

# What is the impact of Chlorhexidine use on the incidence of anaphylaxis?

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## Literature Review

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**Purpose:** The National Health and Medical Research Council (NHMRC) commissioned this independent literature review to provide assurance that the revision of the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2010 Guidelines) is grounded in the most up-to-date and relevant scientific evidence

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# What is the impact of chlorhexidine use on the incidence of anaphylaxis?

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## Background

Chlorhexidine is an antiseptic antibacterial agent that is widely used in healthcare setting. It is commonly used to clean the skin after an injury, before surgery, before an injection and to clean hands before a procedure. Chlorhexidine is available in numerous different forms: Dressing; Gel/Jelly; Lotion; Solution; Liquid; Pad; Sponge; Cream (NHMRC 2010) with many unaware of its presence in the products they use daily (Sharp, Green & Rose 2016). Skin cleansing with chlorhexidine plays an important role in reducing the incidence of hospital-acquired infections (Hijazi et al. 2016; Karki & Cheng 2012). The Australian Guidelines for the Prevention and Control of Infection in Healthcare recommended decontaminating intravascular access devices site using a single-use application of alcohol-based chlorhexidine gluconate solution before device insertion (NHMRC 2010). Increasing chlorhexidine usage by consumers and health-care workers has resulted in a number of different adverse reactions including allergic contact dermatitis, photosensitivity, anaphylaxis and septic shock (Chen, P, Huda & Levy 2016; Chen, X et al. 2016; Hong et al. 2015a, 2015b; Sharp, Green & Rose 2016; Weng, M et al. 2014; Weng, ML et al. 2014). Anaphylactic reactions to chlorhexidine are a rare but potentially life-threatening complication (Stewart & Lenaghan 2015a). Therefore, it is important to examine the impact of chlorhexidine use on anaphylaxis in clinical settings.

## Objectives

The primary purpose of this literature review was to examine the impact of chlorhexidine use on the incidence of anaphylaxis in clinical settings.

Initial inspection of the literature suggested that chlorhexidine-related anaphylaxis was a relatively rare event, so has not been well researched. However, there were a number of case reports that described individual chlorhexidine-related anaphylaxis events. As a result, a broad approach to the literature review was taken. The two questions were:

1. What is the impact of chlorhexidine use with people in health care settings on the incidence of anaphylaxis?
2. What are the characteristics of chlorhexidine-related anaphylaxis in health care settings?

## Methods

As noted above, initial inspection of the literature suggested that evidence about the use of chlorhexidine on the incidence of anaphylaxis in the acute care, residential aged care, paediatric, neonatal and rehabilitation settings was limited. Therefore a broader review methodology was used to explore the incidence of chlorhexidine-related anaphylaxis and to generate a description of anaphylactic events.

### Types of studies

This literature review considered all types of research designs that addressed the above review questions. There were two major sources of evidence for this literature review. Firstly, there was a smaller body of literature that included case series, retrospective surveys and cohort studies that explored anaphylaxis in different health care populations. This body of literature allowed the incidence of chlorhexidine-related anaphylaxis to be investigated. Secondly, a number of case reports on chlorhexidine-related anaphylaxis have been published which allowed a detailed description to be generated about the anaphylaxis, the chlorhexidine products involved and the circumstances of the events. Therefore this review considered:

- Case series reports, retrospective surveys and cohort studies
- Case reports.

### Types of participants and settings

The review included all types of patients/participants including children and adults. The review considered studies that explored chlorhexidine-related anaphylaxis involving people from: acute care; residential aged care; paediatric; neonatal; or rehabilitation settings.

### Types of interventions

The review considered studies that addressed the use of chlorhexidine and anaphylaxis. Chlorhexidine products of interest included any gels, lotions, solutions, liquids, dressings, pads, sponges, creams and impregnated devices.

### Type of Comparison

The review investigated all uses of chlorhexidine in health care in relation to anaphylaxis, and there were no comparisons.

### Types of outcome measures

The review considered any study that focused on the following:

- Anaphylactic reactions (international criteria were used to confirm anaphylaxis)
- Severe allergy or hypersensitivity reactions
- Chlorhexidine product related to anaphylaxis (attribution to chlorhexidine was assessed)
- Procedures being undertaken at time of anaphylaxis
- Mortality rate

### Publication Date and Limits

The focus of the review was on current clinical practice, so the review only considered studies published from 2006 to 2016. The search was also limited to human and English language publications.

### Search Strategy

A broad approach to the search was undertaken that fitted the literature review framework. It was more iterative than the search process used for systematic reviews and entailed a preliminary investigation of databases and search terms by an academic librarian. Given the limited body of literature in the area of chlorhexidine-related anaphylaxis, the search included a comprehensive investigation of the grey literature to identify reports from governments, health departments, research institutes and professional bodies.

