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REVIEW

Antiseptic use in the neonatal intensive care unit - a dilemma in clinical practice: An evidence based review

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Abstract

Infants in the neonatal intensive care unit are highly susceptible to healthcare associated infections (HAI), with a substantial impact on mortality, morbidity and healthcare costs. Effective skin disinfection with topical antiseptic agents is an important intervention in the prevention or reduction of HAI. A wide array of antiseptic preparations in varying concentrations and combinations has been used in neonatal units worldwide. In this article we have reviewed the current evidence of a preferred antiseptic of choice over other agents for topical skin disinfection in neonates. Chlorhexidine (CHG) appears to be a promising antiseptic agent; however there exists a significant concern regarding the safety of all agents used including CHG especially in preterm and very low birth weight infants. There is substantial evidence to support the use of CHG for umbilical cord cleansing and some evidence to support the use of topical emollients in reducing the mortality in infants born in developing countries. Well-designed large multicentre randomized clinical trials are urgently needed to guide us on the most appropriate and safe antiseptic to use in neonates undergoing intensive care, especially preterm infants.

Key words: Antiseptics; Disinfectants; Topical; Neonate; Preterm; Very low birth weight infant; Chlorhexidine; Povidone-iodine; Alcohol

Core tip: Topical antiseptic agents play a crucial role in the prevention of nosocomial infections in infants admitted to neonatal intensive care unit. There is a paucity of good quality studies to guide us on the most effective and safe antiseptic preparation, concentration and combination for use in neonatal skin disinfection. Further research is urgently needed to identify the most appropriate and safe antiseptic use in neonates including preterm and very low birth weight infants.

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INTRODUCTION

Sepsis is one of the leading causes of death in infants admitted to the neonatal unit[1-5]. Neonatal sepsis is also associated with significant morbidity including prolonged hospital stay and increases in health care costs[6,7]. Studies have shown that sepsis in preterm and very low birth weight infants (VLBW) infants could lead to significant neurodevelopmental morbidity secondary to associated white matter injury[8-10]. Healthcare associated infections (HAI) account for vast majority of neonatal sepsis, with Catheter Related Bloodstream Infection (CRBSI) being the most common nosocomial infection[11,12]. The neonatal units, to reduce or prevent the HAI/CRBSI have adopted several strategies and use of an effective topical antiseptic agent is one of the integral components[11,13,14]. Centers for Disease Control and Prevention (CDC)[15] has made a specific recommendation for skin preparation before cannulation and central venous catheter insertion for adults and children 2 mo or older. Similarly United Kingdom national evidence based guidelines[16] recommend the use of 2% chlorhexidine gluconate (CHG) in 70% Isopropyl alcohol for skin antisepsis prior to venous cannulation and Central Venous Catheter (CVC) insertion in the same age group. However there is no specific guidance recommendation on antiseptic of choice for infants less than 2 mo. Wide range of antiseptics has been used in neonatal units all over the world, but good evidence is lacking, and the most appropriate and safe antiseptic solution to use on the skin remains controversial. The purpose of this review is to comprehensively examine the available literature on use of topical antiseptics in neonates and to identify evidence based recommendations for clinical practice. In this review we did not include the evidence of antiseptic use for hand hygiene in neonatal units.

BACKGROUND

HAI is a major problem in neonates that incur significant health and economic burden to the society. Gray *et al*[17] reported that nosocomial infections related to coagulase negative staphylococcus prolonged the hospital stay by 14.0 ± 4.0 d ($P < 0.01$) and an associated increase in hospital charges of $25090 ± 12051 ($P < 0.05$). In another report nosocomial infections were found to increase costs by 26% in < 750 g and 80% in 1250-1500 g infants and the length of stay was increased by 4-7 d in VLBW infants[18].

Preterm neonates are prone for infection because they have functionally immature immune system with extremely low immunoglobulin levels, complement activity, and neutrophil storage pool and function[19]. In addition, preterm infants lack an effective skin barrier. Stratum Corneum, which is responsible for providing an effective epidermal barrier, is not well developed until 32-34 wk of gestation. For babies born < 34 wk, it takes about 4-5 wk for the skin to mature which makes them more vulnerable to infections during this period[20-22]. Other risk factors for hospital-acquired infections include the presence of intravascular catheters, other invasive devices, mechanical ventilation, parenteral nutrition and use of broad-spectrum antibiotics[23].

CRBSI is the most common HAI[12] and is estimated to cause up to 70% of all hospital acquired infections in preterm infants[11]. Catheter hub colonisations followed by exit site were the strongest predictors of CRBSI in NICU[24]. Multi-faceted interventional strategies in the form of care bundles have been developed in neonates worldwide to reduce the HAI. There are several reports from all over the world, that catheter care bundles can reduce the risk of nosocomial and CRBSI[11,13,25]. One of the key steps included within the care bundles is that skin is appropriately disinfected to prevent the entry of microorganisms as well as to reduce the risk of subsequent infection. It is widely accepted; from adult and paediatric studies that CHG is most effective for skin antisepsis[26] and is recommended as best practice in various guidelines[15,16].

Antiseptics used in neonatal units

An ideal antiseptic agent should be effective against a wide range of microorganisms, have an immediate onset of action, have residual and long term effect, not be inactivated by the presence of organic material *e.g.,* blood, have minimum toxic effects on the skin and the organ systems[27,28]. A variety of topical antiseptics have been used in varying concentrations and combinations. Surveys from United States, United Kingdom, Australia and New Zealand showed that CHG, alcohols and Povidone-Iodine (PI) are the most commonly used agents in neonatal units[29-32].

