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

Technical Report

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Contents

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

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Background

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.

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 perform hand hygiene 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 device sites 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 had 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 utilised. 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.

Inclusion and exclusion criteria for considering studies for this review

Review question	Population	Intervention	Outcomes	Study Designs
Q 1	All types of people (adults and children) from the following settings: • Acute care • Residential aged care • Paediatric • Neonatal • Rehabilitation	All types of chlorhexidine, including: • Gels • Lotions • Solutions • Liquids • Dressings, pads & sponges • creams • Impregnated devices	• Anaphylactic reactions / severe allergy or hypersensitivity reactions • Mortality rate • Chlorhexidine products related to anaphylaxis • Procedures being undertaken at time of anaphylaxis	• Case series reports • Retrospective surveys • Cohort studies
Q 2	All types of people (adults and children) from the following settings: • Acute care • Residential aged care • Paediatric • Neonatal • Rehabilitation	All types of chlorhexidine, including: • Gels • Lotions • Solutions • Liquids • Dressings, pads & sponges • Creams • Impregnated	• Demographic data of people who experienced an anaphylactic event • Chlorhexidine products used and exposure details • Procedures being undertaken • Presentation of the anaphylaxis	• Case reports

		devices	• Outcome from anaphylactic event	

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 one or more of following health care settings:

- Acute care
- Residential aged care
- Paediatric
- Neonatal
- Rehabilitation.

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. The review considered any study that focused on the following:

- Any type of chlorhexidine use in relation to the incidence of anaphylaxis.
- Reports about anaphylaxis and hypersensitivity reactions related to the use of any chlorhexidine product.

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

In addition, to develop a description of the chlorhexidine-related anaphylaxis the review considered studies that report the following information:

- Demographics of people who experienced a chlorhexidine-related anaphylactic event
- Chlorhexidine products and details of exposure
- Procedures
- Presentation of the anaphylaxis
- Outcome from anaphylactic event
- Repeat exposure events

Publication Date and Limits

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

Search Strategy

Given the diverse nature of the literature addressing chlorhexidine-related anaphylaxis, a broad approach to the search was utilised, one that better fitted the literature review framework. It was more iterative than the search process used for systematic reviews and entailed a series of preliminary investigations of databases and search terms by an academic librarian. Given the relatively limited body of rigorous research addressing chlorhexidine-related anaphylaxis, the search included a comprehensive investigation of the grey literature to identify reports, alerts, conference abstracts and case 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)

Grey literature

A grey literature was searched to identify studies not indexed in the databases. This search included the following:

- AHRQ (Agency for Healthcare Research and Quality)- www.ahrq.gov
- Grey Literature Report (New York Academy of Medicine) http://greylit.org/
- NICE (National Institute for Health and Clinical Excellence) www.nice.org.uk/
- Open Grey http://www.opengrey.eu/)

Key international infection control and health care organisations were also searched for relevant reports related to one of the review objectives. International organisations searched included:

- USA - Department of Health & Human Services (http://www.hhs.gov/)
- USA - Agency for Healthcare Research and Quality (http://www.ahrq.gov/)
- USA - Infectious Disease Society of America (www.idsociety.org).
- Australia - Department of Health (http://www.health.gov.au/)
- Australia - National Health and Medical Research Council (http://www.nhmrc.gov.au/)
- Australian Institute for Health and Welfare (https://www.aihw.gov.au/)
- Australian Commission on Safety and Quality in Health Care (http://www.safetyandquality.gov.au/)
- NZ – Department of Health (http://www.health.govt.nz/)
- World Health Organization (http://www.who.int/en/)
- Centres for Disease Control and Prevention (http://www.cdc.gov/)
- European Centre for Disease Prevention and Control (http://ecdc.europa.eu/en/Pages/home.aspx)
- European Society for Clinical Microbiology and Infectious Diseases (www.escmid.org)
- British Society for Antimicrobial Chemotherapy (www.bsac.org.uk)
- Infectious Diseases Research Network (www.idrn.org).
- Canada - IPAC (http://www.ipac-canada.org/)
- UK Healthcare Infection Society (https://www.his.org.uk/)
- Therapeutic Goods Administration (https://www.tga.gov.au/)
- Australian Society of Clinical Immunology and Allergy (http://www.allergy.org.au/)
- Allergy & Anaphylaxis Australia (https://www.allergyfacts.org.au/)
- World Allergy Organisation (http://www.worldallergy.org/)
- International Food Allergy & Anaphylaxis Alliance (http://www.foodallergy.org/about/faaalliance)
- American Academy Of Allergy, Asthma & Immunology (https://www.aaaai.org/)
- British Society for Allergy and Clinical Immunology (http://www.bsaci.org/)
- American College of Clinical Pharmacy (https://www.accp.com/index.aspx)

Reference List Search

Finally, 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.

Conference Abstracts

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.

Keywords

Chlorhexidine/ eludril / corsodyl/ Tubulicid/Novalsan/Sebidin/CHX/ MK-412A/MK 412A/MK412A

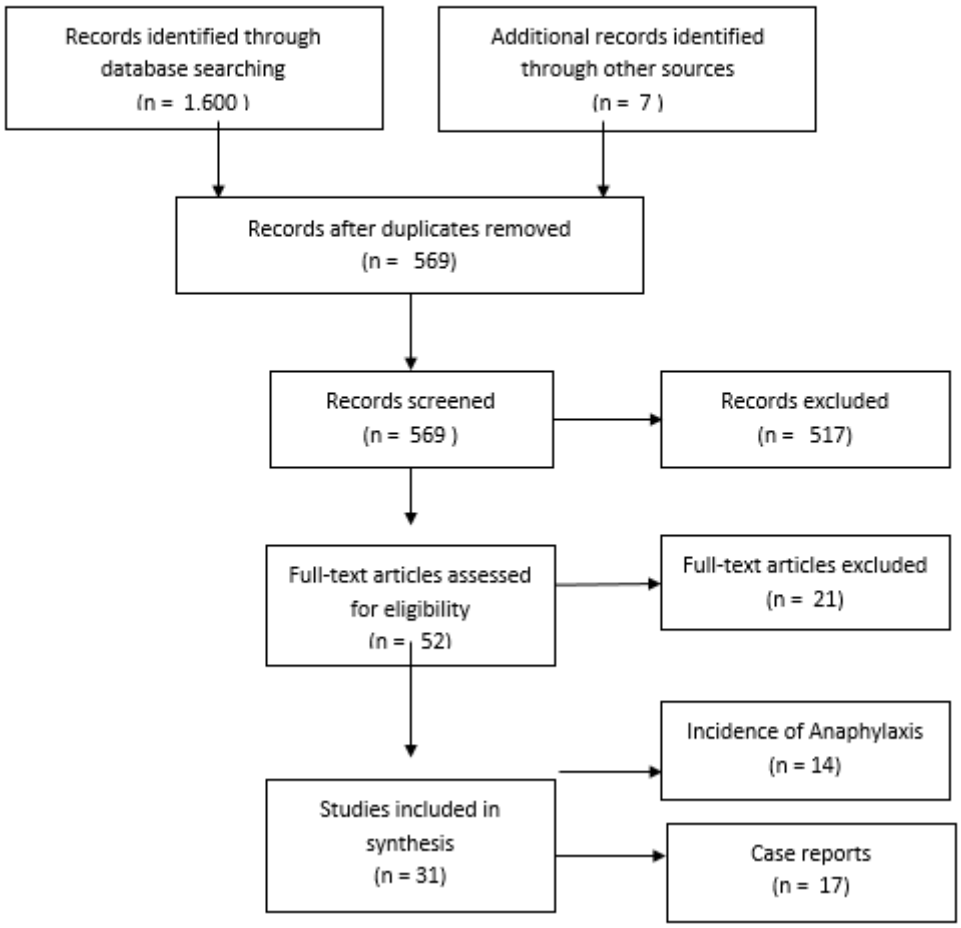
Anaphylaxis/Anaphylactic reaction/Anaphylactic shock/Anaphylactoid reaction/ Allergy/ Hypersensitivity/ adverse reactions/ systemic shock

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.

