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HEALTH TECHNOLOGY ASSESSMENT REPORT

MINISTRY OF HEALTH MALAYSIA

# ANTISEPTICS FOR SKIN PREPARATIONS PRIOR TO PROCEDURES


Health Technology Assessment Section (MaHTAS)

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MINISTRY OF HEALTH MALAYSIA

# Health Technology Assessment Report

# ANTISEPTICS FOR SKIN PREPARATIONS PRIOR TO PROCEDURES

**DISCLAIMER**

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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## DISCLOSURE

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# EXECUTIVE SUMMARY

## Background

According to the definition given by CDC Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008, a germicide is an agent that can kill microorganisms, particularly pathogenic organisms ("germs"). The term germicide includes both antiseptics and disinfectants. Antiseptics are germicides applied to living tissue and skin; disinfectants are antimicrobials applied only to inanimate objects. In general, antiseptics are used only on the skin and not for surface disinfection, and disinfectants are not used for skin antisepsis because they can injure skin and other tissues.

An antiseptic is a substance which inhibits the growth and development of microorganisms. It may be either bacteriocidal or bacteriostatic. Their uses include cleansing of skin and wound surfaces after injury, preparation of skin surfaces prior to injections or surgical procedures, and routine disinfection of the oral cavity as part of a program of oral hygiene. Some commonly used antiseptics for skin cleaning includes chlorhexidine, iodine compounds, and alcohol.

Currently in the Ministry of Health Drug Formulary, the common antiseptics listed are: 70% alcohol; 4% chlorhexidine gluconate scrub; 5% chlorhexidine gluconate solution; 5% chlorhexidine gluconate solution in 70% alcohol; 10% povidone iodine; and 7.5% povidone iodine scrub.

In the last fifty years we have witnessed a significant increase in the number of antiseptics as well as their usage in the healthcare environment. When used appropriately, antiseptics play an important role in controlling infection and reduce the risk of nosocomial infections.

In view of the new development in the area of antiseptic, there is a need to update the evidence available to support the use of these antiseptics in the Malaysian Ministry of Health. Thus, this Health Technology Assessment was undertaken to review the antiseptics currently used for skin preparations especially prior to procedures such as surgery, central venous catheterization, epidural catheterization, urinary catheterization, intradermal, subcutaneous, and intramuscular injection which will help healthcare providers to identify the best intervention strategies in preventing and controlling infections in clinical settings.

## Technical features

Alcohols exhibit rapid broad-spectrum antimicrobial activity against vegetative bacteria (including mycobacteria), viruses, and fungi but are not sporicidal. They are, however, known to inhibit sporulation and spore germination but this effect is reversible. Another antiseptic, chlorhexidine, is probably the most widely used biocide and antiseptic. This is due in particular to its broad-spectrum efficacy, substantively for the skin, and low irritation. Despite the advantages of chlorhexidine, its activity is pH dependent and is greatly reduced in the presence of organic matter.

A new antiseptic, Octenidine dihydrochloride, has activity against Gram-positive and Gram-negative bacteria. Octenidine dihydrochloride is used in concentrations of 0.1% to 2.0% and is similar in its action to the Quaternary Ammonium Compounds (QAC's), but is of somewhat broader spectrum of activity. Currently, it is increasingly being used in continental Europe as a QAC's and chlorhexidine substitute in water-or alcohol-based antiseptic for skin, mucosa and wound. A commonly used antiseptic, iodine, is bactericidal, fungicidal, tuberculocidal, virucidal, and s poricidal. Although aqueous or alcoholic (tincture) solutions of iodine have been used for 150 years as antiseptics, they are associated with irritation and excessive staining. In addition, aqueous solutions are generally unstable; in solution, at least seven iodine species are present in a complex equilibrium, with molecular iodine ($I_2$) being primarily responsible for antimictrobial efficacy. These problems can be overcomed by the development of iodophors ("iodine carriers" or "iodine-releasing agents"); the most widely used are povidone-iodine and poloxamer-iodine in antiseptics.

## Objective

To assess the safety, effectiveness, efficacy and cost-effectiveness of antiseptics for skin preparations prior to five procedures commonly performed in clinical practice.

## Methods

Electronic databases such as MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, HTA databases, EBM Reviews – NHS Economic Evaluation Database, EBM Full Text-Cochrane DSR, ACP Journal Club and DARE were searched. Critical appraisal of all relevant literature was done using Critical Appraisal Skills Programme (CASP) and evidence was graded according to US/Canadian Preventive Services Task Force.

## Results and conclusion

Twenty four potentially relevant articles were retrieved in full text. Of the twenty four full text articles, seventeen articles were included for effectiveness of antiseptics for skin preparations prior to the identified procedures.

Five systematic reviews, eleven randomised controlled trials and one non randomised trial related to the effectiveness of antiseptics for skin preparations prior to procedures were retrieved. However, there was no health technology assessment report retrieved.

The evidence retrieved showed that 0.1% Octenidine in alcoholic solution, 70% alcohol, 10% povidone iodine, iodophor in alcohol, 0.25% chlorhexidine gluconate, 0.5% chlorhexidine gluconate in 70% alcohol, 4% chlorhexidine gluconate, 2% chlorhexidine gluconate in 70% alcohol and alcohol spray are antiseptics commonly used for skin preparations prior to procedures.

The review showed there was strong evidence that:

- Two percent (2%) chlorhexidine gluconate resulted in significant reduction in microbial colonization of the central venous catheter insertion site and the catheter tip as well as local site infection. However, (0.1%) Octenidine in alcoholic solution was superior to 74% alcohol in preventing the central venous catheter associated infections.

- Zero point five percent (0.5%) chlorhexidine in 70% alcohol resulted in significant reduction in microbial colonization of the epidural catheter insertion site.

- Two percent (2 %) chlorhexidine gluconate in 70% alcohol resulted in significant microbial reduction of the preparation sites prior to surgery and surgical site infection.

- Cleansing the periurethral area with sterile water was not inferior to cleansing with antiseptics prior to urinary catheterization.

There was evidence to show that the use or no use of antiseptics on unsoiled skin prior to intradermal, subcutaneous and intramuscular injection does not decrease or increase the risk of infection.

## RECOMMENDATION

Based on the above review, the following antiseptics are recommended for use prior to the following procedures:

i) Central venous catheterization:
Two percent (2%) chlorhexidine gluconate in 70% alcohol is the antiseptic of choice prior to central venous catheterization but 0.1% Octenidine in alcoholic solution is potentially beneficial. However, the retrieved evidence shows that 0.1% Octenidine in alcoholic solution was superior to alcohol. More clinical research is warranted.

ii) Epidural catheterization
Zero point five percent (0.5%) chlorhexidine in 70% alcohol is the antiseptic of choice for skin preparation prior to epidural catheterization.

iii) Surgery:
Two percent (2 %) chlorhexidine gluconate in 70% alcohol is potentially superior to 4% chlorhexidine and povidone iodine solution and may be the antiseptic of choice for skin preparation prior to surgery

iv) Urethral catheterization:
The use of either sterile water or antiseptic for skin preparation prior to urethral catheterization is an acceptable practice.

v) Intradermal, subcutaneous, and intramuscular injection
For unsoiled skin, the use or not use of 70% alcohol swab prior to the above procedures can be practised.

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# ANTISEPTICS FOR SKIN PREPARATIONS PRIOR TO PROCEDURES

## 1 BACKGROUND

According to the definition given by CDC Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008, a germicide is an agent that can kill microorganisms, particularly pathogenic organisms ("germs"). The term *germicide* includes both antiseptics and disinfectants. *Antiseptics* are germicides applied to living tissue and skin; *disinfectants* are antimicrobials applied only to inanimate objects. In general, antiseptics are used only on the skin and not for surface disinfection, and disinfectants are not used for skin antisepsis because they can injure skin and other tissues.[1]

An antiseptic is a substance which inhibits the growth and development of microorganisms. It may be either bacteriocidal or bacteriostatic. Their uses include cleansing of skin and wound surfaces after injury, preparation of skin surfaces prior to injections or surgical procedures, and routine disinfection of the oral cavity as part of a program of oral hygiene. Some commonly used antiseptics are for skin cleansing includes chlorhexidine, iodine compounds, and alcohol.

"Biocide" is a general term describing a chemical agent, usually broad spectrum that inactivates microorganisms. Biocides range in antimicrobial activity. Other terms may be more specific such as "-static," referring to agents which inhibit growth (examples include bacteriostatic, fungistatic, and sporistatic), whereas "-cidal," refers to agents which kill the target organism (examples include sporicidal, virucidal, and bactericidal).[2]

All disinfectants used to disinfect medical appliances are classified as medical device in line with the regulatory bodies globally. As the Medical Device Act is still pending for approval, most disinfectants are not subjected to stringent pre-marketing tests. Only antiseptics used for skin preparations must be registered with Drug Control Authority of Malaysia.

In the last fifty years, we have witnessed a significant increase in the number of antiseptics as well as their usage in the healthcare environment. When used appropriately, antiseptics play an important role in controlling infection and reduce the risk of nosocomial infections.

In view of the new development in the area of antiseptic, there is a need to update the evidence available to support the use of these antiseptics in the Malaysian Ministry of Health. Thus this review was undertaken to review the antiseptics currently used for skin preparations especially prior to procedures such as surgery, central venous catheterization, epidural catheterization, urinary catheterization, intradermal, subcutaneous, and intramuscular injection which will help healthcare providers to identify the best intervention strategies in preventing and controlling infections in clinical settings.

# 2 TECHNICAL FEATURES

Currently in the Ministry of Health Drug Formulary, the common antiseptics listed are: 70% alcohol; 4% chlorhexidine gluconate scrub; 5% chlorhexidine gluconate solution; 5% chlorhexidine gluconate solution in 70% alcohol; 10% povidone iodine; and 7.5% povidone iodine scrub.[3]

## 2.1 Alcohol

Although several alcohols have been shown to be effective antimicrobials, ethyl alcohol (ethanol, alcohol), isopropyl alcohol (isopropanol, propan-2-ol) and *n*-propanol particularly in Europe are the most widely used. [2,4] Alcohols exhibit rapid broad-spectrum antimicrobial activity against vegetative bacteria (including mycobacteria), viruses, and fungi but are not sporicidal. They are, however, known to inhibit sporulation and spore germination [2,5] but this effect is reversible. Because of the lack of sporicidal activity, alcohols are not recommended for sterilization but are widely used for both hard-surface disinfection and skin antisepsis.

## 2.2 Chlorhexidine

Chlorhexidine is probably the most widely used biocide and antiseptic. This is due in particular to its broad-spectrum efficacy, substantively for the skin, and low irritation. Of note, irritability has been described and in many cases may be product specific. [6,7] Despite the advantages of chlorhexidine, its activity is pH dependent and is greatly reduced in the presence of organic matter.[7]

## 2.3 Octenidine dihydrochloride

Octenidine dihydrochloride is a new cationic antiseptic that belongs to the bispyridine class of chemicals. It has activity against Gram-positive and Gram-negative bacteria [8-10] Octenidine dihydrochloride is used in concentrations of 0.1–2.0% and is similar in its action to the Quaternary Ammonium Compounds (QAC's), but is of somewhat broader spectrum of activity. Currently, it is increasingly being used in continental Europe as a QAC's and chlrohexidine substitute in water or alcohol-based antiseptic for use on skin, mucosa and wound. In aqueous formulations, it is often potentiated with addition of 2-phenoxyethanol. A reduction factor of 5 decadic units is achieved even with concentrations of > 0.001% Octenidine dihydrochloride within 1 min. Although the cytotoxicity of the active ingredient in the concentrations necessary for activity is low, it is present even at concentrations higher than 0.001% by weight Octenidine dihydrochloride. Hence there are limits on the use of Octenidine dihydrochloride for example on chronic wounds.

