

REVIEW ARTICLE

Chlorhexidine allergy in the perioperative setting: a narrative review

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Summary

Chlorhexidine is an antiseptic with a broad spectrum of activity and a persistent effect on skin. Consequently, it has become an ubiquitous antiseptic in healthcare and the community. As use has become widespread, increasing numbers of cases of allergy have been reported in the literature, including cases of anaphylaxis to chlorhexidine gels used on mucous membranes, chlorhexidine-impregnated devices such as central venous catheters, chlorhexidine preparations used on wounds and broken skin, and cases after dental procedures. Numerous governmental warnings have been issued over recent decades to warn of the risk of allergy to chlorhexidine on mucosal surfaces or in medical devices. Whilst the number of published cases likely underestimates the true prevalence of reactions, we retrospectively surveyed clinics with experience in investigating perioperative chlorhexidine allergy. Despite differences in investigation practice before the survey took place, 13 clinics responded which together had diagnosed 252 cases of anaphylaxis to chlorhexidine, and cases of delayed allergy. In eight of 13 clinics, chlorhexidine was within the top four most commonly diagnosed causes of perioperative anaphylaxis. Despite this, the incidence of anaphylaxis to chlorhexidine is low given that patients are very commonly exposed. Sensitisation of healthcare workers can occur, but is uncommon. Before exposing patients to this antiseptic, consideration of the potential risk vs benefit should be undertaken, particularly for higher risk exposures, such as mucosal exposure or i.v. exposure via impregnated lines. Difficulties exist in protecting patients with known allergies from re-exposure to chlorhexidine, which would be improved with uniform labelling and chlorhexidine product registers.

Keywords: adverse effects; allergens; anaphylaxis; chlorhexidine; perioperative; drug hypersensitivity; survey

Chlorhexidine (1:6-di-4'-chlorophenyldiguanidohexane) is a synthetic biguanide, broad-spectrum antiseptic and disinfectant used widely in the healthcare sector in many countries

(Fig. 1). This narrative review summarises the current published knowledge on chlorhexidine allergy in the perioperative setting, as it has become one of the most important causes of

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Fig 1. Chemical structure of chlorhexidine. Reproduced with permission from [123rf.com](https://www.123rf.com).

perioperative allergy. Results of a retrospective survey of chlorhexidine allergy in 13 worldwide perioperative allergy clinics are presented.

The appreciation of chlorhexidine's attractive spectrum of activity and persistent effect has seen the use of chlorhexidine increase in recent years.¹ At lower concentrations it is bacteriostatic and at higher concentrations rapidly bacteriocidal.^{2,3} It is active against Gram-negative and -positive bacteria, fungi, and some viruses, but is not sporocidal.⁴ As proteins in the skin are anionic, the positive ammonium charges in chlorhexidine bind well to these, which gives it a persistent effect in the superficial skin layers.⁵

Chlorhexidine has found use in diverse forms both in and outside the perioperative setting including, but not limited to, alcoholic and aqueous surgical skin preps, skin wipes, and lubricant gels for urethral catheterisation and vaginal and rectal examination. It has been impregnated into central venous catheters (CVCs) and other medical devices, and may be found in wound dressings, throat gargles/mouthwashes, toothpastes,

contact lens solutions, and cosmetics. In many of these forms, the presence of chlorhexidine is obvious, however the presence of chlorhexidine is not always obvious (such as in gels, devices, toothpastes, and dressings) leading to its reputation of being an 'occult' or 'hidden' allergen in the healthcare environment.

Initial descriptions of hypersensitivity began in the early 1960s in the UK.^{6,7} In Japan between 1967 and 1984, 50 adverse reactions, many of which were consistent with hypersensitivity, were reported, and in 1984 the Japanese Ministry of Welfare recommended prohibition of the use of chlorhexidine on mucous membranes.⁸ In 1985, the manufacturers of chlorhexidine in Japan recommended that only the lowest bactericidal concentration (0.05%) of chlorhexidine gluconate should be used on wound surfaces.⁸ In 1988, reports of hypersensitivity reactions to chlorhexidine impregnated CVCs led the US Food and Drug administration (FDA) to issue an alert about the risk of anaphylactic reactions.⁹ A similar alert was issued by the Therapeutic Goods Administration in Australia in 2012,¹⁰ and an Australian Adverse Drug Reactions Bulletin warned of reports of anaphylaxis to gels containing lignocaine and chlorhexidine.¹¹ The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK issued an alert in 2012¹² warning about reports of allergic reactions to devices and products containing chlorhexidine. In 2013, New Zealand's regulator reported 69 reports of anaphylaxis over 13 yr.¹³ In 2016, increased reports of allergy (53 to topical non-prescription products) led Canadian authorities to a safety review and updating of product information with allergy concerns.¹⁴ In addition, in 2017, the FDA issued another alert as a result of a recent increase in allergic reactions to chlorhexidine skin antiseptics and a request that manufacturers of over-the-counter antiseptic products containing chlorhexidine gluconate add an allergy warning to their products' Drug Facts labels.¹⁵ These warnings, though important, must be seen in context. The individual patient risk for chlorhexidine allergy is very low (for patients without a history suggestive of chlorhexidine allergy), and its spectrum makes chlorhexidine the antiseptic of choice for many procedures.

