

Chlorhexidine: Uses and Adverse Reactions

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Chlorhexidine is increasingly being used not only as an antiseptic to prevent hospital infections and an adjuvant in oral hygiene but also as a preservative in personal care products. As exposure to the agent becomes more widespread, reports of adverse reactions to it are increasing. Complications range from mild irritant contact dermatitis to life-threatening anaphylaxis. Allergic contact dermatitis in some cases precedes anaphylaxis. It is imperative that physicians be aware of the many possible sources of contact with this antiseptic and be alert to recognize the potentially debilitating and catastrophic reactions that may occur because of chlorhexidine sensitization.

CHLORHEXIDINE IS a biguanide topical antiseptic with broad efficacy against bacteria, yeast, and some viruses that has been in use worldwide since 1954.¹ With antibiotic-resistant organisms emerging in hospital and community settings, chlorhexidine is increasingly recommended in both treatment and prevention protocols. In recent years, its role has expanded for reducing health care-associated infections, a significant cause of patient morbidity, mortality, and medical expenditure. We present here an overview of chlorhexidine's current applications and adverse events that have been described with its use.

Chlorhexidine, usually in the gluconate formulation and less frequently as an acetate or hydrochloride salt,^{2,3} is available in concentrations from 0.05% to 4% in aqueous (aq) or alcohol vehicles alone or with other ingredients, such as surfactants, dyes, fragrances, and anesthetics.¹ It is popular for hand washing,^{1,4} daily bathing of intensive care unit patients,⁵ nursery neonatal umbilical stump care,⁶ preoperative bathing,⁷ and surgical site sterilization.^{1,8} It is widely used for skin antisepsis before placement of epidural, arterial, and central venous catheters.^{1,4,7} It has a role in catheter site maintenance,¹ skin cleansing for venipuncture,⁴ oropharyngeal decontamination in ventilator patients,⁹ burn antisepsis,¹⁰ vaginal sanitation,¹¹ and cleansing before urethral catheter insertion.⁴ Some investigators have advised its use to bathe trauma patients before hospital admission.¹² Chlorhexidine has also been impregnated into medical materials, including vascular cannulae^{4,13} and dressings for both vascular¹⁴ and epidural catheters.¹⁵ It has been used for decades by dentists and oral surgeons to control gingivitis and

periodontitis.^{16,17} Table 1 summarizes the standard roles of chlorhexidine at our regional hospital.

Although hypersensitivity reactions to this antiseptic are uncommon, their number seems to be rising (Fig. 1), and they can be life-threatening. The adverse effect of least concern may be irritant contact dermatitis. Skin disruption occurs frequently at sites of chlorhexidine application around percutaneously inserted central catheters.¹⁸ Although the antibacterial benefits of the compound have prompted recommendation for atotics to bathe with it periodically,¹⁹ further irritation can result from this practice.²⁰ In Japan, questionnaires were mailed to 895 physicians to investigate occupational risk.²¹ Of the 307 completed surveys, 23 reported contact dermatitis from chlorhexidine, without further characterization as irritant or allergic.

Chlorhexidine is also a potential cause of allergic contact dermatitis. Delayed-type hypersensitivity to the agent has been documented by patch testing. When chlorhexidine is included in allergen series applied to consecutive patients, 0.5%²² to 13.1%² of the studied population are reported to be positive (Table 2).^{2,22–28} Highest rates of sensitization to the agent are found among those with leg ulcers and stasis dermatitis^{2,23–25} or with atopic dermatitis.²⁸ 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.^{29–31}

Many case reports have been published describing allergic contact dermatitis to chlorhexidine with patch test confirmation (Table 3).^{3,23,29–42} One patient with severe dermatitis after preoperative skin cleansing not only demonstrated positive patch tests to serial dilutions of chlorhexidine digluconate but also showed photoreactivity at even lower concentrations.³³ Most of these cases illustrate the potential for sensitization by chlorhexidine-containing skin cleansers and topical medications. In other instances, however, individuals have developed allergic contact dermatitis after ocular or oral exposure. In addition, contact lens solutions that incorporate the antiseptic were thought to be the source of conjunctivitis in 5 patients with positive patch tests.^{43,44} Beyond risking

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TABLE 1. Standard Procedures for the Use of Chlorhexidine at 1 Regional Hospital*

