

**Second Meeting of the Subcommittee of the Expert Committee on the Selection
and Use of Essential Medicines**

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**Review of the available evidence on
4% chlorhexidine solution for umbilical cord care
FOR THE WHO MODEL LIST OF ESSENTIAL MEDICINES**

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WHO Model List Application, June, 2008

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1. Summary statement of the proposal

Based on currently available evidence including direct evidence from a single large randomized controlled trial (RCT) (Mullany LC et al, 2006) and indirect evidence from one systematic review of RCTs (Zupan J et al, 2004), two RCTs (Pezzati M et al, 2003; Tielsh JM et al, 2007) and some observational or not randomized studies (Aggett PJ et al, 1981; Belfrage E et al, 1985; Meberg A et al, 1990; Seeberg S et al, 1984), it is proposed to include 4% (free) chlorhexidine for topical umbilical cord care (i.e. equivalent 4% free chlorhexidine in 7.1% digluconate) in the WHO Model List of Essential Medicines (EML 15, revise March 2007) available at the URL:

http://www.who.int/medicines/publications/08_ENGLISH_indexFINAL_EML15.pdf (last accessed 09 June 2008) as in the subsection *15.1 Disinfectants and antiseptics* and in the WHO Model List of Essential Medicines for Children. 1st list., October 2007. Geneva available at: [http://www.who.int/childmedicines/publications/EMLc%20\(2\).pdf](http://www.who.int/childmedicines/publications/EMLc%20(2).pdf)

The proposal is based on the following evidence and considerations:

1. There is a consensus that a topical antiseptic should be applied to the umbilical cord in cases of unclean delivery, and if the traditional practices in place increase the risk of cord infection (Zupan J et al, 2004);
2. There is evidence that 4% chlorhexidine solution reduces the risk of infection of the umbilical cord if used within the first 24 hours of delivery. This evidence is based on a large RCT conducted in Nepal where 80-90% of deliveries occur at home, and where current traditional practices increase the risk of omphalitis (Mullany LC et al, 2006);
3. There is evidence that 4% chlorhexidine solution reduces neonatal mortality (Mullany LC et al, 2006);
4. There is conflicting low-quality evidence (pre post observational studies) that 4% chlorhexidine solution can be effective in preventing omphalitis when used for hospital care of newborns kept in the nursery (not kept with in the room with the mother) in developed countries (Meberg 1985; Belfrage 1985);
5. There is no evidence of side effects when using 4% chlorhexidine solution for umbilical cord care, except a longer cord separation time that does not seem to correlate with increased risk of omphalitis (Mullany LC et al, 2006b);
6. Chlorhexidine could be provided at low cost, and could be distributed for home deliveries and peripheral health facilities as a stand alone product or within a clean delivery kit.

2. Name of the focal point in WHO submitting or supporting the application

Drs. Sue Hill and Matthews Mathai were consulted in the development of this application.

3. Name of the organization(s) consulted and/or supporting the application

The application has been developed by CEVEAS, NHS Centre for the Evaluation of the Effectiveness of Health Care, World Health Organization Collaborating Centre for Evidence Based Research Synthesis and Guideline Development in Reproductive Health. Modena, Italy.

The application is supported and revised by PATH/Healthtech and USAID

4. International Nonproprietary Name (INN, generic name) of the medicine:

Chlorhexidine

Chlorhexidine gluconate, is listed in USP, BP, EP and JP as an aqueous solution containing 20% chlorhexidine digluconate.

5. Formulation proposed for inclusion; including adult and pediatric (if appropriate)

4% chlorhexidine (free)

6. International availability - sources, if possible manufacturers (Annex A)

A list of manufacturers that have active status in the Drug Master File of the Food and Drug Administration is available in Annex A.

Chlorhexidine is registered in many countries in the developed and developing world, in addition to the U.S. The choice of the manufacturer for chlorhexidine will depend on the price and availability at the local or national level.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the Model List of Essential Medicines as an individual medicine.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment on current use, target population)

There are few studies assessing the incidence of umbilical cord infections (omphalitis) in high, middle and low-income countries but it is known that in settings where the neonatal mortality rate (NMR) is very high—around 45 per 1000 live births, as in many parts of Africa and southeast Asia—almost 50% of neonatal deaths are caused by severe infections and tetanus (Lawn JE et al, 2005). In particular, omphalitis and neonatal tetanus contribute significantly to high neonatal mortality in settings where clean delivery, cord care, and maternal immunization against tetanus are not largely implemented and where access to and utilization of public health services is not guaranteed.

The diagnosis of omphalitis is mainly based on the detection of clinical signs; therefore large variations in diagnosis can result from the adoption of different diagnostic criteria (Mullany LC et al, 2006):

- the incidence of omphalitis in low income countries is around 15% when large diagnostic criteria like the presence of moderate or severe redness around the cord are used;
- the incidence of omphalitis in low income countries is around 1% if more strict criteria like severe redness with pus around the cord are used.

At the moment no studies are available indicating the positive predictive value, sensitivity, and specificity of each single sign for omphalitis. Due to the scarcity of studies and unclear diagnostic criteria, the incidence of this condition is not well established. In high income countries the

incidence of omphalitis is estimated around 0.5% in newborns of normal weight and around 2% in premature infants (WHO, 1998). Data from low and middle income countries indicate that of newborns admitted to hospitals for sepsis, cord infection was the origin of the illness in 47% and that 21% of newborns admitted for other reasons presented omphalitis (WHO, 1998). Estimates of incidence in hospital-born infants range from 2 to 77 per 1000 live births (Mullany LC et al, 2006). *S. aureus* is the bacterium most frequently isolated in newborns with cord infections, both in home and hospital deliveries. Other bacteria frequently isolated in hospital settings are *Klebsiella spp* and *E. coli*. *C. tetani* is easily found in cases of unclean deliveries. The risk of umbilical cord infection is greatest during the first three days of life and then decreases as the umbilical cord dries and the stump separates (WHO, 1998). Once the cord is infected disease can progress through umbilical vessels causing septicemia, peritonitis, or involve internal organs such as lungs, heart, and pancreas. Alternatively the infection can remain localized at umbilical level, causing omphalitis, with erythema, oedema, and tenderness of the tissues surrounding the cord. Since inflammation delays the healing of the cord, bleeding can also be present; purulent discharge from the stump can also be present. Neonates with tetanus often also present with cord infection, since the risk factors for the two conditions are the same: unclean deliveries and unhygienic cord care practices. Some traditional practices can increase the risk of omphalitis, like using unclean tools to cut the cord, using roots, reeds, or chewed bark fibers to tie it, or covering the cord with ashes, herbs, animal dung, mud, or mustard oil. Other traditional practices can have beneficial effects, like using new cotton thread to tie the cord, or passing a knife or scissors through a flame before cutting the cord. Staying with the mother (versus being placed in a nursery), skin to skin contact with the mother, and early and exclusive breastfeeding are all well-known protective factors that reduce the incidence of infection and the risk of contamination of the umbilicus with infectious pathogens. The risk of omphalitis can be particularly high in cases of home delivery in settings where traditional practices do not include hygienic deliveries and clean cord care. In some developing countries the rate of home delivery can be high: it is around 90% in Nepal (Mullany LC et al, 2006; Sreeramareddy CT et al, 2006), 85% in Northern Nigeria, with 60% of women not receiving tetanus toxoid in their last pregnancy and 80% of home deliveries assisted by personnel not trained in clean delivery practices (Galadanci HS et al, 2007), 47% in rural areas of Malawi (Kasenga F et al, 2007) and 37% in India (Thind A et al, 2008). In these situations it would be of utmost importance to implement a series of interventions to increase the coverage of maternal immunization against tetanus, training of workers assisting with deliveries, clean deliveries, and hygienic cord care.

Clean cord care at birth includes washing hands with clean water and soap before delivery and again before cutting and tying the cord, laying the newborn on a clean surface, cutting the cord with a sterile instrument and tying/clamping it with a sterile string or clamp. In the postnatal period clean cord care includes washing hands with clean water and soap before and after care of the stump, and keeping the cord dry and exposed to air or loosely covered with clean clothes. When the cord is soiled it should be washed with clean water and soap. The diaper should not cover the umbilicus (WHO, 1998). A clean delivery kit (containing a piece of soap, a sterile blade and tie, a small plastic disc, and a plastic sheet) has been developed to support personnel assisting home deliveries in implementing hygienic practices. Some data indicates that where the clean delivery kit is implemented in conjunction with an educational intervention, it can reduce the rate of cord infection and puerperal sepsis (Winani S et al, 2007), but no conclusive evidence on the impact of the clean delivery kits is available.

9. Treatment details

Chlorhexidine is a bisbiguanide compound that acts by binding to the bacterial cell wall and disrupting its membrane, leading to increased permeability and cell content leakage. It has a shelf life of 20 to 24 months. It is stable at room temperature if stored in an opaque container, and it has no known interactions. It is an antimicrobial for topical use which is active against gram positive and gram negative microbes while it has no effect on clostridia spores (WHO, 1998). It exists as chlorhexidine acetate, diacetate, gluconate, and digluconate, in aqueous or saline solution and in alcoholic solution. Chlorhexidine-containing compounds have been used as topical disinfectants since the middle 1970's. Chlorhexidine has been studied at different concentrations for several utilizations: hand washing before surgery, pre-operative body shower, dental and oral hygiene, vaginal wiping before delivery, newborn wiping, and cord care (McClure EM et al, 2007). Chlorhexidine is included in the WHO Model Formulary 2008 under section 15.1 Antiseptics (WHO, 2008). Chlorhexidine is also incorporated in cosmetic products, where it reportedly functions as a cosmetic biocide. In the early 1990's, the FDA cleared three types of medical devices that incorporate chlorhexidine in the composition of the device: intravenous catheters, topical antimicrobial skin dressings, and implanted antimicrobial surgical mesh. In 1998 the FDA circulated a public health notice of possible serious hypersensitivity reactions to chlorhexidine-impregnated medical devices (available at <http://www.fda.gov/cdrh/chlorhex.html>).

Intrapartum vaginal wipe/irrigation

Chlorhexidine at a concentration ranging from 0.05% to 1% has been used to reduce the risk for the newborn to acquire maternal infection (HIV or streptococcus) during the passage through the birth canal.