Methods

A literature search was conducted using Medline (1946–2018), Embase (1980–2018), Cochrane, CINAHL Complete, and Web of

Table 1 Clinical features of chlorhexidine allergy

Route of exposure	Example	Onset of symptoms after exposure		Severity of reaction		
		Immediate	Delayed	Localised (urticaria)	Generalised (urticaria)	Systemic anaphylaxis
Topical cutaneous	Preoperative whole body wash	Yes	Yes	Yes	Yes	Rare
	Preoperative skin preparation	Yes	Rare	Yes	Yes	Rare
Mucous membrane	Transurethral	Yes	Yes	Rare	Rare	Yes
	Rectal	Yes	Yes	Rare	Rare	Yes
	Vaginal	Yes	Yes	Rare	Rare	Yes
	Oral (mouthwash)	Yes	Rare	Yes	Rare	Rare
	Ophthalmic	Yes	Rare	Yes	Rare	Rare
Parenteral	I.V. cannula preparation	Rare	Yes	Yes	Rare	Rare
	CVC, arterial and epidural catheter insertion	Yes	Yes	Yes	Yes	Yes

* Immediate reactions occur within minutes to 1 hour after exposure, delayed reactions may present hours to days after exposure. CVC, central venous catheter

Science for relevant articles (details of search in [Supplementary Appendix S1](#)). The 238 articles identified were screened for relevance. Articles from exploration of references from key articles were also included.

In order to survey experiences and differences in investigation practices of the experts involved in the International Suspected Perioperative Allergic Reaction (ISPAR) group³ (formed in 2018), a questionnaire was circulated to the 26 members. Information was sought from those with active experience investigating perioperative allergy (maximum of one response per testing location). The survey questions ([Supplementary Appendix S2](#)) and a summary of results is attached ([Supplementary Appendix S3](#)).

Clinical features

The spectrum of symptoms and signs of perioperative chlorhexidine allergy is varied in onset time and severity, and ranges from mild reactions confined to the skin, to life-threatening anaphylaxis. [Table 1](#) summarises common presentations of allergy seen after different routes of chlorhexidine exposure. In the context of chlorhexidine-coated CVC insertion, exposure to the drug is i.v., and can therefore result in immediate anaphylaxis that can be life-threatening.⁵⁷ If the catheter is not recognised as the source of the problem and removed, this can lead to prolonged and intractable anaphylaxis.¹⁷ A slower onset of symptoms occurs when chlorhexidine is administered topically to skin or mucous membranes, and time is required for the drug to reach the vascular system. Allergic reactions to chlorhexidine can thus occur with delayed onset, appearing not to be temporally related to administration of the drug. These atypical presentations can result in diagnostic confusion, with chlorhexidine being overlooked as a potential causal agent, and other drugs incorrectly blamed.

Topical chlorhexidine exposure in the perioperative setting frequently begins with skin cleaning before insertion of a peripheral venous cannula. This may result in only localised reactions, with insufficient exposure, to result in widespread systemic symptoms. These reactions are nevertheless IgE-mediated.¹⁸ typically involving localised urticaria. In a study of 33 patients with positive skin tests to chlorhexidine, 11 had localised urticarial reactions when tested with open application of a chlorhexidine-containing solution.¹⁹ A history of localised reactions such as this can often be found in patients who present later with more severe, systemic reactions^{20,21} and should be actively sought when assessing preoperative allergy status,²² as further exposure to chlorhexidine may result in more severe reactions.

In the UK and many other countries, chlorhexidine is the most frequently used skin disinfectant before regional anaesthesia. For neuraxial techniques this typically involves spraying the whole back, thus exposing the patient to a large mass of drug. Broken or damaged skin allows relatively rapid absorption of chlorhexidine. In addition, there is some evidence that the alcohol contained in cleaning solutions may enhance chlorhexidine absorption through its damaging, drying effect.²³ Further exposure occurs if chlorhexidine-containing skin cleaning preparations are used before surgery where a large area of skin is covered, and surgical incision through the disinfected area may result in a more rapid onset of symptoms.²⁴

Probably the most common cause of perioperative anaphylaxis to chlorhexidine is secondary to its use on mucosal surfaces. Typically, this is associated with insertion

of chlorhexidine-impregnated urethral catheters, or more commonly with the use of chlorhexidine-containing lubricants such as Instillagel[®] and KY Jelly[®]. Allergic manifestations are usually delayed compared with reactions caused by i.v. exposure to allergen. Rapid development of allergic manifestations can occur in cases of urethral chlorhexidine exposure,²⁵ which possibly results from traumatic injury to the urethra during catheterisation facilitating venous uptake of allergen. This is frequently misattributed to other causes, unless the anaesthetist is aware that such lubricants contain chlorhexidine. Other mucosal surfaces that may be exposed to chlorhexidine include rectal (examination or colonoscopy lubricants), vaginal (examination lubricants), ophthalmic (cleaning solutions), and oral (mouthwash). Anaphylaxis after chlorhexidine exposure via mouthwash and oral gels has been reported,^{26,27} though possibly less than would be expected compared with those from other mucosal routes of exposure. Two perioperative fatalities have been reported from anaphylaxis as a result of chlorhexidine use in open dental sockets after surgery,²⁸ though this may be attributable to direct vascular access of allergen through the socket rather than transmucosal absorption.

