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Effect of Chlorhexidine Probably Overestimated Because of Lack of Neutralization after Sampling

To the Editor—I read with interest the concise communication by Veiga et al[1] on the effectiveness of chlorhexidine showers before elective plastic surgery procedures. I think the study has a substantial limitation that stands in the way of the authors' conclusion that skin colonization was reduced by chlorhexidine showers. Patients were asked to shower and use either a detergent that contained 4% chlorhexidine or a placebo detergent. Samples for quantitative skin culture were obtained with a premoistened sterile cotton swab. The swab was placed in saline, which apparently did not contain any neutralizing agents to stop ongoing antimicrobial effects caused by chlorhexidine in the sampling fluid. Any remaining chlorhexidine in the sample continued to have a bactericidal or bacteriostatic effect in the saline after sampling.

The lack of neutralizing agents in sampling fluid has well been described as a source of false-positive efficacy data.[2] The absence of such agents in the sampling fluid more or less ruins the validity of the efficacy data because researchers can no longer distinguish whether the effect (ie, a lower number of colony-forming units in samples from the treatment group) was obtained before or after sampling.[3] A study that uses the number of colony-forming units as an end point to examine the efficacy of chlorhexidine should not survive the peer-review process if a valid method for neutralizing the active agent is not employed; false-positive efficacy data are likely to be obtained, which may lead to misleading and unbalanced recommendations for clinical practice. In the Veiga et al study,[1] samples were processed within 6 hours after they were obtained. This is a relatively long time, during which any remaining chlorhexidine could have significantly reduced the number of susceptible bacterial cells in the sampling fluid. It has previously been shown that only immediate sample processing yields the true number of surviving bacteria.[4] From my point of view, it is fair and scientifically acceptable to conclude that samples from the treatment group yielded a lower number of colonies on culture. It is, however, not scientifically acceptable to conclude that the chlorhexidine shower reduced skin colonization.

To my knowledge, the clinical benefit of topical chlorhexidine has so far only been demonstrated on permanently punctured skin sites surrounding vascular catheters.[5] For all other indications on skin, studies have not shown a benefit for the patient, which also includes the study by Veiga et al[1] If there is no clear benefit, any risk weighs even more heavily. There are some risks associated with the topical use of chlorhexidine in the healthcare setting that should be considered in this context, such as the emergence of resistance, especially among gram-negative bacteria; an increase in the degree of resistance as a result of an overall increase in the use of chlorhexidine; the emergence of cross-resistant bacteria that are resistant to both chlorhexidine and antibiotics; and the possibility of anaphylaxis after use, even when used on intact skin.[6] The recommendation that "chlorhexidine showers should be seriously considered in clinical practice"[1(p79)] certainly cannot be made on the basis of the data provided by Veiga et al, and it does not truly take into account the potential risks that can be associated with the topical use of chlorhexidine.

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Reply to Kampf

To the Editor–Despite Dr. Kampf's extensive experience with studies of antiseptics, he should review his conceptual framework regarding randomized clinical trials before stating that other researchers' data are invalid or criticizing the peer-review process.[1] Dr. Kampf made a major conceptual mistake when he asserted that "a study that uses the number of colony-forming units as an end point to examine the efficacy of chlorhexidine should not survive the peer-review process if a valid method for neutralizing the active agent is not employed."[1(p811)] Our trial was not an efficacy trial at all, but rather an effectiveness trial.[2] Randomized controlled trials are generally described in terms of whether they evaluate the efficacy or the effectiveness of an intervention, and these 2 concepts are frequently misunderstood, just as Dr. Kampf has misunderstood them.[3]

"Efficacy" refers to whether an intervention works for the people who actually receive it, whereas "effectiveness" refers to whether an intervention works for the people to whom it has been offered. Effectiveness trials try to evaluate the effects of the intervention in circumstances similar to those encountered by physicians in their daily practice.[3] Several points corroborate that our study was designed as an effectiveness study. For example, despite receiving instructions, there are individual variations in the way patients take showers. Furthermore, in the control group, each patient followed his or her usual personal hygiene routine on the day of surgery, and this obviously means that a great diversity of methods were used. Such diversity would probably ruin the results of an efficacy study, which should yield an evaluation of the intervention's effects that is not subject to arbitrary variation among participants.[3] However, this diversity does not harm the outcomes of an effectiveness trial, because, if appropriate randomization and allocation of subjects has been performed, the diversity mimics that found in clinical practice—that is, in real life. Typically, effectiveness trials evaluate interventions that have proven efficacious when offered to a group of people under ordinary clinical circumstances.[3] This is the case for chlorhexidine gluconate, the efficacy of which has been well studied.[4]

In our trial, patients were instructed to take a shower in which they used liquid detergent-based chlorhexidine 4% or a placebo solution. They were instructed to thoroughly rinse the detergent solution, and skin swab samples were collected in the operating room at least 2 hours later. The bacteriostatic activity of chlorhexidine begins at a concentration of 1 mg/L, and there is bactericidal activity at a concentration of 20 mg/L or greater.[4] Participants were instructed to rinse after using the cleansing solution, and when Dr. Kampf states that the lack of neutralizing agents in the sampling fluid invalidates our data, he seems to ignore the fact that after rinsing—which minimizes carryover of antiseptic—the concentration of chlorhexidine in the sampling fluid is probably much less than 1 mg/L.

Dr. Kampf also enumerates the following risks associated with the topical use of chlorhexidine: the emergence of resistance among gram-negative bacteria, an increase in the degree of resistance as a result of an overall increase in the use of chlorhexidine, the emergence of cross-resistant bacteria that are resistant to both chlorhexidine and antibiotics, and the risk of anaphylaxis. Except for the last one, these risks are minimized among plastic surgery patients, because chlorhexidine resistance is quite clearly linked only to isolates recovered in hospitals.[4] Patients undergoing plastic surgery are in good to optimal clinical condition, and, most of the time, they are discharged on the first postoperative day. These patients thus have distinctive characteristics that are much different from those of long-term hospital patients, in whom infection due to resistant organisms is more likely to occur. Besides, the patients in our study took a single preoperative shower with chlorhexidine.

Chlorhexidine is an ototoxic agent, and it has been reported to cause injuries to eyes and mucosa. Therefore, its use on periorbital sites, the eyelids, the inner ear, and mucosa should be avoided.[5] Even though hypersensitivity to chlorhexidine is rare, anaphylactic shock has been reported.[6] However, chlorhexidine is one of the most widely used antiseptics,[6] and its use is approved by United States Food and Drug Administration, as well as by the equivalent Brazilian governmental department, Agencia Nacional de Vigilancia Sanitaria. The Centers for Disease Control and Prevention has recommended the addition of preoperative antiseptic showers or baths to the preoperative site preparation regimen.[7] The expected outcome from this added effort is a reduction in the quantity of transient and normal skin flora in the area surrounding the surgical site, that is, a reduction in the number of organisms that contribute to surgical site infection.[8]

However, the effectiveness of these showers is controversial in the literature, and our study was designed to address this