A Cochrane systematic review that included five studies on 2190 term and preterm infants showed that although vaginal chlorhexidine significantly reduces group B streptococcal colonization of neonates, it does not reduce incidence of clinical infections. The authors concluded that currently the use of vaginal disinfection with chlorhexidine in labour for preventing early onset disease is not supported by evidence (Stade BC et al, 2004).

A second Cochrane systematic review including three studies (3012 participants) shows no evidence of an effect of vaginal chlorhexidine during labour in preventing maternal and neonatal infections (HIV and streptococcal infections not assessed). Although the data suggest a trend in reducing postpartum endometritis, the difference was not statistically significant (RR 0.83; 95% CI 0.61 to 1.13). There is a need for a well-designed RCT using appropriate concentration and volume of vaginal chlorhexidine irrigation solution and with adequate sample size (Lumbiganon P et al, 2004). Two ongoing studies in Pakistan and South Africa are addressing this question.

Newborn total body wiping

As results from a single trial conducted in Nepal indicate, washing the newborn with a solution of chlorhexidine 0.25% soon after delivery reduces the rate of skin colonization. Wiping the baby was associated with a reduced neonatal mortality of premature infants, while it had no effect on overall neonatal mortality (Tielsh JM et al, 2007).

Preoperative bathing or showering

A Cochrane systematic review assessed efficacy of 4% chlorhexidine digluconate (*Hibiscrub*) used for preoperative bathing in reducing surgical site infections (SSI). Six trials involving a total of 10,007 participants were included. Three trials (7691 participants) compared chlorhexidine with a placebo: the RR of SSI was 0.91 (95% CI 0.80 to 1.04). When only trials of high quality were included in this comparison, the RR of SSI was 0.95 (95% CI 0.82 to 1.10). Three trials (1443

participants) compared bar soap with chlorhexidine: the RR of SSI was 1.02 (95% CI 0.57 to 1.84). Two trials (1092 patients) compared cleansing with chlorhexidine with no cleansing at all; results were conflicting, with one large study finding a statistically significant difference in favour of bathing with chlorhexidine (RR 0.36, 95%CI 0.17 to 0.79) while the second smaller study did not find a difference between patients who washed with chlorhexidine and those who did not wash preoperatively. Authors concluded that there is no clear evidence of the benefit for preoperative showering or bathing with chlorhexidine over other cleansing products, to reduce SSI (Webster J et al, 2007).

Preoperative skin antisepsis

One Cochrane systematic review assessed efficacy of preoperative antiseptics; it included six RCTs. There was significant heterogeneity between studies and the results could not be pooled. In one study, infection rates were significantly lower when skin was prepared using chlorhexidine compared with iodine. There was no evidence of a benefit in four trials associated with the use of iodophor-impregnated drapes. Authors concluded that there is insufficient research examining the effects of preoperative skin antiseptics to allow conclusions (Edwards PS et al, 2004).

Surgical hand antisepsis

A Cochrane systematic review aimed to assess effectiveness of different hands antiseptics to be used before performing surgical procedures. Ten trials were included in the review. Only one trial reported the primary outcome, rates of SSI, while nine trials gave only a measure of colonization (colony forming units—CFUs).

One trial found N-duopropenide more effective than chlorhexidine and povidone iodine aqueous scrubs. One trial found 45% propanol-2, 30% propanol-1 with 0.2% ethylhexadecyldimethyl ammonium ethylsulfate more effective than chlorhexidine scrubs. One trial found no difference between 1% chlorhexidine gluconate in 61% ethyl alcohol or zinc pyrithione in 70% ethyl alcohol against aqueous povidone iodine. A fourth trial found 4% chlorhexidine gluconate scrubs more effective than chlorhexidine in 70% alcohol rubs. Three trials found chlorhexidine gluconate scrubs were significantly more effective than povidone iodine scrubs. One trial found no difference between chlorhexidine gluconate scrubs and povidone iodine plus triclosan scrubs. Evidence from 4 studies suggests that chlorhexidine gluconate based aqueous scrubs are more effective than povidone iodine based aqueous scrubs in terms of the numbers of CFUs on the hands. There is limited evidence regarding the effects on CFUs numbers of different scrub durations (Tanner J et al, 2008).

Oral and dental health

Two Cochrane systematic reviews aimed to assess the effect of different antiseptics on oral and dental health. In particular one systematic review assessed antiseptic regimens for hygiene in dental implants: this review concluded that there is no evidence from trials that powered or sonic toothbrushes are better than manual brushes and that brushing with a hyaluronic gel outdoes brushing with a chlorhexidine gel. Among the professionally-administered treatments there is no evidence that phosphoric acid excels scaling and polishing, that chlorhexidine enclosed in the inner part of implants is superior to physiologic solution, and that a topical antibiotic inserted submucosally is better than a chlorhexidine gel. However, there is some evidence that Listerine antibacterial mouthwash, used twice a day after brushing can help to keep gums healthy. (Grusovin MG et al, 2008). The second systematic review assessed the effect of antiseptics for chronic periodontitis. The review shows that the treatment effect of full-mouth scaling or full-mouth disinfection compared to conventional scaling and root planing are modest and the implications for periodontal care are not profound. In practice the decision to select one approach to non-surgical

periodontal therapy over another approach should take into account patient preferences and convenience of the treatment schedule (Eberhard J et al, 2008).

Umbilical cord care

A Cochrane systematic review assessing the effect of topical umbilical cord care for preventing cord infection, illness, and neonatal death and including 21 studies (8959 participants) was not able to indicate the best antiseptic treatment: no systemic infections or deaths were observed in any of the studies reviewed (largely coming from high-income countries). Only one out of the 21 studies included in the systematic review used chlorhexidine as the main intervention (Zupan J et al, 2004).

Summarizing the above reported Cochrane systematic reviews, it seems that the available evidence is too scanty and it is generally based on small trials of low quality. Therefore no strong recommendations can be made with respect to one or another antiseptic regimen for any of the above explored indications.

New evidence on chlorhexidine and umbilical cord care

In 2006 the first large RCT on 4% chlorhexidine for umbilical cord care used in a low income country (Nepal) was published (Mullany LC et al, 2006). Results of this study were not included in the Cochrane systematic review, since the latter was published in 2004. The study was a community-based, cluster-randomized trial: 4934 infants were randomized to chlorhexidine treatment, 5107 to cleansing with soap and water and 5082 to dry cord care. Cord was cleansed daily on day 1 through 4, and then on days 6, 8, and 10. The cord was assessed for signs of infection (clinical judgment) on days of treatment and then in follow-up visits on days 12, 14, 21, and 28. Outcomes were incidence of omphalitis and neonatal mortality. Severe omphalitis (severe redness with pus) was reduced by 75% in the chlorhexidine group compared to dry cord care; neonatal mortality was reduced by 24% in the chlorhexidine group. Effects were more marked in infants receiving the assigned treatment within the first 24 hours after birth (see Tables of evidence in Annex D).

Based only on this study, chlorhexidine could be proposed as a treatment for umbilical cord care in settings where the rate of home delivery is high, where clean delivery is not universally guaranteed, and where traditional practices of cord care increase the risk of cord infection. The study from Mullany was conducted in Nepal, where around 90% of deliveries happen at home (Sreeramareddy CT et al, 2006) without any professional assistance, clean delivery is hardly guaranteed, and potentially harmful practices of cord care are very popular (massage of the body and the stump with mustard oil, which is a risk factor for cord infection) (Mullany LC et al, 2007). Based on currently available evidence antiseptic use for cord care is not indicated in other settings.

9.1 Indications for use

The following indications are reported as available from the FDA.

Chlorhexidine gluconate 1% solution and ethyl alcohol 61% w/w (FDA date of approval 2001) is indicated for:

- surgical hand scrub
- healthcare personnel hand wash

Chlorhexidine gluconate 2% (w/v) and Isopropyl Alcohol 70% (v/v) (FDA date of approval 2000) is indicated for:

- preoperative skin preparation

Chlorhexidine oral rinse (0.12% Chlorhexidine gluconate) (FDA date of approval 1995) is indicated for:

- treatment of gingivitis in adult population

9.2 Dosage regimen

The proposed regimen for umbilical cord care is application of a small amount of chlorhexidine to the cord with a cotton ball or other clean cloth once daily. Below is the current indication for dosage regimens for chlorhexidine for existing registered uses.

Adult

a) Gingivitis

15 mL oral rinse 0.12% swish and spit for 30 seconds twice daily

b) Periodontitis

2.5 mg chip inserted to the maximum depth of the periodontal pocket (at least 5 mm); insert a new chip every 3 months; maximum of 8 chips per dental visit (Prod Info PERIOCHIP(R) oral tablets, 2002).

c) Skin cleansing procedure

- general skin or wound cleansing: rinse area to be cleansed, apply minimum amount of 4% solution necessary to cover skin or wound area and wash gently, then rinse (Prod Info HIBICLENS(R) topical cleanser, 2006)
- preoperative skin preparation) 4% solution applied for at least 2 min, dry and repeat for 2 min (Prod Info HIBICLENS(R) topical cleanser, 2006)
- surgical hand scrub) apply 5 mL of 4% solution and scrub for 3 minutes, rinse thoroughly, then repeat, rinse, and dry (Prod Info HIBICLENS(R) topical cleanser, 2006)
- personnel handwash) wet hands, wash with 5 mL of 4% solution for 15 seconds; rinse and dry (Prod Info HIBICLENS(R) topical cleanser, 2006)

Dosage in Renal Failure

With topical use, chlorhexidine gluconate is not absorbed through the intact skin. Oral chlorhexidine mouth rinse is not intended for oral ingestion. Therefore, the dosage of these formulations should not require alteration in patients with renal failure (Prod Info Hibiclens(R), 2000)(Prod Info Peridex(R), 2000a).

Dosage in Hepatic Insufficiency

With topical use, chlorhexidine gluconate is not absorbed through the intact skin. Oral chlorhexidine mouth rinse is not intended for oral ingestion. Therefore, the dosage of these formulations should not require alteration in patients with hepatic insufficiency (Prod Info Hibiclens(R), 2000)(Prod Info Peridex(R), 2000a).

9.3 Duration of therapy

There is not a unanimous consensus on duration of therapy and frequency of application of chlorhexidine for cord care. In Nepal the protocol used a seven day regimen of daily application of chlorhexidine on the umbilical cord over the course of ten days. (Mullany LC et al, 2006). In an Italian study comparing chlorhexidine with salicylic sugar powder, the antiseptic was applied at every change of the diaper until the cord detached (Pezzati M et al, 2003). No direct comparisons are currently available on different regimens of therapy. Ongoing research in Bangladesh is

examining the impact of a one day, seven day application regimens, and control dry cord care regimens nested in a community-based newborn-care intervention package in Bangladesh (Baqui et al, 2008).