Chlorhexidine may also cause contact dermatitis through delayed type IV allergic reactions, and there is evidence that some patients simultaneously have both immediate and contact allergy.²⁹ Patients with delayed-type hypersensitivity to chlorhexidine may develop unpleasant reactions on mucosal exposure and be predisposed to develop IgE-mediated allergy; these patients should be advised to avoid chlorhexidine-containing products.³⁰

Epidemiology

Chlorhexidine-induced perioperative hypersensitivity reactions are reported to account for between 7.7%³¹ and 9% of cases in the UK,³² 9% in Belgium,³³ and 9.6% in Denmark.³⁴ Chlorhexidine appears to be a rare culprit in France.³⁵ It is possible that under-recognition or differences in practice account for the discrepancy. Testing for chlorhexidine allergy in all patients referred with perioperative hypersensitivity reactions increases recognition, particularly in countries where chlorhexidine exposure is highly likely in the operating room.^{22,31,33,34} The true prevalence of chlorhexidine allergy remains unknown, but is likely to be increasing. In the 10-yr period up to 2004, only 50 cases of IgE-mediated reactions were reported.³⁶ Between 2009 and 2013, 104 cases were reported from four UK specialist centres.³⁷

The largest UK study of anaesthetic hypersensitivity reactions to date, the Royal College of Anaesthetists' 6th National Audit Project (NAP6),²² identified 18 cases of chlorhexidine anaphylaxis (overall 9%), the third most common trigger. Most cases were in males (16/18) and urological. Interestingly, in the NAP6 study the anaesthetist only considered chlorhexidine as the cause in five (28%) of the cases. There were 2 298 567 annual exposures to chlorhexidine estimated in the same time period by at least one route, with 74% of all patients being exposed. The NAP6 study estimated the incidence of anaphylaxis to chlorhexidine to be 0.78 per 100 000 exposures, but this may be an overestimate as the denominator is unlikely to reflect all exposures.³²

Multiple reactions and misdiagnoses are common and were confirmed in the NAP6 study.³² One patient with a reported chlorhexidine allergy was re-exposed to chlorhexidine and developed anaphylaxis. In another case, after the

Table 2 Questions to ask for a chlorhexidine allergy history

- Have you ever been told you might be allergic to chlorhexidine or disinfectant/cleaning solutions or lubricant gels?
- Have you ever had swelling in the mouth or developed an itchy rash when you have used mouthwashes?
- Have you ever had swelling or an itchy rash develop when your skin is cleaned before taking blood/putting a drip in?
- Have you ever had swelling or an itchy rash develop after using disinfectant/cleaning solution for minor scratches in the home or when asked to wash in it before surgery?
- Have you ever had a rash or swelling after a procedure in hospital or been told that you have had an allergic reaction during surgery, which was not investigated?

anaphylactic event reported to NAP6 was confirmed to be attributable to chlorhexidine, the patient had a further procedure, was exposed to chlorhexidine, and had another hypersensitivity reaction. A Danish study of 23 patients with confirmed chlorhexidine hypersensitivity showed that one-third were accidentally re-exposed in the healthcare setting.³⁸

Our retrospective survey (Supplementary Appendix S2) of the current investigation practice in centres in the ISPAR group³ returned responses (Supplementary Appendix S3) from 13 clinics involved in the investigation of perioperative anaphylaxis from the UK (2), Europe (7), Australia (2), New Zealand (1), and the USA (1). The total number of cases of perioperative chlorhexidine anaphylaxis diagnosed by these clinics was 252, which is much larger than any previous published series (although some cases may have been reported previously). The clinics with the three largest numbers of cases reported 64 over 19 yr (Denmark), 45 over 17 yr (Belgium), and 42 over 9 yr (Australia), respectively, and all tested for chlorhexidine routinely. Not all centres were able to break down their cases by method of exposure, but mucosal exposure, skin/wound and i.v. catheter site/CVC routes were common. It was interesting to note that as a perioperative allergen, chlorhexidine is now relatively prominent, featuring as the second most commonly diagnosed in two clinics. It ranked third in three clinics and within the top four in eight of 13 clinics. Three centres diagnosed chlorhexidine allergy rarely, however two of these three reported they test for chlorhexidine allergy selectively (rather than routinely), reflecting the lack of standardisation of testing even in specialised centres. Given that exposure to chlorhexidine in the perioperative environment often goes unnoticed, not testing routinely for chlorhexidine may have contributed to under-reporting of chlorhexidine anaphylaxis from those centres.