Refer to the PRISMA chart in Figure 1 for search results.

Figure 1

Search Results Flow Chart



Data collection and analysis

Selection of studies

The titles and abstracts of all search results were reviewed to identify and select potentially relevant studies. Pre-defined inclusion and exclusion criteria were used initially when identifying studies to obtain the full text paper. Full text papers were then screened to determine which studies met the inclusion criteria (see Appendix II).

Appraisal of studies

As noted above, chlorhexidine-related anaphylaxis is a rare event so research evidence is currently quite limited. There were two major sources of evidence for this review; investigations of the incidence of anaphylaxis (via case series, retrospective surveys and cohort studies) and reports about individual anaphylactic events (case reports). In appraising studies, the most critical element in determining the trustworthiness of information related to the confirmation of the anaphylactic event and its attribution to chlorhexidine. Therefore, all studies were appraised against these two issues.

Appraising this collection of literature was quite difficult because the major focus for most studies exploring the incidence of severe hypersensitivity reactions was on the attribution of the allergic reaction to chlorhexidine (and to other agents) rather than on demonstrating that an anaphylactic event had occurred. However, case reports generally provided more informative descriptions of the anaphylactic events.

Anaphylaxis was assessed using the main characteristics of the syndrome, which focused on acute onset, rapid progression of symptoms and multiple system involvement. Current recommendations from key international organisations concerned with anaphylaxis suggest anaphylaxis is present when one of the three following criteria are fulfilled (Ruggeberg et al. 2007; Sampson et al. 2006; Simons et al. 2011):

1. Acute onset (eg. minutes to hours) with involvement of skin, mucosal tissue or both (eg. generalised hives pruritus or flushing, swollen lips-tongue-uvula)

   and at least one of the following:

   a) Respiratory compromise (eg. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia).
   b) Reduced BP or associated symptoms of end organ dysfunction (eg hypotonia [collapse], syncope [fainting], incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen (minutes to hours):
   a) Involvement of skin -mucosal tissue (eg. generalised hives, itch-flush, swollen lips-tongue-uvula),
   b) Respiratory compromise (eg. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia) or
   c) Reduced BP or associated symptoms of end organ dysfunction (eg hypotonia [collapse], syncope [fainting], incontinence), or
   d) Persistent gastrointestinal symptoms (eg. Crampy abdominal pain, vomiting).

3. Reduced BP after exposure to a known allergen for that patient (minutes to hours)

There is no gold standard for the attribution of an allergic reaction to chlorhexidine, and results from the different tests can be contradictory. However, attribution to chlorhexidine was assessed to

ensure formal investigation was undertaken and that this investigation linked the anaphylaxis to chlorhexidine use. Testing included:

- Serum tryptase
- Specific IgE testing
- Skin prick test
- Intradermal test
- Challenge provocation testing
- Basophil activation testing

Data extraction

Data was extracted from studies that met the inclusion criteria. The form in Appendix III was used to extract data from case series reports, retrospective surveys and cohort studies and the form in Appendix IV was used for case reports. Data extraction summary tables were used to present extracted data from all included studies. Any study undergoing the data extraction process and subsequently rejected from the review was recorded in the excluded studies table.

Data analysis

In keeping with the literature review approach, data was summarised using tables and narrative discussion. Initially the analysis of data focused on the incidence of chlorhexidine-related anaphylaxis, then on the characteristics of the anaphylactic events.

To determine the incidence of chlorhexidine-related anaphylaxis, the analysis focused on data related to all populations, all uses of chlorhexidine and all chlorhexidine products. Initial review of the literature suggested that chlorhexidine-related anaphylaxis is a rare event, so research is limited. While the original intent for the analysis was to explore the incidence of anaphylaxis in different health care populations, most identified reports addressed perioperative patients and anaphylaxis related to anaesthesia and surgery.

Based on individual case reports, the characteristics of the chlorhexidine-related anaphylactic events were summarised using tables and narrative discussion. While the original intent was to explore the characteristics of anaphylaxis in different populations, given that the majority of reports involved perioperative patients this was not possible.

Declared interests of the author(s)

Refer to Appendix V and Appendix VI for the declared interests of the author(s) of each paper included in this review.

Results

The database search identified 1600 papers, and removal of duplicates resulted in 562 papers. The grey literature search identified 4 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 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. Refer to Appendix VI provides a brief synopsis for each case report included in the review. Appendix VII lists the excluded studies. 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 six 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. See Appendix VIII for the summary of the assessment of studies and Appendix IX for the summary of the assessment of case reports for confirmation of the anaphylactic event and its attribution to chlorhexidine. 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 in any way to weigh the findings of this review.

The health settings included in the review were:

Acute care	28
Residential aged care	0
Paediatric	0
Neonatal	0
Rehabilitation	0
Other	3

Of the reports from the acute care setting, the perioperative area was the most common (see specialties listed below). However, it should be noted that in addition to the two urology papers, some of the perioperative reports also involved urological procedures and in other reports the anaphylactic event was caused by a urinary catheter insertion during the operation.

Perioperative / anaesthesia	24
Urology	2
ICU	1
General acute care	1

The many reports from the perioperative setting may be reflective of the relatively large number of investigations that have been undertaken into hypersensitivity reactions during surgery and anaesthesia. During these perioperative allergy investigations, other sources of hypersensitivity reactions (such as chlorhexidine) were identified and reported. However, information about the

chlorhexidine-related anaphylaxis in these papers was often quite limited. The type of publications that were included in the review are listed below.

Articles	12
Brief reports	11
Letters	1
Conference abstracts	7

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 setting, including acute care, residential aged care, paediatric, neonatal and rehabilitation. However, most of the studies and case reports included in this review focus on the perioperative area. As a result, caution is needed when translating the findings to other settings.

Appendix I
Example Database Search - Medline

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Pres

Search Strategy:

#	Searches	Results
1	Chlorhexidine/	6947
2	(chlorhexidine or CHG or "mk 412a" or "mk-412a" or mk412a or novalsan or "sebidin a" or tubulicid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10255
3	(Chlorhexamed forte or Chlorohex or Chlorohexidine or Consepsis or Dentosan or Dezin or Eburos or Fimeil or Hexadol or Hexident or Periogard or Promax or Soretol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	441
4	(chlorhexidine and (glutonate or biocide or bactericidal or bacteriostatic or antiseptic or disinfectant or bactericidal)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1709
5	1 or 2 or 3	10608
6	Anaphylaxis/	19241
7	hypersensitivity/	45357
8	drug hypersensitivity/	22029
9	hypersensitivity, immediate/	12131
10	(anaphylactic or allerg* reaction or anaphylaxis or hypersensitivity or systemic shock).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	169763
11	6 or 7 or 8 or 9 or 10	169763
12	5 and 11	202
13	limit 12 to humans	180
14	limit 13 to english language	159

Appendix II
Selection Checklist

Endnote Number	
Author	
Year	

Types of studies		
	• Case series report, retrospective survey or cohort study	
	• Case report.	

