blue FlexTip® ARROWg<sup>+</sup>ard Blue®, 14Ga, Arrow International, Inc. USA) was inserted uneventfully in the right internal jugular vein under local anesthesia. Immediately after CVC placement, the patient complained of convulsion, faintness, unconsciousness, difficulty in breathing. Facial flushing, generalized erythema, periorbital oedema, facial oedema, limbs paralysis and oedema subsequently developed. His blood pressure decreased suddenly and profoundly, from 140/80 to 60/30 mmHg, and then couldn't be recorded. Heart rate increased from 80 to 170 beats/min and the oxygen saturation (SpO<sub>2</sub>) decreased progressively over the next 5 mins to 66%. Anaphylaxis was suspected and an aggressive resuscitation was given to the patient. Oxygen 100% was administered. He received intravenous epinephrine 50 µg × 4, norepinephrine 0.3 µg/kg/min, dexamethasone 5 mg, hydrocortisone 150 mg and normal

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**Table 1.** A list of every worldwide reported case of chlorhexidine CVC allergy

Lead author	Time	Country	Number of patients	Type of CVC	History of allergy	Number of episode and reason	Blood analysis	Skin prick test	The outcome
M. Kluger [3]	2003	New Zealand	1	A four-lumen CVC (ARROW Quad Lumen, Arrow International Inc, PA, U.S.A., CS-25854-E)	Chlorhexidine	One episode	Not done	Not done	recovery
A. Khoo [4]	2011	Australia	1	Arrow-Howes Multi-Lumen CVC set with Blue FlexTip, ARROWgard Blue Catheter, 3-lumen, 30 cm, ARROW international	Tetracycline and contrast medium, An erythematous rash following a chlorhexidine skin preparation	One episode	Mast cell tryptase (MCT): 37.2 ug/L↑↑↑	Not done	recovery
Achyut Guleri [5]	2011	UK	1	ARROWgard® Blue Catheter, Arrow® International [Teleflex® Medical], Research Triangle Park, NC.	A purpuric rash after using 4% chlorhexidine shower gel, Itching after skin preparation using 2% chlorhexidine	One episode	MCT: 35.2 mcg/ml↑↑↑, chlorhexidine-specific IgE: 0.40 kU/L↑	positive	recovery
Achyut Guleri [5]	2011	UK	1	ARROWgard® Blue Catheter, Arrow® International [Teleflex® Medical], Research Triangle Park, NC.	chlorhexidine	One episode	MCT: 114 mcg/ml↑↑↑, chlorhexidine-specific IgE: 4.62 kU/L↑↑↑	Not done	recovery
R. Jee [6]	2013	UK	2	ARROWgard Blue®	no	One episode	MCT: ↑ chlorhexidine-specific IgE: positive	Not done	recovery
Matthew Toomey [7]	2013	USA	1	ARROWg®ard, 9F, Arrow International Inc.	No food and drug allergy His wife disclosed later: a mild rash with hives throughout his body after using the chlorhexidine body cloths	One episode	chlorhexidine-specific IgE: 5.26 kU/L↑↑↑	Not done	recovery
Toshiyuki Oda [8]	1997	Japan	1	ARROWgard Blue™, 14-gauge, Arrow International Inc., Reading, PA	no	Two episode on the same patient But the skin prick test result had not been reported to anesthetists on time.	The second time: Histamine: ↑↑↑, C3, C4, lymphocyte count, IgE: ↓↓	The first time: 1 week later: negative.6 week later: positive.	recovery
Etsuji Terazawa [9]	1998	Japan	1	Arrow gard® Blue, Arrow International Inc., Reading, PA	Allergic rhinitis	Two episode on the same patient The first time: lymphocyte transformation test was positive to cefozopran. Anaphylaxis was attribute to cefozopran	The second time: basophil ↓↓↓, histamine: 80 ng/ml↑	The second time: positive to 0.01% and 0.001% chlorhexidine	recovery
R.Stephens [10]	2001	UK	1	Arrow-Howes™ Quad-lumen Central Venous Catheterization Set with ARROWg®ard Blue® Catheter, Arrow, Reading USA	Penicillin, Itchy rash in his groin after skin preparation using chlorhexidine	Two episode on the same patient The precipitating drug was thought to be the "Savolin" used before urethral catheterization.	The first time: MCT: 157 mg/L↑↑↑, C reactive protein: 7 mg/L↑ The second time: MCT: 68 mg/L↑↑	The first time: positive at 0.4%, 4% dilution. The second time: positive at 0.04%, 0.4%, 4% dilution.	recovery