Table 1 summarises the mechanism of action, spectrum of activity and disadvantages of individual antiseptic agents used in neonates[33,34].

Chlorhexidine: CHG a cationic bisguanide, first discovered in the United Kingdom is the most widely used antiseptic agent[35]. It is effective against gram-positive bacteria, somewhat less active against gram negative but is effective against resistant organisms including Methicillin Resistant Staphylococcus aureus (MRSA), Vancomycin resistant enterococcus (VRE), Streptococci and Pseudomonas[33,34,36]. CHG has significant residual activity and addition of alcohol based preparations results in significantly greater residual activity than alcohol alone. It also acts in the presence of organic material like blood or biofilm[33,34,36]. Its antimicrobial activity is slower than that of alcohols.

Table 1 Characteristics of topical antiseptic agents used in neonates (World Health Organization 2009)

Antiseptic agent	Mechanism of action	Advantages	Disadvantages	Preparations/ compounds
Chlorhexidine	Disruption of cytoplasmic membranes Denaturation of proteins	Broad spectrum antimicrobial activity Kills yeasts Intermediate onset of action Activity not affected by organic material Residual activity	Non-sporicidal Not effective against mycobacteria Local dermatitis Neurotoxicity Non-sporicidal	0.25%, 0.5%, 1%, 2%, 4% - aqueous and alcohol based
Alcohols	Damages cell membrane Denaturation of proteins	Broad spectrum antimicrobial activity Faster onset of action	Not active in presence of organic material No residual activity Skin reactions Systemic absorption	Ethanol, isopropyl alcohol, methanol
Iodine	Forms complexes with proteins and lipids Impaired protein synthesis and alteration of cell membranes	Broad spectrum antimicrobial activity Sporicidal Effective against mycobacteria Has some residual activity	Skin irritation Systemic absorption with hypothyroidism	10% povidone-iodine
Hexachlorophene	Inactivates essential enzyme systems	Good activity against gram positive, weak against gram negative	Residual activity Neurotoxicity	Currently not recommended for bathing neonates

Alcohols: Alcohol can be used alone or in combination with other antiseptics, most common being CHG. Alcohols have excellent *in vitro* germicidal activity against gram positive and gram-negative bacteria including MRSA and VRE, mycobacteria and a variety of fungi. They are most effective between concentrations of 60%-80% and have a faster onset of action but no residual activity. They are not active in the presence of organic material.

Iodine: Iodine has been recognised to have antiseptic properties since 1800s and has now been replaced by iodophors. Iodophors are composed of elemental iodine and a polymer carrier of high molecular weight. The amount of iodine present determines the level of antimicrobial activity[33,37]. Combining iodine with polymers increases the solubility, promotes sustained release of iodine and reduces the skin irritation[33,37]. Most common polymers iodophors used are polyvinyl pyrrolidone (povidone) and ethoxylated non-ionic detergents (poloxamers).

Hexachlorophene: Hexachlorophene is a bisphenol compound with three chlorine molecules. It was widely used in hand washing and routine bathing of neonates in hospitals. It is bacteriostatic and is the weakest of all the antiseptic agents mentioned in the Table 1[33]. It does have some residual activity. Hexachlorophene used for washing and cord care reduced *Staphylococcus aureus (S. aureus)* colonisation and related omphalitis. However in 1970 following cases of vacuolar encephalopathy its use has been withdrawn[38]. Following this a number of investigations have revealed that incidence of *S. aureus* infections had gone up and some places restarted the use of hexachlorophene[39,40].

Octenidine: Octenidine is a bis-pyridine compound, a cationic substance that binds to the microbial envelopes, cell membranes and destroys the cell wall of microorganisms by disrupting their metabolism[41]. It has a broad spectrum antimicrobial activity against gram positive and gram negative bacteria[42,43], is effective against resistant organisms including MRSA, vancomycin resistant *Staphylococcus aureus* (VRSA)[44], extended spectrum beta-lactamase producing bacteriae (ESBL)[45] and pseudomonas[46]. It has a low virucidal activity especially against hepatitis B virus and herpes simplex viruses but has no effect on other viruses, spores or protozoa[41]. Like Chlorhexidine it has significant residual activity up to 24 h[47] and the antiseptic effect is retained even in the presence of organic material[44,48]. Octenidine is often used in combination with alcohol preparations either phenoxyethanol or propanol.

A survey from 90 NICUs in United States on CHG use, reported that 61% of the units used CHG containing preparations. Twenty-one neonatal units used alcohol based CHG preparations[30]. Heron *et al*[31] surveyed the use of antiseptics across 57 neonatal units in the United Kingdom in 2013. They reported seven different antiseptics were in use and 53% of the units used alcohol based CHG preparations in contrast to findings of an early survey from 2007 (14% *vs* 53%). Majority of the units used alcohol based CHG irrespective of GA, birth weight[31]. These surveys actually reflect the changes in clinical practice following national recommendations to use alcohol based CHG antiseptic solutions, the evidence of which is mainly

derived from studies on adults and older children.

ARE THE ANTISEPTICS USED IN NEONATES EFFECTIVE?

Antiseptics have been used in neonates for a range of different procedures and interventions, in different concentrations and combinations. We reviewed the current literature based on their purpose of use and to identify a preferable effective antiseptic type and preparation over other agents.