Types of participants and settings		
	• Acute care	
	• Residential aged care	
	• Paediatric	
	• Neonatal	
	• Rehabilitation	

Types of interventions		
	• Investigation of chlorhexidine and anaphylaxis	
	• Report on anaphylaxis related to chlorhexidine	

Types of outcome measures		
	• Anaphylactic	
	• Severe allergy	
	• Hypersensitivity reactions	

Publication Date and Limits		
	• Publication 2006 or later	

Include	
Exclude	

Appendix III
Data Collection
Cohort Studies, Retrospective Surveys & Case Series

Publication Details			
First Author		Year	

Reference Number	

Setting & Population Demographics		
Country		
Health Service	1. Acute Care 2. Aged Care 3. Paediatrics 4. Neonatal 5. Rehabilitation 6. Other (describe below)	
Population		
Study Aim		

Study Details

Study Design	
Case Series	
Retrospective Survey	
Cohort Study	
Other(describe below)	

Data Source	
Timeframe for Data Collection	
How was Anaphylaxis Determined	

Fulfilled anaphylaxis criteria:	
• Yes	
• No	
• Not Clear	

Was attribution to chlorhexidine investigated	
• Yes	
• No	
• Not Clear	

How was Attribution to Chlorhexidine Determined	

Results	
Anaphylaxis Events	
Chlorhexidine-related Anaphylaxis Events	
Mortality overall	
Chlorhexidine related mortality	
Other Relevant Details	

Appendix IV
Data Collection – Case Report

Publication Details			
First Author		Year	
Reference Number			

Demographics of Person					
Gender		Age		Country	
Health Service	7. Acute Care 8. Aged Care 9. Paediatrics	10. Neonatal 11. Rehabilitation 12. Other			
Acute Care Specialty Service (Y/N)		Type			
History of Atopy (Y/N)		Type			

Chlorhexidine Related Details			
History of Reaction to Chlorhexidine (Y/N)		Product	
Current Reaction - Chlorhexidine Product			
Procedure			
Exposure History			

Anaphylaxis

Time from exposure to Symptom Onset	

Fulfilled anaphylaxis criteria:	
• Yes	
• No	
• Not Clear	

Anaphylaxis:	
• Acute onset	
• Involvement of skin-mucosal tissue	
• Respiratory compromise	
• Reduced BP or associated symptoms	
• Persistent gastrointestinal symptoms	

Anaphylaxis Presentation:	
• Hypotension	
• Tachycardia	
• Cardiac Arrest	
• Hypoxia	
• Difficulty breathing / Bronchospasm	
• Angioedema (swelling)	
• Decreased level of consciousness	
• Uticaria / Erythema / Rash / Flushing	
• Gastrointestinal symptoms	
• Red & itchy eyes	
• Other (describe below)	

Attribution

• Clinical Presentation					
• Serum Tryptase		Positive		Negative	
• Specific IgE testing		Positive		Negative	
• Skin Prick Test		Positive		Negative	
• Intradermal Test		Positive		Negative	
• Challenge Provocation Testing		Positive		Negative	
• Basophil Activation Testing		Positive		Negative	
• Other		Positive		Negative	
Comments:					

Chlorhexidine-related event:	
• Likely	
• Possible	
• Not Likely	
• Not Clear	

Outcome

• CPR	
• Adrenaline / Epinephrine	
• Cardiac Arrest	
• Admission to ICU	

• Death	
• Full recovery with sequelae	
• Full recovery	

Other outcome

Multiple Anaphylactic Events	
• Single anaphylactic event	
• Multiple anaphylactic events	

If multiple events, describe:

Appendix V
Summary Table – Included Studies

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Arochena 2014 (Arochena et al. 2014) Abstract	Retrospective Record Review Case series Level IV evidence	Investigated cause of perioperative allergic reactions	UK	Setting Acute Care / perioperative Population Perioperative patients referred to Allergy Clinic because of allergic reaction Data Source Allergy clinic records Time Frame 2011 to 2013 Definition of Anaphylaxis Not described Attribution to Chlorhexidine Skin prick and intradermal tests, drug provication tests, specific IgE, and tryptase (for some) <u>Declared Interests</u> None declared	Total Population Not known Anaphylactic Events 18 allergic reactions 7 of 18 were anaphylaxis Chlorhexidine-related Events 2 of 18 chlorhexidine related (11.1%) Not clear if these were anaphylactic reactions Mortality Study only involved survivors	

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Bubenhofer 2015 (Bubenhofer et al. 2015) Brief Report	Retrospective Record Review Case series Level IV evidence	To assess circumstances and severity of chlorhexidine related reactions	Switzerland	Setting Based on records of 2 allergy clinics Population All patients with chlorhexidine reaction referred to allergy clinic (included referrals from dental clinics) Data Source Clinic records Time Frame 2005 to 2012 Definition of Anaphylaxis Not clear Attribution to chlorhexidine Skin prick test, patch test, Apecific IgE, tryptase Declared Interests No funding, no conflict of interest	Total Population Not known But more than 32,000 referrals to Allergy Clinics Anaphylactic Events Not reported Chlorhexidine-related Events 16 chlorhexidine related allergies 9 of 16 described as anaphylactic Mortality Study only involved survivors	Other Information Chlorhexidine reactions detected: • 25% (4) during urological proceedings • 37.5% (6) at dental clinics • 19% (3) peri-operatively • 19% (3) at person's home

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Chen 2016 (Chen, X et al. 2016) Article	Retrospective Record Review Case series Level IV evidence	Investigated perioperative anaphylaxis	Singapore	Setting Acute Care / perioperative Population Perioperative patients who experienced an anaphylactic reaction Data Source Hospital's risk management system & medical records Time Frame 2007 to 2012 Definition of Anaphylaxis Used Brighton collaboration anaphylaxis criteria Attribution to chlorhexidine Details limited Declared Interests None declared	Total Population 151,876 surgical patients during review period Anaphylactic Events 16 of 151,876 confirmed anaphylactic events Chlorhexidine-related Events 1 of 16 chlorhexidine related (6,25%) 1 of 151,876 Which is 0.66 events per 100,000 surgical patients Mortality No anaphylactic-related deaths during data collection period	

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Chong 2008 (Chong et al. 2008) Article	Retrospective Record Review Case series Level IV evidence	Investigated anaphylaxis during anaesthesia across a 1 year period	UK	Setting Allergy Clinic records Population Perioperative patients referred to allergy clinic Data Source Allergy clinic records Time Frame 2005 to 2006 Definition of Anaphylaxis Used published hypersensitivity criteria Attribution to Chlorhexidine Allergy investigated in Allergy Clinic against all medications used during the anaesthesia Declared Interests None declared	Total Population Not known Anaphylactic Events 23 anaesthesia related anaphylactic presentations identified Chlorhexidine-related Events 1 of 23 chlorhexidine related (4.3%) Mortality Study only involved survivors Other Information	

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Garvey 2007 (Garvey et al. 2007) Article	Retrospective Record Review Case series Level IV evidence	Investigated hypersensitivity reactions to chlorhexidine (with focus on role of specific IgE testing)	Denmark	Setting Acute Care / perioperative Population Allergy clinic clients with hypersensitivity reaction to chlorhexidine during anaesthesia Data Source Allergy clinic records Time Frame 1999 to 2005 Definition of Anaphylaxis Anaphylaxis graded according to standard criteria Attribution to chlorhexidine Skin testing and investigated use of IgE testing Declared Interests L. H. Garvey has received grant support for a congress registration fee from Phadia and was commissioned to write an article for Phadia. P. S. Skov owns the private company Reflab. L. Venemalm is employed by Phadia. F. Degerbeck is employed by MIAB. The rest of the authors have declared that they have no conflict of interest	Total Population Not known Anaphylactic Events 174 anaesthesia-related hypersensitivity reactions identified Of the 12 chlorhexidine events, 10 were severe or involved cardiac arrest, 1 was a moderation reaction & 1 mild reaction Chlorhexidine-related Events 12 of 174 chlorhexidine-related (6.9%) Mortality Study only involved survivors	

