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EDITORIAL

Caution for chlorhexidine gluconate use for oral care: insufficient data

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Oropharyngeal colonization is a crucial step toward tracheobronchial colonization and pneumonia in critically ill patients. Hence, oropharyngeal decontamination [namely, with antiseptics such as chlorhexidine gluconate (CHX)] has formed the basis of pneumonia prevention. However, the large body of data regarding its efficacy in terms of pneumonia rates reduction is inconclusive. Numerous meta-analyses have explored the existing studies in different ways, and have yielded contrasted conclusions. The more recent ones were more consistent in finding that favorable effects of CHX were limited to surgical patients and with greater CHX concentrations [1, 2]. Despite these controversial data and weak support from evidence, using CHX has been generalized in intra-hospital care to prevent respiratory infections.

If one wishes to pursue the use of CHX for oral care and extend it beyond ventilator-associated pneumonia (for example, to prevent post-operative respiratory complications), one should provide an answer to the question of CHX's efficacy in the critical care setting. And if the answer is unclear, then the question of its potential harm should also be answered.

Although CHX has been used with success for decades to treat periodontal diseases, as mentioned above, the more recent meta-analyses have questioned its efficacy in preventing VAP in critically ill patients, namely in those patients ventilated for more than 48 h and for a medical (as opposed to surgical) reason. Surprisingly, meta-analyses on the subject have outnumbered in-depth, at-the-bedside, studies evaluating CHX microbial efficacy. As a consequence, such basic questions as what are the changes over time of bacterial populations in the oropharynx of a ventilated patient after a CHX mouth rinse, and what is CHX's residual concentration are unanswered. Hence, CHX's efficacy could be called into question because there is not enough of it and/or because bacteria have become less susceptible to CHX. The latter is a matter of concern, both outside the field of ventilated patients [3] but also inside. A decrease in susceptibility to CHX that affected a quarter of bacterial isolates responsible for pneumonia in ICU patients has been reported [4]. In addition, a relationship seems to exist between antibiotic resistance and resistance to CHX. Since pathogens responsible for VAP are becoming increasingly more resistant, one must expect CHX to be similarly affected.

The second question addresses both the "local" and the "systemic" harm. Locally, we have clear evidence that CHX use may lead to mucosal ulcerations, and that the greater the CHX concentration, the poorer the patients' tolerance [5, 6]. Regarding a more systemic harm, the hypothesis was first raised by Klompas et al. [2]. They found an association between CHX use and increased

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mortality in non-cardiac surgery patients. Although the association was not significant, they believed that, because of "the potential public health importance of [their] observation", their findings required careful consideration and further evaluation.

In this issue of *Intensive Care Medicine*, Deschepper et al. strived to provide such an evaluation [7]. By analyzing the data of over 80,000 patients of which over 11,000 (14%) had received CHX oral care, they found that a low-level exposure to CHX ($\leq$300 mg) was associated with increased risk of death (OR 2.61). This association was stronger among patients with an inherently lower risk of death. Unexpectedly, no such signal was found in patients receiving mechanical ventilation. Also, among patients undergoing major cardiothoracic or vascular surgery, as well as among patients receiving mechanical ventilation, CHX did not affect mortality.

These results are provocative and counterintuitive. They are provocative because, as mentioned above, CHX has been used for decades in the periodontology field, and because many of us have a chlorhexidine-based mouth rinse solution in our bathroom cupboard we use more or less frequently. The realization that such a ubiquitous product may be harmful is daunting.

They are also counterintuitive because, if indeed CHX is harmful, one would have expected very opposite findings, i.e., more fragile patients, those with a higher risk of death (obviously including those under mechanical ventilation), would be adversely affected by CHX.

Another significant issue regarding the effect of CHX on outcome is related to total exposure to CHX (time and amount). Although authors try to set a cut-off of 300 mg to define levels of exposure, interactions between LOS of patients, increasing risk for nosocomial infections, higher exposure rates to a potential toxic substance, and compliance with prevention measures are certainly not linear, and effects of CHX on outcome are not properly adjusted for all these aspects. Lack of proper adjustment for exposure is, however, a major flaw in most hospital infection prevention studies, and precludes an appropriate interpretation of this study's findings. The effect of different CHX concentrations was not addressed in this study, so further investigations are necessary to assess this potential factor affecting risk for toxicity. The absence of detailed microbiological assessment of CHX effects also limits the full comprehension of the study.

To date, the few clues we have toward a potential harm of CHX concur for a direct lung toxicity [8–10], as shown in animal models, where administering CHX to the lungs induces injury. In the present study, the hypothesis of micro-aspiration of CHX and direct lung toxicity is—according to the results—not true. Indeed, spontaneously breathing patients, with active swallowing and coughing, hence the ones least exposed to the risks of micro-aspiration are the ones with the increased mortality after CHX exposure, whereas those patients with the greatest risk of micro-aspiration, those that are sedated, sometimes paralyzed, under mechanical ventilation, are not affected by CHX exposure. The possibility that the findings may be related to unidentified biases and confounding effects remains.

So where do we go from here? Given the uncertainties regarding CHX's efficacy (both in terms of oropharyngeal decontamination and of VAP reduction), the changes in pathogens' susceptibility to CHX and the potential harm related to CHX exposure, as intriguingly reported by Deschepper et al. [7], more data are urgently needed in order to guide our preventive strategies and identify specific groups who could benefit from CHX and avoid harming those who would not.

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Compliance with ethical standards

Conflicts of interest
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