Antiseptics use to reduce neonatal skin colonisation

Several interventions have been tried to decrease the colonisation of newborn skin with pathogenic organisms and associated sepsis. There are studies, which looked at the use of emollients, antibiotics, vaginal CHG washes during labour, umbilical cord cleansing and whole body washing to reduce the infection rates.

Vaginal CHG washes during labour: A large randomized clinical trial (RCT) conducted in South Africa, compared 4005 mothers and their 4072 neonates treated with 0.5% CHG wipes against 4006 mothers and 4057 neonates in the control group. Results from this study showed that CHG wipes did not reduce neonatal sepsis (3% *vs* 4%; CI: 19-24; *P* = 0.65) or GBS colonisation in neonates (54% *vs* 55%; efficacy -0.05%; CI: 9.5-7.9)[49]. Saleem *et al*[50] conducted a placebo controlled RCT on 5008 women in labour and their infants, to compare the effect of CHG vaginal and infant wipes, on reduction of neonatal sepsis and perinatal mortality. CHG vaginal and infant wipes did not show a significant reduction in neonatal sepsis and mortality (3.1% *vs* 3.4%; RR = 0.91; CI: 0.67-1.24) or composite outcome of neonatal sepsis and perinatal mortality (3.8% *vs* 3.9%; RR = 0.96; CI: 0.73-1.25)[50].

Ohlsson *et al*[51] conducted a systematic review to determine whether vaginal CHG during labour reduced early onset GBS infections. Authors found that Vaginal CHG washes/gel reduced the GBS colonisation of neonates, however this was not associated with significant reduction in GBS sepsis. Moreover, women who received CHG washes developed mild side effects. The quality of the included studies varied and was low. Therefore authors concluded that use of Vaginal CHG is not currently recommended especially in the era of intrapartum antibiotic prophylaxis.

Topical ointments: Preterm infants are prone for infections as they do not have an effective epidermal skin barrier and topical emollients could theoretically provide an effective barrier to prevent infections. Darmstadt *et al*[52] from Bangladesh, in their prospective RCT involving a total of 497 preterm infants, compared the effect of aquaphor ointment and sunflower oil against controls in reducing the neonatal mortality. Results of the study showed that sunflower oil reduced the mortality by 26% (hazard AR = 0.74; CI: 0.55- 0.99, *P* = 0.04) and aquaphor reduced the mortality by 32% (hazard AR = 0.67; CI: 0.57-0.92; *P* = 0.01). This study did not compare neonatal sepsis rates. In another large RCT, Edwards *et al*[53] compared the mortality and nosocomial bacterial sepsis rates (NBS) following the use of aquaphor ointment in preterm infants with birth weight < 1000 g. This group did not a show a significant reduction in combined death or NBS (33.6% *vs* 30.3%, ARR = 1.07; CI: 0.89-1.27; *P* = 0.22). However, the emollient group was noted to have a higher incidence of NBS and Coagulase negative Staphylococcus infections (18.6% *vs* 13.3%; ARR = 1.4; CI: 1.08-1.83)[53]. In their systematic review, Conner *et al*[54] reported that prophylactic application of topical ointment in preterm infants has been associated with significant increase of coagulase negative staphylococcal (RR = 1.31; 95%CI: 1.02-1.70) and other nosocomial infections. They concluded that topical ointment should not be used routinely in preterm infants.

A recent systematic review[55] including the studies from developing countries, has reported that topical emollient therapy significantly reduced neonatal mortality by 27% (RR = 0.73; 95%CI: 0.56-0.94) and hospital acquired infection by 50% (RR = 0.50; 95%CI: 0.36-0.71). Topical emollient therapy may be a promising intervention to reduce neonatal mortality in developing countries but evidence is against this in developed countries.

Umbilical cord care: Umbilical cord has been recognised as a site of colonisation with bacteria especially *S. aureus* and as a source of infection in neonates. Several studies have reported the prophylactic use of CHG reduced the colonisation rates[55-58]. Verber *et al*[56] in their prospective study on a total of 202 infants, reported that CHG reduced the umbilical cord colonisation rates by more than half, compared to the control group (16% *vs* 41%; RR = 0.39; CI: 0.24-0.64). In another double blind comparative study, Oishi *et al*[58] compared the effect of 80% ethanol in CHG against 80% ethanol alone on a total of 100 infants, in reducing umbilical cord colonisation by *S. aureus*. They identified that ethanol in CHG was more effective than ethanol alone in reducing colonisation with *S. aureus* (25% *vs* 58%; *P* < 0.05). However, concerns have been raised that CHG delays the separation of cord[57,58]. Three large block randomised control trials in developing countries[59-61] have shown that use of 4% CHG for umbilical cord care has significantly reduced the mortality (RR = 0.81; 95%CI: 0.71-0.92) and omphalitis (RR = 0.48; 95%CI: 0.40-0.57) in community settings. A recent Cochrane meta-analysis[62] involving 12 trials all over the world confirmed these benefits in developing countries. However there was no strong evidence to suggest that this might be beneficial in

developed countries due to the lack of high quality studies involved[62,63] and therefore dry cord care is recommended at present.