### 2.4 Iodine and iodophors.

Although less reactive than chlorine, iodine is rapidly bactericidal, fungicidal, tuberculocidal, virucidal, and sporicidal.[11] Although aqueous or alcoholic (tincture) solutions of iodine have been used for 150 years as antiseptics, they are associated with irritation and excessive staining. In addition, aqueous solutions are generally unstable; in solution, at least seven iodine species are present in a complex equilibrium, with molecular iodine ($I_2$) being primarily responsible for antimictrobial efficacy. These problems can be overcomed by the development of iodophors ("iodine carriers" or "iodine-releasing agents"). The most widely used are povidone-iodine and poloxamer-iodine in antiseptics. Iodophors are complexes of iodine and a solubilising agent or carrier, which acts as a reservoir of the active "free" iodine. Although germicidal activity is maintained, iodophors are considered less active against certain fungi and spores than are tinctures.

## 3 POLICY QUESTION

In Ministry of Health hospitals, what are the most appropriate antiseptics to be used for skin preparations prior to five procedures commonly performed in clinical practice such as central venous catheterization, epidural procedure, surgery, urinary catheterization, and parenteral injection?

## 4 OBJECTIVE

The objectives of this report were:-

i. To undertake a systematic review on the effectiveness/efficacy of antiseptics for use in skin preparations prior to the following procedures:-
   a. Central venous catheterization
   b. Epidural catheterization
   c. Surgery
   d. Urinary catheterization
   e. Intradermal, subcutaneous, and intramuscular injection

ii. To determine the safety and cost-effectiveness of the antiseptics studied in (i) above.

# 5 METHODOLOGY

## 5.1 Literature search strategy

Electronic databases were searched for published literatures pertaining to antiseptics use for skin preparations prior to procedures namely central venous catheterization, epidural catheterization, surgery, urinary catheterization, intradermal, subcutaneous, and intramuscular injection.

The following databases were searched including MEDLINE, PubMed, EBM Reviews – Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, HTA Databases, EBM Reviews - NHS Economic Evaluation Database, EBM Full Text–Cochrane DSR, ACP Journal Club and DARE. Additional articles were identified from reviewing the bibliographies of retrieved articles and hand searching of journals.

The following search terms were used either singly or in combination: antiseptic, disinfectants, disinfect*, skin disinfections, skin preparation, central venous catheter OR central lines, intravenous injections, antisep*, parenteral inj*, surgical wound infection, surgical infection, surgical wound, post-operative or postoperative, preoperative care, iodophor* or povidone-iodine or betadine or chlorhexidine or octenidine , alcohol or alcohols or antiseptic*, alcohol based disinfectants, aqueous based disinfectants, antisepsis, effectiveness, cost-effectiveness, safety. The search was limited to human study and year of publication from 2000 to 2010.

## 5.2 Inclusion and exclusion criteria

Based on the policy question the following inclusion and exclusion criteria were used:-

### Inclusion criteria

i. Study design: systematic review, randomised controlled trials and non-randomised controlled trials

ii. Population: patients and healthcare personnel

iii. Setting: healthcare setting

iv. Intervention: antiseptics for skin preparations

v. Outcomes:

Reduction in infection rate (surgical site infection, bloodstream infection etc), bacterial colony counts, adverse events

### Exclusion criteria

Articles for antisepsis or disinfectant on mucosal surfaces such as oral cavities and dental preparations were excluded.

### 5.3. Data extraction strategy

The following data was extracted:-

- Details on methods and study population characteristics
- Details on the intervention and comparator
- Details on individual outcomes for effectiveness, safety, cost-effectiveness of the antiseptics

Data was extracted from included studies by a reviewer using a pre-designed data extraction form (Evidence tables as shown in Appendix 3).

### 5.4. Quality assessment strategy

The methodological quality of all the relevant full text articles retrieved was assessed using Critical Appraisal Skills Programme (CASP) depending on the type of study design [13].

All full text articles related to effectiveness were graded according to US/Canadian Preventive Services Task Force (Appendix 1). The extracted data (Evidence tables) were presented and discussed with the expert committee before deciding on the eligibility of articles to be finally included in this report.

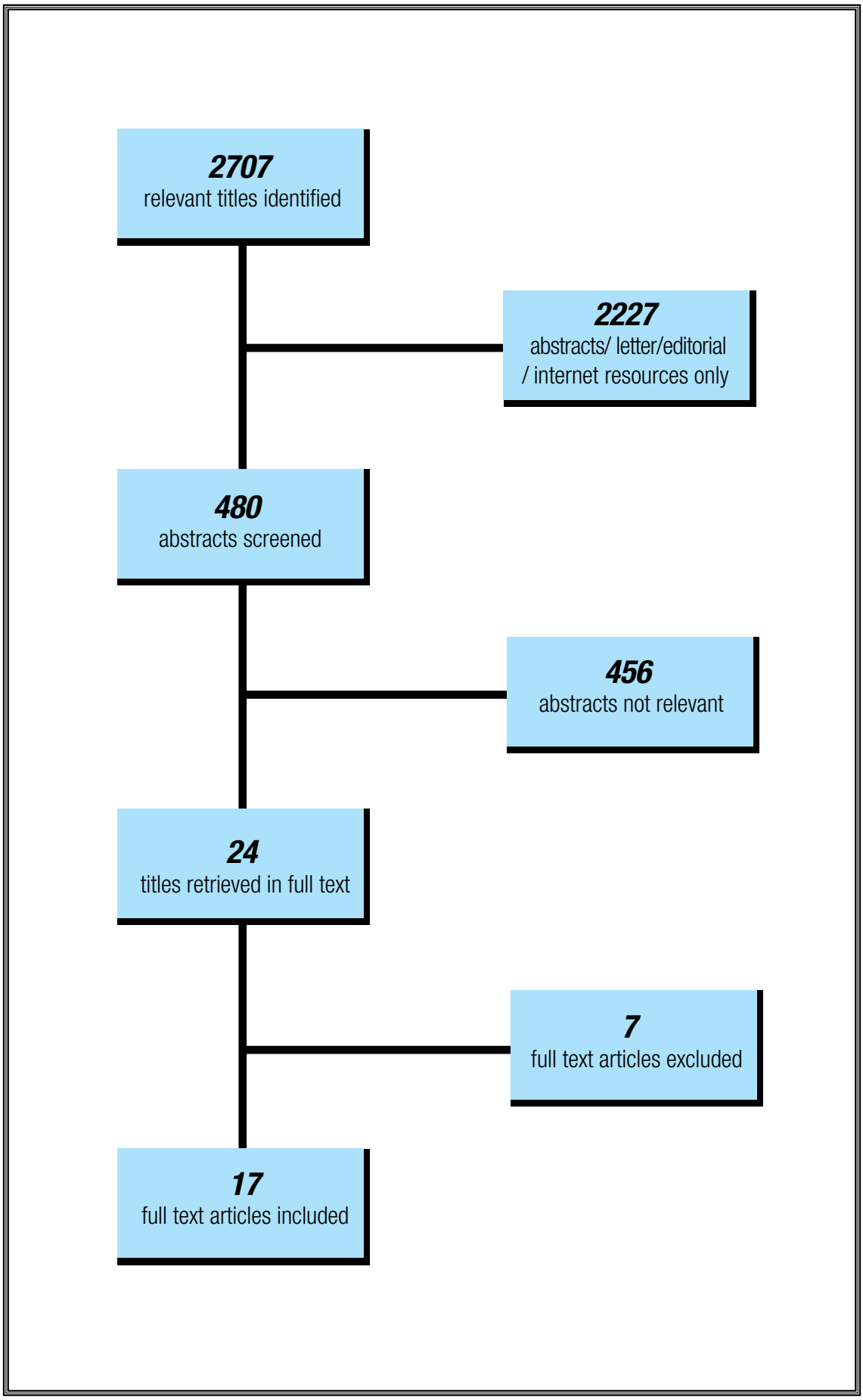
## 6 RESULTS AND DISCUSSION

**S**earch strategies yielded many published articles related to disinfectants and antiseptics. A total of 2707 relevant titles were identified and 480 abstracts were screened using the inclusion and exclusion criteria. Of these, 456 abstract were found to be not relevant. Twenty four potentially relevant articles were retrieved in full text. Of the twenty four full text articles, seventeen articles were included in this systematic review as shown in Figure 1. In total seven full text articles were excluded based on inclusion and exclusion criteria and quality of the studies. These are listed in Appendix 4. Included studies are as shown in Appendix 3.

Seventeen articles were included for effectiveness of antiseptics for skin preparations prior to procedures (such as antiseptics for skin preparations prior to central venous catheterization, prior to epidural analgesia, prior to surgery, prior to urethral catheterization, prior to intradermal, subcutaneous, and intramuscular injection).

Five systematic reviews, eleven randomised controlled trial and one non randomised trial related to the effectiveness of antiseptics for skin preparations prior to procedures were retrieved. However, there was no health technology assessment report retrieved.

Figure 1. Flow chart of retrieval of articles used in the results



## 6.1 EFFECTIVENESS

### 6.1.1 Antiseptic for skin preparations prior to central venous catheterisation

Seven studies evaluated the effect of antiseptics for skin preparations before central venous catheter (CVC) insertion.

Dettenkofer M *et al.* (2009) conducted a double-blind, randomised controlled trial (RCT) using Octenidine dihydrochloride in two university hospitals in Germany and Switzerland. [14 level 1] Four hundred patients who were inserted with CVC were enrolled from May 2002 through April 2005. Both groups were similar in respect of patient characteristics and co-morbidities. The results showed that:

- Skin colonization at the CVC insertion site during the first 10 days was significantly reduced by Octenidine treatment where the relative difference between Octenidine-treated group and control group was 0.21 (95% CI, 0.11–0.39).
- Positive culture of the catheter tip was significantly less frequent in the Octenidine treated group (7.9%) than in the control group (17.8%). The odds ratio (OR) was 0.39 (95% CI, 0.20 – 0.80),
- Patients treated with Octenidine had a non-significant reduction in catheter-associated bloodstream infections when compared to control (4.1% versus 8.3% respectively). The odds ratio was (OR) was 0.44 ( 95% CI, 0.18–1.08).

In another prospective study conducted at Freiburg University Hospital, Germany, by Dettenkofer M *et al.* (2002), 60 patients who received central catheter were alternately assigned to different skin antiseptic regimens at the insertion site. One group (A) received 0.1% Octenidine dihydrochloride in 30% 1-propanol and 45% 2-propanol. Another group (B) received 74% ethanol in 10% 2-propanol. [15 level II-I] In total, 90 cultures were assessed in each group, (i) before catheterization, (ii) following catheterization and (iii) 24 hours after catheter insertion. The median colony-forming unit (cfu) counts per 24 $cm^2$ (group A versus B) were respectively;

(i) Before catheterization: 2,270 cfu versus 2,950 cfu

(ii) Following catheterization: 20 cfu versus 40 cfu, and

(iii) 24 hours after catheter insertion: 860 cfu versus 1,210 cfu

These studies showed that 0.1% Octenidine in propanol was more effective than alcohol alone in reducing skin colonization and the microflora of the skin at the CVC insertion site over a 24-h period.

Olivier Mimoz *et al.* (2007) conducted a RCT at a surgical ICU of a university-affiliated hospital. Skin involved with scheduled central venous catheters insertion into jugular or subclavian veins were consecutively and randomly assigned to be treated with (A) 5% povidone iodine in 70% ethanol or (B) with 0.25% chlorhexidine gluconate in 0.025% benzalkonium chloride, and 4% benzylic alcohol. [16 level1] Of 538 catheters inserted, 481 (89.4%) produced evaluable culture results.