Main exposure routes

Lubricating gels used for urological and gynaecological procedures often contain chlorhexidine and local anaesthetic, but there are aqueous gels without one or both. The predominant surgical specialty associated with chlorhexidine anaphylaxis in the NAP6 study was urology (six cases), and there were cases from cardiac and orthopaedics (three cases each).³² Overall, this is consistent with previous studies reporting the highest prevalence of reactions during urological procedures.^{18,37–39}

Chlorhexidine-coated or -impregnated CVCs are intended to reduce the risk of catheter-associated infection, and clinicians may not be aware of the chlorhexidine coating on these catheters. Reactions to chlorhexidine-impregnated CVCs are often rapid in onset and severe⁴⁰ requiring prompt treatment and removal of the catheter. The line was not removed during resuscitation in two of five cases related to chlorhexidine-coated central venous lines in the NAP6

study.²² Chlorhexidine-free CVCs should be considered where possible. A recent Cochrane review questioned the efficacy of chlorhexidine-coated venous catheters in preventing clinically important morbidity.⁴¹

Chlorhexidine is used widely for skin preparation before surgery or venipuncture. Povidone-iodine and alcohol-based swabs can be used as alternatives. In the NAP6 study, the reported routes of chlorhexidine exposure included skin preparation for cannulation or surgery, coated CVCs, and urethral or similar medical gels. Seven cases had a single route of exposure, while five cases had two, five had three, and one had four, reflecting that exposure is commonly from multiple sites.

Chlorhexidine-containing products are widely used and regarded as the 'gold standard' in dentistry because of their wide antimicrobial spectrum and efficacy. There are multiple preparations including mouthwash or spray solutions, gels, and impregnated chips for use in periodontal pockets. There have been a number of reports of allergies including fatalities linked to dental chair chlorhexidine reactions,²⁸ though possibly less than would be expected compared with those from other mucosal routes of exposure. The main alternative product, hexetidine, has a much weaker evidence base and is considered a poor alternative to chlorhexidine.⁴² Other alternatives for dental use include sodium hypochlorite solution and normal saline.

Challenges in diagnosis of chlorhexidine allergy

The mechanism of immediate-type chlorhexidine allergy has been shown to be IgE-mediated,¹⁸ and methods for diagnosing chlorhexidine allergy are the same as used in other allergy testing: *in vitro* tests [specific IgE test, basophil activation tests (BAT) and histamine release (HR) test] and *in vivo* tests [skin prick test (SPT) and intradermal test (IDT)].³⁴ As no single test has 100% sensitivity or specificity, the results should always be interpreted in the context of a clinical reaction on exposure to chlorhexidine. Sensitivity can be increased by combining several test modalities, and some centres suggest that allergy can be confirmed if two or more test modalities are positive in the light of a relevant clinical reaction.^{34,43} In many countries, chlorhexidine is used routinely in the perioperative setting, and testing for chlorhexidine should always be included in the investigation of suspected perioperative allergic reactions.^{40,44}

A relevant clinical history includes symptoms elicited in a setting of exposure to chlorhexidine. Many patients retrospectively report a minor reaction on previous chlorhexidine exposure, or repeated severe reactions,³⁹ as a result of chlorhexidine being missed as an allergen on initial evaluation. Identifying minor reactions before future exposure is important; Table 2 lists some relevant questions that may help elicit a history of chlorhexidine allergy. On suspicion of allergy to

chlorhexidine, patients should be referred for allergy investigation, preferably in a centre with experience in perioperative allergy investigation, and chlorhexidine should be avoided until investigations are completed.

The commercially available specific IgE analysis for chlorhexidine (ImmunoCAP Allergen C8, Phadia, Uppsala, Sweden) has a recommended cutoff of $0.35 \text{ kU}_A \text{ L}^{-1}$. In patients with high total IgE concentrations, chlorhexidine-specific IgE may be falsely elevated above $0.35 \text{ kU}_A \text{ L}^{-1}$.⁴³ In Denmark, the false positive rate of specific IgE for chlorhexidine is quite low,^{29,38} and the sensitivity and specificity of specific IgE to chlorhexidine has been reported to be very high when sampled in the months after the reaction. Concentrations of IgE are dynamic, showing an increase after exposure followed by a decline over time to concentrations $<0.1 \text{ kU}_A \text{ L}^{-1}$ if exposure is avoided. This means that allergy cannot be ruled out if specific IgE is $<0.1 \text{ kU}_A \text{ L}^{-1}$.^{38,45} For this reason, one study has recommended that the optimal sampling time for specific IgE is 1–4 months after the reaction.³⁸

The BAT and HR test are additional *in vitro* tests that can be carried out in highly specialised centres and require freshly sampled blood for analysis. They are generally used to aid diagnosis in patients where other tests are equivocal or not available. Sensitivities of the BAT and HR test are generally lower than those of other test modalities, but specificity is usually high.^{18,46}

Skin testing is the most common modality in allergy testing. The SPT and IDT are supplementary to each other, as the sensitivity of testing is increased when both tests are performed. As chlorhexidine is a skin irritant, it is important that skin testing is performed with a non-irritant concentration. The recommended maximum skin test concentrations for chlorhexidine are 0.5% (5 mg mL^{-1}) for SPT and 0.0002% (0.002 mg mL^{-1}) for IDT.^{18,47} The skin test response declines over time with lack of exposure, but it is not known how long skin tests stay positive.