### Electronic searches

The following information sources were searched:

- CINAHL (Cumulative Index to Nursing & Allied Health Literature)
- Cochrane Library
- EMBASE-OvidSP
- MEDLINE-OvidSP
- SciFinder
- Scopus
- Science Citation Index Expanded (Web of Science)
- World Health Organization Library Information System(WHOLIS/IRIS)

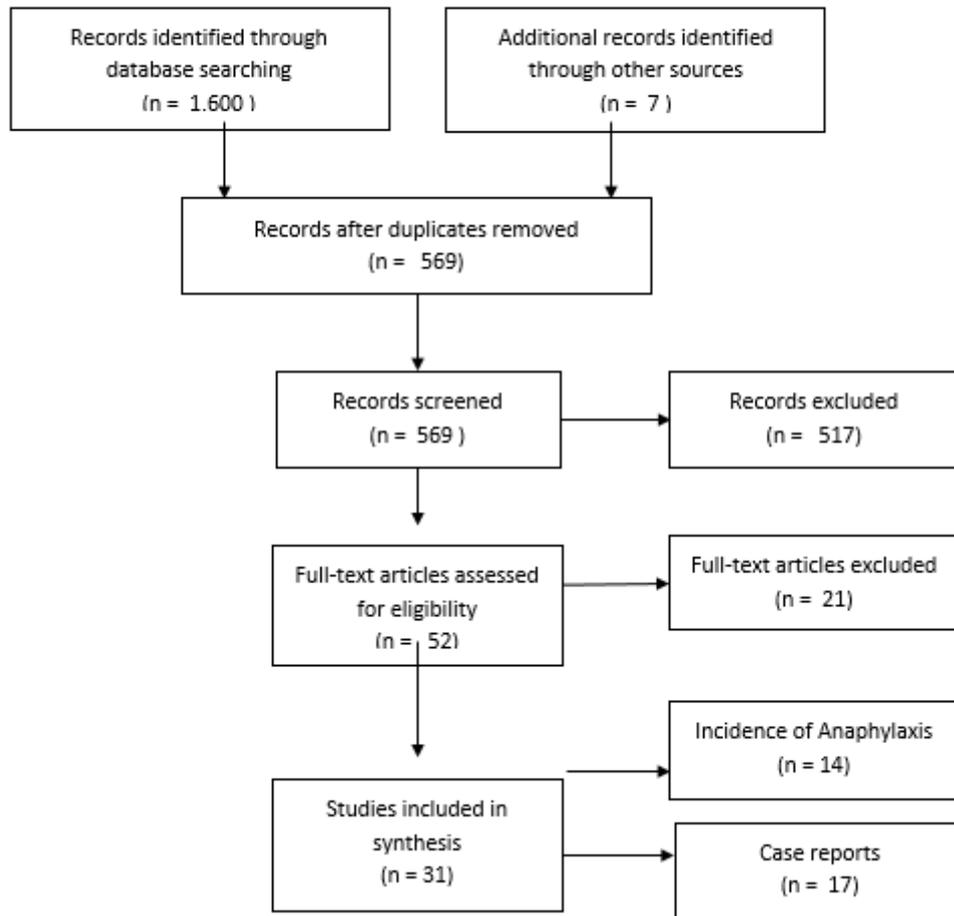
A librarian developed the initial search strategy for MEDLINE, then translated the strategy to other databases using appropriate syntax and vocabulary for those databases. The database search process was more iterative than that of systematic reviews, and some databases listed in the original proposal were deleted from the search as a result of the preliminary investigations of databases because they did not address literature relevant to the review topic. These databases are listed below:

- DARE (Database of Abstracts of Reviews of Effects)
- Joanna Briggs Institute EBP Database
- NCCHTA (National Coordinating Centre for Health Technology Assessment)
- CENTRAL (Cochrane Central Register of Controlled Trials, The Cochrane Library)

Following expert consultation on the draft literature review report, one excluded study was cited in the report because it provided limited information about deaths secondary to chlorhexidine-related anaphylaxis.

