Pitfalls in evidence assessment: the case of chlorhexidine and alcohol in skin antisepsis

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Chlorhexidine has attracted increasing attention for its role in skin antisepsis in recent years. It was tested in several prominent clinical trials and subsequently recommended in important guidelines for blood culture collection, vascular catheter insertion and surgical skin preparation. We noticed and subsequently reported a widespread misinterpretation of evidence surrounding chlorhexidine and its role in skin antisepsis. Multiple clinical trial reports and systematic reviews that had assessed the clinical efficacy of chlorhexidine/alcohol combinations for skin antisepsis had attributed efficacy solely to the chlorhexidine component. This misinterpretation was carried over into the tertiary literature, including evidence-based guidelines. Here we discuss some of the scientific, ethical, patient safety and infection control implications of this misinterpretation, as well as broader implications for evidence-based medicine.

Keywords: povidone–iodine, evidence misinterpretation, skin disinfection

Introduction

Skin antisepsis, also termed skin disinfection, is a simple and effective measure to reduce the risk of contamination or infection from iatrogenic skin breaks. Among the antiseptics, chlorhexidine has attracted considerable attention, as evidenced by numerous presentations at important infection control and infectious diseases conferences in recent years. This was precipitated by findings from prominent clinical studies1–3 and subsequent recommendations in important clinical guidelines.4–6 This led to chlorhexidine being widely promoted as the skin antiseptic of choice for a number of different applications. However, we noticed and subsequently reported a widespread misinterpretation of evidence surrounding this issue.7 The purpose of this article is to discuss some of the scientific, ethical, patient safety and infection control implications of this misinterpretation, as well as broader implications for evidence-based medicine.

Inconsistencies observed in the literature

Our concerns were aroused when we noticed several clinical studies and systematic reviews8–10 that evaluated the clinical efficacy of chlorhexidine/alcohol combinations (i.e. two antiseptics) against povidone–iodine alone (i.e. one antiseptic) and concluded that chlorhexidine per se was superior to povidone–iodine per se (Figure 1). However, this seemed highly implausible, given what is known about the microbiological properties of skin antiseptics.11,12 Alcohols possess the strongest immediate antimicrobial activity, but have no appreciable residual activity on skin. Both chlorhexidine and povidone–iodine have much less immediate efficacy (by a factor of ∏10), but have residual activity, which is small for povidone–iodine but pronounced in the case of chlorhexidine.

Systematic review undertaken

These observations prompted us to perform a systematic review.7 We looked at three applications of skin antisepsis: (i) prior to blood culture collection to prevent blood culture contamination; (ii) prior to vascular catheter insertion and during catheter maintenance to prevent catheter colonization and catheter-related bloodstream infection (CR-BSI); and (iii) prior to surgery to prevent surgical site infections (SSIs). We examined not only the clinical efficacy of chlorhexidine and its combinations, but also the articles’ conclusions (i.e. attribution of efficacy; Figure 1) and whether any incorrect interpretation had been carried over into the tertiary literature.

We found good evidence for the superiority of chlorhexidine/alcohol (two antiseptics) over that of aqueous povidone–iodine (one antiseptic) for all three applications and all assessed study outcomes. However, such evidence of superiority was not found the case of chlorhexidine per se versus povidone–iodine per se.
Our findings indicate that a widespread perception of efficacy of chlorhexidine had arisen that was in significant parts actually based on evidence for the chlorhexidine/alcohol combination. This is also reflected in a recent survey among infection preventionists from 478 US hospitals, in which 98% of respondents indicated strong perceived evidence for ‘chlorhexidine gluconate’ for central venous catheter insertion site skin antisepsis.\(^\text{21}\) We feel that this is of considerable significance. First, it means that a basic error in reasoning has frequently been committed. Effects cannot be attributed to one factor when in fact several factors were tested in combination (Figure 1). Second, this misinterpretation of evidence has caused a potentially mistaken rejection of alternative antiseptics—e.g. iodine–alcohol combinations—on the basis that they do not contain chlorhexidine. This is clearly evident in several articles and guidelines, where the belief in efficacy has been pegged to the presence or absence of chlorhexidine.\(^\text{4,6,13,22}\)