9.4 Reference to existing WHO and other clinical guidelines

Existing WHO relevant documents with related web links (two documents in total) were identified and consulted:

- Care of the umbilical cord; a review of the evidence. Maternal and Newborn Health, Safe Motherhood. Division of Reproductive Health (technical support) Family and Reproductive Health World Health Organization, 1998. Geneva, available at: http://www.who.int/reproductive-health/publications/MSM_98_4/care_umbilcal_cord.pdf
- Postpartum Care of the Mother and Newborn: a practical guide. Maternal and Newborn Health/Safe Motherhood Unit. Division of Reproductive Health (Technical Support) World Health Organization 1998, Geneva, available at: http://www.who.int/reproductive-health/publications/msm_98_3/

Relevant guidelines for cord care are lacking. Only one guideline produced by the Association of Woman's Health Obstetric and Neonatal Nurses (AWHONN) has been identified (see paragraph 10.1 for the search strategy) but it was not possible to assess the full document. By consulting some publications related to the AWHONN guideline it was possible to conclude that the guideline recommends avoiding routine use of isopropyl alcohol for umbilical cord care and to opt, whenever possible, for dry cord care. If an antiseptic is needed, chlorhexidine is preferred (Lund CH et al, 2001; Lund CH et al, 2001b).

- Association of Women's Health, Obstetrics and Neonatal Nurses - AWHONN Neonatal Skin Care, Evidence-Based Clinical Practice Guideline, 2nd Edition (2007). Carolyn Houska Lund, RN, MS, FAAN, Team Leader Joanne Kuller, RN, MS Deborah A. Raines, PhD, RNC Sheila Ecklund, RNC, MSN Melanie Elise Archambault, RN, BN Patricia O'Flaherty, Med, MN, NNPC.

9.5 Need for special diagnostic or treatment facilities and skills

Chlorhexidine management and administration do not require any particular facilities or specific skills.

Chlorhexidine could be provided at low cost, and could be distributed for home deliveries as a stand alone product, within a clean delivery kit or delivered by health workers as part of neonatal health packages.

10. Summary of comparative effectiveness in a variety of clinical settings

Two good quality studies (RCTs) on chlorhexidine use for cord care have been identified (Mullany LC et al, 2006; Pezzati M et al, 2003).

- The Mullany RCT was conducted in Nepal, on 15123 infants born at home. Intervention groups were: chlorhexidine and "water and soap care" that were compared to "dry cord care" (comparison group).

In this study 4% chlorhexidine (7.1% chlorhexidine digluconate), compared to dry cord care, reduces the risk of:

1. Possible omphalitis (moderate or severe redness): RR 0.68 (95% CI 0.58 to 0.80)

2. Probable omphalitis (moderate or severe redness with pus, or severe redness alone): RR 0.46 (95% CI 0.36 to 0.59)
3. Omphalitis (severe redness with pus): RR 0.25 (95% CI 0.12 to 0.53)
4. Neonatal mortality when timing of intervention was early (<24 hours from birth): RR 0.66 (95% CI 0.46 to 0.95)

In addition:

5. The intervention has a marginally significant effect on overall neonatal mortality (early plus late intervention): RR 0.76 (95% CI 0.55 to 1.04).
 6. The intervention increases the time to cord separation: 5.32 ± 2.4 days in the chlorhexidine group versus 4.24 ± 1.6 days in the dry cord care group.
- The Pezzati RCT was conducted in Italy, on 213 hospital-born premature infants. Chlorhexidine was compared against salicylic sugar powder.

In this study 4% chlorhexidine has no effect on incidence of omphalitis (no cases in either intervention group), and on cases of sepsis (one case in each group). Clean conditions at delivery and the number of subjects are probably responsible for the absence of these illnesses. No significant differences were found in the cord colonization for *S. hemolyticus* group B, *E. coli*, *S. aureus*, while a significant higher percentage of colonization with *S. non aureus* and *Enterococcus spp.* was found in the chlorhexidine group.

Chlorhexidine results to increase cord separation time: 9.0 ± 2.0 days in the chlorhexidine group versus 6.0 ± 2.0 days in the salicylic sugar powder group.

From the evidence described above (Mullany LC et al, 2006; Pezzati M et al, 2003), it is possible to conclude that in developing countries, where unclean and unassisted home delivery is common and there is poor access to high quality prenatal care, use of 4% chlorhexidine solution for cord care can have a positive impact on newborn morbidity and mortality. In developed countries, or whenever clean delivery and access to high quality prenatal care can be assured, no antiseptics for cord care are indicated.

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Guidelines were searched through the *National Guideline Clearinghouse* (data last search 26 May 2008). The following search criteria were used:

Keyword: *umbilical cord care*

The search found 16 related guidelines, which are listed in Annex C in order of relevance.

None of the guidelines identified through the *National Guideline Clearinghouse* were relevant for our document.

In addition the scientific database *Medline* have been searched for relevant guidelines (date of last search the 20th of May 2008).

Keyword: "*Umbilical Cord*"[Mesh] AND ("*Guideline* "[Publication Type] OR "*Health Planning Guidelines*"[Mesh] OR *guideline* OR *recommendations*)

36 references were retrieved (listed in Annex C). Based on titles the following references have been identified for further assessment:

1. Mercer JS, Erickson-Owens DA, Graves B, Haley MM. Evidence-based practices for the fetal to newborn transition. *J Midwifery Womens Health*. 2007;52:262-72
2. Trotter S. Management of the umbilical cord--a guide to best care. *RCM Midwives*. 2003;6:308-11
3. Lacour JP, Castanet J, Boutté P, Ortonne JP. [Antiseptic treatment of the umbilical cord in newborns: survey and recommendations] *Arch Pediatr*. 1999;6:631-4

None of the papers were guidelines or contained recommendations. Of interest is the paper from Lacour: it describes the results of a survey conducted in 1996 in 57 maternity units (50 units answered the questionnaire). Six different groups of antiseptics (17 distinct commercial products) were used for the umbilical cord care; products were often used in combination. No coherence between recommendations and practice was observed. Chlorhexidine was the third most frequently prescribed and in 95% of cases it was used in association with other products (Lacour JP et al, 1999).

The guidelines produced by AWHONN were identified since the document was already known by the authors of this proposal.

- Association of Women's Health, Obstetrics and Neonatal Nurses - AWHONN Neonatal Skin Care, Evidence-Based Clinical Practice Guideline, 2nd Edition (2007). Carolyn Houska Lund, RN, MS, FAAN, Team Leader Joanne Kuller, RN, MS Deborah A. Raines, PhD, RNC Sheila Ecklund, RNC, MSN Melanie Elise Archambault, RN, BN Patricia O'Flaherty, Med, MN, NNPC.

The databases **Medline** and **EMBASE** have been searched for **randomized controlled trials**.

Search strategy: *chlorhexidine digluconate* (used as independent terms)

Limits: *human, randomized controlled trial, time limits from 1995.01.01*

168 references were retrieved, largely related to mouth hygiene and plaque prevention. 21 references were selected based on title and abstract assessment.

Abstract of the references selected are reported in Annex C.

10.2 Summary of available estimates of comparative effectiveness (appraisal of quality, outcome measures, summary of results)

Primary studies (RCTs, quasi RCT, pre-post studies) have been synthesized in a table of evidence for effectiveness and safety data (Annex D).

Tables of evidence have been developed using the GRADE profile software (<http://www.gradeworkinggroup.org/toolbox/index.htm>) where a balance between benefits and harms of the intervention are analysed (GRADE working group, 2004; Guyatt GH et al, 2008a; Guyatt GH et al, 2008b; Guyatt GH et al, 2008c; Guyatt GH et al, 2008d; Schünemann HJ et al, 2008).

Each study is tabulated according to the selected outcome (e.g. omphalitis, side effects, cord separation time), and importance is rated in the last column (critical, important, not important).

Quality assessment of the study considered for each outcome takes into account study design, limitations, inconsistency, indirectness, and imprecision. Reasons for judging the quality of the study are reported in footnotes. In the column 'quality', a summary scoring of the study quality for the considered outcome is given: high, moderate, low, or very low.

A summary of findings is given with absolute numbers and estimate of relative (RR) and absolute effects (ARR) of the intervention considered.

11. Summary of comparative evidence on safety

The key studies reviewed indicated that chlorhexidine is safe when used as a topic treatment for cord care (Belfrage E et al, 1985; Seeberg S et al, 1984; Mullany LC et al, 2006), although a full assessment of safety is not currently available. Chlorhexidine can be absorbed when applied to the umbilical cord or more generally to the skin, but the absorption occurs only at trace levels and has no known health effects. Safety studies conducted in the 1970s and 1980s showed that absorption through intact adult skin was minimal (Aly 1973, Case 1976, Withrow 1976). Of the few studies that have examined absorption in newborns, most studied topical chlorhexidine applications to the entire body and trace amounts have been detected in some studies (Wilson 2004, O'Neill 1982, Cowen 1979). Two studies have examined absorption associated with umbilical cord cleansing. Following daily application of 4% chlorhexidine to the umbilical cord of newborn infants (n=21) for 5 days, one infant had trace levels in venous blood, most likely due to contamination from the residue on the skin (Johnson, 1987). Additional studies in preterm and term infants suggested that application of 1% chlorhexidine in ethanol increased the potential for percutaneous absorption of chlorhexidine following application to the umbilical cord of preterm but not term infants (Aggett, 1981). Despite the few cases in which chlorhexidine has been absorbed at trace amounts through newborn skin after umbilical or whole-body cleansing, there have been no reports of negative consequences of chlorhexidine in the newborn circulatory system despite its widespread use for decades (see Mullany 2006b). The only study conducted specifically to investigate the percutaneous absorption of chlorhexidine when used for neonatal cord care was done in 1981 on a small sample of newborns (52 preterm and 25 at term newborns). The study was based on plasma determination of chlorhexidine concentrations at ages 5 and 9 days; it showed that percutaneous absorption of chlorhexidine occurred in preterm neonates treated with a 1% solution of chlorhexidine in ethanol, but not in term infants or in preterm infants treated with a dusting powder containing 1% chlorhexidine and 3% zinc oxide (Aggett PJ, et al 1981).

