5. Blot S. Antiseptic mouthwash, the nitrate-nitrite-nitric oxide pathway, and hospital mortality: a hypothesis generating review. Intensive Care Med. 2021;47(1):28–38.

S. Blot[a,*], M. Deschepper[b]

[a] *Department of Internal Medicine and Pediatrics, Ghent University, Campus UZ Gent, Ghent, Belgium*
[b] *Data Science Institute, Ghent University Hospital, Belgium*

* Corresponding author.
E-mail address: stijn.blot@UGent.be (S. Blot).

https://doi.org/10.1016/j.medin.2022.07.006
0210-5691/

Reply to ''Antiseptic Mouthwashes and Mortality: Look Beyond Chlorhexidine''

Respuesta a ''Enjuagues bucales antisépticos y mortalidad: más allá de la clorhexidina''

Dear Editor:

We have read with great interest the yet unpublished letter from Blot and Deschepper analyzing our article,[1] about oral care with chlorhexidine in critically ill patients, and we have some comments to make regarding the authors' considerations.

Due to the evidence of the association between oral care with chlorhexidine and increased risk of mortality, the International SHEA/IDSA/APIC 2022 Guidelines, in their ventilator-associated pneumonia (VAP) prevention bundles, recommend providing oral hygiene, but without chlorhexidine.[2] However, the pathophysiological mechanisms that explain this association are not well understood.

Indeed, micro-aspirations of chlorhexidine, an acidic substance, which could lead to lung injury, alone do not justify the mechanism of increased mortality. So much so that, in our article,[2] we have presented this as just one, among several, of the possible justifications. Therefore, other theories should be evaluated, including the suggestion by Blot and Deschepper that a disturbance in the enterosalivary nitrate-nitrite-nitric oxide (NO) pathway could help explain the increased mortality risk observed in patients exposed to chlorhexidine mouthwashes. According to the authors, oral antiseptics eradicate the anaerobic bacteria located on the posterior surface of the tongue, interrupting the process of reducing nitrate to nitrite, which occurs in the oral cavity, thus reducing the bioavailability of NO, a condition that could lead to increased mortality due to ischemic events and sepsis.

This theory is attractive, however, it does not fully explain the phenomenon, because: (1) studies evaluating selective oral decontamination with topical antibiotics, in critically ill patients on mechanical ventilation, reported lower hospital mortality[2,3]; (2) reduced bioavailability of the NO could actually be associated with an increased risk for ischemic cardiac events, however, there is evidence of increased mortality with the use of oral chlorhexidine also in young people without heart disease[4] and, in patients undergoing cardiac surgery, the use of oral chlorhexidine is associated with better outcomes[1]; and (3) if, on the one hand, the vasoconstrictor effect of low NO levels can be harmful for septic patients, on the other hand, high levels of this inflammatory mediator are associated with worse outcomes and increased mortality.[5] NO exerts an important role in the pathophysiology of sepsis, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), by causing increased endothelial permeability, vascular leakage, mitochondrial dysfunction, impaired migration of neutrophils to the focus of infection and worsened cardiovascular responsiveness in severe cases of sepsis.[5]

Besides the various possible justifications described in our article,[1] and the NO theorem proposed by Blot and Deschepper, other pathophysiological mechanisms that could explain the increased mortality risk observed in patients undergoing oral care with chlorhexidine should be sought and evaluated.

To our knowledge, there are no studies reporting increased mortality with the use of other oral antiseptics. Therefore, we believe that the issue of not using any antiseptic mouthwash, in the care of critically ill patients, should be explored in research comparing oral hygiene with chlorhexidine, with an alternative antiseptic, and with no antiseptic at all.

Conflict of interest

None.

Funding

None.

References

1. Vieira PC, de Oliveira RB, da Silva Mendonça TM. Should oral chlorhexidine remain in ventilator-associated pneumonia prevention bundles? Med Intensiva (Engl Ed). 2022;46(May (5)):259–68, http://dx.doi.org/10.1016/j.medine.2020.09.010.
2. Klompas M, Branson R, Cawcutt K, Crist M, Eichenwald EC, Greene LR, et al. Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and non-ventilator hospital-acquired pneumonia in acute-care hospitals: 2022 update. Infect Control Hosp Epidemiol. 2022;43(Jun (6)):687–713, http://dx.doi.org/10.1017/ice.2022.88.
3. Price R, MacLennan G, Glen J. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. BMJ. 2014;348:g2197, http://dx.doi.org/10.1136/bmj.g2197.

4. Deschepper M, Waegeman W, Eeckloo K, Vogelaers D, Blot S. Effects of chlorhexidine gluconate oral care on hospital mortality: a hospital-wide, observational cohort study. Intensive Care Med. 2018;44(7):1017–26, http://dx.doi.org/10.1007/s00134-018-5171-3.
5. Spiller F, Oliveira Formiga R, Fernandes da Silva Coimbra J, Alves-Filho JC, Cunha TM, Cunha FQ. Targeting nitric oxide as a key modulator of sepsis, arthritis and pain. Nitric Oxide. 2019;89(Aug):32–40, http://dx.doi.org/10.1016/j.niox.2019.04.011.

P.C. Vieira[a,b,*], R.B. de Oliveira[a,c]

[a] *Intensive Care Unit, Clinical Hospital of Uberlandia, Federal University of Uberlandia, Brazil*

[b] *Health Sciences Post-graduate Program, Federal University of Uberlandia, Brazil*
[c] *Intensive Care Medicine Residency Program, Federal University of Uberlandia, Brazil*

* Corresponding author.
E-mail address: paulacunhavieira@ufu.br (P.C. Vieira).

https://doi.org/10.1016/j.medin.2022.09.002
0210-5691/