Regular bathing with CHG on HAI: In adults and older children in intensive care, daily bathing with CHG washcloths have shown a significant reduction in nosocomial infections (4.78 cases *vs* 6.6 cases per 1000 patient-days, $P = 0.007$)[64] and [4.1 cases *vs* 10.4 cases of primary blood stream infections (BSIs) per 1000 patient-days with CI: 1.2-11.0; $P = 0.01$][65]. Climo *et al*[64] in addition reported that regular CHG bathing reduces the colonisation from multidrug resistant organisms (5.1 cases *vs* 6.6 cases per 1000 patient-days, $P = 0.03$). Spencer *et al*[66] reported a similar finding with use of Octenidine in adults from a surgical intensive care unit, with 75% reduction in MRSA colonisation.

Large randomised controlled trials from Pakistan and South Africa did not show any significant reduction in mortality or sepsis in neonates who had prophylactic whole body cleansing with CHG wipes[49,50]. Quach *et al*[67] who studied the effect of 2% CHG body wash on 195 infants with birth weight of 1000 g or more and a systematic review on whole body cleansing in neonates did not show any beneficial effect on mortality RR = 0.91, CI: 0.8-1.04, however there was a substantial heterogeneity amongst the included studies (I^2 = 80.2%) and therefore evidence is lacking to support CHG washes in neonates at present[68].

Recommendations: (1) There is sufficient evidence to conclude that application of CHG to umbilical cord can prevent omphalitis and neonatal mortality in developing countries (Level 1A). More research is needed regarding the concentration of CHG preparation, duration, frequency and timing of application. In the absence of good evidence to support this in developed countries, dry cord care is recommended (Level 2D); and (2) Vaginal CHG during labour is not recommended based on the available evidence (Level 2B). Topical emollients are not routinely recommended for use in preterm infants in developed countries (Level 2C), however may have an impact in reducing neonatal sepsis and mortality in developing countries with high neonatal mortality rates (Level 2B). We do not recommend regular CHG bathing on the basis of current literature evidence (Level 2C).

Antiseptic use for venepuncture/cannulation/blood culture

Venepuncture and intravenous cannulation breach the skin integrity increasing the risk of hospital acquired infections from invasion of microorganisms colonising the skin and intravenous catheter. Blood culture contamination is a challenging problem in clinical practice with reported contamination rates of 0.6%-6%; that can lead to unnecessary investigation and treatment in otherwise well babies[69,70]. Therefore it is important that we use antiseptics that could prevent HAI and reduce blood culture contamination rates.

Only a few studies were published in literature on use of antiseptics in neonatal population for prevention of infections related to venepuncture, blood culture sampling or cannulation. Malathi *et al*[71] compared the skin clearance using 0.5% CHG in 70% IPA and 10% PI for intravenous cannulation. In the first part skin swabs were taken following routine cannulation and in the second part swabs were taken after skin cleansing with various durations of exposure to either alcoholic CHG or PI. Skin cleansing with antiseptics achieved a reduction of bacterial colony counts in 90%-99% and authors reported no difference between the two groups[71]. Lilley *et al*[72] conducted a prospective randomised controlled trial to compare 0.5% CHG and 0.05% CHG for skin antisepsis prior to intravenous cannulation. A total of 85 neonates were randomly allocated for exposure to different concentrations of CHG and skin surface swabs were taken before and after cannulation. Authors found that 0.5% CHG produced better bacterial clearance than 0.05% CHG (92% *vs* 38%, $P = 0.002$)[72]. Another RCT in neonates with birth weight of $\geqslant$ 1500 g compared the effect of 1% aqueous CHG with 10% PI on blood culture contamination rates[73]. Use of 1% CHG was associated with fewer positive blood culture results in neonates > 1500 g. However this study was non-blinded, did not control drying times and antiseptics were washed off after 30 s. None of the above studies reported clinically relevant outcomes such as sepsis rates, other morbidity or deaths.

A Canadian group[74] is currently conducting a large RCT comparing the efficacy of 2% CHG in 70% IPA against 2% aqueous CHG prior to venepuncture that has recently completed recruitment. Around 460 babies with birth weight of < 1500 g were recruited onto the study and bacterial swabs before and up to 24 h after cleansing were taken for microbiological analysis. While we are still awaiting final study results, interim results showed identical bacterial clearance rates in both groups suggesting that alcoholic component is probably not required in very low birth weight babies. There is not much evidence available in neonates for guidance on appropriate topical antiseptic agent prior to venepuncture, blood culture sampling or intravenous cannulation.

Antiseptic use for PICC/CVC/umbilical catheter insertion

Skin commensals are the most common bacteria to colonise the central venous catheters[75]. Ponnusamy *et al*[76] showed that colonisation rates of proximal catheter segments were higher than catheter tips from asymptomatic infants (78% *vs* 43%, P = 0.004). Same group in their retrospective study on 187 peripherally inserted central venous catheter

(PICC) removals reported that a positive exit site skin swab is associated with an 8 fold increase of catheter colonisation (OR = 2.13; CI: 1.18-3.08; $P \leqslant 0.001$), and a 14 fold increase of CRBSI (OR = 2.00; CI: 0.44-4.14, $P = 0.01$)[77].