Skin preparation procedure using chlorhexidine-containing antiseptic

- Surgical hand scrub for employees
- Showering/bathing protocol for MRSA-exposed employees that test positive
- Preoperative whole body wash at home for patients
- Preoperative skin preparation
- Placement of intravascular or femoral lines†
- Femoral vein catheter insertion and removal
- Central venous, arterial, and epidural catheter insertion†
- Umbilical arterial, umbilical venous, and PICC insertion in the NICU‡
- Pleural and abdominal tunneled catheters
- Cannulation of AV fistula/graft
- Termination of hemodialysis

Equipment preparation procedure using chlorhexidine-containing antiseptic

- Pleural and abdominal tunneled catheters, postinsertion
- Ends of patient's access, before continuous venovenous hemofiltration discontinuation

Catheter care using chlorhexidine-impregnated sterile dressings

- Intravascular catheter insertion site§
- Central venous and arterial catheter insertion site
- Insertion site for nontunneled central and arterial lines, tunneled central lines, PICC lines for pediatric patients||
- Central and umbilical line dressing changes in the NICU‡

*Information obtained from the infection control policies at UMass Memorial Medical Center, Worcester, Massachusetts. Accessed December 20, 2012.

†Except if <2 months of age; povidone iodine if allergic.

‡Povidone iodine for infants <28 weeks and <day of life 6 or who have a known reaction to chlorhexidine.

§Unless contraindicated.

||Chlorhexidine used for skin preparation only in newborns >6 days old and <2 months old. Isopropyl alcohol or povidone iodine was used for skin preparation in newborns <6 days old and <28 weeks gestation.

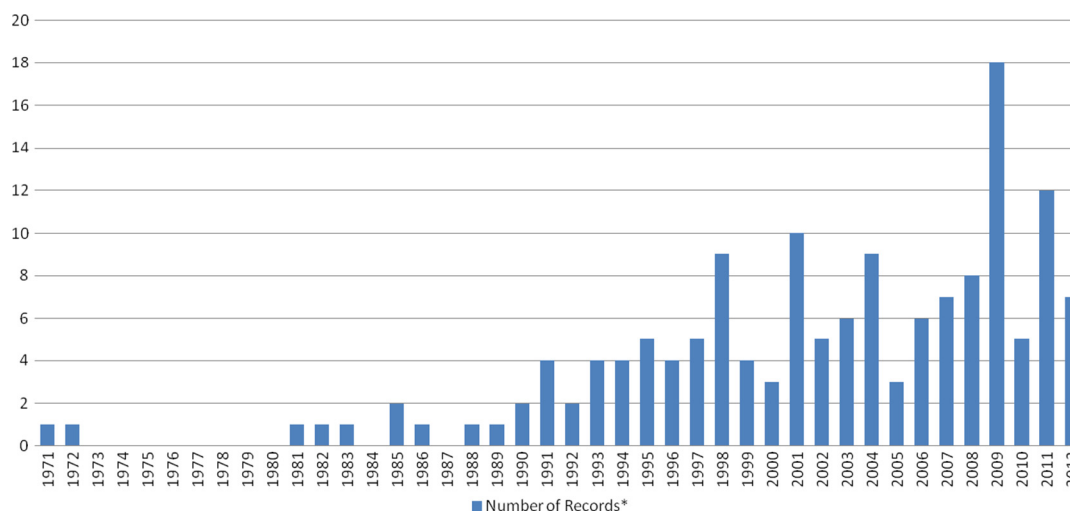
AV, arteriovenous fistula; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; PICC, peripherally inserted central catheter.

dermatitis, chlorhexidine dental rinses can stain teeth,⁴ and in 1 case, it precipitated a fixed drug eruption.⁴⁵

There are also numerous accounts of immediate hypersensitivity reactions to chlorhexidine. Urticaria may occur after application to intact skin^{46,47} or after contact with mucosae through oral,^{41,48}

vaginal,⁴⁹ rectal,⁴⁷ or urethral gels or rinses.^{37,50} In some cases, wheals are accompanied by dyspnea,⁴⁹ angioedema,⁵¹ or syncope.⁴¹

Of greater concern are the multiplying case reports of chlorhexidine-induced anaphylaxis. In some of these, urticaria and generalized flushing heralded the drop in blood pressure,^{51–55} but



*Records include articles, reviews, editorial material, letters, notes, meeting abstracts, proceedings papers and news items.

Figure 1. Number of records containing chlorhexidine and associated hypersensitivity reactions, by year. Data was collected by searching Web of Science records published in all languages from 1965–present, accessed on January 3, 2013, for *chlorhexidine* and the keywords *contact allergic dermatitis* or *allergic contact dermatitis* or *contact allergy* or *delayed hypersensitivity* or *urticaria* or *anaphylaxis* or *immediate hypersensitivity* or *hypersensitivity* or *contact dermatitis* or *contact sensitivity* or *irritant contact* in the topic.

