



Case Report

Chlorhexidine-related refractory anaphylactic shock: a case successfully resuscitated with extracorporeal membrane oxygenation[☆]



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Abstract

Importance: We report a patient with a life-threatening anaphylactic reaction to a chlorhexidine-coated central venous catheter, confirmed with a high serum level of chlorhexidine-specific IgE. To our knowledge, this is the first case successfully resuscitated using extracorporeal membrane oxygenation (ECMO). Great caution is required when using chlorhexidine and chlorhexidine-impregnated catheters, given that its widespread use has the potential to sensitize certain patients and may result in life-threatening anaphylaxis on subsequent exposure.

Observations: A case report of a single patient with life-threatening anaphylactic shock to chlorhexidine, who was successfully resuscitated using ECMO.

Conclusions: We have designed a flowchart for the diagnosis and management of severe anaphylaxis. This case report highlights the potential for chlorhexidine to be a source for the development of refractory anaphylactic shock. We suggest that ECMO may save the lives of patients with severe bronchospasm and refractory anaphylactic shock secondary to chlorhexidine.

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1. Introduction

Chlorhexidine is widely used as a skin antiseptic to facilitate medical and surgical procedures. It is also impregnated in medical devices such as surgical mesh,

dressings, and central venous catheters [1,2]. However, extensive use of chlorhexidine has the potential to sensitize certain patients and may lead to life-threatening anaphylaxis on subsequent exposure [3]. Hypersensitivity reactions to chlorhexidine are being increasingly documented in the medical literature [3–7]. Here, we report a patient with a life-threatening anaphylactic reaction to a chlorhexidine-coated central venous catheter (Fig. 1). This was confirmed by a subsequent high serum level of a high serum level of chlorhexidine-specific IgE. To our knowledge, this is the first such case successfully resuscitated using extracorporeal membrane oxygenation (ECMO).

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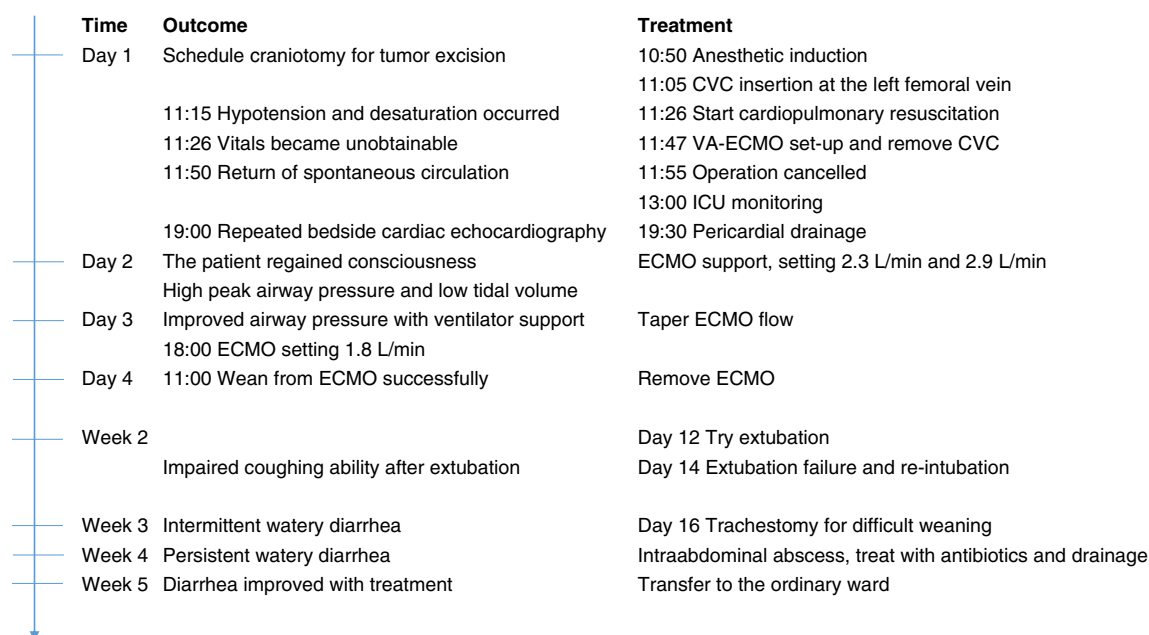


Fig. 1 Timeline for clinical course.

2. Case report

A 54-year-old man was admitted for right clivus chondroma excision. His medical history included hypertension and coronary artery disease. He underwent coronary angioplasty with stent insertion 3 years ago, and his condition was stable thereafter. He had no known allergies. Physical examination revealed clear breath sounds bilaterally, and his preoperative laboratory test results were unremarkable.