Grey literature was searched to identify studies not indexed in the databases. Reference lists were searched to identify studies missed during the database and grey literature searches. Studies were selected based on their title alone, then the full paper was retrieved for those that appeared relevant. During the search a number of conference abstracts were identified. Given that many of these abstracts contained minimal information, an additional search was undertaken to determine if a full report had been published. Refer to the PRISMA chart in Figure 1 for search results

**Figure 1**  
**Search Results Flow Chart**



## Results

The database search identified 1600 papers, and removal of duplicates resulted in 562 papers. The grey literature search identified four abstracts for papers that were also identified during the database search. A search of the Australian Therapeutic Goods Administration Database of Adverse Event Notifications identified two brief reports (one involving a reaction following a central venous catheter (CVC) insertion and another involving chlorhexidine and Lignocaine gel). However, as a result of a lack of detail about the anaphylaxis and attribution to chlorhexidine, neither were included in the review. Reference list searching produced a further seven papers, resulting in 569 papers, of which 52 full papers were screened. Of these 52 papers, 21 were excluded and 31 were included in the review. These papers consisted of 17 case reports and 14 papers that addressed the incidence of chlorhexidine-related anaphylaxis. Of the case reports, four of the 17 papers reported multiple cases (ranging from two to six cases of anaphylaxis). Nearly all papers involved anaphylactic events from the acute care setting (28 of 31). Two papers involved referrals to allergy clinics from all settings, and one paper involved the records of a national allergy register. Reasons for the exclusion of papers included a lack of detail about the anaphylactic event, the attribution to chlorhexidine and the setting. Of these excluded papers, 15 papers addressed case reports and 6 incidence of anaphylaxis. Three papers were excluded because they focused on polyhexanide which is a polymer of chlorhexidine. Of the 21 excluded papers, 14 were conference abstracts and one was a letter to an editor. The most common reason for the exclusion of these abstracts was a lack of detail about the anaphylactic event or the attribution to chlorhexidine, or both. Additional literature searches based on the citation details of the excluded abstracts failed to identify a full published report. Attribution to chlorhexidine in studies and case reports was generally well done, but the confirmation of anaphylaxis was more inconsistent and often relied upon clinical expertise. The inconsistency in confirming anaphylaxis is acknowledged as a limitation in this body of research. However, given that all the research addressing chlorhexidine-related anaphylaxis is quite limited, confirmation of anaphylaxis was not used to weigh the findings of this review.

## Quality of Research

Formal critical appraisal was not undertaken because the preliminary investigation of the literature highlighted that research in the area of chlorhexidine-related anaphylaxis was quite limited. The focus was therefore on how anaphylaxis was defined and how the attribution to chlorhexidine was determined. Attribution to chlorhexidine was generally done quite well in most studies and commonly employed a range of different approaches such as clinical history, tryptase, skin prick tests, intradermal tests and specific IgE. However, the majority of studies were retrospective, so this data was usually collected from patient records when available. Anaphylaxis in many papers was based on the patient assessment by the treating clinicians, typically an anaesthetist for perioperative patients. However, the clinical presentation of anaphylactic reactions was generally well reported in case studies, enabling assessment by the reviewers.

## Setting

It is important to note that the initial focus of the review was on chlorhexidine use in a range of different health care settings, including acute care, residential aged care, paediatric, neonatal and rehabilitation. However, most of the studies and case reports included in this review focused on the perioperative area. As a result, caution is needed when translating the findings to other settings.

## Question 1: What is the impact of Chlorhexidine use with people in health care settings on the incidence of anaphylaxis?

### Incidence of Chlorhexidine-related Anaphylaxis

A number of papers reported data on the frequency of chlorhexidine-related anaphylaxis, but many of these studies had limitations. The most common limitation was the failure of some studies to report the total population number. Lobera et al. (2008) conducted a study involving 71,063 perioperative patients across a five year period and identified 48 anaphylactic events, of which none were related to chlorhexidine. Laguna-Martinez et al. (2014) studied 32,397 perioperative patients across a four year period and identified 12 anaphylactic events, of which none were related to chlorhexidine (see Table 1). From a slightly different perspective, Sperling et al. (2012) conducted a year-long prospective study of the use of Instillagel (2% lignocaine & 0.25% chlorhexidine) with 27,440 urology patients and the application of 57,500 tubes of the gel, and did not identify any adverse events (Sperling, Luemmen & Reubben 2012). However, a retrospective study by Chen et al. (2016) conducted over five years that involved 151,876 perioperative patients identified 16 anaphylactic events, of which one was related to chlorhexidine. This equates to an incidence rate of 0.66/100,000/5 years. However, caution is needed in generalising the findings of Chen et al. (2016) to other settings because the incidence rate is based on data collected retrospectively at a single hospital (refer to Table 1).

These four studies suggest that chlorhexidine-related anaphylaxis is a relatively rare event in health care. However, three of these four studies involved perioperative patients and the fourth involved urology patients so it is difficult to determine if these findings are reflective of other health care populations. It is possible that a large acute care hospital might encounter one or more chlorhexidine-related anaphylactic events each year.

