

# Preoperative Chlorhexidine Anaphylaxis in a Patient Scheduled for Coronary Artery Bypass Graft: A Case Report

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*Chlorhexidine is a synthetic antiseptic and disinfectant that has been widely used in the healthcare setting and in everyday household products. In addition to oral rinses and skin preparations, manufacturers have incorporated chlorhexidine coatings into medical devices such as urinary catheters, endotracheal tubes, and central venous catheters in an effort to reduce infection rates. Despite the ubiquitous use of chlorhexidine, severe reactions, such as anaphylaxis, are relatively rare.*

*This case report describes a 65-year-old patient scheduled for coronary artery bypass graft surgery who preoperatively experienced anaphylaxis to chlorhexi-*

*dine delivered through multiple routes of administration. To our knowledge, this is the first reported perioperative anaphylactic reaction to chlorhexidine in the United States. A review of the anaphylaxis cascade, the prevalence of hospital-acquired infections, and the risks of using chlorhexidine are thoroughly discussed. It must be appreciated that life-threatening reactions to this commonly used agent are more than just a theoretical possibility.*

**Keywords:** Anaphylaxis, central venous catheter, chlorhexidine, hospital-acquired infection.

**A**larming rates of hospital-acquired infections continue to plague the healthcare setting. It has been identified as the most common complication, affecting up to 10% of patients in acute care hospitals.<sup>1</sup> In the past decade, an emphasis has been placed on guidelines and interventions to add to the armamentarium of patient safety and infection control.

Chlorhexidine has become a key component in this process due to its superior antiseptic capabilities compared with povidone-iodine or alcohol.<sup>2-5</sup> More recently, healthcare manufacturers have coated medical devices such as urinary catheters, endotracheal tubes, and central venous catheters (CVCs) with chlorhexidine. It is not only used in the healthcare setting but also frequently found in everyday household items such as toothpaste, mouthwash, and cleaning products. Chlorhexidine has become the antiseptic of choice of our day, just as wine and vinegar were during the Hippocrates era.

Reported anaphylactic reactions to chlorhexidine are rare despite its ubiquitous availability. Isolated cases of perioperative chlorhexidine anaphylaxis have been infrequently reported in the literature in Europe, Australia, and Asia.<sup>6-11</sup> This case report identifies the use of multiple routes of chlorhexidine that resulted in an anaphylactic reaction in a patient scheduled for coronary artery bypass graft surgery. To our knowledge, this is the first reported perioperative anaphylactic reaction to chlorhexidine in the United States.

## Case Summary

A 65-year-old, 178-cm, 142-kg, white man presented to

the emergency department with complaints of chest pain. After evaluation, he was found to have acute coronary syndrome and underwent cardiac catheterization, which revealed multivessel coronary artery disease with preserved left ventricular function. He was subsequently referred to the cardiothoracic surgeon for evaluation.

The patient had no known food or drug allergies. He had a substantial cardiovascular history, which included hypertension dating to his teenage years, a prior septal myocardial infarction, hyperlipidemia, and venous insufficiency. He had a 30 pack-per-year history of smoking but quit at age 50 years. He had been diagnosed with emphysema and slept with oxygen therapy, at 2 L/min, at night. Surgical history included laparoscopic cholecystectomy, lumbar discectomy, and multiple knee arthroscopies. The patient denied any anesthesia complications with all prior surgeries. The patient's current medications included metoprolol, 100 mg twice daily; captopril, 50 mg twice daily; aspirin, 325 mg each morning; atorvastatin, 40 mg each evening; and naproxen, 220 mg twice daily. A preoperative electrocardiogram revealed sinus bradycardia, prior septal myocardial infarction, and anterolateral ischemia. A transthoracic echocardiogram revealed an ejection fraction of 55% with moderate left ventricular hypertrophy.

The night before surgery the patient's chest hair was clipped, and he cleansed himself with preoperative skin cloths containing 2% chlorhexidine gluconate (Sage Products Inc). The following morning, the patient was taken to the preoperative holding area and prepared for surgery. The left forearm was cleansed with a chlorhexidine gluconate and isopropyl alcohol (ChlorPrep) skin

preparation applicator (CareFusion Inc) followed by insertion of a 16-gauge peripheral intravenous (IV) line. Standard monitors were applied, and the patient was premedicated with 1 mg of midazolam and 50 µg of fentanyl by IV injection. The right wrist was then cleansed with ChlorPrep followed by insertion of a 20-gauge arterial catheter placed in the right radial artery. An antimicrobial-coated CVC (ARROWg+ard, 9F, Arrow International Inc) containing chlorhexidine acetate and silver sulfadiazine was placed in the right internal jugular vein using standard sterile technique in addition to cleansing the right side of the neck with a ChlorPrep skin applicator.

