

SKIN STERILITY (Commentary)

Cleaning the skin before undertaking any sterile procedure

Povidone-iodine continues to be quite widely used not just as a vaginal disinfectant but also as a way of cleaning the skin of the baby before undertaking any sterile procedure, although there is substantial evidence that that 0.5% aqueous chlorhexidine is not only more effective (see below) but also safer, especially in the preterm baby where excess iodine exposure can cause transient hypothyroidism.

Safety of povidone-iodine: Studies of the use of povidone-iodine have sometimes come to inconsistent conclusions. Studies in Germany (l'Allemand *et al.*, 1983) and Australia (Smerdley *et al.*, 1989) reported substantial evidence of transient hypothyroidism (TSH levels > 20 mU/l), but these findings were not replicated in some other studies from America (Gordon *et al.*, 1995; Brown *et al.*, 1997). While there is little doubt that the term baby is not at as much risk as the preterm baby (Larson *et al.*, 2003), several papers have been published saying that it should never be used for obstetric or neonatal skin disinfection (Linder *et al.*, 1997; Weber *et al.*, 1998).

Comparative efficacy of chlorhexidine and povidone-iodine: There is substantial evidence that chlorhexidine is at least as effective as povidone-iodine at disinfecting the skin prior to any sterile procedure. Indeed a meta-analysis of seven studies in adults (Chaiyakunapruk *et al.*, 2002) showed that blood-stream infection was half as common when either 2% aqueous, or 0.5% alcoholic, chlorhexidine was used to cleanse the skin before long line insertion instead of 10% povidone-iodine. A 0.5% alcoholic solution of chlorhexidine was also more effective than 10% aqueous povidone-iodine at reducing blood culture contamination following phlebotomy (Mimoz *et al.*, 1999), and in reducing epidural catheter colonisation in children (Kinirons *et al.*, 2001). Many of the comparative studies have used chlorhexidine in alcohol, or 'tincture of chlorhexidine' (Garland, *et al.*, 1995), but superiority has also been demonstrated in at least one large trial that used aqueous chlorhexidine (Maki *et al.*, 1991). There was only 1 catheter-related infection in the 214 patients whose skin was cleaned with 2% aqueous chlorhexidine in the later study, and 6 in 227 where the skin was cleaned with 10% povidone-iodine. Indeed such limited evidence as currently exists all suggests that aqueous 2% chlorhexidine is the product of choice for neonatal use. The FDA in America has not, as yet, approved neonatal use because of a concern that it might cause dermatitis, but there is no evidence that this is a problem. Systemic absorption does occur, and this deserves further study, but there is no evidence as yet that this is a problem either.

Alcoholic solutions: Alcoholic solutions are best avoided in the very preterm baby because sustained soaking can cause serious superficial skin damage (Reynolds *et al.*, 2005; Mannan *et al.*, 2007). All the 'ready to use' formulations of chlorhexidine commercially available in the UK are currently alcohol based, but it is not difficult to make a water based product 'in house'. There is evidence that a 0.5% solution is more effective than a 0.05% solution (Liley *et al.*, 2006), and that a 2% solution may be damagingly strong for some very preterm babies (Anderson *et al.*, 2005). Impregnated wipes are an extremely effective way of cleaning the skin and reducing the risk of neonatal sepsis in developing countries (Mullany *et al.*, 2006), and these usually contain 0.2% or 0.3% chlorhexidine. While the optimum concentration to use is not yet clear, there are good grounds for thinking that it is not necessary, or appropriate, to use more than a 1% solution to cleanse either the vagina before delivery, or the skin of the newborn baby in the first few days of life (Wilson *et al.*, 2004). Staff frequently forget that any product takes a little time to become effective (Malathi *et al.*, 1993). Employ two different swabs, applying each for 10 seconds, and then leave the skin to dry for *at least 30 seconds* before piercing the skin.