Compared with povidone iodine, the chlorhexidine-based solution was associated with:

- 50% decrease in the incidence of catheter colonization rate (11.6% versus 22.2% respectively) [P=0.002];
- a trend toward lower rates of catheter-related bloodstream infection (1.7% versus 4.2% respectively ) [P=0.09]

Similar findings were demonstrated in a systematic review by Sheri M. Carson (2004). [17 level1] All of the studies included in this review carried out at least one insertion site before catheter placement. Many studies checked culture at each dressing change (Garland *et al*., 2001; Hanazaki *et al*., 1999; Maki & Ringer, 1991). In every study, all sites were cultured and then cleansed before catheter removal. After catheter removal, semiquantitative cultures were performed on the distal portion of the catheter (2–5 cm) using the method described by Maki, Weise, and Sarafin (1997). Except for Mimoz *et al.* (1996), who defined significant catheter colonization as a quantitative culture of $\geq 1 \times 10^3$ colony forming units (cfu)/ml, all studies classified a positive catheter culture as ≥15 cfu/ml. Most studies reviewed were RCT (Garland *et al*., 2001; Hanazaki *et al*., 1999; Humar *et al.,* 2000; Kinirons *et al.,* 2001; Maki & Ringer, 1991; Mimoz *et al.,* 1996). Frieberger *et al*. (1992) used a quasi-experimental research design, and Garland *et al*. (1995) conducted a nonrandomized clinical trial. The reviewed studies used similar definitions for many of the dependent variables or outcomes variables. Outcomes variables included were catheter colonization and bacteraemia. Most studies found chlorhexidine to be superior to povidone-iodine for decreasing the risk of local site infection. Hence, chlorhexidine can be used to prevent microbial colonization at CVC insertion sites and catheter tips.

Julia Langgartner *et al.* (2004) did a RCT on one hundred nineteen subjects who needed CVC insertions which compared three different approaches. Patients were scheduled electively to receive 140 CVCs. Skin disinfection was performed with either (i) povidone-iodine 10% (PVP-iodine), (ii) chlorhexidine 0.5%/propanol 70%, or (iii) chlorhexidine 0.5%/propanol 70% followed by PVP-iodine 10%. [18 level 1] Prior to disinfection, a swab from the site of insertion was taken for culture. CVCs were removed if no longer needed or infection was suspected. All catheters were cultured quantitatively after removal. Bacterial growth was found in 30.8% of the catheters placed after skin disinfection with povidone-iodine, in 24.4% after disinfection with propanol/chlorhexidine and in 4.7% after disinfection with propanol/chlorhexidine followed by povidone-iodine (p=0.006). Skin disinfection with propanol/chlorhexidine followed by PVP-iodine was superior in the prevention of microbial CVC colonisation compared to either of the regimens alone.

Bancherd Balamongkhon and Visanu Thamlikitkul (2007), did a study using locally formulated chlorhexidine gluconate for central venous catheter (CVC) site care in intensive care units (ICUs) at Siriraj Hospital, Thailand. [19 level 1] The study was conducted in 312 subjects who needed CVC insertions in three ICUs from January to July 2006. One hundred twenty subjects received 2% chlorhexidine gluconate in 70% alcohol, whereas 192 subjects received 10% povidone-iodine as the antiseptic solution for CVC site care.

The patients were assessed for CVC-related infections and for any adverse effects of 2% chlorhexidine gluconate in 70% alcohol. The incidence of catheter related blood stream infection (CRBSIs) in the indwelling CVC subjects who received 2% chlorhexidine gluconate in 70% alcohol was less than those who received 10% povidone-iodine during the same period, (3.2 versus 5.6 episodes per 1000 CVC days, respectively, P = 0.06). The odds ratio (OR) was 3.26 with 95% CI: 0.97-10.92. No adverse effects related to using 2% chlorhexidine gluconate in 70% alcohol were observed. Hence, the locally formulated 2% chlorhexidine gluconate in 70% alcohol was safe and effective for CVC site care in ICUs at Siriraj Hospital.

Prabha Ramritu *et al.* (2007) did a systematic review and meta-analysis of strategies, hypothesized to reduce risk of catheter-related bloodstream infections and catheter colonization in the intensive care unit setting. [20 level 1] Results from studies of similar interventions were pooled using meta-analyses. Here, three studies compared different types of skin antiseptics were as shown below:

- One RCT (Maki *et al.* 1991) compared 2% aqueous chlorhexidine gluconate with 10% povidone iodine (PI) and 70% isopropyl alcohol. The 2% aqueous Chlorhexidine solution compared to 10% Povidone Iodine reduced colonization by 69% (RR 0.31; 95% CI: 0.17–0.88) but there was no statistically significant reduction for catheter related blood stream infection (CRBSI ) (RR 0.23; 95% CI: 0.03– 1.92). When compared to the 70% alcohol solution, the 2% Chlorhexidine showed no statistically significant difference in colonization (RR 0.38; 95% CI: 0.11–1.33) or CRBSI rates (RR 0.24; 95% CI: 0.02–2.54) where the confidence intervals cuts across the value of 1.
- Another RCT (Humar *et al*. 2000) compared 10% PI solution with 0.5% tincture of Chlorhexidine solution and found no statistical difference in rates of colonization (RR 0.8; 95% CI:0.52–1.26) or CRBSI (RR 1.07; 95% CI: 0.27–4.17 ) where the confidence intervals cuts across the value of 1.
- The third study (Parienti *et al*. 2004) used a cross-over unit-randomized trial to compare 10% aqueous PI solution with 5% PI in 70% ethanol based aqueous solution. Colonization rates were significantly lower for povidone iodine in 70% alcohol than 10% aqueous povidone iodine solution (RR 0.38; 95% CI: 0.22 to -0.65) but there was no significant difference in CRBSI rate (RR 0.3; 95% CI: 0.03–2.4).

### 6.1.2 Antiseptic for skin preparations prior to epidural catheterization

Two studies evaluated the effect of antiseptic for skin preparations prior to epidural analgesia.

Sara J. Robinson (2005) did a systematic review of effectiveness of antiseptics on skin preparation prior to epidural analgesia. [21 level 1] A systematic review on nine reports of trials was completed to examine the efficacy of antiseptics in patients with epidural analgesia. These reports included randomized controlled trials and clinical trials.

They included both pediatric and adult populations undergoing epidural procedures. A systematic search was completed using MEDLINE from 1966 to March week 4 in 2004, EMBASE from 1980 to week 12 in 2004, the Cochrane Library Controlled Trials Register and CINAHL. Three of the studies included in the systematic review examined the effect of chlorhexidine versus povidone iodine as an antiseptic for skin preparation. The results showed that:

- One RCT (Kinirions *et al*. 2001) compared an alcoholic solution of 0.5% chlorhexidine with aqueous solution of 10% povidone iodine. The 0.5% chlorhexidine reduced colonization more effectively than the 10% povidone iodine. The study also showed that chlorhexidine could be colonized one sixth less quickly than povidone iodine when used as skin preparation prior to insertion of catheters (1 of 52 catheters [0.9 per 100 catheter days] *versus* 5 of 44 catheters [5.6 per 100 catheter days] respectively. The relative risk (RR) was 0.2 [95% CI, 0.1-1.0].

- Another RCT ( Kasuda *et al*. 2002) compared 0.5% chlorhexidine in ethanol to aqueous solution of 10% povidone iodine. They found the effect of chlorhexidine to be no different than povidone iodine in reducing epidural catheter colonization. Cultures of catheter insertion sites yielded microorganisms in 7 out of 28 (25%) in the Povidone iodine group and 8 out of 34 (24%) in the Chlorhexidine group.

- The third study (Sato *et al* 1996) compared 0.5% chlorhexidine in ethanol to aqueous solution of 10% povidone iodine. The 0.5% chlorhexidine reduces colonization more effectively then povidone iodine by 2 out of 35 cultures [5.7%]; compared to 11 out of 34 cultures [32.4%] respectively.

David J. Birnbach *et al.* (2003) did a RCT on sixty women in active labour who requested epidural analgesia. [22 level 1] They were randomly assigned to receive skin preparation with either Povidone iodine or Iodophor in Isopropyl Alcohol Solution. A total of three cultures were obtained from each subject. (i)The first was obtained prior to skin antisepsis, (ii)the second was obtained immediately following antisepsis, and (iii) the third was obtained just before removal of the catheter. In addition, the distal tip of the catheter was also submitted for culture. The results showed that:

i) The groups did not differ with respect to the presence of skin organisms at the site of epidural insertion prior to disinfection (90% in each group)

ii) The proportion of subjects with positive skin cultures immediately after skin antiseptic application differed significantly between the Povidone iodine and Iodophor in Isopropyl Alcohol Solution groups (30% and 3%, respectively, p= 0.01). This showed that Iodophor in Isopropyl Alcohol Solution was more effective than povidone iodine.

iii) The number of subjects with any positive skin cultures at the time of catheter removal was greater in the Povidone iodine group as compared to the Iodophor in Isopropyl Alcohol Solution group (97% and 50%, respectively, p = 0.0001). At catheter removal, skin cultures from the Povidone iodine group (mean log CFU=1.93 ± 0.40) differed significantly from those from the Iodophor in Isopropyl Alcohol Solution group (mean log CFU = 0.90 ± 0.23) (P=0.03). Hence, Iodophor in Isopropyl Alcohol Solution showed better efficacy than povidone iodine.

### 6.1.3 Antiseptic for skin preparations prior to surgery

Five studies evaluated the effect of antiseptics for skin preparations prior to surgery. There were three RCT that showed 2 % chlorhexidine gluconate was superior to 4% chlorhexidine or povidone iodine as a skin antiseptic prior to surgery in reducing microbial counts.

Charles E. Edmiston *et al.* (2007) compared the activity of an innovative 2% chlorhexidine gluconate (CHG)-impregnated preoperative skin preparation cloth (PC) with a standard application procedure with a 4% CHG surgical skin preparation (SP). [23 level 1] A paired, randomised, parallel phase III study was conducted to evaluate preoperative skin preparations. Subjects' left and right sides of the inguinal and abdominal skin sites (n= 30) were randomised to either 2% chlorhexidine gluconate (CHG)-impregnated preoperative skin preparation cloth (PC) or 4% CHG surgical skin preparation (SP ) treatment. Following baseline cultures, 2% chlorhexidine gluconate sites were prepared for 3 minutes, and 4% CHG surgical skin preparation sites were prepared for 4 minutes. Skin site cultures were obtained at (i) 10 minutes, (ii) 30 minutes, and (iii) 6 hours post preparation. Bacterial recovery was expressed as $\log_{10}$ colony-forming units (cfu)/$cm^2$ for baseline and post application microbial recovery. The results showed that:

- Mean microbial baseline for 2% chlorhexidine gluconate surgical skin preparation
    - at the abdominal skin sites was 3.36 cfu/$cm^2$ and
    - at inguinal skin sites was 6.15 cfu/ $cm^2$;
- Mean microbial baseline for 4% chlorhexidine gluconate surgical skin preparation
    - at the abdominal skin sites was 3.51 cfu/ $cm^2$ and
    - at inguinal skin sites was 6.16 cfu/ $cm^2$.

There was significant microbial reductions from abdominal-inguinal preparation sites treated with 2% chlorhexidine gluconate and 4% chlorhexidine gluconate compared with baseline, (P <0 .05). However, the 2% chlorhexidine gluconate skin preparation treated inguinal sites at 10 minutes, 30 minutes, and 6 hours post-skin preparation demonstrated significantly greater microbial reductions than did the 4% chlorhexidine treated inguinal sites (P <0 .01) as shown below:

- $Log_{10}$ reduction for 2% chlorhexidine gluconate surgical skin preparation,
  - o abdominal sites at 10 minutes, 30 minutes, and 6 hours post preparation were 2.50, 2.33, and 2.54 respectively;
  - o and inguinal preparation sites at 10 minutes, 30 minutes, and 6 hours post preparation were 3.45, 3.50, and 3.64 respectively.
- $Log_{10}$ reductions for 4% Chlorhexidine gluconate surgical skin preparation,
  - o abdominal preparation sites at 10 minutes, 30 minutes, and 6 hours were 2.18, 2.19, and 2.77 respectively.;
  - o and inguinal preparation sites at 10 minutes, 30 minutes, and 6 hours were 2.78, 2.63, and 3.15 respectively.

