Chlorhexidine – Is It Time To Defend or De-friend?

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Dr Cathryn Murphy is a casual consultant to medical industry and device manufacturers including Mayo Healthcare.
Content

- Incidence, pathophysiology, avoidable costs and preventability of central line associated bloodstream infection (CLABSI)
- Use of Chlorhexidine and CHG-coated central venous catheters
- Chlorhexidine – sensitivity and safety
- CLABSI prevention: a balanced, real-world view
Incidence, Pathophysiology, Avoidable Costs and Preventability of Central Line Associated Bloodstream Infection (CLABSI)
CVC Use & Outcome Varies Across The World

• In Europe – half of all ICU patients have a central venous catheter
• Attributable mortality from CLABSI ranges from 0-11.5%
• Additional length of stay between 9-12 days

Central Line Associated Bloodstream Infection Issues

• 17% of Australian ICU patients receive CVCs
• 17,000 CVCs inserted in NSW annually – 1.2/1000 catheter days
• Clinicians do not comply with evidence-based infection control practice recommendations
  – compliance with the clinician bundle between 61% to 90% & with the patient bundle between 74.1% to 91.8%
  – overall hand hygiene compliance in Australia is only 78.3% (CI 95% 78.2-78.3)
• Limited data regarding line management, securement, access and management


IVD-related BSI Risk Factors

• Underlying disease
• Prolonged hospitalisation before device insertion
• Insertion
  – Site (heavily colonised) and type
• Catheter management
  – Duration of insertion
  – Colonisation of catheter hub from contaminated HCW hands
• Antibiotic use during catheterisation
Potential Sources of Contamination

More Common Mechanisms
1. Pathogen migration **along external surface**
   - more common early
   (< 7 days)
2. Hub contamination with **intraluminal** colonization
   - more common >10 days

Less Common Mechanisms
1. Hematogenous seeding from another source
2. Contaminated infusates
Stages of Biofilm Development

- Exposure of device to bacteria
- Bacterial attachment caused by irregularities on device (within 24 hours of insertion)
- Bacteria produces glycopolysaccharide (slime)
- Slime stabilises cell-to-cell association allowing bacteria to accumulate
- Bacteria sticks to biofilm, absorbs nutrients and multiplies

*NOTE: Staphylococci LOVE biofilm; hence, biofilm plays a major role in catheter-related infections!*
Biofilm Development

*Pseudomonas aeruginosa*

@ 2hrs on 100% Silicone Catheter

@ 18hrs on 100% Silicone Catheter
**Insertion – Access - Removal**

All catheters eventually become colonised after insertion

Probability of infection is proportional to the number of microbes multiplying on the catheter surface

ANZICS’ Eight Easy Steps To CLABSI Prevention

1. Appropriate site & catheter
2. Aseptic technique including hat & mask
3. Maximal barrier precautions including large drape
4. Alcoholic chlorhexidine skin prep & allow to dry
5. Stop if asepsis breached
6. Ensure dressing always intact
7. Hand hygiene prior to any line access
8. Remove ASAP

Simple Facts

- Estimated overall incidence of infection 2.5%\(^1\)
- Fungi as well as gram +ve and gram –ve organisms commonly cause CLABSIs - Vancomycin-resistant enterococci, *Ps. aeruginosa* and *Candida albicans*\(^2\)
- Common skin flora – *S. aureus*, *S. epidermidis* & CNS (gram +ve)
- In one study resistant organisms accounted for 64.4% cultures\(^2\)
- Catheter-related bloodstream infections (CR-BSIs) increase health costs and patient morbidity\(^1\)
- ICU CLs may be accessed > 16 times a shift\(^3\)


Treatment Costs & Microbial Costs

- Excess length of stay 2.4 ICU and 7.5 general ward days
  - ICU bed-day $AUD (2006) 3,021
  - Ward bed-day $AUD (2006) 843
- Diagnostic costs – catheter tip & two blood cultures
- Treatment costs
  - 2 weeks of Vancomycin
  - 10 days of Ticarcillin
  - 4 weeks Fluconazole

3500 cases of bloodstream infections. Most of them are preventable.