Conclusions: Optimising skin sterility is a matter of some importance and there has been surprising little research into the optimum way of achieving this in the preterm baby. Most UK neonatal units now use chlorhexidine in preference to povidone-iodine (Datta and Clarke, 2008), and there is a general recognition that alcoholic solutions can damage the skin of the preterm baby. Such evidence as there is seems to point to 0.5% chlorhexidine in aqueous solution being the most appropriate product.

l'Allemand D, Gruters AJ, Heidemann P, *et al.* Iodine-induced alterations of thyroid function in newborn infants after prenatal and perinatal exposure to povidone iodine. *J Pediatr* 1983;**102**:935–8.

Smerdely P, Boyages SC, Wu D, *et al.* Topical iodine-containing antiseptics and neonatal hypothyroidism in very-low-birthweight infants. *Lancet* 1989;ii:661–4.

Maki DG, Ringer M, Alvarado CJ. Prospective randomised trial of povidone-iodine, alcohol and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* 1991;**338**:339–43. [RCT]

Malathi I, Millar MR, Leeming JP, *et al.* Skin disinfection in preterm infants. *Arch Dis Child* 1993;**69**:312–6.

Vivier PM, Lewander WJ, Martin HF, *et al.* Isopropyl alcohol intoxication in a neonate through exposure: a complication of a culturally-based umbilical care practise. *Pediatr Emerg Care* 1994;**10**:91–3

Garland JS, Buck RK, Maloney P, *et al.* Comparison of 10% povidone-iodine and 0.5% chlorhexidine gluconate for the prevention of peripheral intravenous catheter colonization in neonates: a prospective trial. *Pediatr Infect Dis J* 1995;**14**:10–6. [RCT]

Gordon CM, Rowitch DH, Mitchell ML, *et al.* Topical iodine and neonatal hypothyroidism. *Arch Pediatr Adolesc Med* 1995;**149**:1336–9.

- Brown RS, Bloomfield S, Bednarek FJ, *et al.* Routine skin cleaning with povidone-iodine is not a common cause of transient neonatal hypothyroidism in North America: a prospective controlled study. *Thyroid* 1997;**7**:495–400. [RCT]
- Linder N, Davidovitch N, Reichman B, *et al.* Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997;**131**:434–9.
- Weber G, Vigone MC, Rapa A, *et al.* Neonatal transient hypothyroidism: aetiological study. *Arch Dis Child* 1998;**79**:F20–2.
- Mimoz O, Karim A, Mercat A, *et al.* Chlorhexidine compared with povidone-iodine as skin preparation before blood culture – a randomized controlled trial. *Ann Int Med* 1999;**131**:834–7. [RCT]
- Humar A, Ostromecki A, Drenfeld J, *et al.* Prospective randomized trial of 10% povidone-iodine versus 0.5% tincture of chlorhexidine as cutaneous antiseptics for prevention of central venous catheter infection. *Clin Infect Dis* 2000;**31**:1001–7. [RCT]
- Kinirons B, Mimoz O, Lafendil L, *et al.* Chlorhexidine versus povidone iodine in prevention colonisation of continuous epidural catheters in children – a randomized controlled trial. *Anesthesiology* 2001;**94**:239–44. [RCT]
- Garland JS, Alex CP, Mueller CD, *et al.* A randomized trial comparing povidone-iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. *Pediatrics* 2001;**107**:1431–6. [RCT]
- Garland JS, Alex CP, Mueller CD, *et al.* A randomized trial comparing povidone-iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. *Pediatrics* 2001;**107**:1431–7. [RCT]
- O'Grady NP, Alexander M, Dellinger EP, *et al.* Guidelines for the prevention of intravascular catheter-related infections. *Pediatrics* 2002;**110**:e51. [SR]
- Chaiyakunapruk, NM, Veenstra, DL, Lispy BA, *et al.* Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. *Ann Int Med* 2002;**136**:792–801. [SR]
- Larson C, Hermos R, Delaney D, *et al.* Risk factors associated with delayed thyrotropin elevations in congenital hypothyroidism. *J Pediatr* 2003;**143**:587–91.
- Wilson CM, Gray G, Read JS, *et al.* Tolerance and safety of different concentrations of chlorhexidine for peripartum vaginal and infant washes. HIVNET 025. *J Acquir Immune Defic Syndr* 2004;**35**:138–43.
- Andersen C, Hart J, Vembal P, *et al.* Prospective evaluation of a multi-factorial prevention strategy on the impact of nosocomial infection in very-low-birthweight infants. *J Hosp Infect* 2005;**61**:162–7.
- Reynolds PR, Banerjee S, Meek JH. Alcohol burns in extremely low birthweight infants: still occurring. *Arch Dis Child* 2005;**90**:F11–16.
- Mullany LC, Darmstadt GL, Tielsch JM. Safety and impact of chlorhexidine antiseptics interventions for improving neonatal health in developing countries. *J Pediatr Infect Dis* 2006;**25**:665–75. [SR] (See also 676–9.)
- Lilley C, Powls A, Gray A. A prospective randomised double blind comparison of 0.5% versus 0.05% aqueous chlorhexidine for skin antiseptics prior to line insertion in neonates. *Arch Dis Child* 2006;**91**:A18. [RCT]
- Mannan K, Chow P, Lissauer T, *et al.* Mistaken identity of skin cleansing solution leading to extensive chemical burns in an extremely preterm infant. *Acta Paediatr* 2007;**96**:1536–7.
- Darmstadt GL, Hossain MM, Choi Y, *et al.* Safety and effect of chlorhexidine skin cleansing on skin flora of neonates in Bangladesh. *Pediatr Infect Dis J* 2007;**26**:492–5.
- Datta MK, Clarke P. Current practices in skin antiseptics for central venous catheterisation in UK tertiary-level neonatal units. [Letter] *Arch Dis Child* 2008;**93**:F328.