Matthew D. Saltzman et *al*. (2009) did a randomised controlled trial on 150 consecutive patients undergoing shoulder surgery.[24 level 1] Each shoulder was prepared with one of three randomly selected solutions: (i) ChloraPrep (2% chlorhexidine gluconate in 70% isopropyl alcohol), (ii) DuraPrep (0.7% iodophor in 74% isopropyl alcohol), or (iii) povidone-iodine scrub and paint (0.75% iodine scrub and 1.0% iodine paint). Aerobic and anaerobic cultures were obtained prior to skin preparation for the first twenty patients, to determine the native bacteria around the shoulder, and following skin preparation for all patients. Coagulase-negative Staphylococcus and Propionibacterium acnes were the most commonly isolated organisms prior to skin preparation. The results showed the 2% chlorhexidine gluconate in 70% isopropyl alcohol was more effective than 0.7% iodophor in isopropyl alcohol or povidone-iodine at eliminating overall bacteria from the shoulder region whereby the positive culture rate for the 2% chlorhexidine gluconate in alcohol group was lower than that for the povidone-iodine group ($p < 0.0001$) or the 0.7% iodophor in alcohol group ($p = 0.01$) as shown below:

- 7% in the ChloraPrep treated group (2% chlorhexidine gluconate and 70% isopropyl alcohol).
- 19% in the DuraPrep treated group (0.7% iodophor and 74% isopropyl alcohol) and
- 31% in the povidone-iodine treated group.

The study also showed that 2% chlorhexidine gluconate in alcohol and 0.7% iodophor in alcohol were also more effective than povidone-iodine in eliminating coagulase-negative Staphylococcus from the shoulder region ($p < 0.001$ for both).

Rabih Darouiche *et al*. (2010) randomly assigned adults undergoing surgery in six hospitals to preoperative skin preparation with either 2% chlorhexidine gluconate in 70% isopropyl alcohol scrub or povidone–iodine scrub and paint. [25 level1] The primary outcome was any surgical-site infection within 30 days after surgery. Secondary outcomes included individual types of surgical-site infections. A total of 849 subjects (409 in the chlorhexidine–alcohol treated group and 440 in the povidone–iodine treated group) qualified for the intention-to-treat analysis. The results showed that:

- The overall rate of surgical-site infection was significantly lower in the chlorhexidine–alcohol treated group than in the povidone–iodine treated group (9.5% versus 16.1% respectively; RR, 0.59; 95% CI, 0.41 to 0.85).

- Chlorhexidine–alcohol was significantly more protective than povidone–iodine against both superficial incisional Infections (4.2% versus 8.6% respectively, P = 0.008) and deep incisional infections (1% versus 3% respectively, P = 0.05) but not against organ-space infections (4.4% versus 4.5% respectively).

Similar results were observed in the per-protocol analysis of the 813 patients who remained in the study during the 30-day follow-up period. Adverse events were similar in the two study groups. Hence, preoperative cleansing of the patient's skin with 2% chlorhexidine gluconate in 70% isopropyl alcohol is superior to cleansing with povidone–iodine for preventing surgical-site infection.

Edwards P *et al*. (2009) did a systematic review to determine whether preoperative skin antisepsis prevents post-operative surgical wound infection. [26 level 1] The authors searched the Cochrane Wounds Group Specialised Trials Register (July 2008); the Cochrane Central, Register of Controlled Trials (CENTRAL), Issue 3 2008; OvidMEDLINE, 2005 to July Week 3 in 2008; Ovid EMBASE, 2005 to Week 29 in 2008 and Ovid CINAHL, 2005 to July Week 3 in 2008. In addition they also searched the bibliographies of all retrieved and relevant publications identified by these strategies for further studies. They placed no specific date restriction upon study inclusion. They also contacted manufacturers and distributors of antiseptic agents as well as professional organisations for example Association for Perioperative Practice, Association of peri Operative Registered Nurses (AORN), Royal College of Surgeons of England, The Association of Operating Department Practitioners for details of unpublished and ongoing studies. They did not restrict the search by language or publication status. Randomised controlled trials evaluating the use of preoperative skin antiseptics applied immediately prior to incision in clean surgery were included. There was no restriction on the inclusion of reports based on language of publication, date or publication status. Data extraction and assessment of study quality were undertaken by three authors independently.

In the above study by Edwards *et al* (2009), the antiseptics used differed between studies. The results were as shown below:

- Iodine impregnated incise drapes were evaluated in four trials (Alexander 1985; Dewan 1987; Lorenz 1988; Segal 2002). One study used iodophor-tmpregnated incise drapes on all patients (Roberts 1995). There was some heterogeneity in the comparisons and the results were pooled for three comparisons; (i)iodophor-in-alcohol film forming antiseptic compared with povidone iodine scrub and paint, (ii) drape compared with no drape and (iii) povidone scrub and paint compared with povidone paint. There was no evidence of a benefit in four trials associated with the use of iodophor impregnated drapes.

- In another study, infection rates were significantly lower when skin was prepared using chlorhexidine compared with iodine. Berry 1982 compared povidone iodine (PI) 10% in alcohol with chlorhexidine 0.5% in spirit (Hibitane) in 371 patients undergoing clean surgery. Significantly more patients (28/176; 15.9%) in the Povidone Iodine group developed an infection compared with the patients cleansed with chlorhexidine (8/195; 4.1%). The odds ratio (OR) was (4.42, 95%CI 1.96 to 9.99).

J. Kalantar-Hormozi, and Babak Davami (2005) did a RCT on patients (905 cases) who were all candidates for certain elective outpatient surgery including excision of nevus, scar revision, Z-plasty, excision of benign cysts and tumors of skin, and dermabrasion.[27 level 1] The patients were randomised into two groups according to their time of admission (even or odd days). The first group took a shower with soap and water 2 hours before surgery, and normal saline was used to prepare the site of operation. No antiseptics or antibiotics were used either preoperatively or postoperatively. On the other hand, the second group also took a preoperative shower with soap and water which was then followed by application of povidone-iodine scrub and then the site of operation was painted with povidone iodine. No antibiotics or antiseptics were used postoperatively. There was no significant statistical difference between the two groups ($p > 0.05$). There was no incidence of wound infection noted in either group after 1-month follow-up. A preoperative surgical scrub or shower with antiseptics may not be an obligation in clean wound surgery. Equal results were obtained with the use of normal saline to prepare the surgical site for operation of certain elective outpatient surgery provided meticulous and careful technique was used.

### 6.1.4 Antiseptic for skin preparations prior to urinary catheterization

There were two randomised control trials comparing the use of water against antiseptics prior to urethral catheterization.

Joan Webster *et al.* (2001) did a randomised control trial to compare urinary colonization rates of subjects whose periurethral area was cleaned with water versus 0.1% chlorhexidine before the insertion of an indwelling urinary catheter. [28 level 1] Obstetric patients who required urinary catheterization as part of their routine care were randomly assigned to either the "water" (n=253) or "chlorhexidine" (n=253) group with an opaque sealed-envelope technique. Computer generated random numbers were used for group allocation. A sterile specimen of urine was collected 24 hours after insertion of the catheter. The microbiologist was blinded to the preparation of the solution used. Urine test results from 70 patients were unavailable (36 from chlorhexidine group and 34 from water group) because the catheter was inadvertently removed before urine sample was collected. The results showed that:

- Out of the 436 patients (86.2%) with complete data, the water treated group was 219 and the antiseptic treated group was 217. Thirty eight (8.7%) had urinary tract bacteriuria >106 cfu/L. Rates of urinary tract infection were similar in each group (water treated group, 8.2% versus antiseptic treated group, 9.2%). The odds ratio (OR) was 1.13 with 95% confidence interval 0.58-2.21.

Sami Al-Farsi *et al.* (2009) did a randomized controlled study to compare urinary infection rate in 186 children cleaned with sterile water versus a 10% povidone-iodine before bladder catheterization. [29 level 1] He did a prospective randomized controlled study of children requiring bladder catheterization in the emergency department whose parents consented to the study. The children were randomly assigned to either of two groups, the "sterile water" treated group or the "10% povidone-iodine" treated group for periurethral cleansing prior to catheterization. The sterile water treated group had 92 children and the povidone-iodine treated group had 94 children. Most children (87%) were under 12 months of age. Urine cultures were positive in 16% of children in the povidone-iodine treated group and in 18% in the water treated group. There was no significant difference in signs and symptoms between the two groups. The study concluded that cleaning the periurethral area of children with sterile water prior to catheterization is not inferior to cleaning with povidone iodine. Hence, the practice of periurethral cleaning with an antiseptic did not decrease the rates of infection in these subjects and is probably not useful.

### 6.1.5 Antiseptic for skin preparation prior to intradermal, subcutaneous, and intramuscular injection

Infection Control Team, Healthcare Associated Infection & Infection Control Section, Health Protection Scotland (formerly Scottish Centre for Infection and Environmental Health (SCIEH) (2005) did a systematic review to assess the evidence in relation to skin disinfection prior to intradermal, subcutaneous, and intramuscular injection administration.[30 level 1] The included studies in the systematic review were of low level of evidence. In this systematic review:

- A research conducted by Koivisto & Felig (1978) on diabetic patients (cross sectional study) indicated that although skin preparation with alcohol prior to injection markedly reduced skin bacterial counts, such disinfection is not necessary to prevent infection at injection sites.
- A cross sectional study conducted by McCarthy, Covarrubias & Sink (1993), also involving diabetic patients, supported the above findings and suggested that, generally, there was insufficient contamination of skin to cause infection following intradermal, subcutaneous, and intramuscular injection.
- The cross sectional study by UK Guidance on Best Practice in Vaccine Administration and the Position Statement on Injection Techniques published by the Royal College of Paediatrics and Child Health (March 2002) further reinforced these views by recommending that no formal skin disinfection is required.
- A review of evidence-based best practices by Hutin and colleagues in relation to the prevention of injection associated infection (in the World Health Organisation Bulletin in 2003) concluded that if the skin is 'clean', swab application on the injection sites whether it be the arm, thigh, stomach or other body part was not necessary.
- Also, comments from the Hospital Infection Society's Discussion Forum (2004) suggested that individuals working in the healthcare setting, likewise, consider skin disinfection prior to injection was not necessary.

Hence, from the systematic review of the studies as mentioned above, there appears to be little evidence at this time to support the need for skin antisepsis prior to intradermal, subcutaneous or intramuscular injection if the skin is unsoiled. If soiled, skin should be cleaned with soap and water. There is no clear evidence for the use of antiseptic (alcohol swabs). If skin is visibly unsoiled and antisepsis is still performed according to decisions taken at local level to undertake this practice, care should be taken to prepare the skin area properly with a pre-medicated 70% alcohol swab. The injection site should be cleaned for 30 seconds with an alcohol swab and allowed to dry for a further 30 seconds to ensure bacteria are rendered inactive.

## 6.2 SAFETY

There was no retrievable evidence on safety and adverse events. Although aqueous or alcoholic (tincture) solutions of iodine have been used for 150 years as antiseptics, there were reports that they are associated with minor irritation and excessive staining.

Based on the limited evidence available to us, 0.5% chlorhexidine in 70% alcohol is the optimal skin preparation prior to epidural procedures. The use of a concentration of chlorhexidine gluconate greater than 0.5% cannot be supported; this concentration is evidently effective, but a greater one might increase the risk of neurotoxicity from inadvertent contamination, and should be avoided. With the introduction of higher concentrations of chlorhexidine solution, there will be more chlorhexidine residue left on the skin after the alcohol has dried. This may be introduced into the cerebrospinal fluid (CSF) on the tip of the spinal or epidural needle causing potential arachnoiditis secondary to chlorhexidine contamination.[31-32]

## 6.3 COST/ COST-EFECTIVENESS

There was no retrievable evidence on cost-effectiveness. Currently in Malaysia, the price of a box of alcohol swab is RM 5.52 per 50 pieces; the price of a bottle of 4% chlorhexidine is RM 8.75 per litre, the price of a bottle of 2% chlorhexidine is RM 2.20 per litre and the price of a bottle of povidone iodine is RM 12.20 per litre. Two percent (2%) Octinidine in alcohol is still not available as an antiseptic in Malaysia.

# 7 CONCLUSION

The evidence retrieved showed that 0.1% Octenidine in alcoholic solution, 70% alcohol, 10% povidone iodine, iodophor in alcohol, 0.25% chlorhexidine gluconate, 0.5% chlorhexidine gluconate in 70% alcohol, 4% chlorhexidine gluconate, 2% chlorhexidine gluconate in 70% alcohol and alcohol spray are antiseptics commonly used for skin preparations prior to procedures.