Key studies (RCTs, quasi RCT, pre-post studies) have been synthesized in tables of evidence for effectiveness and safety data (Annex D).

11.1 Estimate of total patient exposure to date

Since its first introduction in the 1970s, chlorhexidine has been widely used all over the world for hand washing, preoperative skin preparation, oral and dental health, and cord care.

11.2 Description of adverse effects/reactions

Chlorhexidine for topical use in cord care has no adverse effects/reactions described from major studies (see paragraph 11) and is extensively used in medical settings, and it is therefore considered safe to be used (McClure EM et al, 2007).

From **MICROMEDEX**®:

Incidence of skin irritation is extremely low. One case of urticaria has been reported. There is significant evidence to support the fact that chlorhexidine can cause rare anaphylaxis or anaphylactoid reactions (see paragraph 15).

From **FDA**:

The only reactions described by the FDA (available at <http://www.fda.gov/cdrh/chlorhex.html>) relate to chlorhexidine used intra-urethrally, on urinary catheters and with chlorhexidine impregnated catheters (see description below from FDA website).

Evidence of Hypersensitivity Reactions

Although the antimicrobial properties of chlorhexidine are well known, it is not as well known that chlorhexidine has been associated with hypersensitivity reactions. Anaphylactoid and other types of reactions have been reported with chlorhexidine used topically, intra-urethrally, as a lubricant on urinary catheters, and with chlorhexidine-impregnated catheters. These incidents have occurred in Japan,¹⁻³ Switzerland,⁴ the United Kingdom,⁵ Australia,⁶ Malaysia,⁷ and the United States.^{8,9}

1. *Immediate systemic hypersensitivity reactions to chlorhexidine gels/lubricants used during urological procedures*
Hypersensitivity reactions associated with chlorhexidine gels/lubricants used during urological procedures have been reported in several countries. (None have been reported thus far in the U.S.) In one case, a 61 year-old man in the Netherlands exhibited a severe allergic reaction associated with a chlorhexidine gel used for an intra-urethral preparation.¹⁰ In another incident in Nedlands, Australia, a 52 year-old man had an anaphylactic reaction to a chlorhexidine lubricant on a urinary catheter While undergoing a temporal lobectomy.¹¹ Six cases of severe allergic reactions to chlorhexidine gel used with urinary catheters have also been reported in Melbourne, Australia.¹²
2. *Immediate systemic hypersensitivity reactions to central venous catheters*
From communication with the Japanese government, FDA became aware that 13 Japanese patients experienced anaphylactoid type adverse events while using central venous catheters impregnated with chlorhexidine. Tachycardia, hypotension and complaints of chest pain were reported. One patient subsequently died, although the exact cause of death is unknown. It is not clear why these reactions occurred in Japanese individuals but not in others; possible explanations include an increased exposure to chlorhexidine-containing products resulting in heightened sensitivity, a genetic predisposition to react to this chemical, or some other factor. Sale of these central venous catheters in Japan began in 1996. The adverse events occurred between June 25, 1996, and June 24, 1997. The World Health Organization issued a notice stating that the manufacturer of the central venous catheters voluntarily withdrew the product from the market in Japan on August 19, 1997.¹³ Approximately 117,000 catheters were sold. To date, FDA has not received any reports of immediate systemic hypersensitivity reactions related to central venous catheters for patients in the United States. (Of the 3 million sold worldwide since 1990, 2.5 million were in the U.S.)
3. *Other types of reactions*
In addition to the immediate systemic hypersensitivity reactions reported with the use of topical chlorhexidine, chlorhexidine gel/lubricant and chlorhexidine-impregnated catheters, other types of reactions have been documented. In one U.S. study, six of 10 neonates weighing under 1000 grams showed local hypersensitivity reactions to chlorhexidine

gluconate-impregnated patches used to secure central venous catheters.¹⁴ Severe contact dermatitis in seven neonates with this type of dressing was also reported in another U.S. study.¹⁵ Two cases of occupational asthma in nurses were reported from chlorhexidine and alcohol aerosols,¹⁶ and bradycardia was reported in a neonate associated with a chlorhexidine spray used on the mother's breasts.¹⁷

11.3 Identification of variation in safety due to health systems and patient factors

Given that the use of topical 4% chlorhexidine for cord care should be considered in unhygienic environments in low-income countries, problems related with correct storage and supply, monitoring of expiring dates, possible contamination, mistakes in dilution, and application with an unclean applicators should be considered (WHO, 1998).

11.4 Summary of comparative safety against comparators

Studies analyzed compared chlorhexidine to water and soap, or to salicylic sugar powder, ethanol, hydrophobic gauze material bandage, benzine, and dry cord care.

Primary studies (RCTs, quasi RCT, pre-post studies) have been synthesized in table of evidence for effectiveness and safety data (Annex D).

12. Summary of available data on comparative costs and cost-effectiveness

The cost of chlorhexidine, available in most cases also as generic formulations, is not an issue in term of access and availability.

12.1 Range of cost of the proposed medicine

Chlorhexidine's cost depends on formulation and presence of a local manufacturer. For example, the manufacturer's recommended price for Savlon® (50ml, 1.5% v/v chlorhexidine gluconate solution) is INR12.50 (Indian Rupee, about 0.18 Euro), and Handirub® (50ml, 0.5% w/v chlorhexidine gluconate solution) is sold at BDT 30 (Bangladeshi Taka, about 0.28 Euro). "Chlorhexidine solution: 5% (digluconate) for dilution" is already included in the WHO EML in the subsection *15.1 Disinfectants and antiseptics*.

12.2 Comparative cost-effectiveness presented as range of cost per routine outcome

"Chlorhexidine solution: 5% (digluconate) for dilution" is already included in the WHO EML in the subsection *15.1 Disinfectants and antiseptics*.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

4% chlorhexidine solution has not been approved for this particular pediatric use by the U.S. FDA because in developed country settings, or whenever clean delivery and access to prenatal care can be assured, no antiseptics for cord care are indicated. However, chlorhexidine solutions of various concentrations are approved in the U.S., and a list of FDA-approved products is available in Annex B. A 5% chlorhexidine digluconate solution for dilution already listed on the WHO Essential Medicine List for general antiseptic use as well as cord care. Based upon available evidence it is

recommended that the 4% chlorhexidine solution replace it for cord care and the 5% solution for dilution be retained for use as a general antiseptic.

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

Chlorhexidine solutions:

- British Pharmacopoeia: Yes
- US Pharmacopoeia: Yes
- European Pharmacopoeia: Yes
- JP Pharmacopoeia: Yes

15. Proposed (new/adapted) text for the WHO Model Formulary

Description:

4% chlorhexidine is a bisbiguanide compound. It is an antimicrobial for topical use being active against gram positive and gram negative microbes, while it has no effect on clostridia spores.

How Supplied:

4% chlorhexidine (free)

Use:

4% chlorhexidine solution can be indicated for cord care in developing countries, i.e. in settings with rudimentary peripheral facilities and unassisted home deliveries are prevalent. In these settings initiation of use of 4% chlorhexidine solution within 24 hours of birth and repeated application of up to seven times or until the cord falls off reduces the risk of omphalitis and neonatal mortality.

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Annex A

1Q2008 ALLEXCEL				
DMF #	SUBMIT DATE	HOLDER	COUNTRY	SUBJECT
5782	8-Apr-1985	XTTRIUM LABS INC	USA	CHLORHEXIDINE GLUCONATE B.P-81
8379	19-Jan-1990	EVONIK DEGUSSA GMBH	GERMANY	CHLORHEXIDINE GLUCONATE AS MFG. IN HANAU, GERMANY
9701	27-May-1992	MEDICHEM SA	SPAIN	CHLORHEXIDINE GLUCONATE MANUFACTURED IN GERONA, SPAIN.
14250	26-May-1999	ECOLAB INC	USA	20% CHLORHEXIDINE GLUCONATE AS MANUFACTURED IN HUNTINGTON IN
18841	3-Oct-2005	BASIC PHARMA LIFE SCIENCE PVT LTD	INDIA	CHLORHEXIDINE HYDROCHLORIDE AS MANUFACTURED IN GUJARAT, INDIA.
19128	24-Jan-2006	JFC TECHNOLOGIES LLC	USA	CHLORHEXIDINE GLUCONATE 20% SOLUTION, USP AS MANUFACTURED IN BOUND BROOK, NJ.
19583	26-Jun-2006	CADILA PHARMACEUTICALS LTD	INDIA	CHLORHEXIDINE GLUCONATE AS MANUFACTURED IN GUJARAT, INDIA.

Source: Drug Master File (DMF), Food and Drug Administration(as of Q1, 2008)

Annex B

FDA Approved Drug Products (as of May 29, 2008)

Drug Name	Company	FDA Application No.	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	Approval Date
AVAGARD	3M	021074	ALCOHOL; CHLORHEXIDINE GLUCONATE	61%; 1%	SOLUTION; TOPICAL	Over-the-counter	7-Jun-01
PERIDEX	3M	019028	CHLORHEXIDINE GLUCONATE	0.12%	SOLUTION; DENTAL	Prescription	13-Aug-86
BIOSCRUB	GRIFFEN	019822	CHLORHEXIDINE GLUCONATE	4%	SPONGE; TOPICAL	Over-the-counter	31-Mar-89
BRIAN CARE	SOAPCO	071419	CHLORHEXIDINE GLUCONATE	4%	SOLUTION; TOPICAL	Over-the-counter	17-Dec-87
CIDA-STAT	ECOLAB	019258	CHLORHEXIDINE GLUCONATE	2%	SOLUTION; TOPICAL	Over-the-counter	22-Jul-86
CHG SCRUB	ECOLAB	019258	CHLORHEXIDINE GLUCONATE	4%	SOLUTION; TOPICAL	Over-the-counter	22-Jul-86
CHLORAPREP ONE-STEP	ENTURIA INC	020832	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	2%; 70% (3ML)	SPONGE; TOPICAL	Over-the-counter	14-Jul-00
CHLORAPREP ONE-STEP	ENTURIA INC	020832	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	2%; 70% (10.5ML)	SPONGE TOPICAL	Over-the-counter	14-Jul-00
CHLORAPREP ONE-STEP	ENTURIA INC	020832	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	2%; 70% (26ML)	SPONGE TOPICAL	Over-the-counter	14-Jul-00
CHLORAPREP ONE-STEP PREPP	ENTURIA INC	020832	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	2%; 70% (1.5ML)	SPONGE TOPICAL	Over-the-counter	14-Jul-00
CHLORAPREP WITH TINT	ENTURIA INC	020832	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	2%; 70% (3ML)	SPONGE TOPICAL	Over-the-counter	14-Jul-00
CHLORAPREP WITH TINT	ENTURIA INC	020832	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	2%; 70% (10.5ML)	SPONGE TOPICAL	Over-the-counter	14-Jul-00
CHLORAPREP WITH TINT	ENTURIA INC	020832	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	2%; 70% (26ML)	SPONGE TOPICAL	Over-the-counter	14-Jul-00
CHLORAPREP ONE-STEP SEPP	ENTURIA INC	021555	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	2%; 70% (0.6ML)	SWAB; TOPICAL	Over-the-counter	7-Oct-02
CHLORAPREP SINGLE SWABSTICK	ENTURIA INC	021555	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	2%; 70% (1.75ML)	SWAB; TOPICAL	Over-the-counter	7-Oct-02
CHLORASCRUB MAXI SWABSTICK	PROF DSPLS	021524	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	3.15%; 70% (5.1ML)	SWAB; TOPICAL	Over-the-counter	3-Jun-05