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Harboe 2010 (Harboe et al. 2010) Article	Retrospective Record Review Case series Level IV evidence	Evaluated frequency and causative agents of allergy to local anaesthetic	Norway	Setting All settings Population Referrals to allergy clinic (referrals came from hospitals, GPs, dentist, etc) Data Source Medical records Time Frame 1995 to 2006 Definition of Anaphylaxis Not defined Attribution to Chlorhexidine Skin prick test, subcutaneous challenge, IgE, Histamine release test Declared Interests This study was funded by Haukeland University Hospital, Bergen, Norway, and the Western Norway Regional Health Authority (Helse Vest RHF), Stavanger, Norway	Total Population Not known Anaphylactic Events 135 allergic reactions identified 7 of 135 were anaphylaxis Chlorhexidine-related Events 5 of 135 were chlorhexidine-related (3.7%) Not clear of these were anaphylaxis Mortality Study only involved survivors	Other Information Researchers conclude that reactions to local anaesthetic are rare, and when they happen are more likely to be the result of other agents such as chlorhexidine

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Krishna 2014 (Krishna et al. 2014) Article	Retrospective Record Review Case series Level IV evidence	Investigated perioperative anaphylaxis. Specific focus was on diagnostic performance of tryptase	UK	Setting 4 regional allergy centres Population Perioperative patients referred to allergy centres for suspected anaphylaxis Data Source Hospital notes and electronic records Time Frame 2005 to 2012 Definition of Anaphylaxis Used World Allergy Organisation anaphylaxis criteria Attribution to chlorhexidine Skin prick testing, intradermal testing, specific IgE, tryptase (taken from records) Declared Interests No conflict of interests to declare.	Total Population Not known Anaphylactic Events 161 anaphylactic events identified Chlorhexidine-related Events 8 of 161 chlorhexidine-related (5%) Mortality Study only involved survivors	Other Information Researchers acknowledge high rate of chlorhexidine-related anaphylaxis

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Laguna-Martinez 2014 (Laguna Martinez et al. 2014) Abstract	Prospective Case Series Level IV evidence	Evaluated the incidence of perioperative anaphylaxis	Spain	Setting Allergy-Anaesthetic Unit Population Perioperative patients who experienced perioperative allergic reaction Data Source Allergy unit records Time Frame 2010 to 2013 Definition of Anaphylaxis Not described, based on referrals Attribution to chlorhexidine tryptase, skin prick test, intradermal test Declared Interests Study support by SEAIC foundation grant	Total Population 32,397 anaesthetic procedures during the study period Anaphylactic Events 30 of 32,397 anaphylactic events 12 of 32,397 confirmed as allergic reaction events 37 per 100,000 anaesthetic procedure allergy-related anaphylactic events Chlorhexidine-related Events No chlorhexidine related events Mortality Study only involved survivors Other Information	

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Leysen 2012 (Leysen et al. 2012) Abstract	Retrospective Record Review Case series Level IV evidence	Surveyed anaphylactic reactions observed during anaesthesia	Belgium	Setting Allergy clinic Population Perioperative patients referred to clinic Data Source Allergy clinic records Time Frame 2001 to 2011 Definition of Anaphylaxis Not clear Attribution to chlorhexidine skin tests, specific IgE, basophil activation test Declared Interests None declared	Total Population Not known Anaphylactic Events 344 perioperative anaphylactic events over the 10 years Chlorhexidine-related Events 24 of 344 chlorhexidine related (7%) Mortality Study only involved survivors	

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Lobera 2008 (Lobera et al. 2008) Article	Prospective Case Series Level IV evidence	Investigated severe adverse reactions during surgery	Spain	Setting Acute Care / perioperative Population perioperative patients Data Source Hospital records and patient assessment Time Frame 1998 to 2002 Definition of Anaphylaxis Used published criteria Attribution to chlorhexidine History, skin prick test, intradermal test, tryptase Declared Interests Financial support by SERIS (Hospital San Pedro/San Millán, Logroño, Spain) and OSAKIDETZA (Hospital Santiago Apóstol, Vitoria, Spain)	Total Population 71,063 surgical interventions during study period Anaphylactic Events 48 of 71,063 severe hypersensitivity events 67.5 severe hypersensitivity events per 100,000 Chlorhexidine-related Events No chlorhexidine related events Mortality No deaths	Other Information Presentation of symptoms: • 83% had skin eruptions • 27% had cardiovascular symptoms (hypotension, tachycardia) • 23% had respiratory symptoms (bronchospasm, increased airway resistance, breathlessness)

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Makina-Kiljunen 2008 (Makinen-Kiljunen & Haahtela 2008) <u>Article</u>	Retrospective Record Review Case series Level IV evidence	To summarised data on severe allergic reactions in Finland across an 8 year period	Finland	<u>Setting</u> National Severe Allergic Reactions Register <u>Population</u> Reviewed first 530 cases in National Register <u>Data Source</u> National Register data for first 530 cases <u>Time Frame</u> 2000 to 2007 <u>Definition of Anaphylaxis</u> Details limited - as reported in register <u>Attribution to chlorhexidine</u> Details limited – as reported in register <u>Declared Interests</u> Article associated with the Finnish Allergy Programme 2008-2018 and World Health Organization Global Alliance against Chronic Respiratory Diseases Project	<u>Total Population</u> Not known <u>Anaphylactic Events</u> 530 records included in review <u>Chlorhexidine-related Events</u> 1 of 530 related to chlorhexidine (0.2%) No information on whether reaction was a severe allergy or an anaphylactic reaction <u>Mortality</u> Study only involved survivors	<u>Other Information</u> The 1 chlorhexidine allergic event identified was caused by skin disinfectant

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
McNeil 2008 (McNeill, Kerridge & Boyle 2008) Article	Retrospective Record Review Case series Level IV evidence	Reviewed frequency of sensitisation to specific agents used in general anaesthetic	Australia	Setting Acute Care / perioperative Population 50 patients referred to Immunology Unit after anaesthetic-related anaphylactic event Data Source Hospital records Time Frame 2000 - 2007 Definition of Anaphylaxis Not well described Attribution to chlorhexidine Skin prick, & intradermal, tryptase (if available) Declared Interests None declared	Total Population Not known Anaphylactic Events 50 anaphylactic events selected from clinic records Chlorhexidine-related Events 2 of 50 related to chlorhexidine (4%) Mortality Study only involved survivors	Other Information 1 of the 2 patients with chlorhexidine-related anaphylaxis experienced a second anaphylactic event during the rescheduled surgery. The surgical team had not realized it was used during the original surgery. Third attempt at surgery was uneventful

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Savic 2013 (Savic et al. 2013) Abstract	Retrospective Record Review Case series Level IV evidence	Explored anaphylaxis during general anaesthesia	UK	Setting Acute Care / perioperative at a single centre Population Perioperative patients who experienced anaphylaxis Data Source Hospital records Time Frame 2008 to 2012 Definition of Anaphylaxis Not described Attribution to chlorhexidine skin prick and intradermal tests, tryptase (for 54% of patients) Declared Interests None declared	Total Population Not known Anaphylactic Events 130 anaphylactic events identified 49 of 130 allergic anaphylaxis Chlorhexidine-related Events 9 of 130 chlorhexidine related (6.9%) No information about chlorhexidine and anaphylaxis Mortality Study only involved survivors Other Information	

Reference Authors / year Type of report	Type of study Level of Evidence (NHMRC)	Study Aim-	Country	Study Information	Results	Conclusions / Other information
Sperling 2012 (Sperling, Luemmen & Reubben 2012) Abstract	Prospective Case Series Level IV evidence	Evaluated the number of adverse events when using a lubricant containing chlorhexidine over a 1 year period(Instillagel - lignocaine & chlorhexidine)	German	Setting 3 major urological clinics Population Patients undergoing urological procedures Data Source Records of the 3 clinics Time Frame 2009 to 2010 Definition of Anaphylaxis Focused on any adverse event Attribution to chlorhexidine Monitored direct use of Instillagel Declared Interests None declared	Total Population Inpatients = 8940 patients Outpatients = 18,500 Tubes of gel used = 57,500 Anaphylactic Events No adverse events of any sort detected Chlorhexidine-related Events nil Mortality No deaths	