A range of other studies also presented data that was more varied (see Table 2). These results show much greater variability, with the rate of all anaphylactic events attributed to chlorhexidine ranging from 0.2% to 7%. However, lack of data about population numbers makes it more difficult to evaluate the magnitude of this relationship. Further, all studies involved a retrospective review of patient records. In addition, six of the seven studies involved perioperative patients, so it is not clear if these findings are generalisable to other health care populations.

**Table 1**  
**Chlorhexidine-related Anaphylaxis**

Citation	Total Population	Time Frame	Anaphylactic Events	Number of Chlorhexidine-related Anaphylactic Events	Incident Rate of Anaphylaxis	Incident Rate of Chlorhexidine-related Anaphylaxis
Lobera 2008	71,063 perioperative patients	1998 to 2002 Prospective Study	48	0	67.5/100,000/3 years	NA
Laguna-Martinez 2014	32,397 perioperative patients	2010 to 2013 Prospective Study	12	0	37.0/100,000/3 years	NA
Chen 2016	151,876 perioperative patients	2007 to 2012 Retrospective Study	16	1 of 16 (6.25%)	10.5/100,000/5 years	0.66/100,000/5 years
Sperling 2012	27,440 urology procedure patients that involve Instillagel	1 year period Prospective Study	0 (No adverse event)	0	NA	NA

**Table 2**  
**Number of Anaphylactic Events**

<b>Citation</b>	<b>Population</b>	<b>Time Frame</b>	<b>Anaphylactic Events</b>	<b>Number of Chlorhexidine-related Anaphylactic Events</b>
Chong 2008	Perioperative patients referred to allergy clinic	2005 to 2006 Retrospective Study	23	1 of 23 (4.3%)
Garvey 2007	Perioperative patients referred to allergy clinic	1999 to 2005 Retrospective Study	174	12 of 174 (6.9%)
Harboe 2010	Perioperative patients who had reaction to local anaesthetic & referred to allergy clinic	1995 to 2006 Retrospective Study	135	5 of 135 (3.7%)
Krishna 2014	Perioperative patients referred to allergy clinic	2005 to 2012 Retrospective Study	161	8 of 161 (5%)
Laysen 2012	Perioperative patients referred to allergy clinic	2001 to 2011 Retrospective Study	344	24 of 344 (7%)
Makinen-Kiljunen 2008	National Severe Allergic Reactions Register	2000 to 2007 Retrospective Study	530	1 of 530 (0.2%)
McNeil 2008	50 perioperative patients referred to Immunology Unit	2000 to 2007 Retrospective Study	50 (selected from all records)	2 of 50 (4%)

## Multiple Anaphylactic Events

From a different perspective, reports also demonstrated that some patients experience multiple hypersensitivity and anaphylactic events during a single hospital admission (Buergi et al. 2014; Guleri et al. 2012; McNeill, Kerridge & Boyle 2008; Nakonechna et al. 2014; Odedra & Farooque 2014; Sijbesma, Rockmann & van der Weegen 2011; Toomey 2013). Case reports were identified that described patients having to undergo three attempts at surgery because the first two attempts were abandoned as a result of hypersensitivity and anaphylactic reactions to chlorhexidine (Buergi et al. 2014; Guleri et al. 2012; Nakonechna et al. 2014; Sijbesma, Rockmann & van der Weegen 2011). These multiple hypersensitivity events occurred in perioperative patients, who sometimes experienced reactions at different stages of their hospitalisation.

For example, Guleri et al. (2012) described one such case involving a 71 year old man admitted to hospital for coronary artery surgery. This man's hypersensitivity events are described below:

- Pre-operatively:  
The man experienced an allergic reaction to skin preparation with 4% chlorhexidine soap
- 1st Surgical Attempt:  
The man experienced a second allergic reaction involving a chlorhexidine impregnated CVC and chlorhexidine skin preparation solution. He had an anaphylactic reaction so the surgery was abandoned. Investigation of the allergic reaction identified a sensitivity to pancuroneum, which was assumed to be the cause of the anaphylaxis.
- 2nd Surgical Attempt  
The patient experienced another allergic reaction during the re-scheduled surgery (one month later), a chlorhexidine impregnated CVC was used again, which produced another anaphylactic reaction. Surgery was abandoned for a second time
- 3rd Surgical Attempt  
Allergy to chlorhexidine was identified. Surgery was completed under local anaesthetic agents without the use of chlorhexidine or pancuroneum and there were no adverse events.

Of note, in some reports an initial mild allergic reaction to a chlorhexidine product was discounted, ignored or not reported by the patient. As a consequence, use of chlorhexidine products was continued leading to an anaphylactic event.