It was then recognized that the patient had not received his preoperative chlorhexidine oral rinse. Once fully awake with airway reflexes intact, the patient was given 15 mL of 0.12% chlorhexidine gluconate oral rinse. Within minutes after the mouth rinse, arterial hypotension developed (decreasing from 149/91 mm Hg to 100/60 mm Hg within 5 minutes), along with tachycardia (120/min) and generalized erythema that was more pronounced in the face and upper part of the chest.

The patient was taken emergently to the operating room for resuscitation and intubation. The patient's blood pressure on arrival to the operating room was approximately 50/30 mm Hg, and he had a heart rate of 120/min. Epinephrine, 16 µg IV; phenylephrine, 200 µg IV; diphenhydramine, 50 mg IV; and hydrocortisone, 100 mg IV, were promptly administered. The patient's blood pressure increased to 90/50 mm Hg after 3 minutes. Anesthesia was induced with etomidate, 28 mg IV, and fentanyl, 50 µg IV. Tracheal intubation was facilitated with succinylcholine, 200 mg IV. Continuous infusions of epinephrine, 6 µg/min, and norepinephrine, 10 µg/min, were initiated to maintain a systolic blood pressure greater 120 mm Hg. Fluid resuscitation was achieved with a total of 4.6 L of multiple electrolytes injection (Normosol-R, Hospira) and 500 mL of 5% albumin. Following stabilization, the patient was transferred to the cardiovascular intensive care unit while receiving controlled ventilation; epinephrine, 6 µg/min; and propofol (Diprivan), 15 µg/kg/min.

The patient was placed on a regimen of hydrocortisone and diphenhydramine and continued epinephrine IV infusion in the cardiovascular intensive care unit (ICU). The events were discussed with the patient's wife, at which point she disclosed that the patient had experienced a mild rash with hives throughout his body the night before after using the chlorhexidine body cloths. It was then recognized that the CVC was coated with chlorhexidine, and it was replaced with a nonantimicrobial-coated catheter. Within hours the patient's hemodynamics stabilized, and the epinephrine infusion was discontinued.

The following day, the patient was extubated using standard ICU protocol. A serum chlorhexidine immuno-

globulin E (IgE) test (IBT Laboratories) was obtained 48 hours after the incident, which revealed a positive result of 5.26 kU/L (reference range < 0.35 kU/L). The surgery was postponed. The patient was discharged to home on the third day following the incident, with instructions for strict avoidance of chlorhexidine-containing products (Figure 1).

## Discussion

Healthcare-associated infections are, unfortunately, a common complication throughout the world. In 2002, there were an estimated 1.7 million healthcare-associated infections per year in the United States.<sup>12</sup> Nearly 100,000 of those infections resulted in death, with 14% attributable to bloodstream infections.<sup>12</sup> It has been estimated that 250,000 cases of catheter-related bloodstream infections occur annually, with a mortality rate of 12% to 25% and a marginal cost of approximately \$25,000 per case.<sup>13</sup> With these staggering numbers in mind, organizations and patient safety programs around the country have promoted initiatives to improve quality of care. In relation to catheter-related bloodstream infections, these programs have recommended chlorhexidine as the superior choice of skin antiseptics.<sup>13-15</sup>

Chlorhexidine is a commonly used synthetic antiseptic and disinfectant that was introduced in the 1950s. It affects both gram-negative and gram-positive bacteria, *Candida albicans*, and some viruses.<sup>9</sup> It has a broad range of uses, including antiseptics of skin and mucosal membranes, as well as disinfection of surgical instruments and surfaces. Recently, manufacturers have incorporated chlorhexidine coatings on indwelling medical devices such as urinary catheters, endotracheal tubes, and CVCs.<sup>9,16,17</sup> The US Food and Drug Administration (FDA) has outlined the use of chlorhexidine as part of a multidisciplinary approach to improve patient outcomes and reduce healthcare costs.<sup>13</sup> A class IA recommendation was issued for the use of chlorhexidine, with emphasis on its use as a cutaneous antiseptic.<sup>13</sup> (A class IA recommendation is strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies.<sup>13</sup>)