Appendix VI
Summary Table – Case Reports

Demographics					
Author	Bae (Bae et al. 2008)	Title	Brief Report A case of anaphylaxis to chlorhexidine during digital rectal examination		
Country	Korea	Gender	Male	Age	54 v
Health Service	Acute Care	Specialty Service	No		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	Yes
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Product: 10mls 0.05% chlorhexidine used as rectal disinfectant Procedure: Onset within 2 minutes of digital rectal examination
Exposure History	Nil Report
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Full recovery involving admission to ICU
Single / Multiple Anaphylactic Event	Single anaphylactic event

Case Reports

Demographics					
Author	Toomey (Toomey 2013)	Title	Article Preoperative chlorhexidine anaphylaxis in a patient scheduled for coronary artery bypass graft: a case report		
Country	USA	Gender	Male	Age	65 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Multiple products 1 - Night before surgery - 2% chlorhexidine skin prep 2 - Prior to surgery - ChloraPrep (chlorhexidine & alcohol) in intravascular devices 3 - Oral rinse with 15mls 0.12% chlorhexidine 4 - CVC impregnated with chlorhexidine Procedure: Initial anaphylactic reaction during anaesthesia started within minutes of CVC insertion. But on night prior experienced a mild erythema and hives over body.
Exposure History	Developed skin reaction to skin prep on the night before surgery which went unreported by patient
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	CVC replaced, surgery postponed.
Single / Multiple Anaphylactic Event	Multiple events: 1. Reaction to chlorhexidine skip prep night before surgery (mild erythema and hives over body). But unreported by patient 2. Multiple exposures to chlorhexidine leading to anaphylaxis

Case Reports

Demographics					
Author	Odedra (Odedra & Farooque 2014)	Title	Article Chlorhexidine: an unrecognised cause of anaphylaxis		
Country	UK	Gender	Male	Age	62 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No competing interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	Yes Had a mild reaction to chlorhexidine skin prep 3 days prior to cardiac surgery during angiogram, but cause not determined at that time.
Current Anaphylactic Reaction	Product: CVC impregnated with chlorhexidine Procedure: Immediate reaction and cardiac arrest after insertion of CVC.
Exposure History	Reaction to chlorhexidine skin prep 3 days before surgery
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Recovered and surgery undertaken after patient stabilised
Single / Multiple Anaphylactic Event	Multiple events: 1 - mild reaction to chlorhexidine skin prep during angiogram 3 days prior to surgery (cause not determined) 2 - post CVC insertion prior to surgery

Case Reports

Demographics					
Author	Dyer (Dyer et al. 2013)	Title	Brief report: Anaphylactic reaction to intra-urethral chlorhexidine: sensitisation following previous repeated uneventful administration		
Country	UK	Gender	Male	Age	84 years
Health Service	Acute care	Specialty Service	Perioperative		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Product: Instillagel (lignocaine 2% and chlorhxidine 0.25%) Procedure: Reaction post urinary catheter insertion using the Instillagel
Exposure History	Had a history of urological procedures and use of Instillagel without any problems
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Recovered
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Pettipher (Pettipher & Duggleby 2015)	Title	Abstract: Chlorhexidine anaphylaxis: The hidden trigger		
Country	UK	Gender	Female	Age	67 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Two Products: 1 - chlorhexidine 2% skin prep 2 - CVC impregnated with chlorhexidine Procedure: Sudden reaction after surgical skin prep and CVC insertion
Exposure History	Nil reported
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Full recovery when CVC replaced with non-chlorhexidine version and admission to ICU
Single / Multiple Anaphylactic Event	Single Event

Case Reports

Demographics					
Author	Qin (Qin & Zeng 2016)	Title	Letter to Editor: Anaphylaxis to chlorhexidine in a chlorhexidine-coated central venous catheter during general anaesthesia		
Country	China	Gender	Female	Age	Not stated
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	Yes
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Product: CVC impregnated with chlorhexidine Procedure: Reaction 2 – 3 minutes after CVC insertion
Exposure History	None reported
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Full recovery after CVC changed and admitted to ICU
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Khoo (Khoo & Oziemski 2011)	Title	Brief Report: Chlorhexidine impregnated central venous catheter inducing an anaphylactic shock in the intensive care unit		
Country	Australia	Gender	Female	Age	84
Health Service	Acute Care	Specialty Service	ICU		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	Yes
Previous Reaction to Chlorhexidine	Previously developed rash after application of chlorhexidine skin preparation
Current Anaphylactic Reaction	Two Products 1 - CVC impregnated with chlorhexidine 2 - skin preparation (chlorhexidine 0.5% & alcohol 70%) Procedure: Reaction with cardiac arrest within 1 minute of skin preparation and CVC insertion
Exposure History	Previously reaction to chlorhexidine
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Full recovery
Single / Multiple Anaphylactic Event	Single event, but with a history of an allergic reaction to chlorhexidine during a previous hospital admission

Case Reports

Demographics					
Author	Stewart (Stewart & Lenaghan 2015b)	Title	Brief Report: The danger of chlorhexidine in lignocaine gel: A case report of anaphylaxis during urinary catheterisation		
Country	Australia	Gender	Male	Age	70 years
Health Service	Acute Care	Specialty Service	No		
Declared Interests	No competing interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Two products: 1 - 0.1% chlorhexidine irrigation solution - for skin prep 2 - x4 10ml tubes of chlorhexidine 0.5% & lignocaine 2% gel Procedure: Reaction during urethral catheterisation and dilation
Exposure History	Past urological procedures, so likely previous exposure
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Recovery
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Khan (Khan, Kazi & O'Donohoe 2011)	Title	Brief Report: Near fatal intra-operative anaphylaxis to chlorhexidine--is it time to change practice?		
Country	UK	Gender	Male	Age	49 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No competing interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Product: Instillagel (chlorhexidine 0.25% & lignocaine 2%) Procedure: Reaction 50 minutes after urological procedure using gel
Exposure History	Nil reported
Anaphylactic Event	Not clear
Caused by Chlorhexidine	Possible

Outcome	
Treatment	Recovery
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Buergi (Buergi et al. 2014)	Title	Brief Report: Severe anaphylaxis: The secret ingredient		
Country	Switzerland	Gender	Male	Age	45 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	The authors declare no conflicts of interest				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Products: Instillagel (chlorhexidine 0.25% & lignocaine 2%) Procedure: Reaction during urological procedure that used the gel, then second reaction during repeat procedure
Exposure History	Nil reported
Anaphylactic Event	Yes
Caused by Chlorhexidine	Yes

Outcome	
Treatment	Procedure eventually completed and patient recovered
Single / Multiple Anaphylactic Event	Multiple events: • 1st attempt at procedure: Anaphylactic reaction - procedure abandoned. Suspected reaction to contrast media • 2nd attempt at procedure: Anaphylactic reaction - procedure abandoned. Referred to immunology clinic - suspected cause was antibiotics (urological team did not realise chlorhexidine was in lubricant gel) • 3rd Attempt at procedure During work-up for procedure tested for chlorhexidine (positive reaction). Chlorhexidine avoided, surgery completed without incident

Case Reports

Demographics					
Author	Liu (Liu et al. 2007)	Title	Brief Report: Rectal stump lavage: simple procedure resulting in life-threatening complication		
Country	Hong Kong	Gender	Male	Age	51 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Products: 0.05% chlorhexidine acetate solution Procedure: Immediate reaction after rectal stump lavage during colorectal resection of bowel
Exposure History	Nil reported
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Restorative anastomosis abandoned and surgery completed rapidly with formation of an end colostomy
Single / Multiple Anaphylactic Event	Single