Drug Name	Company	FDA Application No.	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	Approval Date
CHLORASCRUB SWAB	PROF DSPLS	021524	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	3.15%; 70% (1ML)	SWAB; TOPICAL	Over-the-counter	3-Jun-05
CHLORASCRUB SWABSTICK	PROF DSPLS	021524	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	3.15%; 70% (1.6ML)	SWAB; TOPICAL	Over-the-counter	3-Jun-05
CHLORHEXIDINE GLUCONATE	KENDALL IL	019490	CHLORHEXIDINE GLUCONATE	4%	SPONGE; TOPICAL	Discontinued	N/A
CHLORHEXIDINE GLUCONATE	SAGE PRODS	021669	CHLORHEXIDINE GLUCONATE	2%	CLOTH; TOPICAL	Over-the-counter	25-Apr-05
CHLORHEXIDINE GLUCONATE	BECTON DICKINSON	072525	CHLORHEXIDINE GLUCONATE	4%	SPONGE; TOPICAL	Over-the-counter	24-Oct-89
CHLORHEXIDINE GLUCONATE	ACTAVIS MID ATLANTIC	074291	CHLORHEXIDINE GLUCONATE	0.12%	SOLUTION; DENTAL	Prescription	28-Dec-95
CHLORHEXIDINE GLUCONATE	HI TECH PHARMA	074356	CHLORHEXIDINE GLUCONATE	0.12%	SOLUTION; DENTAL	Prescription	7-May-96
CHLORHEXIDINE GLUCONATE	TEVA	074522	CHLORHEXIDINE GLUCONATE	0.12%	SOLUTION; DENTAL	Prescription	15-Dec-95
CHLORHEXIDINE GLUCONATE	MORTON GROVE	075006	CHLORHEXIDINE GLUCONATE	0.12%	SOLUTION; DENTAL	Prescription	3-Mar-04
CHLORHEXIDINE GLUCONATE	NOVEX	075561	CHLORHEXIDINE GLUCONATE	0.12%	SOLUTION; DENTAL	Prescription	14-Nov-00
CHLORHEXIDINE GLUCONATE	JOHN O BUTLER CO	076434	CHLORHEXIDINE GLUCONATE	0.12%	SOLUTION; DENTAL	Prescription	29-Nov-05
DYNA-HEX	XTTRIUM	020111	CHLORHEXIDINE GLUCONATE	0.75%	SOLUTION; TOPICAL	Over-the-counter	11-Sep-97
EXIDINE	XTTRIUM	019125	CHLORHEXIDINE GLUCONATE	4%	SOLUTION; TOPICAL	Over-the-counter	24-Dec-84
EXIDINE	XTTRIUM	019127	CHLORHEXIDINE GLUCONATE	4%	AEROSOL, METERED; TOPICAL	Over-the-counter	24-Dec-84
EXIDINE	XTTRIUM	019422	CHLORHEXIDINE GLUCONATE	2%	SOLUTION; TPICAL	Over-the-counter	17-Dec-85
HIBICLENS	REGENT	017768	CHLORHEXIDINE GLUCONATE	4%	SOLUTION; TOPICAL	Over-the-counter	17-Sep-76
HIBICLENS	REGENT	018423	CHLORHEXIDINE GLUCONATE	4%	SPONGE; TOPICAL	Over-the-counter	27-Aug-81
HIBISTAT	REGENT	018300	CHLORHEXIDINE GLUCONATE	0.50%	SOLUTION; TOPICAL	Over-the-counter	23-May-80

Drug Name	Company	FDA Application No.	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	Approval Date
MICRODERM	J AND J	072255	CHLORHEXIDINE GLUCONATE	4%	SOLUTION; TOPICAL	Over-the-counter	15-Apr-91
MICRODERM	J AND J	072295	CHLORHEXIDINE GLUCONATE	4%	SPONGE; TOPICAL	Over-the-counter	28-Feb-91
PREVACARE R	J AND J	072292	CHLORHEXIDINE GLUCONATE	0.5%	SOLUTION; TOPICAL	Over-the-counter	28-Jan-92
PERIOCHIP	DEXCEL PHARMA	020774	CHLORHEXIDINE GLUCONATE	2.5MG	TABLET; DENTAL	Prescription	15-May-98
PERIOGARD	COLGATE	073695	CHLORHEXIDINE GLUCONATE	0.12%	SOLUTION; DENTAL	Prescription	14-Jan-94
PHARMASEAL SCRUB CARE	PHARMASEAL	019793	CHLORHEXIDINE GLUCONATE	4%	SPONGE; TOPICAL	Over-the-counter	2-Dec-88

Source: Drugs@FDA, FDA/Center for Drug Evaluation and Research

Annex C

List of guidelines and RCTs

16 guidelines identified through the *National Guideline Clearinghouse*

Keyword: *umbilical cord care*

1. [Caesarean section](#). National Collaborating Centre for Women's and Children's Health - National Government Agency [Non-U.S.]. 2004 Apr. 38 pages. NGC:003544
2. [Postnatal care. Routine postnatal care of women and their babies](#). National Collaborating Centre for Primary Care - National Government Agency [Non-U.S.]. 2006 Jul. 392 pages. NGC:005150
3. [Management of labor](#). Institute for Clinical Systems Improvement - Private Nonprofit Organization. 2005 Oct (revised 2007 Mar). 72 pages. NGC:005587
4. [Management of HIV in pregnancy](#). Royal College of Obstetricians and Gynaecologists - Medical Specialty Society. 2004 Apr. 12 pages. NGC:004475
5. [Cord blood banking for potential future transplantation](#). American Academy of Pediatrics - Medical Specialty Society. 2007 Jan. 6 pages. NGC:005435
6. [Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals](#). American Medical Association - Medical Specialty Society Center for Food Safety and Applied Nutrition - Federal Government Agency [U.S.] Centers for Disease Control and Prevention - Federal Government Agency [U.S.] Food Safety and Inspection Service - Federal Government Agency [U.S.]. 2001 Jan (revised 2004 Apr 16). 33 pages. NGC:003593
7. [Antithrombotic therapy supplement](#). Institute for Clinical Systems Improvement - Private Nonprofit Organization. 2001 Sep (revised 2007 Aug). 64 pages. NGC:005971
8. [Congenital syphilis. Sexually transmitted diseases treatment guidelines 2006](#). Centers for Disease Control and Prevention - Federal Government Agency [U.S.]. 1993 (revised 2006 Aug 4). 4 pages. NGC:005185
9. [Interim guidelines for the evaluation of infants born to mothers infected with West Nile virus during pregnancy](#). Centers for Disease Control and Prevention - Federal Government Agency [U.S.]. 2004 Feb 27. 4 pages. NGC:003471
10. [Growth disturbances: risk of intrauterine growth restriction](#). American College of Radiology - Medical Specialty Society. 1996 (revised 2007). 10 pages. NGC:006006
11. [Ultrasound scanning during pregnancy](#). Finnish Medical Society Duodecim - Professional Association. 2000 Apr 3 (revised 2004 Jun 28). Various pagings. NGC:004106
12. [Practice parameter for the diagnosis and management of primary immunodeficiency](#). American Academy of Allergy, Asthma and Immunology - Medical Specialty Society American College of Allergy, Asthma and Immunology - Medical Specialty Society Joint Council of Allergy, Asthma and Immunology - Medical Specialty Society. 1995 Aug 31 (revised 2005 May). 63 pages. NGC:004445
13. [Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation](#). American Academy of Pediatrics - Medical Specialty Society. 1994 Oct (revised 2004 Jul). 20 pages. NGC:003716

14. [Dystocia and augmentation of labor](#). American College of Obstetricians and Gynecologists - Medical Specialty Society. 2003 Dec. 10 pages. NGC:005722
15. [Vaginal birth after previous cesarean delivery](#). American College of Obstetricians and Gynecologists - Medical Specialty Society. 1999 Jun (revised 2004 Jul). 8 pages. NGC:004043
16. [Screening for sickle cell disease in newborns: U.S. Preventive Services Task Force recommendation statement](#). United States Preventive Services Task Force - Independent Expert Panel. 1996 (revised 2007). 10 pages. NGC:005908

36 guidelines identified through Medline (only titles reported)

Keyword: "*Umbilical Cord*"[Mesh] AND ("*Guideline* "[Publication Type] OR "*Health Planning Guidelines*"[Mesh] OR *guideline* OR *recommendations*)

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- 2: Mercer JS, Erickson-Owens DA, Graves B, Haley MM. Evidence-based practices for the fetal to newborn transition. J Midwifery Womens Health. 2007 May-Jun;52(3):262-72
- 3: Mitchell RT, Thompson R, Thomas S. Surgical retrieval of a transected umbilical artery catheter. Neonatal Netw. 2007 Mar-Apr;26(2):133-4
- 4: Hutchon DJ. NICE is encouraging artificial intervention. BMJ. 2007 Mar 31;334(7595):651
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- 12: Hillemanns P, Strauss A, Hasbargen U, Schulze A, Genzel-Boroviczeny O, Weninger E, Hepp H. Crash emergency cesarean section: decision-to-delivery interval under 30 min and its effect on Apgar and umbilical artery pH. *Arch Gynecol Obstet.* 2005 Dec;273(3):161-5
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- 18: Kwee A, van der Hoorn-van den Beld CW, Veerman J, Dekkers AH, Visser GH. STAN S21 fetal heart monitor for fetal surveillance during labor: an observational study in 637 patients. *J Matern Fetal Neonatal Med.* 2004 Jun;15(6):400-7
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21 RCT selected through the databases **Medline** and **EMBASE**. (abstract reported)

Search strategy, free terms: *chlorhexidine digluconate*

Limits: *human, randomized controlled trial, time limits from 1995.01.01*

1: *Arch Intern Med.* 2007 Oct 22;167(19):2066-72.