TABLE 2. Results of Screening Patch Tests to Chlorhexidine

Lead Author	Period	Allergen	No. Tested	Positive, n (%)	Comments
		Concentration/Vehicle			
Osmundsen ²³	1978–1981	Chlorhexidine gluconate 1% aq	551	20 (3.6)	14 (2.5%) considered relevant; 10/14 had leg ulcers
Bechgaard et al ²⁴	Unknown	Chlorhexidine gluconate 1% aq	2061	48 (2.3)	18 (0.9%) considered relevant; most had leg eczema or ulcer
Lasthein Andersen and Brandrup ²⁵	6/1982–5/1984	Chlorhexidine gluconate 1% aq and 1% pet	1063	52 (4.9)	21/29 (72%) retested later were still positive; other vehicles and concentrations were tested
Bajaj and Gupta ²⁶	1/1980–12/1983	Chlorhexidine powder	314	10 (3.2)	
Knudsen and Avnstorp ²	1987–1989	Chlorhexidine gluconate 1% aq and acetate 1% aq	297	39 (13.1)	24 found relevant; all had leg ulcer or stasis
Perrenoud et al ²⁷	2/1989–1/1990	Chlorhexidine digluconate 0.5% aq	2295	46 (2.0)	Fourth most common of 13 preservatives tested
Hasan et al ²²	1995–1997	Chlorhexidine digluconate	Unknown	1.2%	Noted decreasing prevalence of sensitization
Mailhol et al ²⁸	2000–2002	Chlorhexidine digluconate	Unknown	0.5%	
	1/1997–1/2007	Chlorhexidine digluconate 0.5% aq	641	17 (2.7)	All were atopic children younger than 16 y

in other cases, there was no cutaneous indication of the source of the life-threatening hypotension, bradycardia, or ventricular fibrillation. Anaphylaxis has been described after chlorhexidine application to unbroken skin⁵⁵ and minor wounds,^{51,52,54} whole body bathing,⁵⁶ ophthalmic wash,⁵⁷ and gel for urethral catheterization^{58,59} or digital rectal examination.⁶⁰ The antiseptic has been incorporated into some medical materials. Anaphylactic episodes have occurred upon insertion of chlorhexidine-impregnated central venous catheters^{13,61–63} and application of impregnated dressings to burns or skin graft and donor sites.^{64,65} In 1998, the Food and Drug Administration issued a warning of potential serious hypersensitivity reactions to such impregnated medical devices.⁶⁶

During surgery and other interventional procedures, chlorhexidine may be easily overlooked as the source of shock due to the many potential causes of hypotension.⁶⁷ Intraoperative anaphylaxis may follow its use for cleansing the skin incision site^{68–70} or for lubricating the urethra during catheter placement or cystoscopy.^{4,71} One patient's blood pressure fell during anesthesia after chlorhexidine was applied intranasally to prepare for transphenoidal resection of a pituitary tumor.⁷² When an operative procedure is brief, anaphylaxis from these sources of chlorhexidine exposure may transpire in the recovery room rather than the surgical theater.^{73,74} It is essential for each patient that all exposures to chlorhexidine by any route be tracked to assure prompt and accurate diagnosis and management of critical events.

Of particular interest are the descriptions of patients who have manifested both immediate- and delayed-type hypersensitivity reactions to chlorhexidine. Few allergens have been described that stimulate both types of allergic response in the same individual. Three patients reported with intraoperative urticaria or anaphylaxis were shown on subsequent evaluation to have both

prick or intradermal and also patch tests positive to chlorhexidine.^{46,75} In an early report of 6 patients with anaphylaxis caused by chlorhexidine, one case had a clear history of allergic contact dermatitis after prior use of the antiseptic to his leg and chin.⁵³ Earlier contact sensitization and patch test–confirmed delayed hypersensitivity were present in 3 other patients who developed severe immediate hypersensitivity reactions on subsequent exposure to chlorhexidine.^{37,40,41} These descriptions underscore the importance of careful history taking before applying or prescribing chlorhexidine to an individual.