In addition to its use in the healthcare setting, chlorhexidine is found in many domestic products, including toothpaste, mouth rinse, and cleaning fluids. Inherent to any synthetic product, even the slightest exposure can lead to adverse reactions in certain individuals. Although rare, immediate-type allergic reactions to chlorhexidine have been noted since the 1980s.<sup>9</sup> A higher prevalence has been identified from the mucosal route of administration, especially in persons of Japanese descent.<sup>9</sup> In 1984, this prompted the Japanese Ministry of Health to recommend the avoidance of chlorhexidine in mucosal membranes.<sup>9</sup> Similarly, in 1998, with an increasing number of serious hypersensitive reactions related to chlorhexidine-impregnated medical devices,

the FDA released a public health notice outlining their concerns of this potential risk.<sup>18</sup> Although the amount of chlorhexidine on these coatings is relatively small, unpredictable drug reactions, such as anaphylaxis, are dose independent so even the smallest amount can trigger an IgE-mediated reaction.<sup>19</sup>

A type 1 hypersensitivity reaction, or anaphylaxis, is an immunologic response to a specific triggering substance (antigen). The synthesis of IgE antibodies is what differentiates anaphylaxis from other normal immunologic responses.<sup>20</sup> When certain individuals are exposed to a triggering antigen, their immunologic system activates the production of IgE antibodies from B lymphocytes. A “priming” effect then occurs from the attachment of IgE antibodies to the surface membrane of mast cells.<sup>20</sup> Reexposure leads to rapid binding of the antigen to the IgE antibodies of primed mast cells. This binding activates the mast cell, causing degranulation and release of allergenic mediators such as histamine, cytokines, and leukotrienes, which account for the signs and symptoms of anaphylaxis<sup>20,21</sup> (Figure 2). Specific laboratory tests can identify abnormally elevated levels of IgE antibodies from a particular antigen such as chlorhexidine. This IgE test can be used to support the diagnosis of chlorhexidine anaphylaxis in the presence of clinical manifestations.<sup>22</sup>

Manifestations of anaphylaxis affect the skin (erythema, hives, pruritus, angioedema), the gastrointestinal system (nausea, vomiting, abdominal cramping, diarrhea), the respiratory system (cough, wheeze, stridor, shortness of breath), and the cardiovascular system (arrhythmia, hypotension)<sup>23</sup> (Figure 3). Increased vascular permeability is a characteristic feature produced by allergenic mediators, which can allow for 50% of intravascular fluid to shift into the extravascular space within 10 minutes.<sup>23</sup> As a result, hemodynamic collapse can occur before cutaneous manifestations.<sup>23</sup>

Interestingly, the patient described in this case report did not exhibit signs of bronchospasm as would be anticipated with an anaphylactic reaction. This finding is consistent with similar cases of chlorhexidine anaphylaxis reported in the literature<sup>8,11,18,24</sup> and may be a topic for further investigation.

Several medications used in anesthesia, such as muscle relaxants and hypnotics, can cause nonimmunologic, nonspecific histamine release. As such, mild symptoms of plausible allergic reactions, such as flushing and urticaria, are often disregarded as normal temporary reactions to