A multicentre prospective non-randomised clinical trial was conducted in two epochs by Garland *et al*[78] to compare the effects of CHG and PI on catheter colonisation rates. In a total of 826 catheters in 254 infants 0.5% CHG significantly reduced the catheter colonisation rates (4.7% *vs* 9.8%, RR = 0.5, CI: 0.3-0.9; $P = 0.01$). There were only 2 cases of CRBSI and therefore it was not possible to draw any conclusions on their effect on clinical outcomes[78]. Same group conducted a large multicentre RCT to compare the effect of CHG impregnated dressing and PI on outcomes of CRBSI, CLABSI and Catheter colonisation. Three hundred and thirty-five neonates were randomised to CHG impregnated dressing after 70% alcohol cleansing and 370 to skin disinfection with PI. Neonates randomised to the CHG impregnated dressing had reduced colonisation rates (15% *vs* 24%, RR = 0.6; CI: 0.5-0.9; $P = 0.004$). There were no differences observed in CRSBI or CLABSI. However, significantly more babies < 1000 g (15% *vs* 0%) developed contact dermatitis in the CHG + 70% IPA group. These results suggest that CHG + 70% IPA is more effective but safety issues need to be addressed[79].

Andersen *et al*[37] reported a significant reduction in BSIs (21% *vs* 9%; CI: 0.19-1.0; $P = 0.05$) with 2% CHG compared to PI in two cohorts of VLBW infants ($n = 174$) over 12 mo period before and after implementing multifactorial prevention strategies. However there were 4/36 cases of contact dermatitis in infants with birth weight less than 1000 g and therefore studies on weaker solution was recommended. During this period they also implemented several other interventions including changes in hand washing practice, standardisation of intravascular device insertion with specialised packs and mandatory removal or replacement of peripheral IV after 48 h, to reduce nosocomial infections that could have contributed to the reduction in BSI. Another retrospective study comparing 10% PI and 0.5% CHG in 70% IPA for PICC insertions in two different time periods reported no differences in sepsis or CRBSI rates[80]. Jeffries *et al*[81] in their retrospective study compared the short-term outcomes following use of CHG or PI prior to PICC insertion. There was no observed difference between the two groups in mortality or other short-term outcomes in VLBW infants. Kieran *et al*[82] recently completed a large RCT comparing the efficacy of 2% CHG in 70% IPA with 10% PI to reduce CRBSI in preterm infants. Three hundred and ten preterm infants < 31 wk gestation were randomised to CHG or PI group for PICC/Umbilical catheter insertion. CRBSI rates were similar in both groups. However significant differences were observed in PI group for hypothyroidism (8% *vs* 0%; $P = 0.002$) and all of them required treatment with Thyroxine. No adverse skin reactions were reported[82].

Duration of antiseptic application for effective skin disinfection

In a retrospective study in preterm neonates comparing duration of antiseptic usage with bacterial colony counts in skin swabs, Malathi *et al*[71] have reported that 30 s cleansing with 0.5% CHG in 70% IPA or 10% PI was more effective than 5 or 10 s cleansing in reducing the bacterial colony counts from skin swabs.

CHG vs povidone iodine

There is enough evidence in adults to suggest that CHG containing solutions are more effective than PI for skin preparation for surgery and PICC/CVC insertions[26,83]. But in neonates this has not been studied in great detail. *In vitro* studies to compare the efficacy of CHG against PI on 33 MRSA isolates showed that PI achieved a significantly higher logarithmic reduction factor of >5 (tube dilution method 4.879 *vs* 3.004, $P < 0.001$; microtitre plate dilution method 4.5 *vs* 2.73, $P < 0.001$), suggesting that PI is better than CHG in microbiological studies against MRSA strains[84]. In another microbiological study from Birmingham, United Kingdom, Adams *et al*[85] compared the efficacy of 2% CHG in 70% IPA with 5 different antiseptics (70% IPA, 0.5% CHG, 2% CHG, 0.5% CHG in 70% IPA, and 10% PI) against *S. epidermidis*. They found that 2% CHG in 70% IPA and PI achieved a significant $\log_{10}$ reduction factor of > 5 (4.7 *vs* 2.3-3.6, $P = 0.0001$) against *S. epidermidis* biofilm compared to other antiseptics but there was no statistical difference between CHG and PI (4.7 *vs* 4.4; $P = 0.28$). Clinical studies in neonates involving 0.5% CHG in 70% IPA did not find any significant differences between the two antiseptics in terms of bacterial clearance rates[71,80]. These studies were small and did not include clinical outcomes. A large prospective controlled trial compared the two antiseptics and found that 0.5% CHG in 70% IPA is more effective in reducing the catheter colonisation compared to PI in neonates. There were not enough infection rates to compare between the two groups[78]. A non-blinded RCT showed that 1% CHG achieved better blood culture contamination rates compared to 10% PI[73]. Jeffries *et al*[81] reported no differences between CHG and PI in mortality or other short-term morbidity outcomes in VLBW infants.

In a large RCT on a total of 705 neonates, Garland *et al*[79] compared CHG impregnated dressing followed by IPA cleansing against PI in neonates demonstrated that CHG significantly reduced catheter colonisation (15% *vs* 24%; RR = 0.6; CI: 0.5-0.9; $P = 0.004$)

but there was no difference in CRBSI. A large RCT involving 310 preterm infants comparing 2% CHG in 70% IPA and PI has completed recruitment recently[82], the results are awaited; this might give us further insight about a better choice of antiseptics in preterm infants.

Concentration of CHG 0.5% vs 1% vs 2%

There are a handful of studies in neonates that compared the efficacy of different concentration of CHG. Adams *et al*[85] showed that 2% CHG is more effective than 0.5% CHG in reducing colony forming units. In a prospective RCT 0.5% CHG was found to be superior to 0.05% CHG in bacterial clearance as identified from skin swabs[72].