No reliable challenge test has been identified at the present time. The majority of severe reactions have been triggered by intraurethral or i.v. exposure, and a challenge protocol using these exposures presents difficulties in terms of safe dosing and acceptability to the patient. Other exposure routes, such as intact skin and the mucous membrane in the mouth, are likely to present strong barriers to absorption of allergen and thus are likely to produce false negative challenge responses. The current recommendation is to combine several tests with a relevant clinical history. For patients tested within a few months of the reaction, a combination of a positive SPT and positive specific IgE test has very high sensitivity and specificity.³⁴ When investigations are delayed many months, the IDT may prove more sensitive.³⁷ If clinical suspicion is high and all tests are negative, testing can be repeated some months later, and may then have become positive (LH Garvey, personal communication).

Risk vs benefit in chlorhexidine use

The utility of chlorhexidine as an antiseptic is well established. It is also clear that through the incredibly widespread use of chlorhexidine in many products throughout modern healthcare environments, exposure to chlorhexidine is very common. Whilst the actual denominator is not known, even if the prevalence of chlorhexidine anaphylaxis has increased in recent years, the incidence of hypersensitivity reactions to chlorhexidine is very low. As with all interventions in

healthcare, the aim is to make sure that there is a positive benefit/risk ratio. Given that there is a risk of anaphylaxis with exposure to chlorhexidine, its use should be reserved for situations where benefit is likely to exist. Currently, some exposures to chlorhexidine in the perioperative environment, such as use of chlorhexidine-containing urethral gels, are potentially unnecessary, and if so may carry risk without benefit.

The reduction in catheter-related bloodstream infections (CRBSI), clinically diagnosed sepsis, and associated mortality caused by i.v. access devices such as CVCs and peripheral IV catheters (PIVCs), is a common goal globally. The risk vs benefit of using chlorhexidine skin preparations, chlorhexidine-impregnated CVCs, and chlorhexidine-impregnated dressings has long been debated. The most recent Cochrane reviews suggest that chlorhexidine skin prep may be more effective than povidone-iodine at preventing CRBSI, however the quality of evidence was very low.⁴⁸ Assessment of the value of antimicrobial impregnated CVCs suggested they may decrease CRBSI in adults, but with a number needed to treat for benefit of 50.⁴⁹ The evidence does not suggest a significant decrease in clinically diagnosed sepsis events or mortality.^{41,49} There was moderate quality evidence that impregnated dressings with chlorhexidine or silver may reduce CRBSI.⁵⁰ Given that reported cases of anaphylaxis to chlorhexidine products are increasing and that governmental warnings exist^{10–15} about hypersensitivity reactions, decisions about the use of these products should be made after consideration of allergy history and route of exposure (topical with access to broken skin vs i.v.). Chlorhexidine should be used when the benefit to the patient is likely to be tangible and outweighs the potential risk. It is not recommended to use impregnated CVCs routinely in all settings.⁴⁹

The rate of CRBSI from PIVCs is highly dependent on line duration. For this reason, it may be prudent to reserve the use of chlorhexidine as an antiseptic for PIVCs that are intended to stay *in situ* for several days, and in particular to use 70% alcohol skin swabs as skin prep for day cases or overnight PIVCs. Such a strategy is likely to greatly reduce exposure of patients to a potential allergen where benefit is unlikely to be derived.

Many of the cases of perioperative anaphylaxis resulting from chlorhexidine have originated from lubricant gels, particularly in urology procedures.^{18,37,39} The US Centers for Disease Control and Prevention considers the routine use of antiseptic urethral lubricants ‘unnecessary’,⁵³ suggesting that many of these anaphylactic reactions have occurred unnecessarily. The ISPAR group³ survey (Supplementary Appendices S2 and S3) found that rates of chlorhexidine anaphylaxis have decreased in two large perioperative allergy clinics in Australia in recent years, after local decisions to discontinue the use of chlorhexidine-containing urethral lubrication gels.