General anesthesia was induced with fentanyl 150 µg, propofol 150 mg, and cisatracurium 10 mg. After successful intubation, anesthesia was maintained with an air/oxygen/desflurane mixture. An arterial catheter was placed to monitor his blood pressure intraoperatively. After the skin was cleaned with alcohol and chlorhexidine solution, a central venous catheter (CVC) coated with chlorhexidine and silver sulfadiazine was inserted in his left femoral vein. Five minutes later, tachycardia (118 beats per minute) with hypotension (70/38 mm Hg) and desaturation ($\text{SpO}_2 < 90\%$) developed. High peak airway pressure (42 cm H_2O) and ST-segment elevation at the electrocardiogram (ECG) were also observed. No prophylactic antibiotic or additional medication was administered before the episode. There was no evidence of urticaria, flush, or facial edema. Initially, end-tidal CO_2 increased but soon dropped to 17 to 21 mm Hg. His rhythm on ECG became progressively bradycardic, and his arterial waveform and SpO_2 became unobtainable. Pulseless electrical activity was diagnosed, and cardiopulmonary resuscitation (CPR) was immediately performed. The accumulated dose of epinephrine was 15 mg, and the amount of fluid resuscitation was 2500 mL of crystalloid fluids and 500 mL of hydroxyethyl starch (Voluven) over 20 minutes. An arterial blood gas revealed hypercapnia (PaCO_2 66 mm Hg) and revealed global left ventricular hypokinesia,

no aortic aneurysm or dissection, no visible pulmonary embolism, and mild pericardial effusion. An emergent ECMO system was initiated for severe cardiac dysfunction in shock refractory to aggressive fluid resuscitation, inotropic agents, and vasopressors. Blood pressure (80/50 mm Hg) and saturation (PaO_2 319 mm Hg) were restored after veno-arterial (VA)-ECMO with an initial setting of 2410 rpm and a flow of 2.24 L/min. Because hypersensitivity reaction to CVC coating agents could not be ruled out, we removed the impregnated CVC and replaced it with a noncoated one. Subsequently, 120 mg methylprednisolone was administered intravenously and 2 puffs of inhaled albuterol via an AeroChamber. The operation was canceled, and the patient was transferred to the intensive care unit (ICU) for further management.

In the ICU, initial mechanical ventilation parameters were as follows: pressure control mode, P_i , 30 cm H_2O ; T_i , 1 seconds; rate, 25 beats per minute; and fraction of inspired oxygen, 100%. His airway pressure remained high (peak airway pressure 36 mm Hg) with limited tidal volume in the following 2 days. Positive end-expiratory pressure was set as 5 cm H_2O initially and was titrated up to 12 cm H_2O thereafter. His cardiac output remained low despite VA-ECMO support and high-dose inotropic support. Repeated bedside transthoracic echocardiography on the night of ICU admission revealed no evidence of regional wall motion abnormalities, mild pulmonary hypertension, and massive pericardial effusion. Urgent pericardial drainage yielded 460 mL of sanguineous fluids, suspected secondary to anaphylaxis and systemic inflammatory response syndrome–induced severe capillary leakage of fluid. Cardiac enzyme levels were only minimally elevated as follows: creatine kinase, 131 U/L; creatine kinase-MB, 99 U/L; and troponin I, 0.191 ng/mL. Serial workup of cardiac enzymes revealed decreased proportion of creatine kinase-MB/creatinine