Chlorhexidine-based antiseptic solution vs alcohol-based povidone-iodine for central venous catheter care.

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BACKGROUND: Although chlorhexidine-based solutions and alcohol-based povidone-iodine have been shown to be more efficient than aqueous povidone-iodine for skin disinfection at catheter insertion sites, their abilities to reduce catheter-related infection have never been compared.

METHODS: 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).

RESULTS: Of 538 catheters randomized, 481 (89.4%) produced evaluable culture results. 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 = .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 = .09]; incidence density, 1.4 vs 3.4 per 1000 catheter-days). Independent risk factors for catheter colonization were catheter insertion into the jugular vein (adjusted relative risk, 2.01; 95% confidence interval, 1.24-3.24) and use of povidone-iodine (adjusted relative risk, 1.87; 95% confidence interval, 1.18-2.96). **CONCLUSION:** Chlorhexidine-based solutions should be considered as a replacement for povidone-iodine (including alcohol-based) formulations in efforts to prevent catheter-related infection.

2: Am J Infect Control. 2007 Mar;35(2):89-96.

Comparative of a new and innovative 2% chlorhexidine gluconate-impregnated cloth with 4% chlorhexidine gluconate as topical antiseptic for preparation of the skin prior to surgery.

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BACKGROUND: Decreasing the microbial skin burden reduces the risk of surgical site infection (SSI). The present 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). **METHODS:** A paired, randomized, parallel phase III study was conducted adhering to the Food and Drug Administration (FDA) design criteria for evaluating preoperative skin preparations. 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 postpreparation. Bacterial recovery was expressed as log(10) colony-forming units (cfu)/cm(2) for baseline and postapplication microbial recovery.

RESULTS: 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. Log(10) reduction for PC abdominal and inguinal prepped sites at 10 minutes, 30 minutes, and 6 hours postpreparation were 2.50, 2.33, and 2.54; 3.45, 3.50, and 3.64, respectively. Log(10) 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. **CONCLUSION:** Microbial reductions from abdominal-inguinal PC prepped sites were significantly reduced (P < .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 < .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 ($P < .01$).

3: *Ann R Coll Surg Engl.* 2006 Jan;88(1):13-5.

Comment in:

Ann R Coll Surg Engl. 2007 Mar;89(2):191; author reply 191.

Hand washing rituals in trauma theatre: clean or dirty?

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INTRODUCTION: The aim of this study was to investigate the degree of contamination of a surgeon's hand following use of chlorhexidine gluconate or alcohol gel as disinfectants.

MATERIALS AND METHODS: In this prospective, randomised trial, orthopaedic surgeons were allocated to one of two different hand-washing protocols using a randomisation table. The hand-washing protocol dictated that all surgeons should wash for 5 min with chlorhexidine for their first case. Thereafter, the surgeon was randomised to wash for 3 min with either alcohol gel or chlorhexidine. At the end of each procedure, the gloves of each surgeon were carefully removed and the fingertips from each hand were placed on an agar plate. The number of bacterial colonies present after 24 h and 48 h of incubation were recorded for each agar plate by a microbiologist blinded to the washing protocol used. **RESULTS:** Overall, 41 procedures and 82 episodes of hand washings were included in the study. Two episodes were discarded due to contamination at the time of glove removal. Four hands (8%) were contaminated in the chlorhexidine group compared to 19 (34%) in the alcohol group. Fisher's exact test confirmed a significantly higher risk of contamination using alcohol gel compared to chlorhexidine ($P = 0.002$). In addition, the average bacterial colony count was substantially higher in the alcohol group (20 colony forming units) compared to the chlorhexidine group (5 colony forming units). There was no relationship between the duration of surgery and the degree of contamination ($P = 1.12$). **CONCLUSIONS:** Alcohol gel disinfectant is not a suitable alternative to chlorhexidine when hand washing before surgery. This study has identified a higher risk of bacterial contamination of surgeons' hands washed with alcohol. This may lead to higher levels of postoperative infection in the event of glove perforation.

4: *Arch Pediatr Adolesc Med.* 2005 Apr;159(4):377-83.

Comment in:

Arch Pediatr Adolesc Med. 2005 May;159(5):502-3.

Effect of antiseptic handwashing vs alcohol sanitizer on health care-associated infections in neonatal intensive care units.

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BACKGROUND: The Centers for Disease Control and Prevention, Atlanta, Ga, recommend use of waterless alcohol hand products in lieu of traditional handwashing for patient care, but there are few data demonstrating the impact of this recommendation on health care-associated infections. **OBJECTIVE:** To compare the effect of 2 hand hygiene regimens on infection rates and skin condition and microbial counts of nurses' hands in neonatal intensive care units. **DESIGN, SETTING, AND PARTICIPANTS:** Clinical trial using a crossover design in 2 neonatal intensive care units in Manhattan, NY, from March 1, 2001, to January 31, 2003, including 2932 neonatal hospital admissions (51 760 patient days) and 119 nurse participants. **INTERVENTION:** Two hand hygiene products were tested: a traditional antiseptic handwash and an alcohol hand sanitizer. Each product was used for 11 consecutive months in each neonatal intensive care unit in random order. **RESULTS:** After adjusting for study site, birth weight, surgery, and follow-up time, there were no significant differences in neonatal infections between the 2 products; odds ratios for alcohol compared with handwashing were 0.98 (95% confidence interval [CI], 0.77-1.25) for any infection, 0.99 (95% CI, 0.77-1.33) for bloodstream infections, 1.61 (95% CI, 0.57-5.54) for pneumonia, 1.78 (95% CI, 0.94-3.37) for skin and soft tissue infections, and 1.26 (95% CI, 0.42-3.76) for central nervous system infections. The skin condition of participating nurses was significantly improved during the alcohol phase ($P = .02$ and $P = .049$ for observer and self-assessments, respectively), but there were no significant differences in mean microbial counts on nurses' hands (3.21 and 3.11 \log_{10} colony-forming units for handwashing and alcohol, respectively; $P = .38$). **CONCLUSIONS:** Infection rates and microbial counts on nurses' hands were equivalent during handwashing and alcohol phases, and nurses' skin condition was improved using alcohol. However, assessing the impact on infection rates of a single intervention is challenging because of multiple contributory factors such as patient risk, unit design, and staff behavior. Other practices such as frequency and quality of hand hygiene are likely to be as important as product in reducing risk of cross-transmission.

5: *Am J Obstet Gynecol.* 2005 Feb;192(2):422-5.

Comment in:

Am J Obstet Gynecol. 2006 Aug;195(2):624; author reply 625.

A randomized trial that compared povidone iodine and chlorhexidine as antiseptics for vaginal hysterectomy.

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OBJECTIVE: The purpose of this study was to compare the efficacy of chlorhexidine and povidone iodine for cleansing the operative field for vaginal surgery. **STUDY DESIGN:** This was a randomized controlled trial that compared 10% povidone iodine and 4% chlorhexidine gluconate as surgical scrubs. Our primary end point was the proportion of contaminated specimens (defined as total bacterial colony counts of ≥ 5000 colony-forming units) per group found throughout the surgical procedures. All patients received standard infection prophylaxis that included preoperative intravenous antibiotics. Immediately before antibiotic administration and baseline aerobic and anaerobic cultures of the vaginal flora were obtained, which were followed by cultures at 30 minutes after the surgical scrub and hourly thereafter throughout each patient's surgery. **RESULTS:** A total of 50 patients were enrolled between October 2002 and September 2003. There were no differences between the povidone iodine ($n = 27$) and chlorhexidine ($n = 23$) groups with respect to

age, race, exogenous hormone use, body mass index, gravity, parity, preoperative mean colony counts, or operative time. Among the first set of intraoperative specimens (which were obtained 30 minutes after the surgical scrub), 63% of the cultures (17/27) from the povidone iodine group and 22% of the cultures (5/23) from the chlorhexidine group were classified as contaminated ($P = .003$; relative risk, 6.12; 95% CI, 1.7, 21.6). Subsequent cultures failed to demonstrate significant differences. **CONCLUSION:** Chlorhexidine gluconate was more effective than povidone iodine in decreasing the bacterial colony counts that were found in the operative field for vaginal hysterectomy.

6: JAMA. 2003 Mar 12;289(10):1274-7.

Efficacy of selected hand hygiene agents used to remove *Bacillus atrophaeus* (a surrogate of *Bacillus anthracis*) from contaminated hands.