Prevention of re-exposure to chlorhexidine in patients with a history of hypersensitivity

The widespread use of chlorhexidine in the healthcare and pharmacy environments brings with it a great challenge when trying to avoid re-exposure in allergic patients. Repeated episodes of allergy have been described before or after diagnosis of chlorhexidine hypersensitivity.^{18,38,54–57} Challenges include the easy identification of these products in the absence of standards for clear labelling of the presence of chlorhexidine and the need to remove these products from the environment of allergic patients without affecting access for the vast

Table 3 Important considerations in the management of chlorhexidine allergic patients (adapted from Australian and New Zealand College of Anaesthetists [ANZCA] Guidelines PS60⁵⁸)

- Adequate history taking for all hypersensitivity including to chlorhexidine before exposure
- Single room, removal of all chlorhexidine-containing products from the room
- Development of a chlorhexidine product register for each site. Access to this register in the patient's room
- All products must be checked for absence of chlorhexidine before use
- Clear 'Allergy to Chlorhexidine' signs on the room door, patient notes, and patient's bed
- Medic-Alert®/Patient allergy band in place
- Handover need of chlorhexidine avoidance when patient transferred to other locations in the healthcare facility
- Inform patient to be vigilant towards potential chlorhexidine exposures

majority of patients without a history of hypersensitivity. The Australian and New Zealand College of Anaesthetists has released professional guidelines on the management of patients with suspected or proved hypersensitivity to chlorhexidine;⁵⁸ the key recommendations are summarised in Table 3.

In addition to these recommendations, uniform international regulations requiring clear labelling of the presence of chlorhexidine would provide some additional protection to allergic patients, but would be difficult to achieve. Practically, the maintenance of a high index of suspicion for chlorhexidine as an allergen is important in cases where milder allergic features are noted in patients known to, or suspected to, have recently been exposed to chlorhexidine. If these patients are diagnosed appropriately with chlorhexidine allergy at this time, further more severe reactions may be avoided.

Empowering patients diagnosed with chlorhexidine allergy to be vigilant for products in medical and pharmacy environments and to actively ask healthcare staff to check all products to be used on them is extremely important, as healthcare staff are often unaware of chlorhexidine content in products. In a perioperative environment, the same principles apply as to all healthcare environments, such as the handover of allergy status, and the identification and avoidance of products containing chlorhexidine in the environment. The key differences are that the number of products containing chlorhexidine is many and varied, and the patient is often not conscious and able to be their own advocate. As a result of this, the responsibility for avoiding re-exposure in chlorhexidine allergic patients falls more directly on perioperative staff.

Occupational exposure in healthcare

As the number of patients with allergy to chlorhexidine has increased with increasing utilisation, the question of potential sensitisation and allergy to chlorhexidine in healthcare workers has arisen. Occupational exposure to chlorhexidine may occur directly on the skin through hand disinfectants, soaps, and scrubs used repeatedly throughout the working day. Indirect exposure can occur on skin when handling chlorhexidine-containing dressings, gels, creams, and lotions to be applied to patients.⁵⁹ Lastly, exposure can occur in the respiratory tract via solutions and sprays used for disinfection of equipment.⁶⁰

Chlorhexidine is a known irritant in high concentrations, and irritant contact dermatitis causing localised transient irritation, which disappears spontaneously on avoidance, has been reported in doctors and other healthcare workers.^{61,62} Allergic contact dermatitis with more chronic eczematous reactions and recurrence on repeated exposure has been

described in 2% of 549 healthcare workers presenting with skin symptoms to an Australian occupational dermatology clinic. The rate of sensitisation to chlorhexidine in the general dermatology clinic in the same hospital was 0.24% for comparison.⁵⁹ A Danish study investigating potential allergic sensitisation in 104 healthcare workers who were asymptomatic failed to identify any cases,⁶³ and a more recent study of healthcare workers with self-reported hand eczema identified one case in 120 with concomitant contact dermatitis and immediate-type allergy to chlorhexidine.⁶⁴

In recent years, cases of immediate-type IgE-mediated allergy to chlorhexidine have been reported in healthcare workers with very low frequency when considering the widespread exposure to chlorhexidine. Symptoms in healthcare workers in the workplace range from itching and urticaria on skin exposure^{64,65} to respiratory symptoms such as rhinitis, sneezing, and asthma symptoms.^{66,67} The relative rarity of severe reactions in healthcare workers is probably related to the route of exposure which is mainly via the skin or respiratory tract. In patients, where exposure may occur on mucous membranes in the urinary tract during catheterisation or directly in the bloodstream when inserting chlorhexidine-coated central lines, anaphylaxis with severe circulatory compromise is relatively more common.³⁹ Once sensitised to chlorhexidine, healthcare workers are at risk of severe reactions if they themselves become patients and are accidentally exposed to chlorhexidine. One very rare case of full-blown anaphylaxis occurring in a dentist in the workplace has been reported recently.⁶⁸

There is no evidence for the mechanisms behind allergic sensitisation to chlorhexidine in healthcare workers. Co-sensitisation of healthcare workers can occur,⁴⁵ and it could be speculated that one allergy caused the skin barrier to be impaired leading to the other allergy. High concentrations of chlorhexidine of 2–4% have irritant effects on the skin, again leading to an impaired skin barrier and potentially increasing the risk of allergic sensitisation.⁷⁰ In some countries, 0.5% chlorhexidine is recommended and in others much higher concentrations of 2–4% are used. The issue of potentially increased risk of allergic sensitisation with higher concentrations of chlorhexidine has been raised,²⁴ and the recommendation should be to use the minimum effective concentration of chlorhexidine. Because of the widespread use of chlorhexidine in the health sector, healthcare workers presenting with occupational allergy should always be investigated for chlorhexidine allergy.