In Australia each year there are approximately 3500 cases of bloodstream infections as a result of intravascular catheters. Many of these are central line associated bloodstream infections (CLABSI), and occur in intensive care units. Most of them are preventable.

CLABSIs & Mortality

Relative risk of hospital mortality associated with CR-BSI estimated to be 1.06 or absolute increase in mortality just under 1%

How does that impact the families of the 3500 Australians who develop CLABSI each year?
Current Situation

- Millions of $AUD and hours of manpower invested in understanding and improving practice and reducing healthcare associated infections (HAIs)
- Raised clinician, media and public awareness yet minimal impact in terms of HAI reduction
- Exhausted input from clinicians, government, academics and infection prevention community
- Remaining solutions are technology-based and involve welcoming medical industry to the infection prevention table as equal partners rather than commercially-driven players
Current Beliefs & Focus

• CLABSI prevention is possible
• Requires rigorous policy and guidelines
• Specific education and training
• Continuous implementation of quality improvement initiatives
• Good governance
• Clinician compliance
Examples of Technology Driven CLABSI Solutions

• Easy-to-use skin preparation
• Ultrasound guided insertion
• Securement devices
• Engineered devices eg. Needleless connectors
• Antiseptic impregnated dressings

How do we address the issue of biofilm?
• Nanotechnologies & improved device compositions
• Antiseptic and antimicrobial coated catheters
Use of Chlorhexidine and CHG-coated Central Venous Catheters
Antimicrobial Catheters

• Arrowgard introduced in 1990
• External catheter surface impregnated with combination of silver sulfadiazine (SSD) and chlorhexidine (Chlorhexidine)
• Designed to reduce catheter colonisation
• Demonstrated good in vitro broad spectrum efficacy
• Subsequent publication of additional in vitro and invivo studies as well as economic studies
• Extended dwell times and greater understanding of CLABSI cause lead to 2\textsuperscript{nd} generation
The Scientific “Father” of Infusion Therapy & CLABSI Cause & Prevention

Insertion, antisepsis, management & composition of componentry
Antiseptic catheters were less likely to be colonised at removal than control catheters (13.5 compared with 24.1 colonised catheters per 100 catheters; relative risk, 0.56 [95% CI, 0.36 to 0.89]; P = 0.005) and were nearly fivefold less likely to produce bloodstream infection.

3rd January 2000

- US FDA determines that Arrowg+ard Blue Plus antimicrobial multi-lumen CVC kit has equivalent indications to its predecessor and therefore grant permission to market device in the US

- Generation 2: AGB+ CVCs: Full protection along entire fluid path. Internal impregnation of all channels from hub to tip with Chlorhexidine.
By 2005

• 19 RCTs, 3 meta-analyses & 2 cost-benefit analyses
• CDC recommended use of antimicrobial-impregnated CVCs in selected clinical situations
• 13 of the 17 published studies that examined the effect of antimicrobial-impregnated CVCs on rates of CVC-related BSI found either a statistically significant reduction or a strong trend toward a reduction in rates of BSI
• Evidence that 40% of intravascular device–related BSIs are preventable with the use of antimicrobial-impregnated CVCs
• Support their selective use in situations in which rates of CVC-related BSI remain unacceptably high despite adherence to standard infection-control practices

Current Recommendations

Recommended by CDC

Recommended by ANZICs


2. National Institutes of Health, Bethesda, Maryland
3. Infectious Disease Society of America, Ann Arbor, Massachusetts
4. Greenwich Hospital, Greenwich, Connecticut
5. University of Washington, Seattle, Washington
7. University of Massachusetts Medical School, Worcester, Massachusetts
8. Yale University, New Haven, Connecticut
9. Warren Alpert Medical School of Brown University and Rhode Island Hospital, Providence, Rhode Island
10. Ohio Department of Health, Columbus, Ohio
11. National Cancer Institute, Bethesda, Maryland
12. Centers for Disease Control and Prevention, Atlanta, Georgia
13. The Children’s Hospital, Boston, Massachusetts
14. University of Nebraska Medical Center, Omaha, Nebraska
15. Ann Arbor VA Medical Center and University of Michigan, Ann Arbor, Michigan
16. Australian Commission on Safety and Quality in Health Care