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A. Pittaway [11]	2002	UK	1	Arrow-Howes™ multi-lumen central venous catheter set with ARROWg <sup>®</sup> ard and Blue <sup>®</sup> Catheter, Arrow, Reading, USA.	penicillin	Two episode on the same patient A speculative diagnosis of a non-IgE mediated reaction to atracurium	The first time: MCT: 16.8 ug/L↑ The second time: a raised serum total IgE of 1178 kU/L↑↑	The second time: positive to 1% chlorhexidine	recovery
Achyt Guleri [5]	2011	UK	1	ARROWgard <sup>®</sup> Blue Catheter, Arrow <sup>®</sup> International [Teleflex <sup>®</sup> Medical], Research Triangle Park, NC.	a generalized pruritic maculopapular rash after a shower using a 4% chlorhexidine soap solution	Two episode on the same patient Intradermal testing for pancuronium hypersensitivity was positive, and this drug was considered the antigenic trigger	The first time: MCT: 131 mcg/ml↑↑↑ The second time: MCT > 200 mcg/ml↑↑↑, chlorhexidine-specific IgE: 7.4kU/L↑↑↑	intradermal test with 0.005% chlorhexidine: positive	recovery
R. Jee [6]	2013	UK	2	ARROWgard Blue <sup>®</sup>	no	Two episode on the same patient all antiseptic preparation containing chlorhexidine were removed, but they didn't aware that antiseptic CVC containing chlorhexidine	MCT: ↑ chlorhexidine-specific IgE: positive	Not done	recovery

CVC: central venous catheter; MCT: mast cell tryptase.

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saline 2000 ml. Meanwhile, a radial artery catheter was inserted. Fortunately, his blood pressure was restored to 120/60 mmHg rapidly in 15 min with a heart rate of 150 beats/min. An emergency tracheal intubation was performed using cisatracurium and propofol. After intubation, oxygen saturation remained at 99%. After establishing another two peripheral veins IVs, we removed the CVC. Then the patient gradually became stable without epinephrine and norepinephrine continuous infusion. The surgery was abandoned. The trachea was extubated two hours later in SICU and the patient made a full recovery.

The total IgE concentration was 162 IU/ml (normal range is 0-200 IU/ml) during the resuscitation. A week later, further investigation revealed positive Skin Prick Test (SPT) to chlorhexidine and negative to lidocaine, silver sulphadiazine, iodine, ethanol and latex. SPT for 0.1% chlorhexidine was weakly positive, however SPT for 0.45%, 1% and 2% chlorhexidine were strongly positive. The patient was rescheduled for the surgery. The anesthesia was planned to follow the same procedures used on the previous occasion. This time povidone-iodine was used for skin preparation prior to epidural block, central venous and artery cannulation. The CVC was changed to a non-chlorhexidine catheter (Blue FlexTip®, 14Ga, Arrow International, Inc. USA). He subsequently underwent surgery successfully and uneventfully. Six weeks later, SPT showed a strongly positive reaction to 0.1%, 0.45%, 1% and 2% chlorhexidine, but he was now SPT positive to 0.05% dilution which was previously negative.

