EDITORIAL

Oral care with chlorhexidine: beware!

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Pneumonia in hospitalized patients is usually induced by aspiration of oral pathogens into the lower respiratory system. Oral care with chlorhexidine for the prevention of pneumonia is an appealing alternative because it appears to be safe, effective, and less likely to select for antibiotic resistance than oropharyngeal or digestive decontamination [1, 2].

The evidence that chlorhexidine is safe and effective, however, may be less robust than it seems (Table 1). First, our perception that chlorhexidine oral care prevents ventilator-associated pneumonia (VAP) may be biased. While multiple meta-analyses of randomized controlled trials have reported lower VAP rates, this is not the case if one stratifies by blinding status [3]. Lower VAP rates are only present on meta-analysis of open label studies, not double-blind studies. This suggests a problem with ascertainment bias.

Second, chlorhexidine can have adverse effects on the oral mucosa. Plantiga and colleagues, for example, documented erosive oral lesions, ulcerations, white/yellow plaques, and bleeding mucosa in 9.8% of patients treated with 2% oral chlorhexidine [4]. Fortunately, these lesions disappeared after stopping chlorhexidine.

More disturbingly, two recent meta-analyses of randomized controlled trials and two observational studies have reported that oral chlorhexidine, paradoxically, may *increase* mortality risk [3, 5–7]. The mechanism leading to higher mortality rates is unclear, but it may be that some patients aspirate chlorhexidine and develop acute respiratory distress syndrome [8]. In addition, some patients may suffer allergic reactions, including anaphylaxis [9–11].

Finally, the presumption that oral care with chlorhexidine has no impact on resistance may be incorrect. Biocide and antibiotic efflux pump genes are present in bacteria and can confer resistance to chlorhexidine; widespread use of chlorhexidine may accelerate the spread of acquired resistance [12]. A recent study documented decreased susceptibility to chlorhexidine in a quarter of *Escherichia coli* isolates associated with pneumonia in ICU patients [13].

In an article recently published in *Intensive Care Medicine*, Deschepper et al. [14] add further concern that oral care with chlorhexidine may be harmful in some patients. These investigators performed a hospital-wide retrospective observational cohort analysis on the effects of chlorhexidine oral care on hospital mortality. They included 82,274 patients, of whom 11,138 (14%) received chlorhexidine. Thee results showed that oral chlorhexidine was associated with an increased risk of death (OR 2.92; 95% CI 2.62–3.26). The association was strongest in patients with the lowest baseline risk of death. The

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Table 1 Evidence for and against daily oral care with chlorhexidine in mechanically ventilated patients

	Evidence in favor of oral care with chlorhexidine	Evidence against oral care with chlorhexidine
Randomized controlled trials	A few randomized controlled trials have reported significant decreases in VAP rates Presumed mechanism: chlorhexidine lowers microbial burden in the oropharynx, leading to lower probability of pulmonary inoculation with micro- and macroaspiration	Almost all randomized controlled trials have reported no significant impact on VAP rates VAP is an imprecise diagnosis; high risk of ascertainment bias in open-label studies and misclassification bias in double-blind studies
Meta analyses of randomized controlled trials	Multiple meta-analyses have reported significantly lower VAP rates	No significant decrease in VAP rates on meta-analysis of double-blind studies Meta-analyses suggest higher mortality rates Presumed mechanism: micro- and macroaspiration of chlorhexidine leading to acute lung injury in some patients; allergic reactions including anaphylaxis may also contribute
Observational studies	Multiple observational studies of VAP bundle implementations have reported lower VAP rates; many of these bundles have included oral care with chlorhexidine in addition to other prevention strategies	VAP bundle implementation studies are difficult to interpret—unclear which bundle components are contributing to observed effects and which are not. All studies unblinded, hence high risk of ascertainment bias Observational studies that have tried to determine the individual effect of each bundle component have reported associations between oral chlorhexidine and higher mortality rates

estimated number of patients needed to be exposed to result in one additional fatality was 47.1 (95% CI 45.2–49.1). In contrast to prior studies, however, the authors found no association between oral chlorhexidine and death in patients on mechanical ventilation or among cardiothoracic and vascular surgery patients.

The paper by Deschepper and colleagues extends the existing literature on possible harmful effects of oral chlorhexidine in ventilated patients to include non-ventilated patients outside the ICU as well. It is a provocative analysis that echoes a possible safety signal that has now been observed at least three times in three different studies [5–7]. Nonetheless, this study has important caveats that qualify its interpretation.

First and foremost, this was an observational, retrospective study. Less than 5% of non-ICU patients received chlorhexidine oral care, and the crude mortality for these patients was suspiciously high, at 13.5%. The high mortality rate in the chlorhexidine-exposed population raises the strong possibility of confounding by indication (providers may be more likely to provide chlorhexidine oral care to sicker patients). Indeed, the authors noted that such treatment is often used in their hospital for dependent patients who cannot perform their own oral hygiene. The authors attempted to adjust for confounding by incorporating age, sex, emergency admission, medical or surgical admission, diagnostic category, and predicted risk of death into logistic regression models. They did not, however, include variables for dependency or any other indications for chlorhexidine. Likewise, the authors used All Patient Refined-Diagnosis Related Group (APR-DRG) codes to adjust for severity of illness [15]. These codes correlate with hospital mortality, but they lack the nuance of detailed clinical risk scores. Finally, the authors were not able to precisely quantify patients' exposure to chlorhexidine or demonstrate a dose–response relationship.

In contrast to previous work, the authors found no harmful effect of chlorhexidine in ventilated patients or cardiothoracic and vascular surgery patients. Indeed, the authors reported that chlorhexidine may lower mortality risk by almost 50% in patients ventilated for < 96 h. This is difficult to believe given the large effect size relative to the low attributable mortality of VAP, the inconsistency of this finding with the rest of the study, and the strong possibility of survivor bias (nurses likely had more opportunities to use chlorhexidine in survivors versus those who died soon after intubation or who had care limitations placed due to impending death). Moreover, almost 90% of ventilated patients received chlorhexidine, thereby limiting the capacity to discern effects directly attributable to chlorhexidine in the ventilated population.

So, should clinicians reconsider oral chlorhexidine for VAP/HAP prevention? A growing body of evidence, including the study by Deschepper and colleagues, suggests that indiscriminate use of chlorhexidine oral care may be harmful. Nonetheless, there are important gaps in our current knowledge: the signal is only present on meta-analysis and retrospective observational studies; some meta-analyses reach different conclusions, and the mechanism is uncertain [16]. For the present, however, given the lack of evidence of benefit in double-blind studies and multiple independent signals suggesting the possibility of harm, we believe we should follow the precautionary principle [17]. In our opinion, oral care with chlorhexidine should not be used to prevent pneumonia in non-ventilated or ventilated patients unless and until further data become available.

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