Central Line Insertion and Maintenance Guideline

April 2012
Prevention Strategies: Supplemental

2011 CDC Antimicrobial-Impregnated Catheters

• 2 types with most supporting evidence:
  – Minocycline-Rifampin
  – Chlorhexidine–Silver Sulfadiazine

• Platinum-Silver catheter available but less evidence to support use

• These may be appropriate for patients whose catheter is expected to be used for more than 5 days and when Core strategies have not decreased rates of CLABSI to established goals.
ANZICS Antimicrobial central lines

Antimicrobial central lines\textsuperscript{17,18}

Chlorhexidine and silver sulphadiazine coated lines (not silver-only),\textsuperscript{19} and rifampicin and minocycline lines should be considered

- If the CLABSI rate remains high in spite of good compliance with the insertion and maintenance guidelines
- For patients who will have a central line in-situ >7 days\textsuperscript{20}
- For patients at particular risk of CLABSI, eg. burns, immunocompromised

Other factors to consider are:\textsuperscript{21}

- Both types of catheter have limited antimicrobial action against some organisms.
- If rifampicin and minocycline lines are frequently used, there should be monitoring for the development of resistance.
- Hypersensitivity reactions to chlorhexidine-coated central lines have been reported, albeit rarely.

Chlorhexidine – Sensitivity and Safety
Chlorhexidine Antiseptic Properties

- Been used widely as an antimicrobial agent since mid 1970s
- Mouth rinses, cosmetics, contact lens solution, skin creams
- Used clinically urinary antiseptic/ lubricant, implanted mesh
- Increasing use in clinical settings – skin preparation and hand hygiene solution
- Broad spectrum of action, rapid acting & persistent
Safety When Using Chlorhexidine

- Patient reactions are rare & typically minor
- Staff safety is not an issue
- Manufacturers’ instructions should be followed including paying attention to label warnings
CHG-Associated Anaphylaxis

- Chlorhexidine introduced in 1954
- Adverse reactions (mostly mild and skin related) reported for last 30 years
- Type 1 hypersensitivity first reported 1984
- Over ten years ~ 50 case reports published
- High rate in Japan
- Most anaphylaxis related to anaesthesia and surgery

Common Features of Reports

• Reaction to Chlorhexidine occurs during multi-body site exposure to Chlorhexidine – urinary catheter insertion/ skin preparation & insertion of impregnated CVC

• In multi-case series reports of Chlorhexidine hypersensitivity most reactions occur after urinary tract mucousal contact with Chlorhexidine vs insertion of impregnated CVC¹

• Specific reports of reaction to Chlorhexidine impregnated CVCs are rare and most often Chlorhexidine sensitivity known prior to insertion²

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Four cases of anaphylaxis to chlorhexidine impregnated central venous catheters: a case cluster or the tip of the iceberg?

Editor—We describe four cases of anaphylaxis caused by chlorhexidine in patients undergoing anaesthesia for cardiothoracic procedures in our Trust over a 12 month period. In all of these cases, anaphylaxis was preceded by insertion of a central venous catheter (CVC) impregnated with silver sulphadiazine and chlorhexidine (ARROWgard Blue®). All patients received standard anaphylaxis management including the administration of i.v. epinephrine, steroids, and antihistamines. In each patient, a tryptase increase from baseline was demonstrated in the early postreaction sample, indicating mast cell degranulation and confirming the clinical impression of anaphylaxis. Allergen-specific IgE testing (ImmunoCAP®) to chlorhexidine was also positive in all cases.