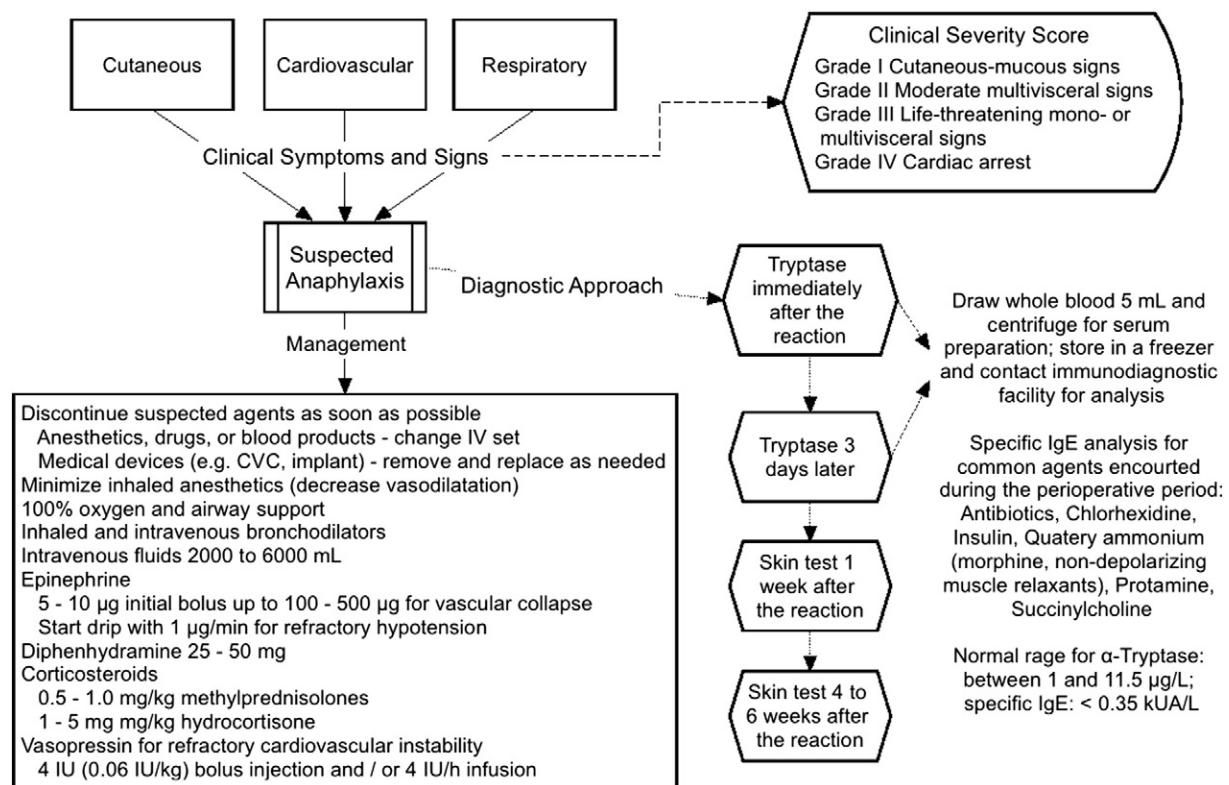


Fig. 2 Flowchart for anaphylaxis in the anesthesia department.

kinase, compatible with postresuscitation myocardial ischemia. VA-ECMO flow was titrated to support the patient's cardiopulmonary condition. For maintenance, the ECMO flow setting ranged from 2.3 to 2.9 L/min over the first 2 days. For anticoagulation management, we used heparin 25 000 U in 250 mL and titrated it to maintain the activated clotting time between 200 and 220 seconds. Serial serum analysis for the mast cell tryptase level (Phadia AB, Uppsala, Sweden) was performed and revealed a remarkable elevation to 33.1 µg/L (reference range, <11.5 µg/L) immediately after the event. This subsequently decreased to 1.72 µg/L 72 hours later. Chlorhexidine-specific IgE also showed a remarkable elevation to 7.21 kU/L (reference range, <0.35 kU/L). Life-threatening anaphylaxis to chlorhexidine was confirmed.

The patient regained consciousness the next day after initiation of ECMO and his arrest, and his condition improved gradually. With VA-ECMO support for 3 days, his airway pressure decreased gradually, and his saturation improved. The ECMO flow setting was tapered on to 1.8 on the third day after the episode. On the morning of weaning from ECMO, his Pao₂ was 135.8 mm Hg with ventilator setting: pressure control mode, P_i, 18 cm H₂O; T_i, 1 seconds; rate, 15 beats per minute; positive end-expiratory pressure, 11 cm H₂O; and fraction of inspired oxygen, 70%. ECMO was successfully removed on the fourth day. An episode of extubation failure developed because of impaired cough function. Tracheostomy was performed for difficult weaning. There was another episode of intraabdominal abscess, and he underwent a

complete course of antibiotics and drainage. He was transferred to the general ward after 5 weeks.

3. Discussion

This case report highlights a potentially life-threatening and protracted anaphylaxis secondary to use of a chlorhexidine-impregnated CVC. The prevalence of patients with sensitization to chlorhexidine may likely increase after the widespread use of chlorhexidine products. This may increase the incidence of life-threatening or fatal anaphylaxis on subsequent exposure. Because the hemodynamic collapse can rapidly occur without cutaneous reactions [5,8], early detection and removal of chlorhexidine-coated products are critical for successful resuscitation.