The review showed there was strong evidence that:

- Two percent (2%) chlorhexidine gluconate resulted in significant reduction in microbial colonization of the central venous catheter insertion site and the catheter tip as well as local site infection. However, 0.1%) Octenidine in alcoholic solution was superior to 74% alcohol in preventing the central venous catheter associated infections.
- Zero point five percent (0.5%) chlorhexidine in 70% alcohol resulted in significant reduction in microbial colonization of the epidural catheter insertion site.
- Two percent (2 %) chlorhexidine gluconate in 70% alcohol resulted in significant microbial reduction of the preparation sites prior to surgery and surgical site infection.
- Cleansing the periurethral area with sterile water was not inferior to cleansing with antiseptics prior to urinary catheterization.

There was evidence to show that the use or no use of antiseptics on unsoiled skin prior to intradermal, subcutaneous and intramuscular injection does not decrease or increase the risk of infection.

## 8 RECOMMENDATION

Based on the above review, the following antiseptics are recommended for use prior to the following procedures:

i) Central venous catheterization:

Two percent (2%) chlorhexidine gluconate in 70% alcohol is the antiseptic of choice prior to central venous catheterization but 0.1% Octenidine in alcoholic solution is potentially beneficial. However, the retrieved evidence shows that 0.1% Octenidine in alcoholic solution was superior to alcohol. More clinical research is warranted.

ii) Epidural catheterization

Zero point five percent (0.5%) chlorhexidine in 70% alcohol is the antiseptic of choice for skin preparation prior to epidural catheterization.

iii) Surgery:

Two percent (2 %) chlorhexidine gluconate in 70% alcohol is potentially superior to 4% chlorhexidine and povidone iodine solution and may be the antiseptic of choice for skin preparation prior to surgery

iv) Urethral catheterization:

The use of either sterile water or antiseptic for skin preparation prior to urethral catheterization is an acceptable practice.

v) Intradermal, subcutaneous, and intramuscular injection

For unsoiled skin, the use or not use of 70% alcohol swab prior to the above procedures can be practised.

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# APPENDIXES

**Appendix 1**

## HIERACHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

## DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

**Appendix 2**
**PTK-FM-2**

# HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL

# ANTISEPTICS FOR SKIN PREPARATIONS PRIOR TO PROCEDURES

## 1. BACKGROUND INFORMATION

According to the definition given by CDC Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008, a germicide is an agent that can kill microorganisms, particularly pathogenic organisms ("germs"). The term *germicide* includes both antiseptics and disinfectants. *Antiseptics* are germicides applied to living tissue and skin; *disinfectants* are antimicrobials applied only to inanimate objects. In general, antiseptics are used only on the skin and not for surface disinfection, and disinfectants are not used for skin antisepsis because they can injure skin and other tissues.

An antiseptic is a substance which inhibits the growth and development of microorganisms. It may be either bacteriocidal or bacteriostatic. Their uses include cleansing of skin and wound surfaces after injury, preparation of skin surfaces prior to injections or surgical procedures, and routine disinfection of the oral cavity as part of a program of oral hygiene. Some commonly used antiseptics for skin cleaning includes chlorhexidine, iodine compounds, and alcohol.

Currently in the Ministry of Health Drug Formulary, the common antiseptics listed are: 70% alcohol; 4% chlorhexidine gluconate scrub; 5% chlorhexidine gluconate solution; 5% chlorhexidine gluconate solution in 70% alcohol; 10% povidone iodine; and 7.5% povidone iodine scrub.

The last fifty years we have witnessed a significant increase in the number of antiseptics as well as their usage in the healthcare environment. When used appropriately antiseptics play an important role in controlling infection and reduce the risk of nosocomial infections.

In view of the new developments in the area of antiseptic, there is a need to update the evidence available to support the use of these antiseptics in the Ministry of Health Malaysia. Thus, this Health Technology Assessment was undertaken to review the antiseptics currently used for skin preparations especially prior to procedures such as surgery, central venous catheterization, epidural catheterization, urinary catheterization, intradermal, subcutaneous, and intramuscular injection which will help healthcare providers to identify the best intervention strategies in preventing and controlling infections in healthcare settings.

## 2. POLICY QUESTION

In Ministry of Health hospitals, what are the most appropriate antiseptics to be used for skin preparations prior to five procedures commonly performed in clinical practice such as central venous catheterization, epidural procedure, surgery, urinary catheterization, and parenteral injection?

## 3. OBJECTIVE

To assess the safety, effectiveness, efficacy and cost-effectiveness of antiseptics for skin preparations prior to five procedures commonly performed in clinical practice.

## 4. METHODOLOGY

### 4.1 Search Strategy

Electronic database will be searched for published literatures pertaining to disinfectants currently available in the Ministry of Health The following sources will be searched:

i. Databases as follows MEDLINE, Pubmed, EBM Reviews – Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, HTA Database EBM Reviews – NHS Economic Evaluation Database, EBM Full Text- Cochrane DSR, ACP journal Club and DARE.

ii. Google was used to search as additional web-based information

iii. Additional articles will be identified from reviewing the bibliographies of retrieved articles.

### 4.2 Inclusion and exclusion criteria

Based on the policy question the following inclusion and exclusion criteria were used:-

#### Inclusion criteria

i. Study design: systematic review, randomised controlled trials and non-randomised controlled trials

ii. Population: patients and healthcare personnel

iii. Setting: healthcare setting

iv. Intervention: antiseptics for skin preparations

v. Outcomes:
Reduction in infection rate (surgical site infection, bloodstream infection etc), bacterial colony counts, adverse events

### Exclusion criteria

Articles for antisepsis or disinfectant on mucosal surfaces such as oral cavities and dental preparations were excluded.

Based on these inclusion criteria, study selection will be carried out independently by two reviewers. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persists after discussion.

## 4.3 Data extraction strategy

The following data will be extracted:

- Details of methods and study population characteristics
- Details of intervention and comparator
- Details of individual outcomes for effectiveness, safety, cost effectiveness

Data will be extracted from included studies by a reviewer using a pre-defined data extraction form and checked by another reviewer. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persists after discussion.

## 4.4 Quality assessment strategy

The methodological quality of all relevant articles will be assessed by using Critical Appraisal Skills Programme (CASP) depending on the type of study design. Quality assessment will be conducted by a reviewer and checked by a second

## 4.5 Methods of analysis / synthesis

Data on clinical effectiveness, safety, and cost effectiveness will be presented in tabulated format with narrative summaries. A decision on whether to pool efficacy, safety and accuracy outcomes will be taken following the updated search and based on clinical and statistical heterogeneity and the range of outcome measures reported. Data will be pooled using fixed model unless statistical heterogeneity between studies is found, in which case random effect model will be used.

# 5. Report writing

## Appendix 3

### Evidence Table : Effectiveness / efficacy of antiseptics for skin preparations prior to procedures

### Question : Are the use of antiseptics for skin preparations prior to central venous catheterization procedures effective?

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| **Bibliographic Citation** | 1). Dettenkofer M, Wilson C, Gratwohl A. et al. Skin disinfection with octenidine dihydrochloride for central venous catheter site care: a double-blind, randomized, controlled trial. Clin Microbiol Infect Diseases. 2009 10.1111/j.1469-0691.2009.02917.x |
| **Study Type / Methodology** | Randomised controlled trial.<br><br>To compare the efficacy of two commercially available, alcohol-based antiseptic solutions for preparation and care of central venous catheter (CVC) insertion sites, with and without octenidine dihydrochloride, a double-blind, randomized, controlled trial was undertaken in the haematology units and in one surgical unit of two university hospitals.<br><br>The study was carried out from 2002 through 2005 in the haematology units of University Medical Center Freiburg (FR; Freiburg, Germany) and University Hospital Basel (BS; Basel, Switzerland) and in one surgical unit (BS). Both institutions are tertiary care facilities. The study was approved by both local ethics committees and entered into the clinical trials registry of the University Medical Center |
| **LE** | I |
| **Number of patients and patient characteristics** | Adult patients with a non-tunnelled CVC were randomly assigned to two different skin disinfection regimens at the insertion site. |
| **Intervention** | 0.1% octenidine with 30% 1-propanol and 45% 2-propanol |
| **Comparison** | 74% ethanol with 10% 2-propanol |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Endpoints were (i) skin colonization at the insertion site; (ii) positive culture from the catheter tip (≥15 CFU); and (iii) occurrence of CVC-associated bloodstream infection (defined according to criteria set by the CDC). Four hundred patients with inserted CVC were enrolled from May 2002 through April 2005. Both groups were similar in respect of patient characteristics and co-morbidities.<br><br>Skin colonization at the CVC insertion site during the first 10 days was significantly reduced by octenidine treatment (relative difference octenidine vs. control: 0.21; 95%CI: 0.11–0.39, p <0.0001).<br><br>Positive culture of the catheter tip was signi.cantly less frequent in the octenidine group (7.9%) than in the control group (17.8%): OR = 0.39 (95%CI: 0.20–0.80, p 0.009).<br><br>Patients treated with octenidine had a non-significant reduction in catheter-associated bloodstream infections (4.1% vs. 8.3%; OR = 0.44; 95%CI: 0.18–1.08, p 0.081). Side effects were similar in both groups.<br><br>This study demonstrate octenidine in alcoholic solution to be better than alcohol alone for prevention of CVC associated infections. |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to central venous catheterization procedures effective?**

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| **Bibliographic Citation** | 2. Dettenkofer M., Jonas D., Wiechmann C. et al. Effect of Skin Disinfection with Octenidine Dihydrochloride on Insertion Site Colonization of Intravascular Catheters. Infection.2002; 30: 282-285 |
| **Study Type / Methodology** | Clinical trial<br>This prospective study was carried out from October 1999 to February 2000 at the Neurosurgery Department of Freiburg University Hospital, Germany.<br>Inpatients receiving either a central venous catheter (CVC) or a peripherally inserted central catheter (PICC) were alternately assigned to different skin disinfection regimens at the insertion site: (A) 0.1% octenidine dihydrochloride with 30% 1-propanol and 45% 2propanol, (B) 74% ethanol with 10% 2-propanol. Quantitative skin cultures were obtained from the insertion site at predetermined intervals. |
| **LE** | II-I |
| **Number of patients and patient characteristics** | Adult inpatients that required catheterization with either a non-tunneled central venous catheter (CVC) or a peripherally inserted central catheter (PICC) prior to neurosurgery.<br>Before catheterization, the entry site was disinfected with the assigned solution on an area > 200 cm2 for at least 1 min. After insertion, which was performed according to a standard written protocol, the catheter was dressed uniformly with sterile gauze. |
| **Intervention** | 0.1% octenidine dihydrochloride with 30% 1-propanol and 45% 2propanol, |
| **Comparison** | 74% ethanol with 10% 2-propanol. |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Three sets of quantitative skin cultures were obtained from each patient from a 6 x 4 cm area of skin around the catheter insertion site (24 $cm^{2.}$ Skin cultures were obtained: (1) before, (2) immediately following and (3) 24 h after insertion. A sterile, moistened cotton applicator was swabbed across the 6 x 4 cm area in a back-and-forth manner, (ten strokes each from top to bottom and from left to right). The applicator was then placed in a tube containing 1.0 ml of 0.01 M PBS and taken to the microbiology laboratory. After vortex mixing and diluting (1:10 in case of skin cultures (1) and (3), respectively), three aliquots of 0.1 ml of the suspension and of the dilution were plated onto blood agar petri dishes. Colonies were counted after incubation at 35 °C for 48 h.<br><br>The number of cfu per area sampled was determined by taking the mean of the three petri dishes. If the catheter dressing had to be removed for clinical reasons prior to skin culture (3), the patient was excluded from the study. To detect a difference in the efficacy of skin decontamination between groups A and B, the results of the quantitative skin culture sets (and the differences between sets) were compared using the Wilcoxon rank sum test.<br><br>A total of 60 patients received 13 CVCs and 47 PICCs (no significant difference with respect to gender, age and catheter type). In total, 90 cultures were assessed in each group. The median colony-forming unit (cfu) counts per 24 $cm^2$ (group A vs B) were 2,270 vs 2,950 before, 20 vs 40 following and 860 vs 1,210 24 h after catheter insertion, respectively. A statistically significant difference in the efficacy of skin decontamination was seen between groups in culture set (3) and in the difference between culture sets<br>(2) and (3) (Wilcoxon rank sum test).<br><br>Octenidine/propanol appears to be more effective than alcohol (ethanol/propanol) alone in reducing microflora of the skin at the PICC/CVC insertion site over a 24-h period. |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to central venous catheterization procedures effective?**