The first patient experienced two separate episodes of chlorhexidine-associated anaphylaxis. He had his initial procedure abandoned after developing anaphylaxis. An ARROWgard Blue® CVC was inserted immediately before his reaction, but the significance was not noted at the time. After investigation under the allergy team, he was found to be positive to chlorhexidine by specific IgE. His surgery was rescheduled and in light of his previous episode, all antiseptic preparations containing chlorhexidine were removed from the theatre. He had a second anaphylactic reaction after insertion of a second ARROWgard Blue® CVC. The external sterile set packaging did not

Chlorhexidine is a chlorophenyl biguanido antiseptic with two identical epitopes. This type of chemical conformation is known to be capable of cross-linking IgE antibodies on the surface of mast cells and basophils, subsequently causing histamine release in sensitized individuals in a manner similar to succinylcholine. Sensitization to chlorhexidine is undoubtedly through exposure, although this does not appear to be more common in health-care professionals who work in an environment where chlorhexidine is ubiquitous.1

First reports of anaphylaxis to this substance appeared in medical literature 25 yr ago2 and subsequent reports have been published sporadically since, mainly involving reactions from topical applications to skin and mucous membranes (ophthalmic wash, urinary catheterization, rectal examination, and intranasal administration).3–7 The severity of these cases prompted the Food and Drug Administration (FDA) in 1998, to issue an alert to the medical community about the potential for serious hypersensitivity reactions to chlorhexidine-impregnated medical devices.8

The incidence of chlorhexidine anaphylaxis is likely to be vastly under-represented; in a world-wide review in 2004, there were only 50 reported cases over a 10 yr period.9 In response to our recent cases, the Immunology Department in Southampton is currently undertaking a historical review of patients who have had an episode of intraoperative allergy. They have so far discovered 19 patients with positive chlorhexidine ‘ImmunoCAP’ tests in Wessex out of 86 cases tested in the last 36 months. Of the 86 patients tested, 16 were anaesthetic referrals and of these seven tested positive for chlorhexidine ‘ImmunoCAP’.

The Importance of Checking Packaging and Patient History

- “…as it was not widely appreciated that central lines may be pre-coated with Chlorhexidine and (as is routine practice) the line was handed to us already open, none of us thought to check the package insert…”

- CHG-impregnated CVCs are contraindicated for patients with known hypersensitivity

UK Medical Device Alert 2012/075

Medical Device Alert
Ref: MDA2012/075  Issued: 25 October 2012 at 12:00

Device
All medical devices and medicinal products containing chlorhexidine

Problem
Risk of anaphylactic reaction due to chlorhexidine allergy

Action
- Be aware of the potential for an anaphylactic reaction to chlorhexidine.
- Ensure that known allergies are recorded in patient notes.
- Check the labels and instructions for use to establish if products contain chlorhexidine prior to use on patients with a known allergy.
- If a patient experiences an unexplained reaction, check whether chlorhexidine was used or was impregnated in a medical device that was used.
- Report allergic reactions to products containing chlorhexidine to the MHRA.

Action by
All medical and nursing staff involved in the use of these devices and medicinal products.

CAS deadlines
Action underway: 22 November 2012
Action completes: 22 January 2013
Note: These deadlines are for systems to be in place to ensure there is continued awareness of this problem.

Recent National Concerns Regarding Chlorhexidine

The Problem

- Australia
  - No central database, but many reports of increasing incidence

- NZ
  - Some centres report their cases of allergy to a central body, the Centre for Adverse Reactions Monitoring (CARM)
  - In the 43 years from 1965 until April 2008, CARM had 54 reports of chlorhexidine reactions.
  - Four years later, by April 2012, these numbers had almost doubled to 100 reports
Recent National Concerns Regarding Chlorhexidine

Chlorhexidine anaphylaxis is increasing
- Be prepared to treat chlorhexidine allergic patients
- Be extra vigilant dealing with known chlorhexidine allergy patients