Hand hygiene

For a commentary on the importance of minimising the risk of cross infection by attention to hand hygiene, and the best way to achieve this, see the web commentary on skin care.

Care of the skin and umbilical stump after birth

Management in a high-income setting: One challenge faced by the first generation of paediatricians to become involved in the care of the otherwise healthy newborn baby immediately after birth was the epidemic of staphylococcal sepsis that was triggered by the rapid shift from home birth to hospital birth in the 1950s and 1960s. It was a problem further compounded by the routine way that babies were separated from their mothers, and herded, often within inches of each other, into small hospital side-wards. Since, as a result, routine care then had to be undertaken by midwifery staff, epidemics of neonatal staphylococcal infection were almost inevitable. While overcrowding was undoubtedly part of the problem, such infection was, all too easily, carried from baby to baby on the hands of attendant staff (Mortimer *et al.* 1966).

Hexachlorophene emerged around this time as a very effective trichlorophenol antiseptic, and came to be very widely used to combat this problem. Babies were immersed in it as part of a daily bathing ritual, and the practise was considered not just safe but highly beneficial. It certainly managed to reduce the incidence of staphylococcal infection then prevalent (Gezon *et al.*, 1864), and the drug's effectiveness was enhanced by its adherence to the skin – little came off with rinsing. What was not initially realised was that it was also absorbed *through* the skin (Curley *et al.*, 1971), especially in the preterm baby (Kopelman *et al.*, 1973). Significant absorption occurred when preterm infants were bathed in a 3% hexachlorophene solution, or washed with hexachlorophene soap. Absorption was later also found to have occurred in older infants exposed to batches of talcum powder that had become accidentally contaminated with 6% hexachlorophene (Martin-Bouyer *et al.*, 1982).