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| **Bibliographic Citation** | 3) Mimoz O, Villeminey S, Ragot S et al. Chlorhexidine-Based Antiseptic Solution versus Alcohol-Based Povidone-Iodine for Central Venous Catheter Care. Arch Intern Med. 2007;167(19):2066-2072 |
| **Study Type / Methodology** | The trial was conducted from May 14, 2004, through June 29, 2006, at a surgical ICU of a university-affiliated hospital. All consecutively scheduled nontunneled central venous catheters expected to remain in place for 3 or more days were eligible for the study.<br><br>Consecutively scheduled central venous catheters inserted into jugular or subclavian veins were randomly assigned to be disinfected with 5% povidone-iodine in 70% ethanol or with a combination of 0.25% chlorhexidine gluconate, 0.025% benzalkonium chloride, and 4% benzylic alcohol. Solutions were used for skin disinfection before catheter insertion (2 consecutive 30-second applications separated by a period sufficiently long to allow for dryness) and then as single applications during subsequent dressing changes (every 72 hours, or earlier if soiled or wet). |
| **LE** | I |
| **Number of patients and patient characteristics** | All consecutively scheduled nontunneled central venous catheters expected to remain in place for 3 or more days were eligible for the study.<br>A total of 538 catheters were randomised to the 2 antiseptic groups. |
| **Intervention** | A combination of 0.25% chlorhexidine gluconate, 0.025% benzalkonium chloride, and 4% benzylic alcohol. |
| **Comparison** | 5% povidone-iodine in 70% ethanol |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Results:<br>Of 538 catheters randomized, 481 (89.4%) produced evaluable culture results.<br>Compared with povidone-iodine, the chlorhexidine-based solution was associated with a 50% decrease in the incidence of catheter colonization (11.6% vs 22.2% [P=0.002]; incidence density, 9.7 vs 18.3 per 1000 catheter-days) and with a trend toward lower rates of catheter-related bloodstream infection (1.7% vs 4.2% [P=0.09]; incidence density, 1.4 vs 3.4 per 1000 catheter-days).<br><br>Independent risk factors for catheter colonization were catheter insertion into the jugular vein (adjusted relative risk, 2.01; 95% confidence interval, 1.243.24) and use of povidone-iodine (adjusted relative risk, 1.87; 95% confidence interval, 1.18-2.96).<br><br>Chlorhexidine-based solutions should be considered as a replacement for povidone-iodine (including alcohol-based) formulations in efforts to prevent catheter-related infection. |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to central venous catheterization procedures effective?**

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| **Bibliographic Citation** | 4) Carson SM. Chlorhexidine versus Povidone-Iodine for Central Venous Catheter Site Care in Children. Journal of Pediatric Nursing.2004: 19 (1) |
| **Study Type / Methodology** | Systematic review<br>FOCUSED CLINICAL QUESTION<br><br>In hospitalized children, is chlorhexidine gluconate a more effective antiseptic solution than Povidone-iodine in preventing CVC-related site infections and bacteremias?<br><br>Electronic literature searches were conducted for research evidence. Hand literature,searches were also conducted. Search for best clinical practice evidence was done from The websites from the National Institutes for Health, the Centers for Disease Control and Development, (CDC), and the National Guide Clearinghouse. |
| **LE** | I |
| **Number of patients and patient characteristics** | |
| **Intervention** | |
| **Comparison** | |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Most studies reviewed were true experimental designs with randomized, controlled trials (Garland et al., 2001; Hanazaki et al., 1999; Humar et al., 2000; Kinirons et al., 2001; Maki & Ringer, 1991; Mimoz et al., 1996). Frieberger et al. (1992) used a quasi-experimental research design, and Garland et al. (1995) conducted a nonrandomized clinical trial.<br><br>Most studies found chlorhexidine to be superior to povidone-iodine for preventing microbial colonization of the CVC insertion site and the catheter tip, and for decreasing the risk of local site infection. Based on the evidence presented here, chlorhexidine gluconate appears to be a safe and effective solution for CVC site care in older infants and children. Because of the findings by Garland et al. (1995, 2001), which state that chlorhexidine can cause severe local contact dermatitis in low-birthweight infants, further study is necessary before practice changes can be made for low-birth-weight infants or infants born at less than 37 weeks gestation |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to central venous catheterization procedures effective?**

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| **Bibliographic Citation** | 5) Langgartner J, Linde, Lehn N et al. Combined skin disinfection with chlorhexidine/ propanol and aqueous povidone-iodine reduces bacterial colonisation of central venous catheters. Intensive Care Med. 2004; 30:1081-1888 |
| **Study Type / Methodology** | The prospective, randomised study was conducted from May, 1999, to August, 2002, at the Medical Centre of the University of Regensburg, Germany.<br><br>At the time of insertion, each catheter was randomised to one of three disinfection regimens:<br>1. povidone-iodine 10% aqueous solution for 1 min<br>2. propanol 70%/chlorhexidine 0.5% for 1 min<br>3. propanol 70%/chlorhexidine 0.5% for 1 min followed by PVP-iodine 10% (Betaisodona) disinfection for 1 min<br><br>One hundred nineteen patients scheduled electively to receive 140 CVCs. |
| **LE** | I |
| **Number of patients and patient characteristics** | One hundred nineteen Adult in-patients scheduled for elective CVC placement (140 CVC's) during normal working hours were eligible for participation in the study. Patients from normal wards as well as from the intensive care units were included |
| **Intervention** | |
| **Comparison** | |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Bacteria could be isolated from 20.7% of the catheter tips Bacterial growth was found in 30.8% of the catheters placed after skin disinfection with povidone-iodine, in 24.4% after disinfection with propanol/ chlorhexidine and in 4.7% after disinfection with propanol/chlorhexidine followed by povidone-iodine (p=0.006). In 15 cases, the same organism was isolated from the skin swab and the catheter tip. Ten of these paired isolates showed the same pattern in a pulsed-field gel electrophoresis analysis.<br><br>Skin disinfection with propanol/chlorhexidine<br>followed by PVP-iodine was superior in the prevention of microbial CVC colonisation compared to either of the regimens alone. These results support the concept that catheter infections can originate from bacterial translocation at the time of catheter insertion. |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to central venous catheterization procedures effective?**

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| **Bibliographic Citation** | 6) Balamongkhon B, Thamlikitkul V. Implementation of chlorhexidine; gluconate for central venous catheter site care at Siriraj Hospital, Bangkok, Thailand. Am J Infect Control. 2007;35: 585-588.8. |
| **Study Type / Methodology** | The objective of the study was to implement locally formulated chlorhexidine gluconate for central venous catheter (CVC) site care in intensive care units (ICUs) at Siriraj Hospital. Methods:<br><br>The study was conducted in 312 subjects who needed CVC insertions in 3 ICUs from January to July 2006. One hundred twenty subjects received 2% chlorhexidine gluconate in 70% alcohol, whereas 192 subjects received 10% povidone-iodine as the antiseptic solution for CVC site care. The patients were assessed for CVC-related infections and for any adverse effects of 2% chlorhexidine gluconate in 70% alcohol. (Since Chlorhexidine solution for use as skin antisepsis for CVC site care is not available in Thailand. Therefore, the Pharmacy Department was asked to formulate 2% chlorhexidine gluconate in 70% alcohol for CVC site care. |
| **LE** | I |
| **Number of patients and patient characteristics** | The study sites were a medical ICU and 2 surgical ICUs. The study was conducted during January to July 2006. The study subjects were adult patients hospitalized at 3 study ICUs who needed CVC insertion. |
| **Intervention** | 2% chlorhexidine gluconate in 70% alcohol,<br>(The formulation was made by diluting 20% chlorhexidine gluconate and 95% ethyl alcohol in puri.ed water to achieve 2% chlorhexidine gluconate in 70% alcohol. The solution was found to contain good antimicrobial activity up to 6 months after production.) |
| **Comparison** | 10% povidone-iodine as the antiseptic solution |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Results:<br>The incidence of catheter-related bloodstream infections (CRBSIs) in the indwelling CVC subjects who received 2% chlorhexidine gluconate in 70% alcohol was less than those who received 10% povidone-iodine during the same period, 3.2 versus 5.6 episodes per 1000 CVC days, respectively (P 0 .06; OR, 3.26; 95% CI: 0.97-10.92). No adverse effects related to using 2% chlorhexidine gluconate in 70% alcohol were observed.<br><br>The locally formulated 2% chlorhexidine gluconate in 70% alcohol was safe, effective, and efficient for CVC site care in ICUs at Siriraj Hospital. |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to central venous catheterization procedures effective?**

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| **Bibliographic Citation** | 7) Ramritu P, Halton K, Cook D et al. Catheter-related bloodstream infections in intensive care units: a systematic review with meta-analysis. Journal of Advanced Nursing. 2007; 62(1): 3–21 |
| **Study Type / Methodology** | Aim: This paper is a report of a systematic review and meta-analysis of strategies, other than antimicrobial coated catheters, hypothesized to reduce risk of catheter-related bloodstream infections and catheter colonization in the intensive care unit setting.<br><br>A systematic review of studies published between January 1985 and February 2007 was carried out using the keywords 'catheterization – central venous' with combinations of infection*, prevention* and bloodstream*. All included studies were screened by two reviewers, a validated data extraction instrument was used and data collection was completed by two blinded independent reviewers. Risk ratios for catheter-related bloodstream infections and catheter colonization were estimated with 95% CI for each study. Results from studies of similar interventions were pooled using meta-analyses. |
| **LE** | I |
| **Number of patients and patient characteristics** | |
| **Intervention** | |
| **Comparison** | |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Results :<br>Twenty-three studies were included in the review. The strategies that reduced catheter colonization included insertion of central venous catheters in the subclavian vein rather than other sites, use of alternate skin disinfection solutions before catheter insertion and use of Vitacuff in combination with polymyxin, neomycin and bacitracin ointment. Strategies to reduce catheter-related bloodstream infection included staff education multifaceted infection control programmes and performance feedback.<br><br>Three studies compared different types of skin disinfectants. One RCT (Maki et al. 1991) compared 2% aqueous chlorhexidine (Chl) gluconate to 10% povidone iodine (PI) and 70% isopropyl alcohol. The 2% aqueous Chl solution compared to 10% PI reduced colonization by 69% (RR 0.31; 95% CI: 0.17-0.88; P =0.01) but there was no statistically significant reduction for CRBSI (RR 0.23;95% CI 0.03-1.92; P = 0.14) Compared to alcohol 70% solution the 2% chlorhexidine showed no statitistically significant difference in colonization (RR 0.38;95% CI 0.11-1.33 P=0.11)or CRBSI rates (RR 0.24; 95% CI 0.02-2.54 P=0.24). Another RCT (Humar et al 2000) compared 10% PI with 0.5% tinc Chlorhexidine and found no diffence in rates of colonization or CRBSI (RR0.8; 95% CI 0.52-1.26;P=0.22; RR 1.07; 95% CI 0.27-4.17; P=0.6 respectively). The third study (Parieti et al 2004) used a cross-over RCT to compare 10% aqueous PI with 5% PI in 70% ethanol. Colonization rates were significantly lower for alcoholic PI (RR0.38; 95% CI 0.22-0.65;P<0.001) but there was no significant difference in CRBSI rate (RR 0.3; 95% CI: 0.03-2.4;P=0.21) |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to epidural catheterization procedures effective?**