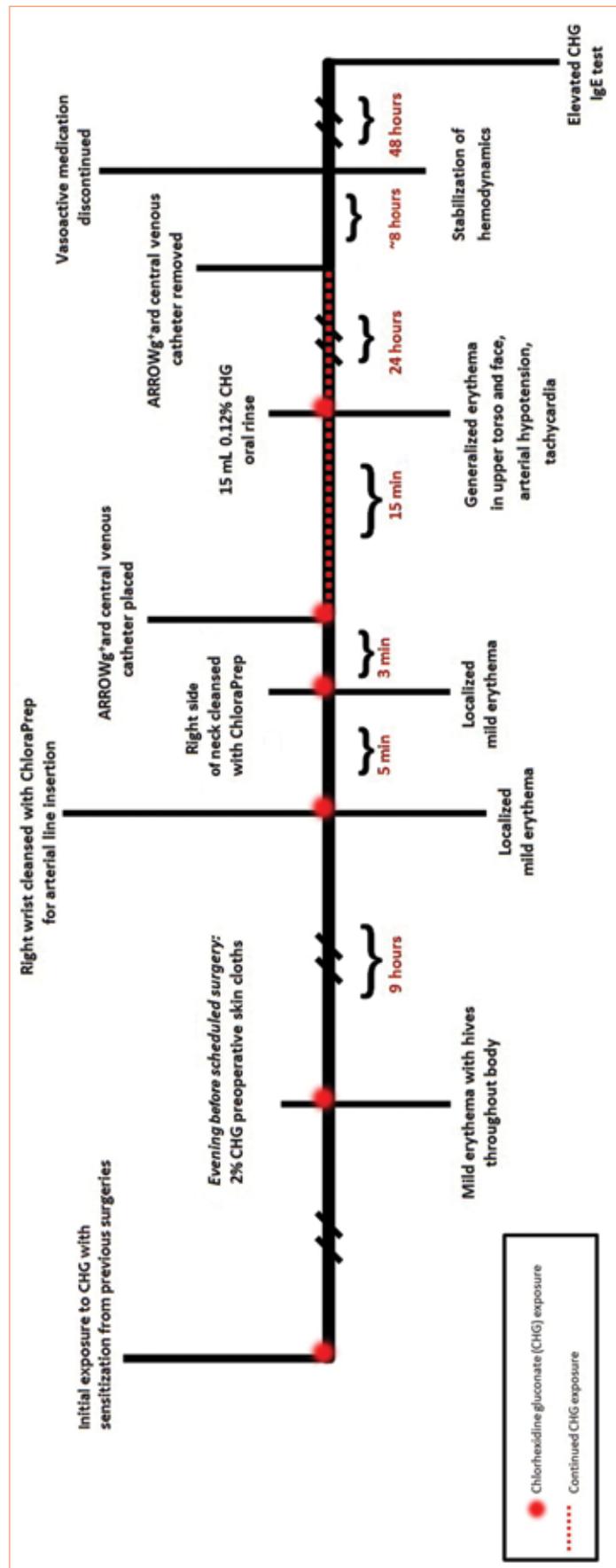


Figure 1. Timeline of Chlorhexidine Exposure with Subsequent Clinical Manifestations