Case Reports

Demographics					
Author	Sijbesma (Sijbesma, Rockmann & van der Weegen 2011)	Title	Brief Report: Severe anaphylactic reaction to chlorhexidine during total hip arthroplasty surgery. A case report		
Country	Netherlands	Gender	Male	Age	51 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No conflict of interests, no financial or other form of compensation				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Products: Chlorhexidine gel Procedure: Two reactions during urinary catheter insertion in different surgical procedures
Exposure History	Nil reported, but previous surgical procedures noted
Anaphylactic Event	Likely 1st reaction not clearly if anaphylactic, but 2nd reaction was anaphylaxis
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Surgery abandoned twice, then referred for allergy testing, surgery completed on third attempt
Single / Multiple Anaphylactic Event	Multiple events: • 1st Surgery Hypotensive / desaturation event 20 minutes into surgery, procedure abandoned. Chlorhexidine used for urinary catheter insertion • 2nd Surgery Anaphylactic event, surgery abandoned & referred for allergy testing. Chlorhexidine had been used again for catheter insertion. Referred for investigation of allergy • 3rd Surgery Chlorhexidine not used, surgery uneventful

Case Reports

Demographics					
Author	Sheth (Sheth & Silviu-Dan 2007)	Title	Abstract: Anaphylaxis to a commonly used antiseptic: Chlorhexidine		
Country	Canada	Gender	Male	Age	49
Health Service	Acute care	Specialty Service	Perioperative		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Products: Gel (chlorhexidine 0.05% & xylocaine) Procedure: Reaction 30 minutes after urinary catheterisation using gel
Exposure History	Nil reported
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Full recovery
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Weng (Weng, ML et al. 2014)	Title	Brief Report: **Weng - Case 1 of 2** Life-threatening anaphylactic shock due to chlorhexidine on the central venous catheter: a case series		
Country	China	Gender	Male	Age	48 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No conflict of interest				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Two products: 1 - Skin prep (iodine 0.2%, chlorhexidine 0.45% & alcohol 65%) 2 - CVC impregnated with chlorhexidine Procedure: Reaction immediately with cardiac arrest after skin prep and insertion of CVC
Exposure History	Nil reported
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Recovery with admission to ICU. Re-scheduled surgery was uneventful with chlorhexidine avoidance
Single / Multiple Anaphylactic Event	Single

Case Reports

Demographics					
Author	Weng (Weng, ML et al. 2014)	Title	Brief Report: **Weng - Case 2 of 2** Life-threatening anaphylactic shock due to chlorhexidine on the central venous catheter: a case series		
Country	China	Gender	Female	Age	34
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No conflict of interest				

Anaphylaxis	
History of Atopy	Yes
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Products: CVC impregnated with chlorhexidine Procedure: Immediate reaction following CVC insertion
Exposure History	Nil reported
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Full recovery. Re-scheduled surgery was uneventful with chlorhexidine avoidance
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Parkes (Parkes et al. 2009)	Title	Brief Report: **Parkes 1 of 3** Anaphylaxis to the chlorhexidine component of Instillagel: a case series		
Country	UK	Gender	Male	Age	33 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	Yes
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Products: Instillagel (chlorhexidine 0.25% & lignocaine 2%) Procedure: Reaction after transfer to recovery following a urological procedure that used the gel
Exposure History	Nil reported
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Full recovery
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Parkes (Parkes et al. 2009)	Title	Brief Report: **Parkes 2 of 3** Anaphylaxis to the chlorhexidine component of Instillagel: a case series		
Country	UK	Gender	Female	Age	39
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	Yes
Previous Reaction to Chlorhexidine	Not clear - reported previous hypersensitivity reaction during surgery, but cause not identified
Current Anaphylactic Reaction	Products: Instillagel (chlorhexidine 0.25% & lignocaine 2%) Procedure: Reaction 20 minutes after a urological procedure that used the gel
Exposure History	Nil reported, but previous surgical procedures and a history of a hypersensitivity reaction
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Full recovery
Single / Multiple Anaphylactic Event	Single event

Demographics					
Author	Parkes (Parkes et al. 2009)	Title	Brief Report: **Parkes 3 of 3** Anaphylaxis to the chlorhexidine component of Instillagel: a case series		
Country	UK	Gender	Male	Age	61 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	None declared				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Products: Instillagel (chlorhexidine 0.25% & lignocaine 2%) Procedure: Reaction 10 minutes after a urological procedure that used the gel
Exposure History	Nil reported
Anaphylactic Event	Not clear
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Full recovery
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Guleri (Guleri et al. 2012)	Title	Brief Report: **Guleri 1 of 3** Anaphylaxis to chlorhexidine-coated central venous catheters: a case series and review of the literature		
Country	UK	Gender	Male	Age	71 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No competing financial interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	Yes. During current admission experienced a pre-operative skin reaction (rash) after skin preparation with 4% chlorhexidine soap
Current Anaphylactic Reaction	Products: • 4% chlorhexidine soap • chlorhexidine impregnated CVC (on two occasions) • chlorhexidine skin preparation solution Three procedures: 1. Allergic reaction preoperatively to skin preparation with 4% chlorhexidine soap 2. During surgery, reaction immediately after chlorhexidine impregnated CVC and also to chlorhexidine skin preparation solution 3. During re-scheduled surgery chlorhexidine impregnated CVC used again producing another anaphylactic reaction
Exposure History	Nil reported prior to this admission
Anaphylactic Event	Not clear - details limited
Caused by Chlorhexidine	yes
Declared Interests	None declared

Outcome	
Treatment	Surgery attempted and abandoned twice, then completed the third attempt under local anaesthetic
Single / Multiple Anaphylactic Event	Multiple reactions during coronary artery surgery: • Pre-operatively: Allergic reaction preoperatively to skin preparation with 4% chlorhexidine soap • 1st Surgery: Second allergic reaction to chlorhexidine impregnated CVC and also to chlorhexidine skin preparation solution. Anaphylactic event, surgery abandoned. Investigation of allergic reaction also identified a sensitivity to pancuroneum,

	which was thought to be the cause of the anaphylaxis. • 2nd Surgery Third event during re-scheduled surgery 1 month later, chlorhexidine impregnated CVC used again producing another anaphylactic reaction and surgery abandoned again • 3rd Surgery Surgery completed under local anaesthetic agents without use of chlorhexidine or pancuroneum without any adverse events

Case Reports

Demographics					
Author	Guleri (Guleri et al. 2012)	Title	Brief Report: **Guleri 2 of 3** Anaphylaxis to chlorhexidine-coated central venous catheters: a case series and review of the literature		
Country	UK	Gender	Male	Age	26
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No competing financial interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No - 1st stage of surgery previously undertaken without incident
Current Anaphylactic Reaction	Products: • chlorhexidine gel • chlorhexidine skin preparation • CVC impregnated with chlorhexidine Procedure: • Pre-operatively - chlorhexidine gel used as soap in shower, which produced a rash • During Surgery - Skin preparation with chlorhexidine prior to anaesthetic - patient complained of itchiness. Then insertion of a CVC impregnated with chlorhexidine which immediately resulted in anaphylactic reaction
Exposure History	1st stage of surgery previously undertaken without incident
Anaphylactic Event	Not clear - details limited
Caused by Chlorhexidine	Yes

Outcome	
Treatment	Surgery completed 2 weeks later avoiding chlorhexidine without incident
Single / Multiple Anaphylactic Event	Multiple allergic reactions • Pre-operatively - chlorhexidine gel used as soap in shower produced a rash. No follow up • During Surgery - patient complained of itchiness following chlorhexidine skin preparation. No action taken. • CVC impregnated with chlorhexidine inserted which produced an immediate anaphylactic event • Rescheduled surgery - chlorhexidine avoided and procedure was uneventful