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| **Bibliographic Citation** | 1 Robinson SJ. A systematic review of effectiveness of disinfectants on skin preparation and dressings in patients receiving epidural analgesia. Acute Pain. 2005; 7:177-183 |
| **Study Type / Methodology** | Systematic Review<br>Objective of the study was to summarize what is known regarding the effectiveness of disinfectants on skin preparation and dressings in patients receiving epidural analgesia.<br><br>Methods: A systematic review of nine reports of trials was completed to examine the efficacy of disinfectants in patients with epidural analgesia.<br><br>These reports included randomized controlled trials and clinical trials. |
| **LE** | I |
| **Number of patients and patient characteristics** | Systematic review of randomized controlled trials (RCT) and clinical trials included both pediatric and adult populations undergoing epidural analgesia foe a surgical procedure. |
| **Intervention** | |
| **Comparison** | |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Results:<br>Findings indicated that chlorhexidine has been proven to be just as, if not more effective than povidone iodine in reducing microbial colonization of epidural catheters when utilized as a skin disinfectant [Kinirons B, Mimoz O, Lafendi L, Naas T, Meunier J, Nordmann P. Chlorhexidine versus povidone iodine in preventing colonization of continuous epidural catheters in children: a randomized, controlled trial. Anesthesiology 2001;94(2):239—44; Sato S, Sakuragi T, Dan K. Human skin as a potential source of epidural abscess. Anesthesiology 1996;85(6):1276—82; Sakuragi T, Higa K, Dan K, Okubo M. Skin floras on the human back and disinfection with alcoholic chlorhexidine, povidone iodine, and ethyl alcohol. Pain Clin1986/1987;1(3):183-8]<br><br>Moreover, when used in impregnated dressings, it may further reduce microbial colonization of epidural catheters [Mann T, Orlikowski C, Gurrin L, Keil, A. The effect of the biopatch, a chlorhexidine impregnated dressing, on bacterial colonization of epidural catheter exit sites. Anaesth Intensive Care 2001;29(6):600—3; Shapiro J, Bond E, Garman K. Use of a chlorhexidine dressing to reduce microbial colonization of epidural catheters. Anesthesiology 1990;73:625—31].<br><br>Chlorhexidine could be considered the cutaneous antiseptic of choice prior to epidural insertion, |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to epidural catheterization procedures effective?**

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| **Bibliographic Citation** | 2) Birnbach DJ, Meadows W, Stein DJ. et al. Comparison of Povidone Iodine and DuraPrep, an Iodophor-in-Isopropyl Alcohol Solution, for Skin Disinfection Prior to Epidural Catheter Insertion in Parturients. Anesthesiology. 2003; 98:164–169 |
| **Study Type / Methodology** | Randomised control trial.<br>Sixty women in active labor who requested epidural analgesia were randomly assigned to receive skin preparation with either PI or DuraPrep solution. A total of three cultures were obtained from each subject. The first was obtained just prior to skin disinfection, the second was obtained immediately following antisepsis, and the third was obtained just before removal of the catheter. In addition, the distal tip of the catheter was also submitted for culture. |
| **LE** | I |
| **Number of patients and patient characteristics** | Sixty women with American Society of Anesthesiologists physical status I or II in active labor and requesting labor analgesia were enrolled and randomly assigned via an envelope system to undergo skin decontamination prior to epidural anesthesia with either 10% PI or DuraPrep. |
| **Intervention** | (DuraPrep) which contains an iodophor in isopropyl alcohol |
| **Comparison** | povidone iodine (PI). |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Results:<br>The clinical characteristics and the risk factors for infection were similar in the two groups.<br><br>The proportion of subjects with positive skin cultures immediately after skin disinfection differed significantly between the PI and DuraPrep groups (30 vs. 3%, respectively, P= 0.01). The number of subjects with any positive skin cultures at the time of catheter removal was greater in the PI group as compared to the Dura- Prep group (97 vs. 50%, respectively, P= 0.0001), as was the number of organisms cultured from skin (log CFU 1.93± 0.40 vs. 0.90± 0.23, respectively, P= 0.03). Six catheters, all from the PI group, yielded positive cultures by the roll-plate technique. Conclusion: As compared to PI, DuraPrep solution was found to provide a greater decrease in the number of positive skin cultures immediately after disinfection, as well as in bacterial regrowth and colonization of the epidural catheters |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to surgery effective?**

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| **Bibliographic Citation** | 1) Edmiston CE, Seabrook GR, Johnson CP et al. Comparative of a new and innovative 2% chlorhexidine gluconate-impregnated cloth with 4% chlorhexidine gluconate as topical antiseptic for reparation of the skin prior to surgery. Am J Infect Control. 2007; 35:89-96. |
| **Study Type / Methodology** | Randomised control trial.<br><br>Decreasing the microbial skin burden reduces the risk of surgical site infection (SSI). This study compares the activity of an innovative 2% chlorhexidine gluconate (CHG)-impregnated preoperative skin preparation cloth (PC) with a standard application procedure with a 4% CHG surgical skin preparation (SP).<br><br>A paired, randomized, parallel phase III study was conducted Subjects' left and right sides of the inguinal and abdominal skin sites (n = 30) were randomized to either PC or SP treatment. Following baseline cultures, PC sites were prepped for 3 minutes, and SP sites were prepped for 4 minutes. Skin site cultures were obtained at 10 minutes, 30 minutes, and 6 hours post preparation. Bacterial recovery was expressed as log10 colony-forming units (cfu)/cm2 for baseline and post application microbial recovery. |
| **LE** | I |
| **Number of patients and patient characteristics** | Thirty overtly healthy volunteer subjects completed the protocol, and their collected sample data were used in the analysis of the study. |
| **Intervention** | 2 % chlorhexidine gluconate (CHG)-impregnated preoperative skin preparation cloth (PC) |
| **Comparison** | a standard application procedure with a 4% CHG surgical skin preparation (SP). |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Results:<br>Mean microbial baseline for the abdominal and inguinal skin sites were as follows: PC = 3.36 cfu/$cm^2$ and 6.15 cfu/$cm^2$; SP = 3.51 cfu/$cm^2$ and 6.16 cfu/$cm^2$, respectively.<br><br>Mean microbial baseline for the abdominal and inguinal skin sites were as follows: PC= 3.36 cfu/cm2 and 6.15 cfu/cm2; SP = 3.51 cfu/cm2 and 6.16 cfu/cm2, respectively. Log10 reduction for PC abdominal and inguinal prepped sites at 10 minutes, 30minutes, and 6 hours postpreparation were 2.50, 2.33, and 2.54; 3.45, 3.50, and 3.64, respectively. Log10 reductions for SP abdominal and inguinal prepped sites at 10 minutes, 30 minutes, and 6 hours were 2.18, 2.19, and 2.77; 2.78, 2.63, and 3.15, respectively.<br><br>Microbial reductions from abdominal-inguinal PC prepped sites were significantly reduced ($P<0.05$) compared with baseline, exceeding the FDA log-reduction criteria for a preoperative topical skin preparation. Compared with baseline, microbial reductions at the SP-prepped abdominal-inguinal sites were significant ($P<0.05$). SP abdominal-prepped sites met the FDA log-reduction criteria; inguinal sites, however, failed to meet expected FDA log-reduction criteria at 10 minutes postpreparation. The PC-treated inguinal sites at 10 minutes, 30 minutes, and 6 hours post-skin preparation demonstrated significantly greater microbial reductions than did the SP-treated inguinal sites ($P<0.01$). |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to surgery effective?**

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| **Bibliographic Citation** | 2) Saltzman MD, Nuber GW, Gryzlo SM et al. Efficacy of Surgical Preparation Solutions in Shoulder Surgery. J Bone Joint Surg Am.2009; 91:1949-53 |
| **Study Type / Methodology** | Prospective study RCT<br>Between September 2007 and February 2008, 150 consecutive patients undergoing shoulder surgery were enrolled in the present prospective randomized study.<br><br>Each shoulder was prepared with one of three randomly selected solutions: ChloraPrep (2% chlorhexidine gluconate and 70% isopropyl alcohol), DuraPrep (0.7% iodophor and 74% isopropyl alcohol), or povidone-iodine scrub and paint (0.75% iodine scrub and 1.0% iodine paint). Aerobic and anaerobic cultures were obtained prior to skin preparation for the first twenty patients, to determine the native bacteria around the shoulder, and following skin preparation for all patients. |
| **LE** | I |
| **Number of patients and patient characteristics** | All procedures were performed at one institution by one of three surgeons (J.L.K., G.W.N., and S.M.G.). One hundred and thirty-seven of the 150 procedures were done entirely arthroscopically. Four of the patients had shoulder arthroplasties, none of which were revision in nature. Institutional review board approval was obtained, and every patient gave informed consent to participate in the study. |
| **Intervention** | |
| **Comparison** | |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Coagulase-negative Staphylococcus and Propionibacterium acnes were the most commonly isolated organisms prior to skin preparation.<br><br>The overall rate of positive cultures was 31% in the povidone-iodine group, 19% in the DuraPrep group, and 7% in the ChloraPrep group. The positive culture rate for the ChloraPrep group was lower than that for the povidone-iodine group ($p < 0.0001$) and the DuraPrep group ($p = 0.01$).<br><br>ChloraPrep and DuraPrep were more effective than povidone-iodine in eliminating coagulase-negative Staphylococcus from the shoulder region ($p < 0.001$ for both). No significant difference was detected among the agents in their ability to eliminate Propionibacterium acnes from the shoulder region. No infections occurred in any of the patients treated in this study at a minimum of ten months of follow-up.<br><br>ChloraPrep is more effective than DuraPrep and povidone-iodine at eliminating overall bacteria from the shoulder region. Both ChloraPrep (2% chlorhexidine gluconate and 70% isopropyl alcohol), and DuraPrep (0.7% iodophor and 74% isopropyl alcohol), are more effective than povidone-iodine at eliminating coagulase-negative Staphylococcus from the shoulder. |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to surgery effective?**

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| **Bibliographic Citation** | 3) Darouiche R et al. Chlorhexidine Chlorhexidine–Alcohol versus Povidone–Iodine for Surgical-Site Antisepsis. N Engl J Med. 2010; 362:18-26. |
| **Study Type / Methodology** | RCT<br>randomly assigned adults undergoing clean-contaminated surgery in six hospitals to preoperative skin preparation with either chlorhexidine–alcohol scrub or povidone–iodine scrub and paint. The primary outcome was any surgical-site infection within 30 days after surgery. Secondary outcomes included individual types of surgical-site infections. |
| **LE** | I |
| **Number of patients and patient characteristics** | |
| **Intervention** | 2% chlorhexidine gluconate and 70% isopropyl alcohol (ChloraPrep, |
| **Comparison** | aqueous solution of 10% povidone–iodine |
| **Length of follow up** | 30 days after surgery |
| **Outcome measures / Effect size** | A total of 849 subjects (409 in the chlorhexidine–alcohol group and 440 in the povidone–iodine group) qualified for the intention-to-treat analysis. The overall rate of surgical-site infection was significantly lower in the chlorhexidine–alcohol group than in the povidone–iodine group (9.5% vs. 16.1%; P = 0.004; relative risk, 0.59; 95% confidence interval, 0.41 to 0.85). Chlorhexidine–alcohol was significantly more protective than povidone–iodine against both superficial incisional infections (4.2% vs. 8.6%, P = 0.008) and deep incisional infections (1% vs. 3%, P = 0.05) but not against organ-space infections (4.4% vs. 4.5%). Similar results were observed in the per-protocol analysis of the 813 patients who remained in the study during the 30-day follow-up period.<br><br>Preoperative cleansing of the patient's skin with chlorhexidine–alcohol is superiorto cleansing with povidone–iodine for preventing surgical-site infection after cleancontaminated surgery. |
| **General Comments** | |