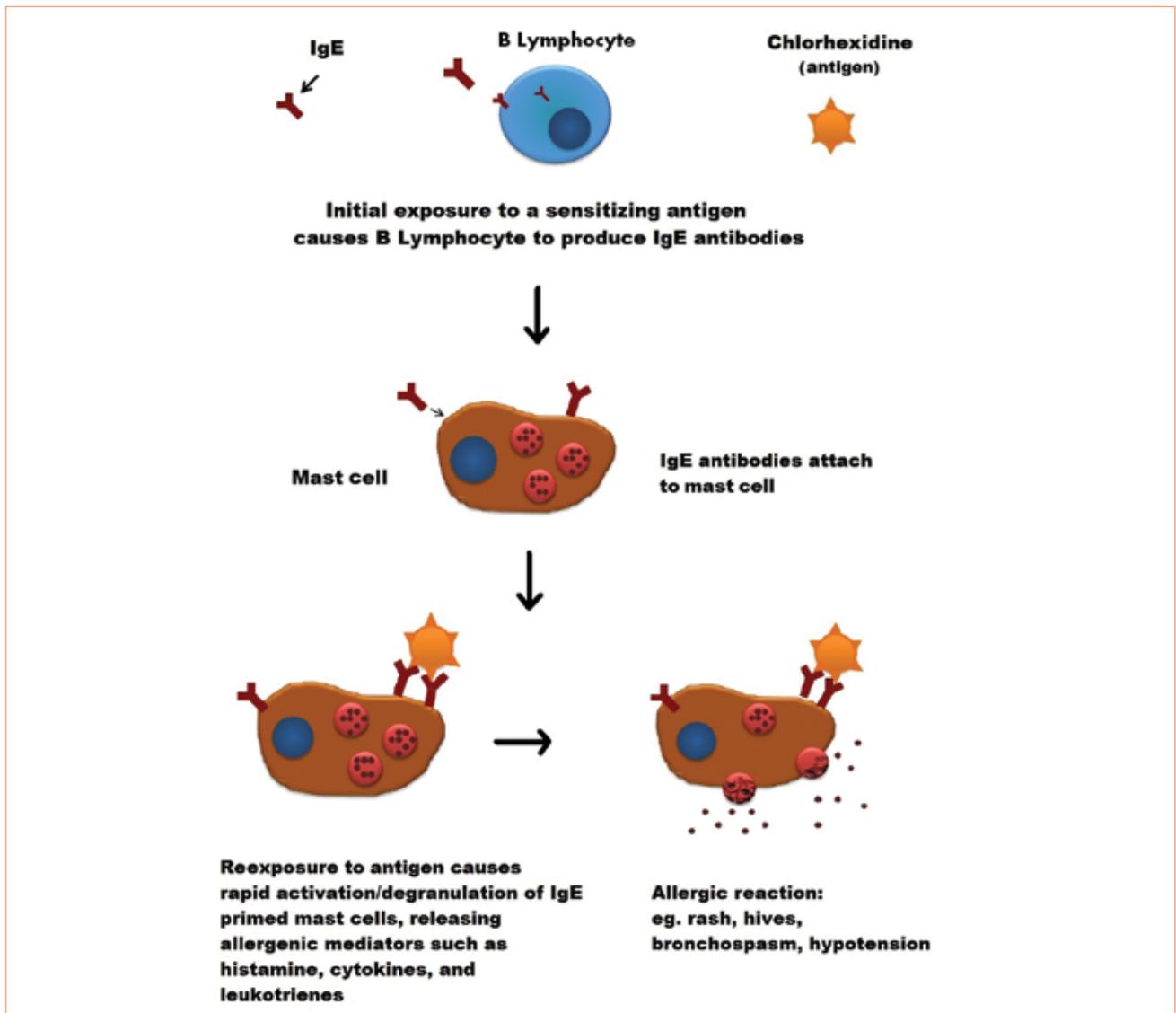


Figure 2. IgE-Mediated Inflammatory Cascade with Chlorhexidine as the Presenting Antigen