Case Reports

Demographics					
Author	Guleri (Guleri et al. 2012)	Title	Brief Report: **Guleri 3 of 3** Anaphylaxis to chlorhexidine-coated central venous catheters: a case series and review of the literature		
Country	UK	Gender	Male	Age	73
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No competing financial interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Products: • 2% chlorhexidine skin preparation solution • CVC impregnated with chlorhexidine Procedure: • 1st reaction during Coronary Angiogram: 2% chlorhexidine skin preparation solution - produced cutaneous allergic reaction • 2nd reaction immediately following insertion of CVC during cardiac surgery
Exposure History	Nil reported
Anaphylactic Event	Not clear - details limited
Caused by Chlorhexidine	Yes

Outcome	
Treatment	After anaphylactic event during surgery, patient put on emergency cardiopulmonary bypass and surgery completed
Single / Multiple Anaphylactic Event	Multiple allergic reactions: • Surgical Work-up - 1st reaction during Coronary Angiogram to 2% chlorhexidine skin preparation solution which produce a cutaneous allergic reaction • Pre-operative – patient used chlorhexidine soap during shower with no allergic reaction • During cardiac surgery immediate anaphylactic reaction following insertion of chlorhexidine impregnated CVC

Case Reports

Demographics					
Author	Nakonechna (Nakonechna et al. 2014)	Title	Article **Nakonechna 1 of 6** Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom		
Country	UK	Gender	Male	Age	50
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No financial or commercial interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	No
Current Anaphylactic Reaction	Products: Chlorhexidine impregnated CVC Procedure: Reaction during cardiac surgery 10 minutes after CVC insertion
Exposure History	Nil reported
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	• Resuscitated and surgery continued. CVC remained in place • Experienced a second anaphylactic reaction when transferred to the surgical recovery area - CVC was then withdrawn at this point
Single / Multiple Anaphylactic Event	Single event related to CVC, but two anaphylactic reactions

Case Reports

Demographics					
Author	Nakonechna (Nakonechna et al. 2014)	Title	Article: **Nakonechna 2 of 6** Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom		
Country	UK	Gender	Male	Age	78
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No financial or commercial interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	Yes, had previously developed urticaria following Corsodyl mouth wash (which contains chlorhexidine). But this was not identified until after surgery (and after the anaphylaxis)
Current Anaphylactic Reaction	Products: Two events, but not clear which product caused reactions. It was assumed that patient was exposed to chlorhexidine during the two procedures. Two allergic events: • Reaction 10 minutes into a Coronary angiogram • A few months later, a reaction 10 minutes into a coronary angioplasty
Exposure History	Nil reported
Anaphylactic Event	Not clear (details limited)
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Details limited
Single / Multiple Anaphylactic Event	Multiple events • Coronary Angiogram 10 minutes into procedure became breathless and developed urticarial. Thought to be a response to the dye, but not investigated • Coronary Angioplasty 10 minutes into procedure became breathless and developed urticarial. Surgery abandoned Testing identified a sensitivity to chlorhexidine, so assumed he was exposed to it during both procedures

Case Reports

Demographics					
Author	Nakonechna (Nakonechna et al. 2014)	Title	Article : **Nakonechna 3 of 6** Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom		
Country	UK	Gender	Male	Age	72
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No financial or commercial interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	Unclear It was noted that patient may possibly have had an allergic reaction 30 years earlier (collapsed & rash) following a urological procedure.
Current Anaphylactic Reaction	Products: Instillagell (0.25% chlorhexidine gluconate and 2% lignocaine) Procedure: Cystoscopy under general anaesthetic which was uneventful. At end of procedure urinary catheter inserted using Instillagel and patient experienced an anaphylactic reaction 10 minutes later
Exposure History	Nil reported (other than possible event 30 years earlier)
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Details limited
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Nakonechna (Nakonechna et al. 2014)	Title	Article : **Nakonechna 4 of 6** Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom		
Country	UK	Gender	Male	Age	73 years
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No financial or commercial interests				

Anaphylaxis	
History of Atopy	No
Previous Reaction to Chlorhexidine	Yes, but not identified until after procedure (and after anaphylaxis). Patient had a past allergic event post bladder instillation with chlorhexidine during surgery, patient developed rash and swollen face.
Current Anaphylactic Reaction	Products: No product was specifically identified Procedure: Anaphylaxis 20 minutes into surgery for resection of bladder tumour.
Exposure History	Nil reported (but history of previous allergic event noted)
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Details limited
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Nakonechna (Nakonechna et al. 2014)	Title	Article : **Nakonechna 5 of 6** Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom		
Country	UK	Gender	Male	Age	73
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No financial or commercial interests				

Anaphylaxis	
History of Atopy	Yes (allergic event 1 month earlier)
Previous Reaction to Chlorhexidine	Yes, but not identified until after the procedure (and after the anaphylaxis). A month earlier had a reaction post catheter insertion which Instillagel was used (patient felt unwell and light-headed).
Current Anaphylactic Reaction	Products: Instillagel (0.25% chlorhexidine gluconate and 2% lignocaine) Procedure: During surgery for resection of bladder tumour, urinary catheter inserted at end of procedure, anaphylactic reaction 10 minutes later
Exposure History	A month earlier had Instillagel used during a catheter insertion
Anaphylactic Event	Likely
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Details limited
Single / Multiple Anaphylactic Event	Single event

Case Reports

Demographics					
Author	Nakonechna (Nakonechna et al. 2014)	Title	C Article : **Nakonechna 6 of 6** Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom		
Country	UK	Gender	Male	Age	60
Health Service	Acute Care	Specialty Service	Perioperative		
Declared Interests	No financial or commercial interests				

Anaphylaxis	
History of Atopy	Yes
Previous Reaction to Chlorhexidine	Yes, but only noted after procedure (and after anaphylaxis). 4 years previously had an allergic reaction to Savlon wipes (which contain chlorhexidine)
Current Anaphylactic Reaction	Products: Cathojell (0.05% chlorhexidine and 2% lignocaine) Procedure: Cystoscopy under anaesthetic, anaphylactic reaction 10 minutes after use of Cathojell
Exposure History	Previous surgery and use of chlorhexidine
Anaphylactic Event	Details limited
Caused by Chlorhexidine	Likely

Outcome	
Treatment	Details limited
Single / Multiple Anaphylactic Event	Single event

Appendix VII
Summary Table – Excluded Studies

Case Reports

Author	Year	Publication Type	Country	Health Service	Reason for Exclusion	Summary
Ahmed	2014	Abstract	USA	Acute care	Lack of detail	Report a case of two episodes of anaphylaxis in same person on different occasions during CVC insertions as a result of un-recognised presence of chlorhexidine
Chiarella	2014	Abstract	Spain	Acute Care	Detail of case too limited. Involved Prontosan which contained Polyhexidine rather than chlorhexidine (it described as a chlorhexidine polymer).	Reports an anaphylactic reaction following application of Prontosan during a dressing of an ulcer on the foot of a 77 year old female.
Ebo	2006	Abstract	Belgium	Acute Care	Detail too limited, no information about anaphylaxis	Present 4 cases of chlorhexidine related anaphylaxis, 3 from skin disinfection and 1 from urethral gel

