

Title

**CATHETER SEPSIS AND ANTISEPSIS: MATTERS OF LIFE, DEATH,
OBSCURITY, AND RESISTANCE**

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PC is current grant holder for the NIHR-funded ARCTIC feasibility study (Project ref: PB-PG-1013-32076) which is comparing the safety and efficacy of two skin antiseptics for catheter insertion. Website: www.npeu.ox.ac.uk/arctic Twitter:

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The very lines inserted daily to provide nutrition to neonates during intensive care remain associated with real risks of both mortality and life-impacting brain injury from associated sepsis. But most cases of central line-associated bloodstream infection (CLABSI) are preventable. There is now compelling observational evidence that adoption of catheter-care 'bundles' markedly reduces rates of CLABSI in the NICU.[1,2] Catheter-care bundles represent grouped evidence-based interventions for good catheter insertion and maintenance practices which, collectively implemented, reduce infection rates compared with individual component interventions. North American centres have shown that, by utilising bundles in conjunction with dedicated personnel, enhanced education, documentation, and a continuous focus on the gravity of the whole catheterisation process, it is possible to achieve zero CLABSI rates for protracted periods - even as long as 1-2 years.[3] In the most recent published UK survey, however, only 70% of tertiary-level UK NICUs had catheter-care bundles in place.[4] Current evidence implies that infants cared for on Units that have not yet implemented best practice guidelines may be at an increased risk of CLABSI;[2] such hospitals may be vulnerable to possible litigation in cases of damaging late-onset sepsis.

Furthermore, there is still debate as to preferred choice and accuracy of CLABSI working definition, inconsistency in definitions used to report CLABSI rates, and concern about data reliability.[2,5] The National Neonatal Audit Programme's latest report (2016) shows that data entry was considered complete and reliable enough to allow inter-unit comparisons of CLABSI rates for only 22 (14%) of the 182 individual NICUs audited.[5] So while many US centres have raced to slash their CLABSI rates, sometimes spurred on by the Medicare health insurance

programme's withholding of funding for hospital-acquired CLABSI cases,[6] it appears that most UK units do not even know their baseline CLABSI rates with any degree of accuracy. Also, reflecting the most widely-used CLABSI definition,[7] headline CLABSI rates are currently provided only as a composite for all types of central catheters present. Yet umbilical catheters each have very different characteristics of use, dwell time, and infection risk, compared with peripherally-inserted central venous catheters or surgical catheters. Future reporting of neonatal CLABSI rates should ideally include subdivisions according to catheter type to facilitate more valid comparisons between centres and studies.[8]

Catheter-care bundles alone do not provide the complete answer to the CLABSI problem; they leave room for improvements which must come from careful research - the individual components have not been subject to rigorous evaluations in neonates. Arguably the most important component is the antiseptic chosen for skin disinfection before catheter insertion, because skin bacterial density at the insertion site is a major risk factor for CLABSI and the main mechanism of infection of short-term catheters is via extraluminal colonisation.[7,9] Major questions remain over the ideal antiseptic agent to use in neonates: which is the safest and most effective preparation to use on the vulnerable skin of preterm neonates and in what concentration? At the last count seven different preparations were being used in UK units.[4] The predominating active agent was chlorhexidine gluconate (CHG), with or without isopropyl alcohol, and CHG concentrations varied 133-fold (between 0.015% and 2%). One unit was still using povidone-iodine; none was using octenidine, an agent popular in Europe for its supposedly better safety profile[10] but lacking any RCT evidence in neonates.

Use of an inferior, weak antiseptic agent may be safer considering the risk of skin morbidity, but may confer an increased risk of life-threatening CLABSI. Conversely, a stronger, more effective agent may significantly reduce the risk of CLABSI but at the expense of an increased risk of skin chemical injury. With a dearth of guiding research in this area, it is welcome that two studies in the present issue now report on the safety and efficacy of different skin antiseptics in preterm neonates.

Janssen and colleagues present retrospective observational data comparing CLABSI rates and skin dermatitis severity with two different CHG concentrations for placement of umbilical catheters and peripherally-inserted central venous catheters in neonates <26 weeks' gestation. In the first epoch they used the antiseptic combination 0.5%CHG with 70% alcohol; in the second epoch when using 0.2%CHG acetate alone they recorded fewer skin reactions while CLABSI rates stayed constant. Relative proportions of umbilical and peripheral catheters inserted are not detailed, though almost all skin lesions were peri-umbilical. A striking finding was the apparent high number of infants (7/41; 17%) with skin lesions classed "severe" in the first epoch. This contrasts starkly with only 4 cases of suspected chlorhexidine neonatal chemical skin burns/disorders (3 peri-umbilical) reported to Medicines and Healthcare products Regulatory Agency (MHRA) as occurring since its 2014 Drug Safety Update alert (Personal written communication, Vigilance and Risk Management of Medicines - MHRA, 17th July 2017).[11] Such wide variance suggests significant over-reporting, under-reporting, or both.