As other preservative systems, such as thimerosal, parabens, formaldehyde releasers, isothiazolinones, and methyl dibromoglutaconitrile lose favor with manufacturers, chlorhexidine is gaining use as a biocidal ingredient in shampoos, conditioners, hair color, sunscreens, mouthwashes, contact lens solutions, eye creams, antiwrinkle creams, moisturizers, first aid ointments, sinus decongestants, personal lubricants, and hand sanitizers.^{3,76} In the decade preceding 2009, the Helsinki Asthma and Allergy Association reported that 153 (1.9%) of 8012 cosmetic products contained chlorhexidine.³¹ Table 4 lists examples of commercial products containing chlorhexidine that are currently available in the United States.

With the increasing exposure of individuals to chlorhexidine both in and out of the hospital, it is likely that the prevalence of sensitization will rise. Physicians should expect to see more sensitized individuals manifesting with immediate- or delayed-type hypersensitivity. In 2009, the American Contact Dermatitis Society proposed a core series of 80 patch test allergens, which included chlorhexidine digluconate 0.5% aq.⁷⁷ It is critical for practitioners to recognize that even a mild allergic contact dermatitis to chlorhexidine may indicate the potential for a severe immediate-type reaction upon subsequent exposure.^{40,47,51,69} Individuals with a history

TABLE 3. Literature Review of Positive Patch Test Confirmed Cases of Allergic Contact Dermatitis to Chlorhexidine

Case	Lead Author	Age/Sex	Source (Route) of Initial Chlorhexidine Exposure
1	Calnan ³²	—	—
2	Wahlberg and Wennersten ³³	31 y/M	—
3	Ljunggren and Möller ³⁴	78 y/F	Hibitane (cutaneous ulcer)
4	Roberts et al ³⁵	36 y/M	—
5	Osmundsen ²³	78 y/M	Chlorhexidine-containing cream (cutaneous ulcer)
6	Shoji ³⁶	40 y/M	Chlorhexidine solution (cutaneous wound)
7	Shoji ³⁶	64 y/M	Unspecified source (cutaneous ulcer)
8	Shoji ³⁶	59 y/M	Chlorhexidine solution (cutaneous wound)
9	Bergqvist-Karlsson ³⁷	66 y/M	Chlorhexidine-containing plaster (cutaneous dermatitis)
10	Reynolds and Harman ³⁸	74 y/M	Likely topical antiseptic solution (cutaneous dermatitis)
11	Rapaport ³⁹	20 y/F	Contact lens cleansing solution (conjunctiva)
12	Ebo et al ⁴⁰	43 y/M	Likely preoperative cleansing solution (cutaneous)
13	Thune ⁴¹	14 y/F	Antiacne preparation (cutaneous)
14	Barrazza ⁴²	40 y/M	Chlorhexidine-containing lubricant gel (cutaneous)
15	Goon et al ³	27 y/F	Hibisol, Hibiscrub (cutaneous)
16	Goon et al ³	54 y/F	Chlorhexidine spray (cutaneous)
17	Goon et al ³	39 y/M	Medicated cream (cutaneous dermatitis)
18	Goon et al ³	3 y/F	Likely Salvon cream (cutaneous wound)
19	Goon et al ³	58 y/M	Perioperative and postoperative topical antiseptic solution (cutaneous wound)
20	de Waard-van der Spek and Oranje ²⁹	4 y/M	Topical antiseptic solution (cutaneous)
21	Le Corre et al ³⁰	23 mo/M	Biseptine (cutaneous umbilical stump)
22	Liippo et al ³¹	39 y/F	Sibicort, cosmetics (cutaneous)
23	Liippo et al ³¹	75 y/F	Chlorhexidine-containing hand scrub (cutaneous)
24	Liippo et al ³¹	48 y/M	Duocort (cutaneous)
25	Liippo et al ³¹	42 y/F	Sibicort, chlorhexidine-containing hand scrub (cutaneous)
26	Liippo et al ³¹	84 y/F	Sibicort, cosmetics (cutaneous)
27	Liippo et al ³¹	52 y/M	Sibicort, cosmetics (cutaneous)
28	Liippo et al ³¹	70 y/M	Chlorhexidine-containing hand scrub (cutaneous)
29	Liippo et al ³¹	51 y/M	Sibicort, cosmetics (cutaneous)
30	Liippo et al ³¹	52 y/F	Mouthwash, cosmetics (oral mucosa, cutaneous)
31	Liippo et al ³¹	13 y/M	Duocort, surgical cleaner (cutaneous)
32	Liippo et al ³¹	56 y/F	Sibicort, cosmetics (cutaneous)
33	Liippo et al ³¹	24 y/M	—
34	Liippo et al ³¹	79 y/F	Sibicort (cutaneous)
35	Liippo et al ³¹	57 y/M	Sibicort (cutaneous)
36	Liippo et al ³¹	32 y/M	Sibicort (cutaneous)
37	Liippo et al ³¹	61 y/M	Duocort, Sibicort (cutaneous)
38	Liippo et al ³¹	67 y/M	—
39	Liippo et al ³¹	65 y/F	Mouthwash (oral mucosa)
40	Liippo et al ³¹	60 y/M	Sibicort, cosmetics (cutaneous)
41	Liippo et al ³¹	45 y/M	Sibicort (cutaneous)
42	Liippo et al ³¹	19 y/F	Duocort (cutaneous)
43	Liippo et al ³¹	80 y/M	Duocort (cutaneous)
44	Liippo et al ³¹	22 y/F	Sibicort (cutaneous)
45	Liippo et al ³¹	74 y/F	Sibicort (cutaneous)
46	Liippo et al ³¹	80 y/F	Sibicort (cutaneous)
47	Liippo et al ³¹	65 y/F	Mouthwash (oral mucosa)
48	Liippo et al ³¹	68 y/M	—
49	Liippo et al ³¹	77 y/F	Sibicort (cutaneous)
50	Liippo et al ³¹	44 y/F	Chlorhexidine-containing hand scrub (cutaneous)
51	Liippo et al ³¹	63 y/F	Sibicort (cutaneous)
52	Liippo et al ³¹	56 y/F	Sibicort, Duocort (cutaneous)
53	Liippo et al ³¹	39 y/F	Sibicort (cutaneous)