### Scientific implications

For comparisons against competitor/alcohol combinations. For blood cultures and surgery, we found no evidence indicating that chlorhexidine without alcohol was effective. For vascular catheters, aqueous chlorhexidine was better than aqueous povidone–iodine for preventing catheter colonization, but not for preventing CR-BSI. When we looked at the articles’ conclusions, we found that between 29% and 43% (among the three applications) of clinical trial reports and systematic reviews incorrectly attributed efficacy of the combination solely to chlorhexidine, and an additional 8%–35% were classified as ‘intermediate’ (i.e. when attribution was ambiguous). Overall, only ~35% of articles both (i) correctly listed the antiseptics that had been tested and (ii) correctly attributed efficacy to the actual antiseptics that had been used. In addition, we found multiple examples in the tertiary literature—including narrative reviews, formal clinical practice recommendations and strict evidence-based guidelines—\(^\text{4,6,13,14}\)—that appeared to have propagated this misinterpretation. Since our review was published, a few articles have specifically considered the possible clinical impact of alcohol in chlorhexidine/alcohol skin antiseptics,\(^\text{15,16}\) while several others have continued to attribute clinical efficacy to chlorhexidine alone.\(^\text{17–20}\)

### Patient safety and infection control implications

There are also implications for patient safety and infection control. First, recommendations to use ‘chlorhexidine’ (without mentioning alcohol) for skin antisepsis are very common. Caregivers following such recommendations may incorrectly use chlorhexidine on its own. This may expose patients to an increased risk of infection, either due to insufficient microbial killing at the skin site or because chlorhexidine—which is a relatively weak antiseptic—may become contaminated with microorganisms.\(^\text{23}\) Although it appears likely that the majority of instances of such incorrect use would go unnoticed and unreported, we are aware of several recent case series of bloodstream infections with non-fermentative Gram-negative bacteria (including *Burkholderia cepacia* complex and *Achromobacter xylosidans*) that were apparently caused by the use of contaminated aqueous chlorhexidine for skin antisepsis at vascular catheter insertion sites.\(^\text{24–28}\) The chlorhexidine had become contaminated by dilution with non-sterile water or been filled in non-sterile containers. Measures that terminated the outbreaks included switching to sterile water or sterile containers, disinfecting the water sources, and/or switching to povidone–iodine or chlorhexidine/alcohol. Second, there is now increasing concern about the possible emergence of bacterial clones with acquired ‘resistance’ (better termed ‘reduced susceptibility’) to chlorhexidine among important nosocomial pathogens.\(^\text{29,30}\) Thus, there is an imperative to limit its use to applications where its benefits have been proven. Nevertheless, it appears plausible that its use in classical skin antisepsis would have a much lesser impact than in more extensive applications, such as preventative antiseptic whole-body washing or multiresistant pathogen decolonization.\(^\text{31,32}\)

### Implications for evidence-based medicine

We think that the chlorhexidine case contains important lessons for evidence-based medicine. What has unfolded while investigating this issue is a story of how subjective perception and preconceived notions clouded and skewed evidence assessments, even in cases where strict evidence-based protocols were followed. The chlorhexidine misinterpretation has affected a significant proportion of the medical literature and contaminated the entire path of evidence assessment, from clinical trials, systematic reviews, narrative reviews, keynote presentations at conferences and simple clinical practice recommendations all the way through to evidence-based clinical practice guidelines. How could this have happened? We speculate that authors may have viewed the alcohol as a mere solvent for chlorhexidine, as expressed in the commonly used term ‘chlorhexidine in alcohol’. This is despite a vast supporting microbiological evidence base that shows alcohol to be a highly potent antiseptic.\(^\text{11,12}\) Unfortunately, this literature pool would likely have been missed by a purely clinical
evidence-based search for articles that assessed clinical outcomes. From our reading, it appears that clinical trial and systematic review authors were frequently unaware of this entire branch of the medical literature.