Alcoholic vs aqueous CHG preparations

Studies have shown in adults and children that Alcohol containing CHG solutions are more effective than aqueous solution[86]. However, up to date there are no studies to support this in neonates. On the other hand, serious concerns have been raised from several case reports that alcoholic component is associated with severe chemical burns in neonates particularly in extreme preterm and VLBW infants (Table 2). *In vitro* studies have shown that alcohol based CHG achieved better bactericidal activity than aqueous CHG of the same concentration[85]. Shah *et al*[74] completed a RCT comparing the efficacy and safety of aqueous CHG against alcoholic CHG in preterm neonates. Preliminary results showed similar bacterial clearance, which may suggest that aqueous CHG is as effective as alcoholic CHG.

Octenidine

Octenidine, as a topical antiseptic agent has been used in some European countries for more than 2 decades for prevention of skin, wound and oral cavity infections. Efficacy studies involving Octenidine have largely been restricted to *in vitro* microbiological studies or involving adult patients; studies on octenidine use in term or preterm neonates are scarce.

In vitro study by Junka *et al*[46] compared the efficacy of Octenidine, Ethacridine and Povidone Iodine against the biofilms of pseudomonas and *S. aureus*. Authors reported that Octenidine was effective in eradicating the bacteria from biofilms made by pseudomonas in 30 min and was more efficient than ethacridine and PI (100% OH *vs* 66% PI *vs* 0% ethacridine). Similarly Octenidine was as effective as PI (100% in 1 min) and more efficient than ethacridine (100% *vs* 60%) in clearing the biofilms by *S. aureus*.

In another *in vitro* study by Amalaradjou *et al*[44] Octenidine hydrochloride was effective not only in preventing the biofilm formation but also in rapidly inactivating the pre-formed biofilms by *S. aureus*, MRSA, VRSA. Goroncy-Bermes *et al*[45] have showed similar results with Octenidine against ESBL producing bacteria in comparison with CHG and polyhexamethylen biguanide.

Clinical studies have been noticeably small in numbers evaluating Octenidine as an antiseptic agent in comparison with other agents such as CHG. Octenidine has been shown to be effective in preventing MRSA colonisation as well as in eradicating MRSA when used as whole body wash[87]. Spencer *et al*[66] in their 2 year retrospective uncontrolled study on daily bathing with Octenidine for adults in intensive care unit reported a significant reduction in MRSA acquisition from 25 to 6 (Mean reduction 76%, CI: 42%-90%, $P < 0.01$) and an associated reduction in MRSA bacteremia from 3 to 0. A recent study from Lithuania evaluating Octenidine's effect on MRSA decolonisation showed that Octenidine was completely effective in decontaminating 67% of adult patients and was very well tolerated[88]. In a recent cluster cross over study on 10936 patients who received either soap and water or Octenidine body wash for 6 mo period found that there was no significant difference between the two groups in MRSA colonisation (3% *vs* 3.3%; OR = 0.89; CI: 0.72-1.11; $P = 0.31$)[89]. There were no studies that compared Octenidine with other antiseptic agent in RCTs.

A pilot study by Dettenkofer *et al*[90] in 2002 showed that Octenidine was more effective than ethanol in reducing the CVC insertion site colonisation rates. Tietz *et al*[91] also reported similar observations in an uncontrolled observational study in immunocompromised patients. Dettenkofer *et al*[92] in their RCT compared the efficacy of Octenidine against 74% ethanol when used as a skin antiseptic agent for CVC/PICC insertion in 400 adult patients. Authors reported that Octenidine combination with 30% propanol and 45% propanol was superior to 74% ethanol with 10% propanol combination in reducing the skin colonisation rates around CVC (OR = 0.21; CI: 0.11-0.39; $P < 0.0001$), catheter tip colonisation rates (7.9% *vs* 17.8%; OR = 0.39; CI: 0.2-0.8; $P = 0.009$) and catheter related bloodstream infections (OR = 0.44; CI: 0.18-1.18; $P = 0.08$)[90]. Bilir *et al*[93] in their non-blinded randomised trial on 57 patients reported that CHG was more effective than Octenidine or Povidone Iodine in reducing CVC insertion site colonisation rates, catheter hub colonisation and CRBSI rates.

These studies have been conducted in adult population and there has been a noticeable lack of studies involving Octenidine use in term and preterm neonates.

RECOMMENDATIONS

Based on current evidence

It is possible to conclude CHG may be a better option compared to PI given that PI is associated with

