Commentary

Acetaminophen in critically ill patients, a therapy in search for big data analytics

Sven Van Poucke, Willem Boer

Department of Anesthesiology, Critical Care, Emergency Medicine and Pain Therapy, Ziekenhuis Oost-Limburg, 3600 Genk, Belgium
Correspondence to: Sven Van Poucke. Department of Anesthesiology, Critical Care, Emergency Medicine and Pain Therapy, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. Email: svanpoucke@gmail.com.

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Young *et al.* presented a study of randomly assigned ICU patients (n=700), with fever (body temperature ≥38 ℃) and known or suspected infection to receive either 1 g of intravenous acetaminophen or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death. The primary outcome was ICU-free days (days alive and free from the need for intensive care) from randomization to day 28. Early administration of acetaminophen to treat fever due to probable infection did not affect the number of ICU-free days.

Concluding that early administration of acetaminophen does not affect the number of ICU-free days should be viewed in perspective of the study limitations. The authors used a temperature ≥38 ℃ to classify patients with fever (1). Taking into consideration the variance related to the anatomical location of the measurement, the diurnal temperature cycle, and the technology applied, using 38 ℃ instead of 38.3 ℃ might be of limited importance. However, no mention is made of this choice of threshold or its possible consequences. Study inclusion too deserves further scrutiny. Out of a total of 3,601 patients meeting inclusion criteria only 700 underwent randomization spread over 23 adult ICU's, though 1,053 eligible patients were not enrolled. Protocol violations, in this case open-label acetaminophen administration, were high in both the acetaminophen (30%) and placebo (29%) groups, predominantly in the latter phases of ICU treatment. Use of the study drug before randomisation or after discharge from ICU was not reported. Finally, study drug administration was short compared to length of ICU stay. These combined weaknesses undermine the findings of the study, watering down any possible differences between the two study groups. In view of these shortcomings it is understandable that no considerations have been made on a potential extrapolation of the use of oral acetaminophen in this patient population (2).

However, the question posed by this study is clinically relevant. It might appear reasonable to give acetaminophen to patients in whom the fever is causing distress but it is similarly reasonable to withhold it in patients who are not distressed. In suspected infection, mild to moderate fever may prove beneficial in fighting infection. Evidence proving benefit of treatment for mild to moderate fever is scarce, apart from in cardiogenic shock, extreme hypoxemia or acute brain injury (3). A study *in vitro* demonstrated that differentiation of $CD8^+$ T cells into effector cells is enhanced by physiological range hyperthermia, with optimal enhancement at 39.5 ℃ (4). Similar advantageous effects were demonstrated in macrophages which play a pivotal role in innate immunity, enhancing early immunological responses to infection. In a murine model, LPS was utilized to model an aseptic endotoxin-induced inflammatory response studying the effects of elevation in body temperature to fever range. Fever enhanced and prolonged subsequent responsiveness of macrophages to the endotoxin challenge (5).

The methodology and its apparent shortcomings limit the value of findings and demand further discussion. Undoubtedly much time and effort has been invested and the abovementioned, often unavoidable, shortcomings must frustrate those who designed the study, begging the

question: what alternatives are there? (6). Predictive analytics could stimulate the transformation of reactive medicine (fever means acetaminophen treatment) towards more predictive, preventive and personalized medicine (PPPM) , ultimately affecting both cost and quality of care (7-9). However, high-dimensionality and high-complexity of the data involved, prevents data-driven methods from easy translation into clinically relevant models. Additionally, the application of cutting edge predictive methods and data manipulation require substantial programming skills, limiting its direct exploitation by medical domain experts. The existing, large databases providing inclusion of more patients (e.g., MIMIC-III database) (10) and the use of open, visual environments, suited to be applied by the medical community could stimulate the meaningful use of data from critical care patients. This could minimize the gap between potential and actual data usage (11).

In conclusion, Young *et al.* have reopened an important debate questioning the routine use of acetaminophen for fever control in the setting of infection. Studying the use of a drug which is so ingrained in clinical practice will always be arduous. Novel predictive analytics in large databases may provide a timely new tool for further study. Though it seems that this study has too many shortcomings to be able to change clinical practice once and for all, the clinician is right to question the use of acetaminophen in mild and moderate fever in patients in no apparent distress.

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Footnote

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References

1. Varghese GM, Trowbridge P, Doherty T. Investigating and managing pyrexia of unknown origin in adults. BMJ 2010;341:C5470.
2. Ripouteau C, Conort O, Lamas JP, et al. Effect of multifaceted intervention promoting early switch from intravenous to oral acetaminophen for postoperative pain: controlled, prospective, before and after study. BMJ 2000;321:1460-3.
3. Gozzoli V, Schöttker P, Suter PM, et al. Is it worth treating fever in intensive care unit patients? Preliminary results from a randomized trial of the effect of external cooling. Arch Intern Med 2001;161:121-3.
4. Mace TA, Zhong L, Kilpatrick C, et al. Differentiation of CD8+ T cells into effector cells is enhanced by physiological range hyperthermia. J Leukoc Biol 2011;90:951-62.
5. Lee CT, Zhong L, Mace TA, et al. Elevation in body temperature to fever range enhances and prolongs subsequent responsiveness of macrophages to endotoxin challenge. PLoS One 2012;7:e30077.
6. Husain AA, Martin GS. What is old is new again: acetaminophen as a novel approach to treating sepsis. Crit Care Med 2015;43:698-9.
7. Van Poucke S, Thomeer M, Hadzic A. 2015, big data in healthcare: for whom the bell tolls? Crit Care 2015;19:171.
8. Ghassemi M, Celi LA, Stone DJ. State of the art review: the data revolution in critical care. Crit Care 2015;19:118.
9. Golubnitschaja O, Kinkorova J, Costigliola V. Predictive, Preventive and Personalised Medicine as the hardcore of 'Horizon 2020': EPMA position paper. EPMA J 2014;5:6.
10. Zhang Z, Chen L, Ni H. Antipyretic therapy in critically ill patients with sepsis: an interaction with body temperature. PLoS One 2015;10:e0121919.
11. Ritthoff O, Klinkenberg R, Fisher S, et al. YALE: Yet Another Learning Environment. LLWA'01 – Tagungsband der GI-Workshop-Woche Lernen– Lehren – Wissen Adaptivitat. University of Dortmund, Dortmund, Germany. Technical Report 2001;763:84-92. Available online: http://www-ai.cs.uni-dortmund.de/PublicPublicationFiles/mierswa_etal_2003a.pdf