**Question : Are the use of antiseptics for skin preparations prior to surgery effective?**

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| **Bibliographic Citation** | 4) Edwards P, Lipp A, Holmes A. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. Cochrane Database of Systematic Reviews. 2009, Issue 3. Art. No.: CD003949. DOI: 10.1002/14651858.CD003949. |
| **Study Type / Methodology** | Systematic review: The aim was to determine whether preoperative skin antisepsis prevents post-operative surgical wound infection.<br><br>Search strategy : For the update of this review the author searched the CochraneWounds Group Specialised Trials Register(July2008); the Cochrane Central Register of Controlled Trials (CENTRAL), Issue 3 2008; Ovid MEDLINE, 2005 to July Week 3 2008;Ovid EMBASE, 2005 to 2008 Week 29 and Ovid CINAHL, 2005 to July Week 3 2008.<br><br>Selection criteria : Randomised controlled trials evaluating the use of preoperative skin antiseptics applied immediately prior to incision in clean surgery. There was no restriction on the inclusion of reports based on language of publication, date or publication status. |
| **LE** | I |
| **Number of patients and patient characteristics** | |
| **Intervention** | |
| **Comparison** | |
| **Length of follow up** | |
| **Outcome measures / Effect size** | For this first update the author identified one additional trial resulting in seven eligible RCTs evaluating preoperative antiseptics. There was some heterogeneity in the comparisons and the results were pooled for three comparisons; iodophor-in-alcohol .film forming antiseptic compared with povidone iodine scrub and paint, drape compared with no drape and povidone scrub and paint compared with povidone paint. In one study, infection rates were significantly lower when skin was prepared using chlorhexidine compared with iodine. There was no evidence of benefit trials associated with the use of iodophor impregnated drapes.<br><br>There was insufficient research examining the effects of preoperative skin antiseptics to allow conclusions to be drawn regarding their effects on post-operative surgical wound infections. Further research is needed.<br><br>There is insufficient evidence from randomised trials to support or refute the use of one antiseptic over another. There is no evidence to show that iodophor impregnated incise drapes reduce infections when compared to using no incise drape. Patients' skin at the operation site is routinely cleaned with antiseptic solutions before surgery. One study found that there were fewer surgical site infections when the skin was prepared using chlorhexidine in comparison with preparation using iodine. |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to surgery effective?**

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| **Bibliographic Citation** | 5) Kalantar-Hormozi A. J, Davami B. Need for Preoperative Antiseptics in Elective Outpatient Plastic Surgical Operations: A Prospective Study. Plast. Reconstr. Surg. 2005;116:529 |
| **Study Type / Methodology** | Randomised control trial:<br><br>All of the operations were performed in only one hospital (15 Khordad Hospital). All the procedures and preoperative and postoperative care were performed by a single team. In both groups, tissues were handled gently and meticulously.<br>Follow-up was performed as visits on a regular basis weekly up to a month in both groups |
| **LE** | I |
| **Number of patients and patient characteristics** | The patients (905 cases) were all candidates for elective outpatient surgery, including excision of nevus, scar revision, Z-plasty, excision of benign cysts and tumors of skin, and dermabrasion. The patients were randomised into two groups according to their time of admission (even or odd days). |
| **Intervention** | The first group took a shower with soap and water 2 hours before surgery, and we used normal saline irrigation to prepare the site of operation. No antiseptics or antibiotics were used either preoperatively or postoperatively. |
| **Comparison** | The second group also took a preoperative shower with soap and water. We used povidone-iodine to scrub and then paint the site of operation. No antibiotics or antiseptics were used postoperatively. |
| **Length of follow up** | There was no significant statistical difference between the two groups (p=0. 0.05). There was no incidence of wound infection noted in either group after 1-month follow-up.<br><br>Preoperative showering with chlorhexidine gluconate, Betadine, or medicated bar soaps is routinely practiced to reduce skin colonization at the site of surgical incision. Antiseptics have the potential to cause corneal toxicity and have adverse effects on cultures of fibroblasts and keratinocytes.Although preoperative cleansing with povidone-iodine surgical scrub followed by povidone-iodine antiseptic solution is an effective, nonirritating bactericide regimen for use at surgical incision sites, it has been shown that this agent significantly reduces wound strength. In this postoperative surveillance of 905 patients with elective outpatient clean wound surgery, betadine, chlorhexidine, or medicated soap as a preoperative shower or as a surgical scrub was not used and the study showed no incidence of wound infection. The patients were advised to take a shower with soap and water and prepared the site of surgery with normal saline.<br><br>A preoperative surgical scrub or shower with antiseptics is not an obligation in clean wound surgery; equal results can be obtained with the use of normal saline to prepare the surgical site for operation if meticulous and careful technique is used. |
| **Outcome measures / Effect size** | |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to urinary catheterization effective?**

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| **Bibliographic Citation** | 1) Joan Webster, Webster J,Hood RH , Christine A et al. Water or antiseptic for periurethral cleaning before urinary catheterization: A randomized controlled trial. Am J Infect Control. 2001; 29:389-94. |
| **Study Type / Methodology** | Randomised control trial:<br>The purpose of this study was to compare urinary colonization rates of subjects whose periurethral area was cleaned with water versus chlorhexidine 0.1% before the insertion of an indwelling urinary catheter.<br><br>Methods: Obstetric patients who required urinary catheterization as part of their routine care were randomly assigned to either the “water” or “chlorhexidine” group with a sealed envelope. A sterile specimen of urine was collected 24 hours after insertion of the catheter. |
| **LE** | I |
| **Number of patients and patient characteristics** | The sample was drawn from pregnant women admitted for delivery at the Royal Women’s Hospital (RWH), Brisbane between October 1999 and April 2000. The only criterion for enrollment was that an indwelling catheter be a required part of routine management |
| **Intervention** | Water |
| **Comparison** | chlorhexidine 0.1% |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Results:<br>Of the 436 patients (86.2%) with complete data (water group, 219; antiseptic group, 217), 38 (8.7%) had urinary tract bacteriuria >106 cfu/L. Rates of urinary tract infection were similar in each group (water group, 8.2%; antiseptic group, 9.2%; odds ratio 1.13; 95% confidence interval 0.58-2.21).<br><br>The practice of periurethral cleaning with an antiseptic did not decrease the rates of bacteriuria in this population and is probably not useful |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to urinary catheterization effective?**

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| **Bibliographic Citation** | 2) Al-Farsi S, Oliva M, Davidson R et al. Periurethral Cleaning Prior to Urinary Catheterization in Children: Sterile Water versus 10% Povidone-Iodine. Clinical Pediatrics. 2009; 48(6) |
| **Study Type / Methodology** | Prospective randomized controlled study to compare urinary infection rate in children cleaned with sterile water versus a 10% povidone-iodine before bladder catheterization.<br>The study was conducted in the emergency department of a tertiary care pediatric hospital with about 50,000 annual patient visits and over 2000 urinary catheterizations per year.<br><br>Methods. Prospective randomized controlled study of children requiring bladder catheterization in the emergency department whose parents consented to the study were randomly assigned to either of 2 groups, in which sterile water (the “sterile water” group) or 10% povidone-iodine (the “10% povidone-iodine” group) was to be used for peri-urethral cleansing prior to catheterization. |
| **LE** | I |
| **Number of patients and patient characteristics** | Prospective randomized controlled study of children requiring bladder catheterization in the emergency department whose parents consented to the study |
| **Intervention** | Sterile water (the “sterile water” group |
| **Comparison** | 10% povidone-iodine (the “10% povidone-iodine” group) |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Results. The sterile water group had 92 patients and the povidone-iodine group had 94. Most children (87%) were under 12 months of age. Urine cultures were positive in 16% of children in the povidone-iodine group and in 18% in the water group. There was no significant difference in signs and symptoms between the 2 groups. There was no significant association between solution preparation and cultures on univariate regression analysis.<br><br>Cleaning the periurethral area of children with sterile water prior to catheterization is not inferior to cleaning with povidone-iodine. |
| **General Comments** | |

**Question :** **Are the use of antiseptics for skin preparations prior to intradermal, subcutaneous or intramuscular injection effective?**

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| **Bibliographic Citation** | 1) Infection Control Team, Healthcare Associated Infection & Infection Control Section, Health Protection Scotland (formerly Scottish Centre for Infection and Environmental Health (SCIEH)). Skin disinfection prior to intradermal, subcutaneous, and intramuscular injection administration. ICT Review of Skin Injection 080604 2005 SCIEH |
| **Study Type / Methodology** | Systematic review<br>To assess the evidence in relation to skin disinfection prior to intradermal, subcutaneous, and intramuscular injection administration. |
| **LE** | I |
| **Number of patients and patient characteristics** | |
| **Intervention** | |
| **Comparison** | |
| **Length of follow up** | |
| **Outcome measures / Effect size** | Research conducted by Koivisto & Felig (1978) with diabetic patients indicated that although skin preparation with alcohol prior to injection markedly reduced skin bacterial counts, such disinfection is not necessary to prevent infection at injection sites. More recently, a study conducted by McCarthy, Covarrubias & Sink (1993), also involving diabetic patients, corroborated these findings and suggested that, generally, there was insufficient contamination of skin to cause infection following injection without disinfection and that skin cleansing was an unnecessary procedure. Further studies have since suggested that there is no increased risk of infection if skin disinfection is not undertaken .<br><br>UK Guidance on Best Practice in Vaccine Administration and the Position Statement on Injection Techniques published by the Royal College of Paediatrics and Child Health (March 2002) further reinforces these views by recommending that no formal skin disinfection is required. Comments from the Hospital Infection Society's Discussion Forum (2004) suggest that individuals working in the healthcare setting, likewise, consider skin disinfection prior to injection not to be necessary. Hutin and colleagues carried out a review of evidence-based best practices in relation to the prevention of injection associated infection which appeared in the World Health Organisation Bulletin in 2003. Their review led to the conclusion that if the skin is 'clean' there should be no need to swab the injection site whether it be the arm, thigh, stomach or other body part.<br><br>There was little evidence to support the need for disinfection of the skin prior to any intradermal, subcutaneous or intramuscular injection. If soiled, however, skin should be cleaned, based on basic commons standards, with soap and water. If skin is visibly unsoiled and disinfection is still performed, according to decisions taken at local level to undertake this practice, care should be taken to disinfect the area properly with a pre-medicated 70% alcohol swab. The injection site should be cleaned for 30 seconds with an alcohol swab and allowed to dry for a further 30 seconds to ensure bacteria are rendered inactive and injections are given safely. |
| **General Comments** | |

## Appendix 4

## LIST OF EXCLUDED STUDIES


1. Mcgrath DR and Mccrory D. An Audit of Pre-Operative Skin Preparative Methods. Ann R Coll Surg Engl. 2005; 87: 366–368

2. Maenthaisong R, Chaiyakunapruk N, Thamlikitkul V. Cost-effectiveness analysis of chlorhexidine gluconate compared with povidone-iodine solution for catheter-site care in Siriraj Hospital, Thailand. Journal of the Medical Association of Thailand. 2006; 89(S5): S94-S101

3. Jones CA. Central venous catheter infection in adults in acute hospital settings. British Journal of Nursing. 2006; 15(7)

4. Camargo L.F.A, Marra A.R, Bu¨chelea G.L. *et al.* Double-lumen central venous catheters impregnated with chlorhexidine and silver sulfadiazine to prevent catheter colonisation in the intensive care unit setting: a prospective randomised study. Journal of Hospital Infection.2009;72, 227-233

5. Garland JS, Alex CP, Mueller CD *et al*. A Randomized Trial Comparing Povidone-Iodine to a Chlorhexidine Gluconate-Impregnated Dressing for Prevention of Central Venous Catheter Infections in Neonate. Pediatrics. 2001;107:1431-1436

6. Small H, Adams D, Casey AL *et al.* Efficacy of Adding 2% (w/v) Chlorhexidine Gluconate to 70% (v/v) Isopropyl Alcohol for Skin Disinfection Prior to Peripheral Venous Cannulation. Infection Control And Hospital Epidemiology.2008; 29(10)

7. Gupta C, Czubatyj A.M., Briski L.E. *et al.* Comparison of two alcohol-based surgical scrub solutions with an iodine-based scrub brush for presurgical antiseptic effectiveness in a community hospital Journal of Hospital Infection.2007; 65: 65-71