Another aspect is that evidence assessments do not commonly take functional and physiological characteristics into account. The requirement for persistency on skin—which is the major advantage provided by chlorhexidine—increases from blood culture collection (which has none) through surgery (for which it is typically several hours) to vascular catheters (which stay in place several to many days). Consequently, one would expect that the relative importance of chlorhexidine increases accordingly for the three applications, being greatest for catheters. The clinical findings of our systematic review\(^7\) are entirely consistent with these expectations, as are the findings of another systematic review on blood cultures,\(^33\) which found no clear difference between iodine-containing and chlorhexidine-containing antiseptics as long as they were alcohol-based. Therefore, we think that such functional aspects constitute important information for guiding clinical decisions.

**Clinical and microbiological evidence for antiseptics**

What information can be obtained from microbiological antiseptic testing versus clinical trials? Microbiological testing, both in vitro and under realistic conditions on human skin, has been used for many decades. It has been incorporated into US and European testing standards and has become part of regulatory requirements for product approval.\(^34,35\) Microbiological comparisons can be very detailed, include many different compounds, and can be used to optimize antimicrobial performance during product development. It also does not expose patients to the risk of real infections should the tested antiseptic be suboptimal. However, it does not measure clinical endpoints and therefore is not entirely predictive of what will happen in clinical practice. In comparison, clinical trials provide information on patient-important outcomes, and when combined in systematic reviews and meta-analyses can provide the strongest possible direct evidence. However, clinical trials are limited in the numbers of possible comparisons; each comparison of antiseptics potentially requires the enrolment of hundreds, if not thousands, of patients. In addition, some measured study outcomes, such as CR-BSIs and SSIs, are potentially life-threatening events. Clearly, both microbiological and clinical evaluations constitute complementary sources of evidence. As an example, a sequential Phase 1–3 approach has been proposed by the European Committee for Standardization (CEN) Technical Committee (TC) 216 for antiseptics and disinfectants, where Phases 1 and 2 are microbiological laboratory tests and Phase 3 tests are ‘field trials’ (in loco tests).\(^36\) However, at this point the Committee has concentrated on standardizing microbiological tests and not yet provided any specific recommendations for field tests. Randomized clinical trials would, of course, constitute the gold standard for field testing, but other approaches are possible.

**Ethical considerations**

The question arises whether it is ethical to conduct a clinical trial measuring potentially serious outcomes when microbiological testing predicts a performance difference of ~10:1 between trial arms. Such a difference applies to some of the published trials, e.g. those comparing chlorhexidine/alcohol with aqueous povidone–iodine. Again, the results of our meta-analyses of clinical outcomes reflect these microbiologically predicted performance differences very well.\(^7\) We do not have a definite answer to this ethical question, but we believe that it is essential for the medical community to be aware of and to be asking such questions. As one step towards addressing this issue, we propose that antiseptic products should be subjected to standardized microbiological testing—including assessment of persistent action where applicable—before proceeding with clinical trials that measure potentially serious clinical outcomes, and that such information should be made available as part of the trial registration procedures. Again, this would be consistent with a sequential microbiological and clinical assessment.

**Concluding remarks and role of biological plausibility**

The case of the chlorhexidine attribution error appears to be unique, both in terms of its large scale and in that it seems to have been caused by genuine misinterpretation by article authors. Other cases of evidence skewing through commercial interests are increasingly attracting attention.\(^36,37\) The chlorhexidine misinterpretation definitely has the potential to benefit chlorhexidine manufacturers, but until recently the misinterpretation per se did not seem to be driven by commercial influence. However, this assessment may change, and there are recent allegations that a major chlorhexidine/alcohol manufacturer may have inappropriately influenced guideline development by the US National Quality Forum towards its particular formulation.\(^38\) The question then arises whether the relative uniqueness of the chlorhexidine attribution error would mean that similar evidence skewing is unlikely to happen again in other contexts. This is unknown, but we are not confident.

Another aspect comes to mind. In a famous article published in 1965, Sir Austin Bradford Hill\(^19\) proposed a set of nine view-points—commonly termed the ‘Hill criteria’—that can help distinguish association from causation in epidemiological research. One of these criteria was biological plausibility. As discussed, it is implausible that clinical trial outcomes from a mixture of two effective agents should solely be due to one of the two. We postulate that, if more authors had been guided by the Hill criteria and checked relevant biological background knowledge, the magnitude of this error might have been reduced. We note that checking for biological plausibility is currently not part of formal evidence assessments.\(^30,41\)

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References