To our knowledge, this is the first case of successful ECMO resuscitation of a patient with life-threatening anaphylaxis to chlorhexidine. VA-ECMO support aided the management of refractory circulatory shock and subsidence of refractory bronchospasm. This patient in the case report may not survive from refractory hypotension, deteriorated desaturation, and repeated prolonged CPR if there were no VA-ECMO maintained during the subsequent 4 days. It may result in severe myocardial injury, overt systemic inflammatory response, and enormous reperfusion injury. ECMO was indicated for this patient because of the following complications: First, the shock was

profound and refractory in spite of aggressive fluid supplementation as well as repeated dosing of epinephrine during resuscitation. We emphasize to remove the coated catheter and replacement with a noncoated catheter as soon as possible despite many previous cases reported clinical signs of anaphylaxis could subside with the catheter still indwelled [6,9]. In our case, the coated CVC remained in situ for 30 minutes. It could not to be excluded if it might result in difficult resuscitation until VA-ECMO set up. Second, myocardial contractility may have been affected by underlying coronary artery disease in this patient. ST-segment elevation was noted on ECG during resuscitation, and this may have led to low cardiac output. Third, the follow-up transthoracic echocardiography revealed mild pulmonary hypertension with a peak systolic tricuspid pressure gradient of 40 mm Hg. During resuscitation, bronchospasm may aggravate pulmonary hypertension and result in decreased venous return to the left atrium. Finally, cardiac tamponade developed after CPR and chest compression. Timely diagnosis and urgent drainage to relieve tamponade would also play a role in saving his life.

There is increasing concerns of unrecognized and underestimated allergic reactions to chlorhexidine currently [10]. Without definite diagnosis or successful resuscitation, life-threatening or fatal chlorhexidine anaphylaxis may be underestimated worldwide. We have designed a flowchart for the diagnosis and management of severe anaphylaxis at our institution (Fig. 2). This flowchart also points out a prompt diagnostic approach to confirm anaphylaxis and to identify the suspected allergens. According to a recent study [11], extremely high value of tryptase increases specificity of diagnosis. There is a relationship between immunoassay results (such as histamine or tryptase levels) and severity of anaphylaxis. As most of the immunoassay for human tryptase or specific IgE are time consuming and not available during resuscitation, continued medical education is required to raise further awareness of chlorhexidine anaphylaxis. We suggest that timely diagnosis and early removal of allergen are important to treat

chlorhexidine-related anaphylactic shock and severe bronchospasm, and ECMO may save the lives of patients in extremely critical condition.

References

- [1] Montecalvo MA, McKenna D, Yarrish R, Mack L, Maguire G, Haas J, et al. Chlorhexidine bathing to reduce central venous catheter-associated bloodstream infection: impact and sustainability. *Am J Med* 2012;125(5):505-11.
- [2] Darouiche RO, Wall MJ Jr, Itani KM, Otterson MF, Webb AL, Carrick MM, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. *N Engl J Med* 2010;362(1):18-26.
- [3] Guleri A, Kumar A, Morgan RJ, Hartley M, Roberts DH. Anaphylaxis to chlorhexidine-coated central venous catheters: a case series and review of the literature. *Surg Infect* 2012;13(3):171-4.
- [4] Nakonechna A, Dore P, Dixon T, Khan S, Deacock S, Holding S, et al. Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom. *Allergol Immunopathol (Madr)* 2012.
- [5] Jee R, Nel L, Gnanakumaran G, Williams A, Eren E. Four cases of anaphylaxis to chlorhexidine impregnated central venous catheters: a case cluster or the tip of the iceberg? *Br J Anaesth* 2009;103(4):614-5.
- [6] Stephens R, Mythen M, Kallis P, Davies DW, Egner W, Rickards A. Two episodes of life-threatening anaphylaxis in the same patient to a chlorhexidine-sulphadiazine-coated central venous catheter. *Br J Anaesth* 2001;87(2):306-8.
- [7] Terazawa E, Shimonaka H, Nagase K, Masue T, Dohi S. Severe anaphylactic reaction due to a chlorhexidine-impregnated central venous catheter. *Anesthesiology* 1998;89(5):1296-8.
- [8] Lieberman Phillip, Kemp Stephen F, Oppenheimer John, Lang David M, Bernstein I Leonard, Nicklas Richard A, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115(3 Suppl. 2):S483-523.
- [9] Oda T, Hamasaki J, Kanda N, Mikami K. Anaphylactic shock induced by an antiseptic-coated central venous [correction of nervous] catheter. *Anesthesiology* 1997;87(5):1242-4.
- [10] Silvestri DL, McEnery-Stonelake M. Chlorhexidine: uses and adverse reactions. *Dermatitis* 2013;24(3):112-8.
- [11] Laroche D, et al. Diagnostic value of histamine and tryptase concentrations in severe anaphylaxis with shock or cardiac arrest during anesthesia. *Anesthesiology* 2014;121(2):272-9.