For example, Buergi et al. (2014) reported the case of a 45 year old urological patient:

- 1st attempt at procedure:  
The man experienced an anaphylactic reaction during the first attempt at the urological procedure, so the procedure was abandoned. Suspected cause of the reaction was the contrast agent that was used, so no action was taken and allergy testing was not done.

- 2nd attempt at procedure:  
The man experienced a second anaphylactic reaction during the re-scheduled procedure, so the procedure was abandoned for a second time. The patient was referred to an immunology clinic for a suspected allergy to antibiotics. Chlorhexidine allergy was not tested because the urological team did not realise it was in the lubricant gel.
- 3rd Attempt at procedure  
During the work-up for the third attempt at the procedure, the patient was tested for a sensitivity to chlorhexidine (which was positive). Therefore chlorhexidine was avoided and the third attempt at the surgery was completed without incident.

In another case, Nakonechina et al. (2014) described anaphylaxis secondary to a CVC catheter impregnated with chlorhexidine. The anaphylaxis was treated, but the CVC line was left in situ which resulted in a repeat anaphylaxis. Similarly, Khoo & Oziemski (2011) reported the case of an 84 year old female with a known allergy to chlorhexidine who experienced anaphylaxis with cardiac arrest secondary to the insertion of a CVC catheter impregnated with chlorhexidine. In another case report, Nakonechina et al. (2014) reported the case of a 78 year old male who experienced two anaphylactic reactions separated by several months. The patient subsequently tested positive to a chlorhexidine allergy, so it was assumed that the man was exposed to chlorhexidine during both procedures. However, the specific chlorhexidine product was not able to be identified by the health care team. Toomey (2013) reported the case of a 65 year old man who developed a rash over his body after cleaning himself with a 2% chlorhexidine solution the night before his surgery ). The patient did not report the mild allergic reaction and then experienced anaphylaxis during surgery. In a similar case, a 26 year old man experienced a rash the night before surgery following the use of 'chlorhexidine soap' in the shower, then complained of itchiness in the operating theatre following skin preparation with chlorhexidine prior to anaesthesia (Guleri et al. 2012). Neither allergic reaction was investigated, and the man then experienced anaphylaxis following the insertion of a CVC impregnated with chlorhexidine.

These reports highlight the danger for people who have an allergy to chlorhexidine in areas such as operating theatres where exposure to chlorhexidine can occur from any one of a large number of products. When exposure to a chlorhexidine product occurs, it is not always known by the health care team. When a hypersensitivity reaction occurs, chlorhexidine is sometimes not considered as a possible cause.

## **Mortality**

No deaths secondary to chlorhexidine-related anaphylaxis were identified during this review. Two deaths were reported in an excluded paper (Pemberton & Gibson 2012). These deaths occurred during dental treatments, but details about the deaths were minimal. However the link to chlorhexidine-related anaphylaxis was made by a coroner rather than by clinicians, and appears to be the result of speculation by the coroner rather than testing for allergy. Thus, the significance of these two reported deaths in the context of chlorhexidine-related anaphylaxis is difficult to

determine. More recently, a Drug Safety Communication release by the USA Food and Drug Administration reported two deaths associated with the use of chlorhexidine skin antiseptic (FDA 2017). While details are limited, it does further highlight the risk associated with anaphylactic events that are caused by chlorhexidine.

However, as allergy testing occurs only in those patients who survive anaphylaxis, and the majority of studies in this review were retrospective reviews of allergy clinic records, it is possible that studies could have missed cases of mortality resulting from an anaphylactic reaction to chlorhexidine. However, given that chlorhexidine-related anaphylaxis appears to be a relatively rare event, this number would likely be small.

## Question 2: What are the characteristics of chlorhexidine-related anaphylaxis in health care settings?

Studies investigating the incidence of anaphylaxis provided little specific information about individual patients or anaphylactic events. However, a number of case reports were identified that provided information about individual chlorhexidine-related anaphylaxis. While this level of evidence is limited, these reports enable a description of anaphylactic events linked to chlorhexidine products to be developed.

### Demographics

Case reports on chlorhexidine-related anaphylaxis came from 7 different countries, with 7 reports coming from the United Kingdom”

United Kingdom	7
Australia	2
China	2
Canada	1
Hong Kong	1
Netherlands	1
Switzerland	1
Korea	1
USA	1

The 17 case reports included in this review described a total of 27 different anaphylactic events. The average age of patients was 58 years, and ranged from 26 to 84 years. Most people in the case reports were male (81%), and 89% were perioperative patients.

In terms of history of allergy, 26% had a documented history of atopy. However given the retrospective nature of data collection, it was difficult to determine how complete this information was for the population. Similarly, information about exposure was less reliable because some reports highlighted that health care workers did not always recognize when chlorhexidine exposure had occurred (Nakonechna et al. 2014). In 11% of cases, a documented history of an allergic reaction

to chlorhexidine went undetected until after the patients had experienced an anaphylactic event (Nakonechna et al. 2014).

