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To counteract or to clear high-mobility group box-1 protein in influenza A (H1N1) infection? That may become the question

Patrick M. Honore*, Rita Jacobs, Inne Hendrickx, Elisabeth De Waele, Viola Van Gorp and Herbert D. Spapen

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Up to one third of patients with influenza A (H1N1) virus require intensive care unit (ICU) admission because of severe pneumonia, sepsis, or acute respiratory distress syndrome or a combination of these. Still, in-ICU mortality rate remains excessively high despite the deployment of maximal therapeutic support, often including extracorporeal membrane oxygenation [1].

In this perspective, the recently published experimental findings of Nosaka and colleagues in *Critical Care* may represent an important therapeutic breakthrough [2]. These investigators show that an anti-high-mobility group box-1 (anti-HMGB-1) monoclonal antibody suppresses the H1N1-induced immuno-inflammatory response, resulting in significant attenuation of lung injury and improved survival [2].

This study underscores that pharmacological inhibition of key inflammatory cytokines, despite offering equivocal or no additional benefit in sepsis, might be useful for treatment of specific infections that are accompanied by intense systemic inflammation. However, such therapy is expensive and not widely available, and little is known about eventual unwarranted side effects or late-onset complications in critically ill subjects.

Although its relatively small molecular weight does not prohibit removal by routine convective hemofiltration, HMGB-1 is effectively cleared by highly adsorptive dialysis membranes (HADMs) [3]. HADMs, in particular the surface-treated acrylonitrile 69 filter, are increasingly used for continuous renal replacement therapy (CRRT) in ICU patients [4] and may offer a valuable, more easily accessible, and potentially cheaper alternative to inhibit HMGB-1 activity in life-threatening influenza (H1N1) virus infection.

Authors' response

Nobuyuki Nosaka, Masato Yashiro, Hirokazu Tsukahara, Masahiro Nishibori and Tsuneo Morishima

We thank Honore and colleagues for their helpful comments on our article on the suppressive effects of HMGB-1 monoclonal antibody against H1N1-induced pneumonia [2]. They suggest that CRRT with HADMs may be beneficial to suppress HMGB-1 activity against H1N1 infection not only with regard to effectiveness but also accessibility, safety and cost. We agree that adjunctive therapy with HADMs holds promise against severe influenza and are interested in future research investigating systemic and local HMGB-1 clearance efficiency in influenza patients; however, we would like to comment from the pediatrician's viewpoint.

The clinical course of influenza infection is usually severe in infants, as in the 2009 pandemic. Therefore, young children should be focused on when preparing for future influenza outbreaks. Although anti-HMGB1 monoclonal antibody might be administered in cases of severe infection in general clinical settings, CRRT requires intensive care, resulting in higher medical costs. Moreover, CRRT is difficult to administer to children, especially those less than 10 kg, because of the lack of trained staff or appropriate equipment [5]. Given the estimates for the challenging demands for mechanical ventilators in a future severe pandemic [6], the feasibility of a stable supply of CRRT equipment or HADMs is questionable.

We have reported the possible therapeutic options for severe influenza pneumonia [2, 7] and believe that the preparation of a range of therapeutic choices will be crucial for future influenza outbreaks to protect the next generation.

* Correspondence: patrick.honore@az.vub.ac.be
Intensive Care Unit Department, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, 101, Laarbeeklaan, 1090 Jette (Brussels), Brussels, Belgium

Abbreviations
CRRT: Continuous renal replacement therapy; H1N1: influenza A; HADM: Highly adsorptive dialysis membrane; HMGB-1: High-mobility group box-1; ICU: Intensive care unit.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
PMH and HDS designed the manuscript and participated in drafting it. RJ, IH, EDW, and VVG participated in drafting the manuscript. All authors read and approved the final manuscript.

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