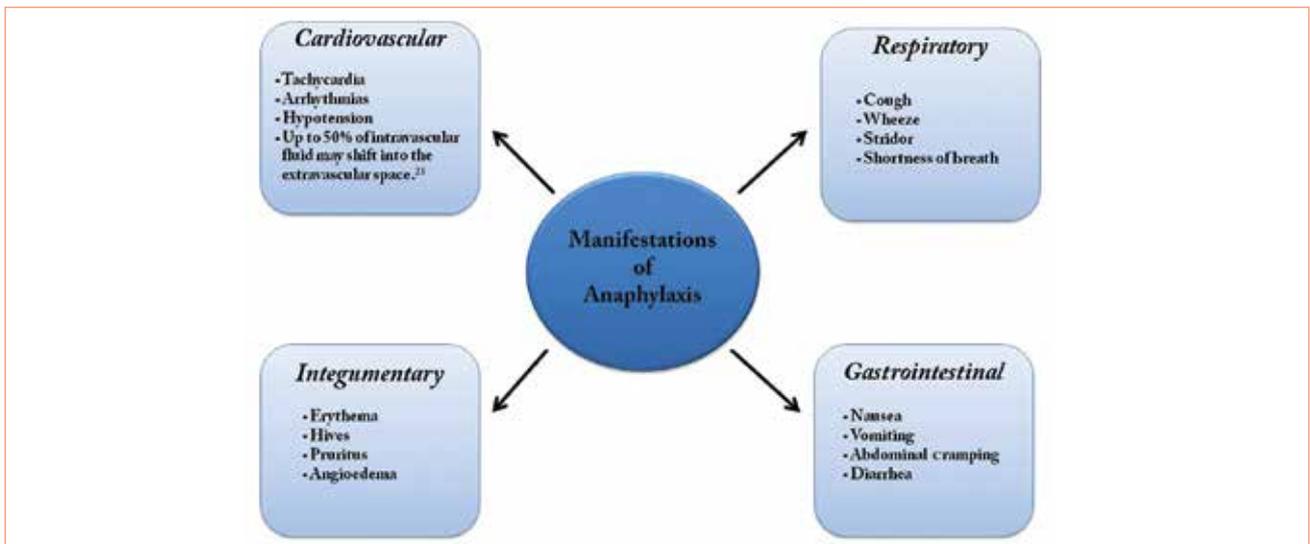


Figure 3. Manifestations of Anaphylaxis

Category	Product (manufacturer)	Notes
Oral rinse	Peridex (3M)	0.12% chlorhexidine gluconate
	Periogard (Colgate-Palmolive)	0.12% chlorhexidine gluconate
Skin antiseptic	Avagard (3M)	1% chlorhexidine gluconate + 61% ethyl alcohol; frequently used as presurgical hand preparation
	Betasept (Purdue Pharma)	4% chlorhexidine gluconate
	ChlorPrep (CareFusion)	2% chlorhexidine gluconate + 70% isopropyl alcohol; various applicator available; often contains green or orange tint
	Prevantics (PDI)	3.15% chlorhexidine + 70% isopropyl alcohol
	Hibiclens (Mölnlycke Health Care)	4% chlorhexidine gluconate
	Hibistat (Mölnlycke Health Care)	0.5% chlorhexidine + 70% isopropyl alcohol
	Sage patient preoperative skin cloth (Sage Products)	2% chlorhexidine gluconate; equivalent to 500 mg of chlorhexidine gluconate per cloth
Supplies and equipment	ARROWg+ard Blue PLUS-central venous catheter (Arrow International)	20-cm catheter contains an average of 9.3 mg chlorhexidine, 0.63 mg silver, and 1.5 mg sulfadiazine
	ArrowEVOLUTION with Chlorag+ard (Arrow International)	40-cm, 50-cm and 55-cm peripherally inserted central lines containing 13.7 mg, 17 mg, and 18.6 mg of chlorhexidine, respectively
	GORE DUALMESH PLUS (Gore Medical)	Chlorhexidine gluconate + silver; biomaterial used for surgical repair of hernia
Antimicrobial dressing	BioPatch protective disk with CHG (Ethicon)	Range of 52.5 mg to 92 mg chlorhexidine gluconate among 6 barrier disk sizes; intended for use in combination with transparent occlusive dressing
	Tegaderm CHG (3M)	Transparent adhesive dressing with integrated gel pad containing 2% chlorhexidine gluconate

**Table.** Examples of Products in the Healthcare Setting That Contain Chlorhexidine

Abbreviation: CHG, chlorhexidine.

these medications. However, observed cutaneous reactions in response to chlorhexidine exposure may only be the tip of the iceberg. Clinicians must respect these manifestations as potential indications of impending cardiovascular collapse.

Chlorhexidine is found in many preparations throughout the healthcare setting (Table). In particular, patients can be exposed to chlorhexidine in several places at once during anesthesia and surgery. It may be used for skin antisepsis before the insertion of arterial and central venous lines, in presurgical hand scrubs, as surgical preparations on body parts, and even within lubricating gels used in the placement of urinary catheters. The combined amount of chlorhexidine absorption from these multiple routes of exposure can lead to an anaphylactic reaction in sensitized patients.

In the case described, the patient was repetitively exposed to multiple routes of administration followed by continued exposure from the CVC. The patient's condition did not improve until even the slightest exposure source was removed.

The decisions for an antiseptic alternative in a patient with suspected chlorhexidine sensitization should be based on scientific evidence. Various studies have shown that alcohol produces synergistic antiseptic properties

when combined with other products such as chlorhexidine and iodophors.<sup>2-5,13,25</sup> Alcohols have a rapid onset of action but alone do not demonstrate persistent, cumulative activity compared with chlorhexidine and povidone-iodine.<sup>2-5,25,26</sup> Although chlorhexidine-alcohol solutions have demonstrated superior antiseptic properties, an alcohol-based iodophor solution would be a safe and effective alternative in patients with a known chlorhexidine sensitivity.<sup>13,25,26</sup>

Anaphylaxis related to chlorhexidine was suspected in this patient for several reasons. First, the patient's wife revealed the presence of a rash with hives after the patient used presurgical chlorhexidine body wipes the night before the surgery. Second, acute hemodynamic instability requiring the use of multiple vasopressors was noted immediately after the administration of the presurgical mouth rinse containing chlorhexidine. Third, there was rapid improvement in the patient's condition after removing the chlorhexidine-impregnated CVC. Finally, a chlorhexidine IgE test was performed, with a value of 5.26 U/L (reference range < 0.35 U/L). The results suggest an IGE-mediated anaphylactic response.

## Conclusion

Alarming rates of hospital-acquired infections continue

to afflict patients in the acute care setting. Organizations, programs, and clinicians have focused on preventive measures to help reduce these complications. Since its initial introduction in the 1950s, chlorhexidine has demonstrated superior antisepsis compared with other commonly used products and is an effective adjunct to the infection control armamentarium. Hypersensitivity responses are relatively rare considering its ubiquitous use both in and outside the healthcare setting. As such, the risks of its use are often hidden. An increasing number of manufacturers are incorporating chlorhexidine into their products, and clinicians may not be fully aware of this. As discovered in this case, as well as others in the literature, it must be appreciated that these life-threatening reactions to this commonly used agent are more than just a theoretical possibility.

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