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CONTEXT: The intentional use of *Bacillus anthracis* transmitted via the US mail in October-November 2001 resulted in 22 people developing inhalation or cutaneous anthrax. Glove use with handwashing prior to and after contact with potential contaminated environmental surfaces and cutaneous lesions has been recommended. However, only limited data are available on the susceptibility of *B anthracis* to antiseptics. **OBJECTIVE:** To evaluate the efficacy of several hand antiseptics (interventions) and soap and water (control) against *Bacillus atrophaeus*, a surrogate of *B anthracis*. **DESIGN, SETTING, AND PARTICIPANTS:** Challenge study conducted among healthy adult volunteers, using the Standard Test Method for Evaluation of the Effectiveness of Health Care Professional Handwash Formulations (American Society for Testing and Materials E 1174-94) to determine the efficacy of various hand hygiene products at wash times of 10, 30, and 60 seconds. Volunteers were excluded if they had eczema, psoriasis, or other chronic skin conditions; nonintact skin; or allergies to any study agent. Study agents were a waterless rub containing 61% ethyl alcohol, a 2% chlorhexidine gluconate preparation, and an antibacterial microfiber towel that releases hypochlorite. A nonantimicrobial soap was used as a control. **MAIN OUTCOME MEASURE:** Reduction of *B atrophaeus* spores (\log_{10} CFU/mL) on contaminated hands. **RESULTS:** Washes of 10, 30, and 60 seconds with either soap and water or 2% chlorhexidine gluconate eliminated 1.5 to 2.0 \log_{10} CFUs/mL of *B atrophaeus* spores at wash 3. Mean reductions (95% confidence intervals) with 10-, 30-, and 60-second washes with soap and water were 2.4 (2.2-2.5), 2.3 (2.2-2.4), and 2.1 (1.9-2.4) \log_{10} CFUs/mL, respectively; and with 2% chlorhexidine gluconate, 2.1 (2.0-2.3), 1.8 (1.5-2.0), and 1.7 (1.5-1.9) \log_{10} CFUs/mL, respectively. Handwashing with chlorine-containing towels was increasingly effective as the wipe time increased; reductions at 10, 30, and 60 seconds were 1.3 (1.1-1.5), 1.6 (1.2-2.0), and 2.2 (2.1-2.2) \log_{10} CFUs/mL, respectively. A waterless rub containing 61% ethyl alcohol was ineffective in eliminating *B atrophaeus* spores at all times tested (0 [-0.1 to 0.1], -0.2 [-0.3 to -0.1], and 0 [-0.2 to 0.2] \log_{10} CFUs/mL). **CONCLUSIONS:** In this evaluation of hand hygiene agents, handwashing with soap and water, 2% chlorhexidine gluconate, or chlorine-containing towels reduced the amount of *B atrophaeus* spore contamination, whereas use of a waterless rub containing ethyl alcohol was not effective in removing spores.

7: Infect Control Hosp Epidemiol. 2002 Jul;23(7):397-401.

Skin antiseptics kits containing alcohol and chlorhexidine gluconate or tincture of iodine are associated with low rates of blood culture contamination.

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OBJECTIVE: Skin preparation is an important factor in reducing the rate of blood culture contamination. We assessed blood culture contamination rates associated with the use of skin antiseptics kits containing either 2% alcoholic chlorhexidine gluconate or 2% alcoholic tincture of iodine. **DESIGN:** Prospective, blinded clinical trial. **SETTING:** Tertiary-care teaching hospital. **PATIENTS:** Adult patients in medical wards, the medical intensive care unit, and the cardiac intensive care unit who needed paired, percutaneous blood cultures. **INTERVENTIONS:** House officers, medical students, and healthcare technicians drew the blood for cultures. We prepared sacks containing all of the necessary supplies, including two different types of antiseptic kits. In each sack, one kit contained 2% chlorhexidine in 70% isopropyl alcohol and the other contained 2% tincture of iodine in ethyl alcohol and 70% isopropyl alcohol. Each patient received chlorhexidine at one site and tincture of iodine at the other. **RESULTS:** Four (0.9%) of 430 blood culture sets from 215 patients were contaminated. The contamination rate when using alcohol and chlorhexidine (1 of 215, 0.5%) did not differ significantly from the contamination rate when using tincture of iodine (3 of 215, 1.4%; $P = .62$, McNemar test). There was an 87% probability that the two interventions differed by less than 2% in their rate of contamination. **CONCLUSIONS:** Both of these antiseptic kits were highly effective for skin preparation prior to drawing blood for cultures. The use of these kits may have contributed to the low contamination rate observed in this study.

8: Crit Care Med. 2001 May;29(5):944-51.

Comment in:

Crit Care Med. 2001 May;29(5):1083-4.

Assessment of two hand hygiene regimens for intensive care unit personnel.

Larson EL, Aiello AE, Bastyr J, Lyle C, Stahl J, Cronquist A, Lai L, Della-Latta P. Columbia University School of Nursing, New York, NY, USA.

OBJECTIVE: To compare skin condition and skin microbiology among intensive care unit personnel using one of two randomly assigned hand hygiene regimens: a 2% chlorhexidine gluconate (CHG)-containing traditional antiseptic wash and a waterless handrub containing 61% ethanol with emollients (ALC). **DESIGN:** Prospective, randomized clinical trial. **SETTING:** Two critical care units (medical and surgical) in a large, metropolitan academic health center in Manhattan. **SUBJECTS:** Fifty staff members (physicians, nurses, housekeepers, respiratory therapists) working full time in the intensive care unit. **INTERVENTIONS:** One of two hand hygiene regimens randomly assigned for four consecutive weeks. **MEASUREMENTS AND MAIN RESULTS:** The two outcomes were skin condition (measured by two tools: Hand Skin Assessment form and Visual Skin Scaling form) and skin microbiology. Samples were obtained at baseline, on day 1, and at the end of wks 2 and 4. Participants in the ALC group had significant improvements in the Hand Skin Assessment scores at wk 4 ($p = 0.04$) and in Visual Skin Scaling scores at wks 3 ($p = 0.01$) and 4 ($p = 0.0005$). There were no significant differences in numbers of colony-forming units between participants in the CHG or ALC group at any time period. The ALC regimen required significantly less time than the CHG regimen (mean: 12.7 secs and 21.1 secs, respectively; $p =$

0.000) and resulted in a 50% reduction in material costs. CONCLUSIONS: Changes in hand hygiene practices in acute care settings from the traditional antiseptic wash to use of plain, mild soap and an alcohol-based product should be considered. Further research is needed to examine the association between use of antiseptic products for hand hygiene of staff and reductions in nosocomial infection rates among patients.

9: *J Hosp Infect.* 1997 May;36(1):49-65.

An evaluation of five protocols for surgical handwashing in relation to skin condition and microbial counts.

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Five protocols for surgical handwashing (scrubbing) were evaluated for their efficiency of removal of micro-organisms and their drying effect on the skin. The scrubbing protocols tested were: (1) an initial scrub of 5 min and consecutive scrubs of 3.5 min with chlorhexidine gluconate 4% (CHG-5); (2) an initial scrub of 3 min and consecutive scrubs of 2.5 min with chlorhexidine gluconate 4% (CHG-3); (3) an initial scrub of 3 min and consecutive scrubs of 2.5 min with povidone iodine 5% and triclosan 1% (PI-3); (4) an initial scrub of 2 min with chlorhexidine gluconate 4% followed by a 30 s application of isopropanol 70% and chlorhexidine gluconate 0.5%, and a 30 s application of isopropanol 70% and chlorhexidine gluconate 0.5% for consecutive scrubs (IPA); and (5) an initial scrub of 2 min with chlorhexidine gluconate 4% followed by a 30 s application of ethanol 70% and chlorhexidine gluconate 0.5%, and a 30 s application of ethanol 70% and chlorhexidine gluconate 0.5% for consecutive scrubs (EA). A convenience sample of 23 operating theatre nurses completed each scrub protocol for one week in a randomized order. A week of normal work activities intervened between each protocol. Subjects were assessed before commencing and after completing the week of each protocol to determine changes in the microbial counts and skin condition of the hands. Specimens for microbial analysis were collected before, immediately after and 2 h after an initial scrub, and 2 h after a consecutive scrub. The CHG-5, CHG-3 and PI-3 protocols, which used detergent-based antiseptics only, were compared with protocols incorporating an alcohol-based antiseptic (IPA and EA). The protocols incorporating alcohol-based antiseptics and the CHG-5 protocol were generally associated with the lowest post-scrub numbers of colony forming units (cfu). No difference between the CHG-5 protocol and the alcohol-based antiseptics was found at the beginning of the test week, but after exclusive use of the respective protocols for a week, the alcohol-based antiseptics were associated with significantly lower cfu numbers in two out of the three post-scrub samples ($P = 0.003$, $P = 0.035$). Although virtually no statistically significant differences in skin condition were found, many subjects reported the alcohol-based antiseptic protocols to be less drying on the skin. The findings of this study support the proposition that a scrub protocol using alcohol-based antiseptics is as effective and no more damaging to skin than more time-consuming, conventional methods using detergent-based antiseptics.

10: *Acta Paediatr.* 1994 Sep;83(9):923-6.

Prevention of neonatal infections by vaginal chlorhexidine disinfection during labour.

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Comparison of two different methods of vaginal disinfection was made with regard to prevention of neonatal infections. In method I, an antepartum vaginal douche with a chlorhexidine solution was used; method II involved the use of chlorhexidine gluconate obstetrical gel during vaginal exploration. We studied 2853 normal deliveries from a total number of 3236 deliveries: 1467 deliveries were allocated randomly to receive a vaginal douche whereas 1386 underwent vaginal exploration using chlorhexidine gel. A total of 203 neonates were transferred to the neonatal unit (120 males and 83 females): 101 belonged to the group where the mothers were subjected to method I, whereas in 102 method II had been used. Within 48 h postpartum 30 neonates from the method I group and 34 neonates from the method II group received systemic antibiotics. There was a tendency towards a higher proportion of full-term neonates with verified septicaemia in the method II group (6 versus 2), whereas the numbers of probable infections were 8 versus 12. The corresponding total numbers in preterm infants were 3 and 2, respectively. These differences were not statistically significant. We conclude that the use of chlorhexidine douche compared with vaginal exploration with chlorhexidine gel provides no additional advantages.

11: *Int Urol Nephrol.* 1993;25(4):359-67.

The use of intermittent chlorhexidine bladder irrigation in the prevention of post-prostatectomy infective complications.

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The efficacy of peri-operative intermittent bladder irrigation with 0.05% chlorhexidine gluconate solution in the prevention of post-prostatectomy infective complications was assessed in men with pre-operative indwelling urinary catheters. Thirty-two consecutive patients undergoing transvesical prostatectomy were randomly allocated to the test group (chlorhexidine irrigation) and control group (saline irrigation). Pre-operatively, intermittent chlorhexidine bladder irrigation achieved sterile urine in only 3 of 13 patients, in the rest bacteriuria persisted. However, the irrigation was able to reduce significantly ($P < 0.05$) the incidence of intra-operative bacteraemia and severe wound infection. Furthermore, septicaemia was absent and post-operative urinary catheter requirements and hospital stay were shortened. Histology of bladder mucosal biopsies revealed that 0.05% chlorhexidine used on intermittent basis caused no injuries.

12: *Oncol Nurs Forum.* 1991 Sep-Oct;18(7):1207-13.

Efficacy of chlorhexidine gluconate use in the prevention of perirectal infections in patients with acute leukemia.