Conclusions

Chlorhexidine is widespread in the perioperative environment, an excellent antiseptic, and generally well-tolerated. True

allergy is rare, however increases in numbers of diagnosed cases have seen it elevated from an obscure cause of perioperative allergy to the second to fourth most commonly diagnosed cause of perioperative allergy in clinics around the world (Supplementary Appendix S3). Delays between exposure and allergic features and the lack of recognition of chlorhexidine as an allergen remain barriers to successful diagnosis of chlorhexidine allergy, and multiple reactions can occur before diagnosis. Difficulty in identifying the wide range of healthcare products containing chlorhexidine is an obstacle to successfully avoiding inadvertent exposure to chlorhexidine in those patients with a diagnosed allergy. Healthcare workers frequently exposed to chlorhexidine occupationally may also be sensitised. Progress towards standardisation of the labelling of chlorhexidine-containing products is needed. Evaluation of the risk vs benefit of using chlorhexidine as an antiseptic in common procedures should be investigated to minimise both infection and unnecessary chlorhexidine exposure.

Authors' contributions

Contributed to the conception and design of the study, data collection, analysis, and interpretation, and drafting of the manuscript, and approved the final version of the manuscript: all authors

Declarations of interest

LHG: Consultant and adjudication committee member for Merck, Kenilworth, NJ, USA and Novo Nordisk, Bagsvaerd, Denmark. Other authors have no conflicts to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2019.01.033>.

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Appendix 1 - Literature search protocol

MEDLINE 1946 to May 31, 2018 on Ovid platform

- 1 Chlorhexidine/
- 2 (chlorhexidine or "ay 5312" or ay5312 or bidex or boston conditioning lotion or chlorhex or chlorhexidin or chlorohex or chlorohexydine or clohexidine or lisium or nibitane or nolvasan or nolvascin or rotersept or sterilon or tubilicid or tubulicid or umbipro or "mk 412a" or mk412a or novalsan or "sebidin a" or tubulicid).mp.
- 3 1 or 2
- 4 exp Hypersensitivity/
- 5 Allergens/
- 6 Histamine/
- 7 Histamine Release/
- 8 (allerg* or hypersensitive* or anaphyla*).mp.
- 9 4 or 5 or 6 or 7 or 8
- 10 3 and 9

Embase 1980 to 2018 Week 22 on Ovid platform

- 1 chlorhexidine/
- 2 (chlorhexidine or "ay 5312" or ay5312 or bidex or boston conditioning lotion or chlorhex or chlorhexidin or chlorohex or chlorohexydine or clohexidine or lisium or nibitane or nolvasan or nolvascin or rotersept or sterilon or tubilicid or tubulicid or umbipro or "mk 412a" or mk412a or novalsan or "sebidin a" or tubulicid).mp.
- 3 1 or 2
- 4 exp hypersensitivity/
- 5 allergy patient/
- 6 exp allergy test/
- 7 allergen/
- 8 histamine/
- 9 histamine release/
- 10 (allerg* or hypersensitive* or anaphyla*).mp.
- 11 4 or 5 or 6 or 7 or 8 or 9 or 10
- 12 3 and 11

Cochrane on Wiley platform

- #1 MeSH descriptor: [Chlorhexidine] explode all trees
- #2 chlorhexidine or "ay 5312" or ay5312 or bidex or boston conditioning lotion or chlorhex or chlorhexidin or chlorohex or chlorohexydine or clohexidine or lisium or nibitane or nolvasan or nolvascin or rotersept or sterilon or tubilicid or tubulicid or umbipro or "mk 412a" or mk412a or novalsan or "sebidin a" or tubulicid:ti,ab,kw
- #3 #1 or #2 3447
- #4 MeSH descriptor: [Hypersensitivity] explode all trees
- #5 MeSH descriptor: [Allergens] explode all trees
- #6 MeSH descriptor: [Histamine] this term only
- #7 MeSH descriptor: [Histamine Release] this term only
- #8 allerg* or hypersensitive* or anaphyla*:ti,ab,kw
- #9 #4 or #5 or #6 or #7 or #8
- #10 #3 and #9

CINAHL Complete on EBSCO platform

- S1 (MH "Chlorhexidine")
- S2 chlorhexidine or "ay 5312" or ay5312 or bidex or boston conditioning lotion or chlorhex or chlorhexidin or chlorohex or chlorohexydine or clohexidine or lisium or nibitane or nolvasan or nolvascin or rotersept or sterilon or tubilicid or tubulicid or umbipro or "mk 412a" or mk412a or novalsan or "sebidin a" or tubulicid

S3 S1 OR S2
S4 (MH "Hypersensitivity")
S5 (MH "Allergy and Immunology")
S6 (MH "Allergens")
S7 (MH "Histamine")
S8 allerg* or hypersensitive* or anaphyla*
S9 S4 OR S5 OR S6 OR S7 OR S8
S10 S3 AND S9

Web of Science

(chlorhexidine or "ay 5312" or ay5312 or bidex or "boston conditioning lotion" or chlorhex or chlorhexidin or chlorohex or chlorohexydine or clohexidine or lisium or nibitane or nolvasan or nolvascin or rotersept or sterilon or tubilicid or tubulicid or umbipro or "mk 412a" or mk412a or novalsan or "sebidin a" or tubulicid) AND TOPIC: (allerg* or hypersensitive* or anaphyla*)
Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC.