Table 2 Studies reporting adverse effects of chlorhexidine use in neonates

Ref.	Design/type	Patient characteristics (*n*)	Type of antiseptic used	Purpose of antisepsis	Adverse reaction	Systemic effects	Comments
Garland *et al*[78]	Prospective study	Neonates (*n* = 111)	0.5% CHG in 70% IPA	PICC insertion	None reported	Not reported	GA not reported
Garland *et al*[79]	RCT	Neonates (*n* = 335, including 98 babies < 1000 g)	0.5% CHG and 70% IPA, CHG impregnated dressing after cleansing	PICC insertion	19 cases of contact dermatitis of which 15 are < 1000 g	Not reported	Occlusive dressing could be the cause of contact dermatitis
Bührer *et al*[102]	Prospective study	Preterm < 27 wk GA (*n* = 24)	2% phenoxyethanol and 0.1% octenidine	Skin care	Transient erythema in a 23 wk gestation baby	Absorbed systemically but no adverse effects reported	
Pezzati *et al*[57]	RCT	Preterm < 34 wk (*n* = 101)	4% CHG aqueous solution	Umbilical cord care	None	Not reported	Mostly above 28 wk
Andersen *et al*[37]	Prospective study	VLBW < 1500 g (*n* = 36)	2% aqueous CHG	PICC, cannula insertion	Skin erythema and burn	Not reported	Recommended alternative safer agent
Visscher *et al*[22]	Pilot study	Neonates (*n* = 40; 14 of which < 30 wk)	2% CHG in 70% IPA	PICC insertion	Erythema and dryness	Not reported	Could be from dressing
Schick *et al*[98]	Case report	Preterm < 28 wk GA (*n* = 2)	IPA	Umbilical catheterisation	Skin burn (2^{nd}/3^{rd} degree burn)	Not reported	
Harpin *et al*[95]	Case report	Preterm 27 wk GA (*n* = 1)	Methylated spirit (95% ethanol and 5% wood naptha)	Umbilical catheterisation	Haemorrhagic skin necrosis	Very high ethanol and methanol levels in blood	Use of alcohol antiseptics in preterm neonates potentially dangerous
Watkins *et al*[99]	Case report	Extreme LBW babies (*n* = 2)	Iso propyle alcohol	Umbilical catheterisation	Skin burns	Not reported	Care must be taken in selection of such solutions
Brayer *et al*[100]	Case report	Preterm at 35 wk (*n* = 1)	Isopropyl alcohol	Umbilical catheterisation	Severe skin burn	Not reported	
Reynolds *et al*[96]	Case report	Preterm infants 24 wk (*n* = 2)	0.5% CHG + 70% methanol	Umbilical catheterisation	Extensive abdominal skin burns	Not reported	Avoid pooling of the antiseptic solution and use Saline for cleaning to wash antiseptic
Mannan *et al*[101]	Case report	Preterm 26 wk GA (*n* = 1)	0.5% CHG + 70% alcohol	Umbilical catheterisation	Extensive abdominal skin burns	Not reported	Alcohol containing preparations should be avoided in NICUs
Bringué Espuny *et al*[97]	Case report	Preterm 26 wk (*n* = 2)	0.5% CHG + methanol	Umbilical catheterisation	Skin burns	Not reported	Use of alcoholic preparations should be avoided in preterm
Lashkari *et al*[103]	Case report	Preterm 25 wk GA (*n* = 1)	2% aqueous CHG	Umbilical catheterisation	Skin burn	Not reported	Cleansing with Normal saline could potentially reduce the exposure and burns

CHG: Chlorhexidine; GA: General availability; NICU: Neonatal intensive care unit; IPA: Iso propyle alcohol; PICC: Peripherally inserted central venous catheter; VLBW: Very low birth weight infants; RCT: Randomized controlled trial.

significant systemic absorption and hypothyroidism. However safety issues of CHG preparations still remain a concern. Results from a recently completed RCT[82] may give us a definitive answer.

Aqueous or alcohol based CHG is as effective - results of the on-going trial would hopefully give us some answers.

It is not possible to recommend a one particular concentration of CHG is better than the others in preterm infants because of its mutually conflicting efficacy and safety profile.

Are the antiseptics used in clinical practice safe in neonates?

Topical antiseptic agents used in adults and older children have been considered safe with no significant adverse effects noted. Studies have reported that Chlorhexidine has been well tolerated and is safe in term neonates following exposure for vaginal washing, umbilical cord care and whole body cleansing[57,94]. However, safety profile of antiseptics has not been extensively studied in preterm neonates. Skin of a preterm infant is immature, lacks an effective barrier

and is vulnerable to local damage and systemic absorption of toxic chemicals.

Local adverse reactions: Local adverse reactions have been reported with almost all the topical disinfectants used in neonatal population. Skin irritation in form of erythema and contact dermatitis is the most commonly reported adverse event after a topical antiseptic use. A national survey in the United States reported that 51% (28 of 55) of NICUs using CHG noted adverse reactions involving the skin and none of them reported systemic side effects[30]. Chemical burns were reported by 61% (17 of 28) of NICUs using CHG and 13 of the 17 centres (76%) reported that burns occurred in neonates with birth weight < 1500 g. In another survey from the United Kingdom[31] 30 of 57 (53%) neonatal units used alcohol based antiseptic agents and 7 of 57 (12%) NICUs reported skin burns.

In Table 2 we have summarised the studies that evaluated side effects of aqueous and alcoholic antiseptic preparations in neonates. An RCT, few prospective studies and several case reports have reported chemical skin burns in extreme premature babies secondary to use of methylated spirit[95], methanol[96,97], IPA[98-101] and 2-phenoxyethanol with 0.1% Octenidine[102]. In all of these case reports skin damage was attributed to the alcohol component of the antiseptic. However, a prospective study on VLBW infants reported local reactions to aqueous based 2% CHG preparation[37]. Similarly another case report of an extensive chemical burn related to the use of 2% aqueous CHG in an extreme preterm infant was reported and attributed this to excessive application and prolonged skin exposure to CHG[103].