Author	Year	Publication Type	Country	Health Service	Reason for Exclusion	Summary
Ferrarino	2006	Letter	Switzerland	Paediatric	No information about attribution to chlorhexidine Involved Polyhexanide (a polymer of chlorhexidine)	A 14 year old boy with fractured femur experienced an immediate reaction following a surgical wound washing with a solution that contained Polyhexanide.
Gohara	2014	Poster Abstract	Japan	Acute Care	Lack of detail	Anaphylactic reaction in a 53 year old man following use of 0.02% chlorhexidine (assumed as a skin disinfectant)
Hodge	2012	Abstract	UK	Acute Care	Lack of detail	Report a case of perioperative pulseless electrical activity in a person who was subsequently found to be allergic to chlorhexidine (and one of the anaesthetic agents)
Hong	2015	Article	Singapore	Acute Care	Very complex case with multiple events, so difficult to extract data related specifically to chlorhexidine	A 66 year old man with significant past medical history presenting with necrotising fasciitis in leg and shock. A diagnosis of septic shock was questioned after allergy to chlorhexidine identified. Reconstructive surgery successfully undertaken avoiding all use of chlorhexidine.
Kautz	2010	abstract	Germany	Not clear	Focus on polyhexanide (a polymer of chlorhexidine)	Presented case of anaphylactic reaction by 81 year old female following use of a brand of wet toilet paper that contained polyhexanide as a disinfectant

Author	Year	Publication Type	Country	Health Service	Reason for Exclusion	Summary
Koch	2014	Article	Germany	Dental	Involves hypersensitivity rather than anaphylaxis	Dental patient experienced a reaction following application of chlorhexidine containing product (Chlorhexamed 1% gel).
Lloyd-Lavery	2012	Abstract	UK	Not clear	Lack of detail	Presented a case of a 27 year old man who experienced anaphylaxis post mouth wash with a chlorhexidine containing solution (Corsodyl)
Mohedano	2009	Abstract	Portugal	Paediatric	Detail of case too limited, not clear if anaphylactic event	Reports the case of an 11 year old girl with a history of atopy experiencing an allergic reaction following an oral table containing chlorhexidine (Angileptol)
Navarro	2015	abstract	Korea	Acute Care	Too little detail about cases	Present two cases, a 3 year old and a 77 year old female, who experienced anaphylaxis related to chlorhexidine use
Noel	2012	Brief Report	UK	Acute Care	Lack of detail about the anaphylaxis	Present a case of a 67 year old experiencing anaphylaxis following use of Instillagel for urethral catheterisation
Pemberton	2012	Article	UK	Dental	Lack of detail	Present two brief cases 1. A 63 year old man who died in hospital following an anaphylactic reaction during a dental procedure when chlorhexidine was used to irrigate a tooth socket. 2. A 30 year old female died following the use of a chlorhexidine mouth wash during a dental treatment.

Author	Year	Publication Type	Country	Health Service	Reason for Exclusion	Summary
Wittczak	2013	Article	Poland	Acute care	Focus on staff allergies rather than patient anaphylaxis.	Present 3 cases of health workers with allergies related to chronic occupational exposure to chlorhexidine.

Incidence of Anaphylaxis

Author	Year	Publication Type	Country	Health Service	Reason for Exclusion	Summary
Bubenhofer	2013	Abstract	Switzerland	Not clear	Lack of detail	Present 20 cases identified from the records of two allergy clinics
Kourosh	2016	Abstract	USA	Paediatric	Lack of detail	Review of records for 1 year period at paediatric hospital identified 8 episodes of perioperative anaphylaxis. Chlorhexidine identified as one of the causative agents.
Nagendran	2009	abstract	UK	Acute Care	Focus on allergy of health care workers, not anaphylaxis. Detail limited	Present findings of a survey and the results of skin prick & Specific IgE tests of health workers for chlorhexidine allergy
Purmer	2015	abstract	Netherlands	Acute Care	Focus on allergy not specifically on anaphylaxis. Details of results limited.	Present finding of a multicentre retrospective review of suspected allergic reactions related to general anaesthesia
Vesel	2014	Poster Abstract	Slovenia	Acute Care	Focus on all perioperative allergic reactions, not specifically chlorhexidine. Details very limited	Prospectively reviewed 13 children referred to Allergology department for perioperative hypersensitivity reaction.
Wills	2009	Letter to Editor	NZ	Not clear	Lack of detail	Reviewed records of allergy clinic and identified 26 cases that were consistent with chlorhexidine-related anaphylaxis

Appendix VIII
Appraisal of Included Studies

Paper	Anaphylaxis	Attribution to Chlorhexidine
Arochena 2014	Not described	Attribution to chlorhexidine Skin prick and intradermal tests, drug provication tests, specific IgE, and tryptase (for some)
Bubenhofer 2015	Not clear	Skin prick test, patch test, Apecific IgE, tryptase
Chen 2016	Used Brighton collaboration anaphylaxis criteria	Details limited
Chong 2008	Used published hypersensitivity criteria	Allergy investigated in Allergy Clinic against all medications used during the anaesthesia
Garvey 2007	Anaphylaxis graded according to standard criteria	Skin testing and investigated use of IgE testing
Harboe 2010	Not defined	Skin prick test, subcutaneous challenge, IgE, Histamine release test
Krishna 2014	Used World Allergy Organisation anaphylaxis criteria	Skin prick testing, intradermal testing, specific IgE, tryptase (taken from records)
Laguna-Martinez 2014	Not described, based on referrals	Tryptase, skin prick test, intradermal test
Leysen 2012	Not clear	Skin tests, specific IgE, basophil activation test
Lobera 2008	Used published criteria	History, skin prick test, intradermal test, tryptase
Makina-Kiljunen 2008	Details limited - as reported in register	Details limited – as reported in register
McNeil 2008	Not well described	Skin prick, & intradermal, tryptase (if available)
Savic 2013	Not described	Skin prick and intradermal tests, tryptase (for 54% of patients)
Sperling 2012	Focused on any adverse event	Monitored direct use of Instillagel

Appendix IX
Appraisal of Included Case Reports

Paper	Anaphylactic Event	Caused by chlorhexidine
Toomey 2013	Likely	Likely
Odedra et al 2014	Likely	Likely
Dyer et al. 2013	Likely	Likely
Pettipher et al 2015	Likely	Likely
Qin & Zeng 2016	Likely	Likely
Khoo et al 2011	Likely	Likely
Stewart et al 2015a	Likely	Likely
Khan et al 2011	Not clear	Possible
Buergi et al. 2014	Yes	Yes
Liu et al. 2007	Likely	Likely
Sijbesma 2011	1st reaction not clearly 2nd reaction was anaphylaxis	Likely
Sheth et al 2007	Likely	Likely
Weng, ML et al. 2014 Case 1	Likely	Likely
Weng, ML et al. 2014 Case 2	Likely	Likely
Parkes et al. 2009 Case 1	Likely	Likely
Parkes et al. 2009 Case 2	Likely	Likely
Parkes et al. 2009 Case 3	Not clear	Likely
Guleri et al. 2012 Case 1	Not clear, details limited	Yes
Guleri et al. 2012 Case 2	Not clear, details limited	Yes
Guleri et al. 2012 Case 3	Not clear, details limited	Yes
Nakonechna et al. 2014 Case 1	Likely	Likely
Nakonechna et al. 2014 Case 2	Not clear, details limited	Likely
Nakonechna et al. 2014 Case 3	Likely	Likely
Nakonechna et al. 2014 Case 4	Likely	Likely
Nakonechna et al. 2014 Case 5	Likely	Likely
Nakonechna et al. 2014 Case 6	Not clear, details limited	Likely

Note – Information about the attribution to chlorhexidine was varied in case reports, and sometimes quite limited. So a system of attribution of *Yes, Likely or Possible* was used to reflect the reviewers confidence in the attribution to chlorhexidine in the report. *Yes* indicated clear attribution, *Likely* indicated information to suggest attribution chlorhexidine was likely, and *Possible* indicated only a limited suggestion that it may be attributed to chlorhexidine. Confirmation of the anaphylactic event was also limited in many papers, so a similar system was used to serve as a guide for readers.

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