### **Specific Populations**

As previously noted, nearly all reports involving chlorhexidine-related anaphylactic events came from the acute care setting (28 of 31 papers). Of these acute care reports, most involved perioperative patients. There were no other specific populations (such as immunosuppressed patients) identified in reports. However, the relatively large number of reports about patients who experienced multiple anaphylactic events highlights the risk of anaphylaxis faced by people with chlorhexidine hypersensitivity.

### **Chlorhexidine Products**

In terms of the type of product that caused the anaphylaxis, in 63% of cases a single chlorhexidine product was identified. In 7.4% of cases, no specific product was identified and it was assumed that some form of exposure had occurred during the perioperative period (Nakonechna et al. 2014). Urinary lubricants contributed to 44.4% of the reported cases, and skin preparation products contributed to 37% of cases (see Table 3). (Note that some anaphylactic events involved two or more products)

Based on the information in case reports, it appears chlorhexidine impregnated CVCs can produce the most rapid onset and severe anaphylaxis. Case reports described immediate onset of anaphylaxis after CVC insertion (Guleri et al. 2012; Odedra & Farooque 2014; Pettipher & Duggleby 2015; Weng, ML et al. 2014) or within minutes (Khoo & Oziemski 2011; Qin & Zeng 2016; Toomey 2013). Some case reports also described a full recovery after CVC replacement (Pettipher & Duggleby 2015; Qin & Zeng 2016). One report described a second episode of anaphylaxis when the CVC line was not removed after the initial event (Nakonechna et al. 2014). However in one report, the anaphylaxis was described as not happening until 10 minutes after CVC insertion (Nakonechna et al. 2014).

Anaphylaxis secondary to urinary application of chlorhexidine was reported in a number of papers, but the anaphylactic events were not described as 'immediate' or 'within minutes'. However, one paper described a sudden anaphylactic event following a rectal examination with the use of chlorhexidine lubricant (Bae et al. 2008). Skin preparation containing chlorhexidine has also been linked to anaphylaxis. However skin preparations were often used in combination with other chlorhexidine containing products, so their risk was more difficult to assess.

Caution is needed when interpreting this information because evidence from case reports is very limited and difficult to generalise beyond the case being reported. In addition, the use of multiple chlorhexidine products were described in some case reports (Khoo & Oziemski 2011; Pettipher & Duggleby 2015; Toomey 2013; Weng, ML et al. 2014), making it difficult to assess the risks associated with individual products.

Table 3  
Products That Caused Hypersensitivity Reactions

Citation	Population
Urinary lubricant (12 cases)	Instillagel - lignocaine 2% and chlorhexidine 0.25% (Buergi et al. 2014; Dyer et al. 2013; Khan, Kazi & O'Donohoe 2011; Nakonechna et al. 2014; Parkes et al. 2009)
	Chlorhexidine gel (Sijbesma, Rockmann & van der Weegen 2011)
	0.05% chlorhexidine and 2% lignocaine (Nakonechna et al. 2014; Sheth & Silviu-Dan 2007)
Skin preparation (10 cases)	Iodine 0.2%, chlorhexidine 0.45% & alcohol 65% (Weng, ML et al. 2014)
	2% chlorhexidine skin prep (Guleri et al. 2012; Pettipher & Duggleby 2015; Toomey 2013)
	ChlorPrep (chlorhexidine & alcohol) (Toomey 2013)
	Chlorhexidine 0.5% & alcohol 70% (Pettipher & Duggleby 2015)
	0.1% chlorhexidine irrigation solution (Stewart & Lenaghan 2015b)
	Chlorhexidine skin prep (Guleri et al. 2012)
	4% chlorhexidine soap (Guleri et al. 2012)
	Chlorhexidine gel (used as soap in shower) (Guleri et al. 2012)
CVC Impregnated with chlorhexidine (8 cases)	(Guleri et al. 2012; Khoo & Oziemski 2011; Nakonechna et al. 2014; Pettipher & Duggleby 2015; Qin & Zeng 2016; Weng, ML et al. 2014)
Other products (3 cases)	Oral rinse with 15mls 0.12% chlorhexidine (Toomey 2013)
	0.05% chlorhexidine used as rectal disinfectant (Bae et al. 2008)
	Rectal stump lavage with 0.05% Chlorhexidine Acetate solution (Liu et al. 2007)

## Procedures

Anaphylaxis occurred during a range of different procedures, and in some case reports the anaphylaxis was attributed to a number of different chlorhexidine exposures. Most reports were from the perioperative area, highlighting that chlorhexidine-related anaphylaxis appears to most often occur with anaesthetic/surgical patients. In terms of specific procedures, urinary interventions such as catheter insertion were the most common procedure (cited in 44.4% of case reports), and the chlorhexidine product used in these cases was chlorhexidine/lignocaine gel. The insertion of chlorhexidine impregnated CVCs was the next most common procedure, cited in eight case reports. Chlorhexidine skin preparation prior to surgery was also commonly cited, often as a second point of exposure to chlorhexidine during a surgical procedure.