Systemic absorption: Studies have reported that CHG can be absorbed in term neonates comparable to those in adults and not have any significant side effects[104]. Few studies have reported systemic absorption of CHG in preterm infants. Milstone *et al*[105] demonstrated that Chlorhexidine inhibits L1 cell adhesion molecule mediated neurite growth of cerebellar granule neurons. This along with hexachlorophene's vacuolar encephalopathy raised concerns regarding neurotoxicity. In the reported studies, although CHG is detected in their bloods, none of them have reported any side effects including neurotoxicity or skin toxicity[106-108]. However the sample population in these studies did not include extreme preterm infants and only very few babies had their levels checked during the first 2 wk when skin is most immature. Safety of systemic absorption in preterm infants has not been studied in great detail and significance of raised CHG concentrations is yet to be determined in clinical studies.

Further research should focus on differences in CHG absorption between aqueous and alcohol based CHG preparations, to identify the strength of solution that is safe and effective to be used on preterm infants, on potential toxicity of absorbed CHG to identify a threshold at which this could occur.

Alcohol based preparations: Studies on systemic absorption of alcohol in neonates following topical antisepsis are very limited. Harpin *et al*[95] in 1982 reported very high levels of methanol and ethanol in a 27 wk gestation baby following use of methylated spirit on skin for antisepsis.

Iodine containing preparations: Preterm infants are vulnerable to iodine exposure than term infants because of increased skin permeability, immaturity of thyroid gland and Wolff-Chaikof effect, and reduced renal clearance. Smerdely *et al*[109] reported 50 times higher urinary iodine levels, raised thyrotropin levels above 36micromoles/L and significantly lower thyroxine levels in 25% of infants iodine exposed (n = 36) preterm infants compared to CHG exposed (n = 27) infants. In a cohort study comparing 73 preterm infants exposed to iodine containing antiseptics against 55 exposed to CHG antiseptics, mean thyrotropin levels were significantly higher in iodine group (15.4 mIU/L *vs* 7.8 mIU/L, $P < 0.01$)[80]. Khashu *et al*[110] reported hypothyroidism in an extreme preterm infant following repeated and prolonged use of topical povidone iodine for wound cleaning. This required treatment with thyroxine and took 8 wk to resolve. There are a few other studies and several case reports of hypothyroidism following use of Iodine containing topical antiseptics in neonates especially preterm infants. Aitken *et al*[111] in their systematic review reported that there is evidence of thyroid dysfunction in preterm infants exposed to iodinated antiseptics with an incidence ranging from 12-33 per 100 infants. However, none of the studies reported long term neurodevelopmental outcomes. Authors concluded that it was not possible to establish relationship between exposure of iodine and occurrence of hypothyroidism due to the quality of studies included. They concluded that use of iodine containing solutions should be restricted in preterms with CHG being an alternative.

Octenidine containing preparations: Octenidine when used in adults for body wash was well tolerated and did not cause any adverse effects[87]. Bührer *et al*[102] in their prospective study reported the use of Octenidine in extreme preterm infants born before 27 wk gestation for routine skin antisepsis during the first week. They found that Octenidine was well tolerated with only one infant developing a transient erythematous rash. However, phenoxyethanol was absorbed into the systemic circulation but readily excreted in urine. Although there were no systemic side effects noted authors suggested using Octenidine without phenoxyethanol combination in neonates.

Wagner *et al*[112] in their *in vitro* study on impact of antiseptic agents on radical metabolism, antioxidant stress and genotoxic stress in human blood cells

compared Octenidine with PI. They reported that PI reduced superoxide dismutase (SOD) activity by 40%, Glutathione peroxidase activity (62%) and alpha tocopherol more than Octenidine. There were no differences observed in Total antioxidative capacity or malondialdehyde in ghosts. Authors concluded that exposure of healthy blood cells to Octenidine concentrations up to 0.05% for 30 min were safe compared to PI.

Recommendations

CHG and Alcohol preparations have been associated with severe local reactions, whereas Iodophors are associated with increased risk of systemic absorption and potential toxicity. Large studies are urgently needed to establish the safety of topical antiseptics used in neonates especially in preterm infants with focus on following: (1) differentiate Aqueous or alcoholic component of CHG as the reason for skin irritation in preterm neonates; (2) ideal CHG concentration that can be safely used in preterm neonates; (3) CHG concentrations in blood and their effect on long-term neurodevelopment outcomes; (4) isopropyl alcohol absorption studies and effect on short term and long term outcomes; and (5) systemic absorption of topical iodine containing solutions and their effects on thyroid function and long-term neurodevelopmental outcomes.

In the meantime we recommend the following on the basis of current evidence: (1) Extreme caution is recommended for use of topical antiseptics particularly alcohol based preparations in extreme preterm infants (Level 2D); (2) Care must be taken to avoid pooling of the solution under infant and washing with normal saline after cleansing with topical antiseptic may prevent severe chemical burn in extreme premature babies (Level 2D); and (3) Povidone Iodine for skin antisepsis should be avoided in extreme preterm infants (Level 2C).

CONCLUSION

Skin disinfection with an effective topical antiseptic agent could be useful in prevention of HAI. Although many antiseptics have been used in neonates for several decades, there is no clear guidance regarding the best antiseptic for use in neonatal intensive care unit. Current evidence based on their efficacy and safety studies, does not support the use of one antiseptic agent over another. Two large RCTs have completed recruitment, but few more large multicentre trials are warranted to determine the most effective antiseptic preparation, concentration and combination for use in neonatal skin disinfection. Large trials are also needed to study the adverse effects of different antiseptics, effects of systemic absorption on developing organ systems in preterm infants with a particular focus on long term neurodevelopmental outcomes.

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