Risk versus benefit
- Still remains the most effective antiseptic
- Rethink use of chlorhexidine for low infection risk
CLABSI Prevention: A Balanced, Real-world View
Ensure CLABSI Prevention Efforts Target All Potential Sources
CVAD Post Insertion Management

• Single use 2% chlorhexidine gluconate in 70% isopropyl alcohol solution is the preferred antiseptic agent for insertion and dressing of CVADs
  • If this is not available, chlorhexidine 0.5% in 70% alcohol or iodine in alcohol should be used
  • Solutions must not be decanted into smaller containers and unused portions must be discarded.
Where a patient demonstrates chlorhexidine sensitivity topical povidone iodine 10% in 70% alcohol may be used

Anaphylaxis to CHG-coated CVCs: Current Thinking

BACKGROUND: Anaphylactic reactions to chlorhexidine are rare but are being reported increasingly in association with a variety of products.

METHODS: We report three cases of anaphylaxis to chlorhexidine in patients presenting for cardiac surgery.

RESULTS: In each case, anaphylaxis was precipitated by the insertion of a central venous catheter impregnated with chlorhexidine acetate. Subsequent investigations confirmed chlorhexidine as the causal agent.

CONCLUSION: Extensive use of chlorhexidine to reduce hospital-acquired infections has the potential to sensitise a small proportion of patients, leading to life-threatening anaphylaxis on subsequent exposure.

Suggested Mechanism of Anaphylactic Response To CHG-Coated CVC

Repeated Chlorhexidine exposure

Pt becomes sensitised

Delayed minor cutaneous reaction not ascribed to Chlorhexidine hypersensitivity

Subsequent exposure to Chlorhexidine through CVC

Anaphylaxis

The Effectiveness of C-SS Impregnated Catheters

**Table 1 - Colonization of catheter surface by slime positive *S.epidermidis*. [Time (days of immersion in PBS before the infection): 0 catheter fragments not immersed in PBS; 1, 2, 7, ... days of immersion].**

<table>
<thead>
<tr>
<th>Time (days in PBS)</th>
<th>Polyurethane catheter</th>
<th>C-SS impregnated catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.04x10^5</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.41x10^5</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2.00x10^5</td>
<td>0</td>
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<tr>
<td>21</td>
<td>2.09x10^6</td>
<td>1.17x10^4</td>
</tr>
<tr>
<td>28</td>
<td>9.33x10^5</td>
<td>3.72x10^3</td>
</tr>
</tbody>
</table>

Outstanding Questions

- Do some races have a genetic predisposition to Chlorhexidine hypersensitivity?
- Is the true incidence of Chlorhexidine anaphylaxis under reported?
- If repeated exposure is a pre-cursor why do healthcare workers show no greater risk or incidence?
- Why do clinicians continue to fail to take preventative action when most cases have previous known history of Chlorhexidine sensitivity?
Don’t Throw The Baby Out With The Bath Water
Anaphylactic reaction to Chlorhexidine impregnated central line – 1: 1,000,000
Catheter related bloodstream infection – 1:100
Precautionary Measures

• Take a careful medical history
• Do not use CHG-impregnated CVCs in patients with known or possible hypersensitivity
• Be familiar with all products and labels/warnings
• Immediately withdraw CHG-impregnated devices in the event of anaphylaxis
Summary

- Anaphylaxis is serious and should be avoided where possible
- The risk of anaphylaxis from CHG-impregnated CVC is rare ~ 2.02 cases per million units sold & 30 million units sold worldwide
- CLABSI in Australia is more common than anaphylaxis from CHG-impregnated CVCs
- In the past five years Australian clinicians have invested countless hours, dollars and effort into reducing CLABSI
- Compliance with standard infection prevention measures is less than ideal
- Where all non-technological avenues of CLABSI prevention have been exhausted and where patients are at increased risk of CLABSI & have no history of Chlorhexidine sensitivity it is recommended that antimicrobial CVCs are used
Conclusion
References