### Case 2

A healthy 34-year-old woman with chloramphenicol allergy had general anaesthesia for elective left retroperitoneal mass resection. Povidone-iodine was used for skin preparation. The insertion of CVC was performed before administration of any other intravenous agent. Immediately after CVC placement, the patient became irritable and felt nausea. Then she began coughing and produced white foaming sputum. The patient became hypertensive (195/145 mmHg), tachycardic (156 beats/min). We gave phentolamine 0.5 mg twice, propofol 40 mg and methylprednisolone 40 mg immediately. Then cyanosis and clammy skin developed, and oxygen saturation (SpO<sub>2</sub>) fell down to 77% quickly.

Auscultation showed both lungs full of moist rales. Her blood pressure decreased suddenly and profoundly and then couldn't be recorded until femoral arterial catheter was inserted. The first invasive pressure was 54/13 mmHg with heart rate of 150 beats/min. The patient was successfully resuscitated with epinephrine, fluid, emergency tracheal intubation and withdrawal of CVC, and surgery was postponed. A week later, the skin prick test with 0.1%, 0.45%, 1% and 2% chlorhexidine were strongly positive. She subsequently underwent uneventful surgery following strict avoidance of chlorhexidine exposure. Postoperative pathology was retroperitoneal neurofibroma. Six weeks later, SPT showed a positive reaction to 0.1%, 0.45%, 1% and 2% chlorhexidine as before, but she was now skin test positive to 0.05% dilution which was previously negative.

### Discussion

The life-threatening clinical manifestations in two cases can be considered as anaphylactic shock to chlorhexidine for the following reasons. First, the clinical features (hypotension, tachycardia, erythema, shortness of breath) are the typical manifestation of anaphylaxis. Second, during the resuscitation epinephrine, corticosteroid and large amount of fluids were effective. Third, the cardiovascular collapse occurred immediately after CVC placement. Fourth, using non-chlorhexidine CVC didn't cause anaphylaxis in the rescheduled surgery. Fifth, the SPT was positive to chlorhexidine. Sixth, the CVC was closely inspected and found to be chlorhexidine coated, with a warning on the packing urging extreme caution in chlorhexidine sensitive patients.

Acute anaphylactic reactions to chlorhexidine are rare and the precise incidence is unknown, as many of them are underreported or underestimated. The concentration of chlorhexidine in antiseptics and the estimated frequency varies vastly from different countries [2]. We made a table in which we endeavor to collect every reported case of chlorhexidine CVC allergy and list each case report with the number of patients, the type of CVC, history of allergy, the number of episode, diagnosis test and the outcome [3-11]. Over the past 14 years, 14 case reports of chlorhexidine-coated CVC anaphylaxis were published worldwide. There are 2 cases in Japan, 9 cases in U.K., 1 case in

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America, 1 case in Australia and 1 case in New Zealand (**Table 1**). High prevalence of chlorhexidine sensitization in some European countries may correlate with the availability of over the counter hydrocortisone-chlorhexidine combination creams widely used in atopic dermatitis [12]. All the cases were limited to the Arrow product, and all the patients made a good recovery.

Since chlorhexidine was introduced in 1954, it has become a key component in reducing infection rate due to its superior antiseptic efficacies compared with povidone-iodine or alcohol [13]. Its ubiquitous use in countless surgical, interventional procedures and everyday household raise the possibility of sensitization in a large proportion of general population. The first case of chlorhexidine-coated CVC anaphylaxis was reported in Japan in 1997 [8]. A cluster of anaphylactic reactions due to central lines in Japan prompted a withdrawal of chlorhexidine from in 1990s and a FDA alert in 1998 [9].