Regrettably, it was only after hexachlorophene had been in widespread use for almost ten years that clinicians came to realise that it could be extremely neurotoxic. Symptoms were first seen in patients whose burns were washed with 3% hexachlorophene (Larson, 1968). Rats fed hexachlorophene were later shown to develop vacuoles in the myelin sheathing their nerves (Kimbrough & Gaines, 1972), and similar lesions were soon found in the brains of preterm babies who had been bathed regularly in hexachlorophene (Powell

et al., 1973; Shuman *et al.*, 1974). Older children even developed signs of an acute encephalopathy similar to that seen in rats (Goutieres & Acardi, 1977). Not surprisingly the neonatal use of hexachlorophene was abandoned very abruptly once this was realised the routine separation of the babies from their mothers, and their herding, within inches of each other, into a small hospital side-ward, but only after its use had almost certainly killed many babies. Even after this salutary lesson struck home, it took many years for clinicians to realise that other antiseptics, such as iodine, can also be absorbed through the skin to a dangerous degree – particularly in the preterm baby (Parravicini *et al.*, 1996).

Even when staff came to accept that most of the skin did not require special treatment after birth, the umbilical stump continued to be the focus of special attention and subject to a wide range of antiseptic treatments. It is now slowly coming to be accepted that, while many of these treatments do reduce bacterial colonisation they do not, when used in an a first world setting, reduce the incidence of sepsis (Zupan *et al.*, 2004). Indeed, with a plastic clamp in place for 24 hours, the umbilical stump heals rapidly and naturally if cut short and kept dry. While colonisation can be reduced in a number of ways, a policy of only treating those stumps that look inflamed reduces overt sepsis just as effectively as a policy of routine universal prophylaxis. Hexachlorophene powder (Ster-Zac[®]) is widely used, and limited use does not cause the damaging systemic absorption that was seen when babies were immersed in this antiseptic. Treatment with spirit merely delays cord separation.

Management in a low-income setting: Now, after almost half a century, thinking has come full circle, and people are beginning to realise that, in the developing world, simple antiseptic routines can save life. Of the four million babies who currently die in the world each year, 99% live in developing countries, often in small rural communities, and a third of these deaths are probably caused by infection (Lawn *et al.*, 2005). The small group headed by Garry Darmstadt have, in the last few years, almost single-handedly changed everyone's approach to this daunting challenge.

In a cluster-randomised controlled trial from Nepal involving over 15,000 infants published in the *Lancet* in 2006 (Mullany *et al.*, 2006), this group showed that cleaning the umbilical stump daily with 4.0% chlorhexidine reduced in the incidence of severe cord stump infection (omphalitis) by 75% (RR = 0.25 [0.12, 0.53]) and also reduced neonatal mortality in those so treated within 24 hours of birth by 34% (RR = 0.66 [0.46, 0.95]). Whole body cleaning using a cloth wipe impregnated with 0.25% chlorhexidine soon after home birth also reduced neonatal mortality in a sub-set of low birth weight babies by 28% (RR = 0.72 [0.55, 0.95]). Other smaller studies have looked at the potential value of cleaning the vagina before birth as well as the baby after birth with cotton wool balls liberally soaked in 0.6% aqueous chlorhexidine (Goldenberg, *et al.*, 2006; McClure *et al.*, 2007; Saleem *et al.*, 2007). Much needs to be done to confirm the outcome of these studies in other settings and to determine whether there really are advantages in routinely cleaning the whole of the skin rather than just the umbilical stump, and whether vaginal cleansing might also be of value especially for mothers delivering in the home or in a community setting. Much will also need to be done to ensure that such care is offered to all who stand to benefit if these findings can be confirmed.

Gezon HM, Thompson DJ, Rogers RD, *et al.* Hexachlorophene bathing in early infancy: effect on staphylococcal disease and infection. *N Engl J Med* 1964;**270**:379–86.

Mortimer EA, Wolinsky E, Gonzaga AJ, *et al.* Role of airborne transmission in staphylococcal infections. *BMJ* 1966;1:319–???

Larson DL. Studies show hexachlorophene causes burn syndrome. *Hospitals* 1968;**42**:63–4.