Appendix 2: Chlorhexidine Survey Questions

1. Do you test for chlorhexidine as an allergen in the workup of perioperative hypersensitivity?

Yes, routinely

If yes, how long has this been routinely performed? _____

Selectively, if mentioned in referral/suspected as a cause

No

2. What diagnostic methods do you use to investigate possible chlorhexidine hypersensitivity? (tick all that apply):

SPT

IDT

sIgE

BAT

Challenge. If so describe the technique briefly:

None, history only

3. Please list your diagnostic criteria for a positive test for all that apply to you:

SPT: _____

IDT: _____

sIgE: _____

4. How many cases of confirmed hypersensitivity has your institution/group diagnosed, and over what time period? (e.g. 13 cases of anaphylaxis, 2 delayed hypersensitivity over 5 years). If known, what was the route of exposure to chlorhexidine?

	Total	IV	Mucosa	Skin
Anaphylaxis:	_____	_____	_____	_____
Delayed hypersensitivity:	_____	_____	_____	_____
Other (describe):	_____	_____	_____	_____
Time period:	_____	_____	_____	_____

5. Where does chlorhexidine rank as a cause of anaphylaxis for you?
(please use broad groups – e.g. “third after NMBAs”, antibiotics, “fifth after antibiotics, latex, NMBAs, NSAIDs”, or “so rare it’s hard to rank”)

6. Is there any other information you think is relevant to pass on to the
“Chlorhexidine narrative review” team?
7. What types of chlorhexidine exposure are common in your patient population?
(tick all that apply):

Handrubs
Surgical skin preps
Skin swabs (pre-IV)
Impregnated CVADs/CVCs
Urethral gels
Mouthwashes
Impregnated dressings
Toothpastes
Other:

ISPAR Group Chlorhexidine survey results

Q1 Frequency of Chlorhexidine testing

Testing location	Routinely	Selectively	No
1	x		
2	x		
3	x		
4	x		
5	x		
6	x		
7	x		
8		x	
9		x	
10	x		
11	x		
12	x		
13	x		

Q2 What diagnostic methods are used to investigate possible chlorhexidine hypersensitivity?

Testing location	SPT	IDT	slgE	BAT	Challenge	Other
1	x	x	x			Hist. release
2	x	x	x			
3	x	x	x			
4	x	x	x			
5	x	x	x			
6		x	x		x (skin)	
7	x	x	x			
8	x	x				
9	x		x	x		
10	x	x	x			
11	x	x	x			
12	x	x	x	x		
13	x		x			

3. Diagnostic criteria for tests

Testing location	SPT	IDT	slgE	Comments
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1	Wheal + 3mm	Wheal + 3mm	>0.35 kUA/L	if 2 tests pos
2	Wheal + 3mm	Double bleb or +3mm	>0.35 kUA/L	
3	Wheal + 3mm	Wheal + 3mm	>0.35 kUA/L	
4	Wheal + 3mm	Double bleb or +3mm	>0.35 kUA/L	
5	>1/2 PC and >NC +3mm	Double bleb	>0.35 kUA/L	
6		> 8mm wheal	>0.01 kUA/L	
7	Wheal +4mm	Wheal + 3mm	>0.35 kUA/L	
8	Wheal + 3mm	Wheal + 3mm, duplicated		
9	Wheal + 3mm with itch		>0.01 kUA/L	
10	Wheal + 3mm	Wheal + 3mm	>0.20 kUA/L	
11			>0.35 kUA/L	
12	Wheal + 3mm	Double bleb or 8mm	>0.35 kUA/L	if 2 tests pos
13			>0.35 kUA/L	

4. Number of cases diagnosed

Testing location	Total Anaphylaxis	IV/CVC	Mucosa	Skin/wound	Delayed	Time Period (yrs)
1	64					19
2	8					5
3	13		3	10		5
4	42					9
5	1		1			1
6	31	8	19	4	8	18
7	10	1	4	1		2
8	1			1		unspecified
9	1					5
10	18	7	3	8	1	12
11	0					unspecified
12	45					17
13	18					20

5. Where does Chlorhexidine rank as a cause of anaphylaxis?

Testing location	Rank	1	2	3
1	2nd	Antibiotics	Chlorhexidine	
2	4 th /5th	NMBAs	Antibiotics	Gelofusine
3	3rd	Antibiotics	NMBAs	Chlorhexidine
4	3rd	NMBAs	Antibiotics	Chlorhexidine
5	rare			
6	4th	NMBAs	Antibiotics	Sugammadex
7	4th	NMBAs	Antibiotics	NSAIDs
8	too rare to rank			
9	too rare to rank			

13		x				x			
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