While the switch to using a lower CHG concentration and/or alcohol-free agent *may* have contributed to fewer recorded skin reactions in the second epoch, the reduction may just have reflected the increased awareness of antiseptic-related skin reactions which had prompted the unit's change in antiseptic agent in the first place, perhaps coinciding with a more sparing antiseptic usage/exposure. Claiming that introducing the weaker, alcohol-free CHG solution resulted in a reduced incidence of skin lesions is unjustified. The data are of interest, but they do not warrant the proposal that 0.2%CHG acetate now be considered a preferred option for extremely preterm infants or any recommendation to change practices. For this was a small observational study which relied on retrospective validation of skin reactions and had other inherent confounders; most importantly numbers were way too small to detect any impact on CLABSI incidence.

Kieran and colleagues deserve praise for having completed one of only very few antiseptic RCTs ever done in neonates for skin disinfection prior to central venous catheter insertion. Studying a large cohort of preterm neonates <31 weeks' gestation, and with excellent follow up rates, they present data suggesting that the 2% CHG-70% isopropyl alcohol combination seems comparable in efficacy against CRBSI as 10% povidone-iodine solution. As acknowledged, their main research question - assessing whether 2% CHG-70% isopropyl alcohol significantly reduces CLABSI rates compared with 10% povidone-iodine - was unfortunately unanswered because the study was markedly underpowered. The power calculation was based on very high baseline (35%) and target (20%) CLABSI rates, both much higher than rates actually seen in the study arms (5-7%). These figures were derived from historic eras with much higher rates of late-onset infection instead of from more

recent pre-existing local or international data for the planned study population. This provides another illustration of the importance of individual centres knowing their own accurate, up-to-date baseline CLABSI rates.

The trial presents some basic safety data which suggest that a 'stronger' antiseptic (2% CHG-70% isopropyl alcohol), already shown to be superior in adults, may be used in preterm infants without causing significant skin injury if a strict procedure to limit topical application and exposure is followed. Yet the lack of robust, active safety surveillance by dedicated research personnel and of any prospective, routine recording of skin integrity and adverse reactions inevitably limits generalisability of safety findings. Future antiseptic studies in neonates must use appropriate methodology to assess skin safety outcomes rigorously, thus allowing firm conclusions to be drawn about the relative safety and efficacy of different antiseptic solutions.

One important finding is that significantly more babies exposed to povidone-iodine antiseptic developed low thyroid status which needed treatment. Given the suggestion of similar efficacy of the antiseptics tested and of similar reassuring skin safety profiles, this finding has implications for current practice. It adds weight to the existing body of evidence of thyroid dysfunction in preterm neonates caused by topical iodine exposure,[12] and renders any ongoing use of topical iodine-based antiseptics very difficult to justify in preterm neonates.

An important but hitherto little-considered issue concerning antiseptic safety is the potential for the emergence of antiseptic resistance. The global antibiotic resistance

crisis is widely appreciated and is a major cause of concern. Use of antiseptics to prevent infection developing in the first place is now more crucial than ever.

However, there are signs that pathogens may also be evolving *antiseptic* resistance.[13] This potentially represents a huge issue given the reliance placed on antiseptics in many medical settings including NICUs.

Bacterial resistance to antimicrobials can occur as a result of various mechanisms, some of which are not specific to single classes of antibiotic. For example, bacteria can over-produce membrane transporters that pump out multiple toxic molecules; often these pumps can recognise and export antiseptics as part of their repertoire. The 'qac' (quaternary ammonium compound) family of genes are known to export chlorhexidine and other related compounds and their presence is increasing in some species.[14] The clinical impact of this is however currently unclear.[15]

There is currently no standard surveillance for antiseptic resistance in routine isolates and little research into the potential for different antiseptic formulations to select for resistance. These knowledge gaps are worrying when trying to define best practice for antiseptics. Future work in this area is therefore imperative to allow full confidence in any antiseptic agents and concentrations chosen for inclusion in care bundles.

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