Curley AQ, Kimbrough RD, Hawk RE, *et al.* Dermal absorption of hexachlorophane in infants. *Lancet* 1971;ii:296–7.

Kimbrough RD, Gaines TB. Hexachlorophene effects on the rat brain: study of high doses by light and electron microscopy. *Arch Environ Health* 1972;**23**:114–22.

Alder VG, Burman D, Corner BD, *et al.* Absorption of hexachlorophene from infants' skin. *Lancet* 1972;ii:384–5.

Kopelman AE. Cutaneous absorption of hexachlorophene in low birthweight infants. *J Pediatr* 1973;**82**:972–5.

Powell H, Swarmer O, Gluck L, *et al.* Hexachlorophene myelinopathy in premature infants. *J Pediatr* 1973;**82**:976–81.

Shuman RM, Leech RW, Alvord EC. Neurotoxicity of hexachlorophene in the human. A clinicopathologic study of 248 children. *Pediatrics* 1974;**54**:689–95.

Goutieres F, Aicardi J. Accidental percutaneous hexachlorophene intoxication in children. *BMJ* 1977;**2**:663–5.

Martin-Bouyer G, Lebreton R, Toga M, *et al.* Outbreak of accidental hexachlorophene poisoning in France. *Lancet* 1982;i:91–5.

Lane AT, Drost SS. Effects of repeated application of emollient cream to premature neonates' skin. *Pediatrics* 1993;**92**:415–9. [RCT]

Nooper AJ, Horii KA, Sookdeo-Drost S, *et al.* Topical ointment therapy benefits premature infants. *J Pediatr* 1996;**128**:660–9. [RCT] (See also **130**:330–4.)

Parravicini E, Fontana C, Paterlini GL, *et al.* Iodine, thyroid function, and very low birth weight infants. *Pediatrics* 1996;**98**:730–4.

Zupan J, Garner P, Omari AAA. Topical umbilical cord care at birth. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art No.:CD001057.

Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? where? why? *Lancet* 2005;**365**:891–900.

Mullany LC, Darmstadt GL, Khatry SK, *et al.* Topical applications of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern Nepal: a community-based, cluster-randomised trial. *Lancet* 2006;**367**:910–8. [RCT]

Mullany LC, Darmstadt GL, Tielsch JM. Safety and impact of chlorhexidine antiseptics interventions for improving neonatal health in developing countries. *Pediatr Infect Dis J* 2006;**25**:665–75. [SR]

Mullany LC, Darmstadt GL, Khatry SK, *et al.* Impact of umbilical cord cleaning with a 4.0% chlorhexidine on time to cord separation among newborns in southern Nepal: a cluster-randomized, community-based trial. *Pediatrics* 2006;**118**:1864–71. [RCT]

- Goldenberg RL, McClure EM, Saleem S, *et al.* Use of vaginally administered chlorhexidine during labour to improve pregnancy outcomes. [Review] *Obstet Gynecol* 2006;**107**:1139–46.
- Saleem s, Reza T, McClure EM, *et al.* Chlorhexidine vaginal and neonatal wipes in home births in Pakistan. A randomized controlled trial. *Obstet Gynecol* 2007;**110**:977–85. [RCT]
- McClure EM, Goldenberg RL, Brandes N, *et al.* The use of chlorhexidine to reduce maternal and neonatal mortality and morbidity in low-resource settings. *Int J Gynaecol Obstet* 2007;**97**:89–91.
- Tielsen JM, Marnstadt GL, Mullany LC, *et al.* Impact of newborn skin-cleansing with chlorhexidine on neonatal mortality in southern Nepal: a community-based, cluster-randomized trial. *Pediatrics* 2007;**119**:e330–40. [RCT]
- Darmstadt GL, Hossain MM, Choi Y, *et al.* Safety and efficacy of chlorhexidine skin cleansing on skin flora of neonates in Bangladesh. *Pediatr Infect Dis J* 2007;**26**:492–5.

Rewritten commentary
first posted June 2008
and updated September 2009