Hypersensitivity reactions to chlorhexidine include delayed and immediate type allergies. Delayed minor allergic reaction may be overlooked or erroneously ascribed to other agents. Subsequent exposure may then lead to severe, immediate and life-threatening anaphylaxis [14]. Koo. A and Guleri. A both reported that their patients developed an erythematous rash following a chlorhexidine skin preparation [4, 5]. But these minor cutaneous reactions were unnoticed. Life threatening anaphylaxis was preceded by insertion of chlorhexidine-coated CVC. Six cases reported fatal anaphylaxis happened twice in the same patient by an antiseptic coated CVC, until second time antigenic trigger was found [5, 6, 8-11]. In these case antigenic trigger were erroneously attributed to cefozopran, "Savlon", atracurium, and pancuronium, resulting in severe hypersensitivity reaction on the second exposure. Despite the warning marked on the product packing, clinicians are often unaware of that, as we were on these occasions. Kluger. M and Guleri. A respectively reported a patient with allergy history to chlorhexidine, but they didn't aware that antiseptic CVC containing chlorhexidine [3, 5]. Until anaphylaxis happened again, a further review of all potential triggers was done and a warning on the packing was found. Our patients were exposed to chlorhexidine during skin antiseptics and within chlorhexidine coated CVC.

The combined amount of chlorhexidine led to an anaphylactic shock in our sensitized patients. It is imperative to consider chlorhexidine as a causative agent in unexplained fatal anaphylaxis.

There are several interesting features of these two cases.

In the second case, immediately after the insertion of CVC, the patient became hypertensive (195/145 mmHg) and tachycardic. At that time we thought the adrenal mass might be a pheochromocytoma, so we gave phentolamine 0.5 mg twice. Then we found that was a misinformation, hypertension might be caused by irritation and convulsion. And the misinformation further worsened the anaphylactic shock. Therefore, early and correct recognition of the reaction is the key to successful outcome.

Anaphylaxis is a severe systemic allergic reaction that affects the skin, the respiratory system, the cardiovascular system and the gastrointestinal system. Anaphylaxis is considered when two or more body systems are noted [15]. In the first case, the patient had cardiovascular collapse, difficulty in breathing, rash and convulsion, without bronchospasm and airway obstruction. In the second case, the patient had cardiovascular collapse, severe respiratory symptoms and nausea, without skin manifestations or bronchospasm. Interestingly, these two cases didn't exhibit signs of bronchospasm, nor of the 14 cases we collected [3-11]. Bronchospasm was not a prominent feature in these cases.

The diagnosis of anaphylaxis is by measuring specific IgE to chlorhexidine, serum tryptase, skin prick test and intradermal testing [16]. It is recommended the serum tryptase is measured approximately 2 h after onset of anaphylaxis. The identification of specific IgE during the diagnosis of chlorhexidine is a reliable tool with high specificity and sensitivity [17]. In the first case, the total IgE concentration was 162 IU/ml (normal range 0-200 IU/ml). IgE in the patients with a type I allergic reaction usually shows high plasma concentration. Interestingly, Watkins described that 10-20% of the population exhibits low IgE concentrations [18]. This should not rule out an allergy as our reaction occurred through a direct non-IgE-mediated anaphylactic response [19]. Skin Prick Test has better sensi-

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tivity and plays an important role in the investigation of anaphylaxis [20]. All potential causative agents should be investigated. The SPTs in two cases were positive to chlorhexidine, and negative to all administered anaesthetic agents. It is interesting both SPTs at 1 week were negative to 0.05% chlorhexidine, but both second tests at 6 week were positive. The optimal time to skin prick test is uncertain, but most allergist wait 4-6 weeks after the episode in order to avoid false negative results [21]. Our result was similar to the literature reported by Stephen R and Oda T [8, 10].

In conclusion, Chlorhexidine coated CVC should be used with caution, and a careful history should be taken before applying it. The warning marked on the packaging should be apparent, amplified and highlighted. Clinicians should be aware that chlorhexidine coated CVC can trigger rare but potentially life-threatening hypersensitivity reaction in susceptible individuals. Allergic reaction to chlorhexidine must be recorded clearly in their case notes and wristbands. Chlorhexidine-allergic patients should be advised to avoid exposure to chlorhexidine containing products. An alcohol-based iodophor solution would be a safe and effective alternative to those patients [22].

### Disclosure of conflict of interest

None.

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