## Presentation of Anaphylaxis

Given that most case reports were from the perioperative setting, description of the presentation of anaphylaxis focused primarily on haemodynamic and respiratory parameters such as hypotension, hypoxia, respiratory distress and wheezing, and tachycardia. However, anaphylaxis secondary to chlorhexidine impregnated CVC insertions were different from others in that they were more often described as an immediate reaction, or within a minute or two of the catheter insertion (Guleri et al. 2012; Khoo & Oziemski 2011; Odedra & Farooque 2014; Qin & Zeng 2016; Toomey 2013; Weng, ML et al. 2014). As previously noted, in one case a 50 year old male experienced an anaphylactic reaction 10 minutes after the insertion of a CVC during cardiac surgery (Nakonechna et al. 2014). The man was resuscitated, the CVC left in place and the surgery continued. However, he experienced a second anaphylactic event in the recovery room and at that point the CVC was removed.

## Outcome

Detailed information about outcomes was not included in most papers, but no deaths were reported in any of the included papers. A number of reports described two or three attempts at a surgical procedure before it was successfully completed (Buergi et al. 2014; Guleri et al. 2012; Sijbesma, Rockmann & van der Weegen 2011).

## Discussion

While evidence about chlorhexidine-related anaphylaxis is limited, it appears to be a relatively rare event. When it occurs, current evidence suggests that it most often involves perioperative patients. This may be a consequence of the greater use of chlorhexidine products in perioperative areas. It may also reflect the more invasive use of chlorhexidine products with these patients, such as CVC insertions, skin washes, urinary catheterizations, bladder irrigations and bowel washouts. It is not possible to determine the incidence of chlorhexidine related anaphylaxis with any confidence, however studies suggest that chlorhexidine-related anaphylaxis may account for between 0.2% and 7% of cases of anaphylaxis. Based on the findings of one study, the incidence rate for chlorhexidine-related anaphylaxis was 0.66/100,000/5 years (Chen, X et al. 2016).

A range of different chlorhexidine products and procedures were linked to anaphylaxis. However, when CVCs that are impregnated with chlorhexidine were used for patients with an allergy to chlorhexidine, a number of papers reported that they produced an immediate and severe anaphylactic reaction (Khoo & Oziemski 2011; Odedra & Farooque 2014; Qin & Zeng 2016). If the CVC was not removed, one paper reported that it produced another anaphylactic reaction (Nakonechna et al. 2014).

Case reports also highlight the danger of multiple anaphylactic reactions for individuals. A number of accounts were identified reporting repeated exposure to chlorhexidine and multiple hypersensitivity reactions. In some of these reports, chlorhexidine was not suspected as the cause of the anaphylaxis; in others the health care team was not aware of the exposure to chlorhexidine (Buergi et al. 2014; Guleri et al. 2012; Nakonechna et al. 2014). In one case report, the authors noted that information about chlorhexidine impregnation was not readily apparent on the CVC insertion package (Guleri et al. 2012). When mild allergic reactions to chlorhexidine occurred, they were

sometimes ignored by the patient or the health care team (Guleri et al. 2012). When perioperative patients had a history of allergic reactions to chlorhexidine, this was not always detected prior to surgery (Nakonechna et al. 2014).

Despite the seriousness of the anaphylactic reactions, and the fact that some involved cardiac arrest, no reports of death secondary to a chlorhexidine-related hypersensitivity reaction were identified in any included paper. However, deaths linked to chlorhexidine were identified in other documentation, but limited information made it difficult to determine their significance. As previously noted, the methods used to investigate chlorhexidine-related anaphylaxis may not identify patients who died secondary to an anaphylactic reaction.

### **Clinical Implications**

There are a number of important implications for clinical practice to emerge from this review and these are summarized below.