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The frequency of rectal infections is increased in patients with acute leukemia. Complications associated with rectal lesions may be severe enough to cause life-threatening septicemia. Clinical research evaluating the effects of preventive perirectal skin care is scarce. This study's purpose was to determine whether using chlorhexidine gluconate (CHG) in a prophylactic perirectal skin-care

regimen decreases perirectal infections and whether it produces more skin irritation than a nonmedicated skin cleanser. The sample consisted of 40 patients, 16 of whom were randomized to use chlorhexidine and 24 of whom were randomized to use nonmedicated skin cleanser. Chi-square and t-tests were used to analyze the incidence of skin breakdown and rectal infections; the correlation between the two factors; a positive history of rectal infections, fissures, or hemorrhoids; presence of hemorrhoids; severity of diarrhea; and duration and severity of granulocytopenia. A positive relationship was found between the severity of granulocytopenia and the incidence of rectal infections ($p = 0.02$). No significant difference was seen in the occurrence of perirectal infections ($p = 0.35$) or skin breakdown ($p = 0.18$) between the two groups. The data suggest that CHG does not offer increased protection against perirectal infections in patients undergoing intensive chemotherapy, nor is it more irritating than a nonmedicated skin cleanser. Further studies are needed to examine the efficacy of hygienic measures such as using skin disinfectants to prevent infections in patients who are immunocompromised.

13: J Hosp Infect. 1990 Aug;16(2):161-6.

Surgical hand disinfection: effect of sequential use of two chlorhexidine preparations.

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The antimicrobial efficacy of three 'two-phase' surgical hand disinfection procedures was compared, in a volunteer study, to 60% n-propanol, applied for 5 min, which is the reference hand-disinfection procedure used in Austria and West Germany (FRG). The procedures involved sequential use of unmedicated soap or a disinfectant-detergent containing 4% chlorhexidine gluconate (CHX; 'Hibiscrub') followed by a handrub preparation containing 70% w/w isopropanol plus 0.5% CHX ('Hibisol'). The immediate and sustained effects (3 h) of washing with unmedicated soap (3 min) followed by rubbing on 'Hibisol' (4 min) were significantly smaller (log₁₀ reductions of 1.72 and 1.12) than with each of the other procedures. Use of 'Hibiscrub' (3 min) and 'Hibisol' (4 min) produced log₁₀ reductions of 2.50 and 1.71, equalling those of the reference procedure with n-propanol (2.49 and 1.78). When 'Hibisol' was used for 5 min rather than 4 min, a considerable, though not significant, increase in effect was achieved (log₁₀ reductions of 2.90 and 2.07). Replacement of unmedicated soap by 'Hibiscrub' could significantly improve the effectiveness of the hand disinfection procedure commonly used by surgeons in German-speaking countries; namely to wash hands first with soap and then disinfect them with an alcoholic preparation. It may also be of additional advantage as this adds another 'layer' of CHX when 'Hibisol' rather than alcohol alone is used.

14: J Hosp Infect. 1990 Aug;16(2):141-9.

Hygienic hand disinfection tests in three laboratories.

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A comparative study was made in three laboratories of a test for hygienic hand disinfection. *Staphylococcus aureus* was applied to the fingertips of a total of 74 volunteers (49 female and 25 male) and the effect of washing with three chlorhexidine preparations and one non-medicated soap

was assessed after one and five applications. Fingertip inoculation is convenient and is a realistic representation of the in-use situation. Although significant differences were obtained between log₁₀ reductions in test organisms using the same formulation in different centres, and different periods in the same centre, the maximum differences after a single application of a preparation were small, e.g. between centres 0.39 and between periods in the same centre 0.55, and after multiple applications the maximum difference between centres was 0.42 and between periods in the same centre it was 0.51. The differences between preparations were similar in all centres. This test compares well with other similar tests and products can be placed in rank order of effectiveness. It is concluded that this test, if carried out under the controlled conditions described, is sufficiently reproducible between laboratories and repeatable within laboratories to be used as a standard test.

15: J Hosp Infect. 1988 May;11(4):310-20.

A comparison of the effects of preoperative whole-body bathing with detergent alone and with detergent containing chlorhexidine gluconate on the frequency of wound infections after clean surgery. The European Working Party on Control of Hospital Infections.

Rotter ML, Larsen SO, Cooke EM, Dankert J, Daschner F, Greco D, Grönross P, Jepsen OB, Lystad A, Nyström B.

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In a prospective, randomized, double-blind, placebo-controlled study involving 27 surgical units in six European countries, the effect of preoperative whole-body bathing on two occasions with a detergent containing chlorhexidine (CHX+) on the incidence of wound infection in elective, clean surgery was compared with two bathings with a detergent without chlorhexidine (CHX-). In the CHX+ group 2.62% of 1413 patients and in the CHX- group 2.36% of 1400 patients subsequently became infected. The infection rate in the CHX+ group was 1.11 times that in the CHX- group with 95% confidence limits ranging between 0.69 and 1.82. Consequently, bathing patients twice preoperatively with chlorhexidine-detergent did not reduce the incidence of infection of clean wounds.

16: J Hosp Infect. 1988 Apr;11 Suppl B:5-9.

Prevention of intraoperative wound contamination with chlorhexidine shower and scrub.

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In a prospective, controlled, clinical trial, we found that preoperative showering and scrubbing with 4% chlorhexidine gluconate was more effective than povidone-iodine or triclocarban medicated soap in reducing skin colonization at the site of surgical incision. Mean log colony counts of the incision site were one half to one log lower for patients who showered with chlorhexidine compared to those who showered with the other regimens. No growth was observed on 43% of the post shower skin cultures from patients in the chlorhexidine group compared with 16% of the cultures from patients who had povidone-iodine showers and 5% of those from patients who used medicated soap and water. The frequency of positive intraoperative wound cultures was 4% with

chlorhexidine, 9% with povidone-iodine and 14% with medicated soap and water. This study demonstrates that chlorhexidine gluconate is a more effective skin disinfectant than either povidone-iodine or triclocarban soap and water and that its use is associated with lower rates of intraoperative wound contamination.

17: *Antimicrob Agents Chemother.* 1987 Oct;31(10):1572-4.

Comparison of four antiseptic products containing chlorhexidine gluconate.

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The purpose of this study was to compare the antimicrobial efficacies of four formulations of chlorhexidine gluconate (CHG) for handwashing under frequent-use conditions. Fifty volunteers were assigned by block randomization to one of five products: one of two liquid detergents containing 4% CHG, a liquid detergent containing 2% CHG, a foam containing 4% CHG, and a nonantiseptic soap (control). Subjects washed their hands by a standardized technique 15 times per day for 5 days. After days 1 and 5 of handwashing, there was a significant reduction in log CFU for subjects using all four CHG-containing products compared with subjects using control soap and for subjects within each group after days 1 and 5 compared with the base-line CFU counts (all P less than 0.05). There were no significant differences between the four CHG products at any testing time. We conclude that all four formulations are satisfactory for clinical use.

18: *J Hosp Infect.* 1987 Sep;10(2):165-72.

A placebo-controlled trial of the effect of two preoperative baths or showers with chlorhexidine detergent on postoperative wound infection rates.

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The effect of preoperative whole-body washing with chlorhexidine detergent on the incidence of postoperative wound infection was assessed in a placebo-controlled trial of 1989 patients. Patients bathed or showered with chlorhexidine, placebo, or conventional bar soap, on two occasions in the 24 h before operation. The overall infection rate for patients treated with chlorhexidine was 9%, against 12.8% in the bar soap and 11.7% in the placebo groups; in the 'clean' surgery group infections were 7.2% against 10.2% and 10%, respectively. The *Staphylococcus aureus* infection rate in the 'clean' group was 3% for chlorhexidine against 6% for bar soap.

19: *Cutis.* 1987 Jun;39(6):551-3.

Efficacy of 4 percent chlorhexidine gluconate skin cleanser in the treatment of acne vulgaris.

Stoughton RB, Leyden JJ.

We conducted three controlled, comparative studies to assess the effectiveness of a 4 percent chlorhexidine gluconate skin cleanser (Hibiclens) for the treatment of acne lesions in patients with acne vulgaris. In all studies, the chlorhexidine gluconate formulation achieved statistically

significant reduction of the papules plus pustules count, which is generally accepted as the principal criterion of efficacy.

20: Burns Incl Therm Inj. 1984 Oct;11(1):35-40.

Prospective comparison of silver sulfadiazine 1 per cent plus chlorhexidine digluconate 0.2 per cent (Silvazine) and silver sulfadiazine 1 per cent (Flamazine) as prophylaxis against burn wound infection.

Inman RJ, Snelling CF, Roberts FJ, Shaw K, Boyle JC.

Patients with fresh full-thickness burn wounds were randomly assigned to receive wound treatment with daily applications of either 1 per cent silver sulfadiazine plus 0.2 per cent chlorhexidine digluconate cream (Silvazine) or 1 per cent silver sulfadiazine (Flamazine). Fifty-four patients treated with Silvazine were comparable to 67 treated with Flamazine with respect to extent and distribution of burn, age and all aspects of wound and associated treatment. Overall incidence of wound bacterial colonization was less in the Silvazine treated patients (65 per cent versus 88 per cent; $P = 0.002$). With Silvazine, wound colonization by *Staphylococcus aureus* was less (41 per cent versus 64 per cent; $P = 0.01$). Clinical wound infection with *Staph. aureus* developed in one Silvazine treated patient and five Flamazine treated patients ($P = 0.16$). Colonization by and infection due to all other organisms did not differ in the two groups. The incidence of graft failure was similar with both agents. In future increasing the concentration of chlorhexidine digluconate above 0.2 per cent might produce an improved prophylactic effect against Gram negative bacteria reported by other authors using the combined agent in in vitro and clinical trials. Silvazine was effective in reducing the incidence of *Staph. aureus* burn wound colonization without fostering supervening opportunistic infection.

21: Pathol Biol (Paris). 1984 Jun;32(5 Pt 2):604-6.

[Comparison of 2 antiseptic soaps used for preoperative showers]

[Article in French]

Enjalbert L, Levade Y, Marchetti P.

This study was carried out in cardiovascular surgery wards and a single operating room. Two different antiseptic scrubs, A and B, were used for two showers given 48 and 24 hours respectively prior to surgery. A scrub (chlorhexidine digluconate 40 mg/ml) was used in 61 patients and B scrub (benzalkonium chloride 5 mg/ml) in 52, for a total of 113 participants. Clinical and bacteriological evaluations show statistically significant superiority of A scrub.