(Continued on next page)

TABLE 3. (Continued)

Case	Lead Author	Age/Sex	Source (Route) of Initial Chlorhexidine Exposure
54	Liippo et al ³¹	18 y/F	Sibicort (cutaneous)
55	Liippo et al ³¹	63 y/M	Sibicort, Duocort (cutaneous)
56	Liippo et al ³¹	49 y/M	Sibicort, Duocort (cutaneous)
57	Liippo et al ³¹	58 y/M	—
58	McEnery-Stonelake ⁷⁸	40 y/F	Mouthwash (oral mucosa)

Biseptine liquid (Laboratoires Roche Nicholas, Gaillard, France), chlorhexidine gluconate 0.25%; *Duocort cream* (Orion Pharma, Espoo, Finland), chlorhexidine digluconate 10 mg/1 g of cream; *Hibiscrub liquid* (Molnlycke Health Care, Gothenburg, Sweden), chlorhexidine gluconate 4% wt/vol in an aqueous base; *Hibisol liquid* (Molnlycke Health Care), chlorhexidine gluconate 0.5% wt/vol; *Hibitane liquid* (Molnlycke Health Care), chlorhexidine digluconate 5% wt/vol; *Salvon cream* (Novartis Consumer Health UK Ltd, Horsham, United Kingdom), chlorhexidine gluconate 0.1% wt/wt; *Sibicort cream* (Orion Pharma), chlorhexidine digluconate 10 mg/1 g of cream.

TABLE 4. Examples of Commercially Available Chlorhexidine-Containing Products⁷⁶

Amplify Color XL Conditioner
Astroglide Personal Lubricant Gel
Aveeno Continuous Protection Sunblock Lotion Face SPF 30
Bausch and Lomb Boston Advance Contact Lens Conditioning Solution
Biologie by Matrix Forte Therapie Intensive Strengthening Masque
Biologie by Matrix Smoothing Shine Milk
Cetaphil Therapeutic Hand Cream
CVS Lubricating Jelly
Garnier Fructis Fortifying Cream Conditioner
Garnier Nutrisse Nourishing Color Cream
K-Y Jelly Personal Lubricant
L'Oreal Advanced Revitalift Eye Cream
L'Oreal Ever Strong Conditioner, Rosemary Mint
L'Oreal Excellence Crème Haircolor
L'Oreal Kids Extra Gentle Conditioner, Grape
L'Oreal Preference Haircolor
L'Oreal Vive Pro Hydra Gloss Moisturizing Conditioner
Redken Guts 10 Volume Spray Foam
ROC Retinol Correxion Eye Cream
Walgreens Personal Lubricating Gel

of dermatitis at any site of previous chlorhexidine use should undergo patch testing with the allergen. Patients who develop urticaria or anaphylaxis related to a procedure should be tested for immediate hypersensitivity to chlorhexidine, especially if the history suggests or confirms chlorhexidine exposure. Increased use of allergy testing to chlorhexidine could facilitate appropriate counseling and potentially prevent dermatitis, urticaria, and catastrophic anaphylaxis.

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