- The major finding to emerge from this review is that chlorhexidine-related anaphylaxis appears to be a relatively rare event in health care. The limited nature of the evidence makes it difficult to determine the clinical significance of the findings. However, given the incident rate of chlorhexidine-related anaphylaxis identified from one study, it is possible that a large acute care surgical hospital might encounter one or more events each year. However, more research is needed to better understand the magnitude of the problem.
- While information is very limited, it seems that the severity of allergic reactions is greatest when the exposure is a result of a chlorhexidine impregnated CVC. In addition, failure to remove the chlorhexidine impregnated CVC after an anaphylactic event results in continuing exposure to chlorhexidine and the possibility of further anaphylaxis.
- Some studies and case reports referred to chlorhexidine as a shampoo, soap, disinfectant and skin preparation. As a result, some chlorhexidine products appeared to be applied or administered in a casual fashion. But given the severity of anaphylaxis, it may be more appropriate to treat chlorhexidine as a medication, and so include it in the quality use of medicines framework. This may help limit the unrecognized exposure to chlorhexidine that was reported in some perioperative case reports.
- Greater recognition of the potential for chlorhexidine-related anaphylaxis is needed. As part of this, it is important to consider chlorhexidine products when investigating hypersensitivity reactions.
- Findings highlight the importance of all allergic reactions in clinical practice, and the need to investigate the cause whenever possible. Linked to this, the review also highlighted the importance of communicating all allergies to treating clinicians.
- It is important to note that the initial focus of the review was on the use of chlorhexidine in a range of different health care settings. These settings included acute care, residential aged care, paediatric, neonatal and rehabilitation. However, most of the studies and case reports included in this review focused on the perioperative area. As a result, caution is needed when interpreting the findings.

## Research Implications and Opportunities

There are a number of implications for research to emerge from the findings of this review.

- The most important finding from this review is that more research is needed on chlorhexidine-related anaphylaxis to better understand the nature, risks and magnitude of the problem. Further information is also needed about the different types of exposure and the risks that accompany them.
- A common limitation of many studies and reports identified by this review was how anaphylaxis and the attribution to chlorhexidine were defined. Clearer definitions and better reporting are needed in future research.
- Clearer documentation is needed of exposures at the time of the anaphylactic event, and the exposure prior to the event is also needed in reports to help understand the nature of the hypersensitivity reactions. As part of this, better reporting of the chlorhexidine products involved is needed, and greater description of the actual exposures.

## Limitations

There were a number of important limitations related to the research exploring chlorhexidine-related anaphylaxis and they are summarized below. These limitations highlight the need for more research, clearer definitions of anaphylaxis and better reporting of exposures.

- Chlorhexidine anaphylaxis appears to be a relatively rare event, so few prospective studies have been conducted. Most research has been retrospective, so has relied on the records of hospitals and allergy clinics for descriptions of anaphylaxis and its attribution to chlorhexidine. As a result, information in published reports was often very limited. Differences in the proportion of anaphylactic events that are related to chlorhexidine differ considerably between reports (from 0.2% to 7%). Given that many investigations used allergy clinic records, it is possible that some people who experience anaphylaxis were not referred to the clinic, so were not captured in the data. In support of this, case studies in this review noted that not all allergic reactions were investigated (Buerger et al. 2014; Nakonechna et al. 2014). Therefore, current research does not give us a reliable indication about the incidence of chlorhexidine-related anaphylaxis. Several studies suggest it is a rare event, but further research is needed to better understand the magnitude of the problem.
- Most studies and case reports in this review involved perioperative patients, with little information about other settings. However, this is likely to reflect the primary use of chlorhexidine as a preparation agent for surgery and invasive procedures. Some studies focused on all perioperative anaphylactic events, so chlorhexidine-related events were opportunistic discoveries. However, a review of records at two allergy clinics identified cases of hypersensitivity reactions and anaphylaxis to chlorhexidine from dental clinics and people's home. Current evidence does not allow us to assess whether chlorhexidine related anaphylaxis is occurring in health care settings other than the perioperative area.
- Information in many reports about anaphylactic events and exposure to chlorhexidine was very limited. Identification of anaphylaxis was often based on expert opinion rather than clearly defined criteria. In other reports, *severe hypersensitivity reactions* and anaphylaxis

were included in the data, making the reports difficult to assess. Limited information about exposure made it difficult to evaluate the impact of different procedures. Based on information from case reports, it appears that the insertion of a CVC impregnated with chlorhexidine into a person with a chlorhexidine allergy may produce a quicker reaction that is of much greater severity than other types of exposure. However, it is not possible to translate the information from a few case reports to the broader population. There is a need for greater rigour and clearer definitions when investigating chlorhexidine related anaphylaxis, and more detailed recording about the exposure.

- Many of the papers identified during the literature search took the form of conference abstracts, brief reports and letters to the editor. As a result, information about the anaphylaxis was limited. Additional literature searches failed to find full reports for most of these abstracts. While these reports helped generate a description of the anaphylactic events, it is difficult to determine the implications of this information for other populations.

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