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EDITORIAL

Association of prior antiplatelet agents with mortality in sepsis patients

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Platelet activation is not only an essential component of primary hemostasis but also plays a critical role in disease progression during sepsis. Sepsis involves inflammatory processes through releasing of several inflammatory mediators, such as interleukin (IL)-1β, IL-8, monocyte chemotactic protein 1, and tumor necrosis factor alpha [1], and then influences microvascular thrombosis formation and both innate and adaptive immunity [2]. Thus, attenuation of platelet activation is suggested to be one possible treatment option for sepsis in preclinical studies [1]. Some retrospective observational studies have also revealed that prehospital antiplatelet use was associated with decreased mortality rate in sepsis patients [3–6], but there is still a place for argument until studies provide strong evidence to support whether antiplatelet drugs are a possible adjuvant treatment choice in sepsis (Table 1).

In a recent article in *Intensive Care Medicine*, Dr. Wiewel and colleagues introduced a prospective observational cohort study to determine the association between pre-existing antiplatelet treatment and outcome of sepsis [16]. This study enrolled patients with strict diagnostic criteria of sepsis and reported that chronic antiplatelet treatment was not associated with the development of organ failure or shock during intensive care unit (ICU) stay or mortality after admission. It also disclosed no differences in 19 biomarkers between antiplatelet users and non-users during ICU stay. Although the robustness of this study is strengthened by well-defined sepsis diagnosis and documentation of relevant molecular biomarkers as an indicator of host immune response during sepsis, several concerns should be clarified.

First, in the study by Wiewel et al. [16], the size of only 150 patients per group who remained after propensity score matching is too small relative to the expected size of population (>2000) to detect differences in both groups. The definite impact (neutral, harm, or benefit) of antiplatelet agents on sepsis may not be determined thoroughly in this study because it is underpowered. This is not the only negative report with the same concern about inadequate sample size. Valerio-Rojas et al. [8] investigated 651 sepsis patients with similar study design and reported insignificant association between antiplatelet treatment and mortality. However, they also addressed the limitation and concern about inadequate patient number and power. With an eye toward improving reliability, the number of patients should be expanded to reach sufficient power in the further studies.

Second, given lack of details of antiplatelet prescription (dose and duration) and unknown baseline biomarker levels prior to antiplatelet drugs, we could not exclude that this flaw may elicit an unexpected finding of insignificant difference of 19 biomarkers between antiplatelet users and non-users with sepsis, possibly as a result of antiplatelet drug resistance or inappropriate dosing. Besides, there are more than 170 different putative biomarkers linked to sepsis, but most of them serve as predictors rather than as therapeutic guidance [17]. Those biomarkers that were reported to be associated with aspirin administration in sepsis, such as inhibition of nuclear factor kappa B [18], production of nitric oxide, and production of lipoxin [7, 10], were not investigated by the current study. The lack of difference in 19 currently used biomarkers between antiplatelet users and non-users may therefore not represent a lack of benefit.

Moreover, the lack of data regarding timing of antiplatelet administration or discontinuation does not allow

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Table 1 Brief summary of recent cohort studies on the association between antiplatelet therapy and sepsis

Literature	Study design	Agent	Date	Patient	Investigation	Outcome	Limitation
Eisen et al. [4]	Retrospective cohort	ASA	2000–2009	5523 patients with SIRS; 2082 on ASA; propensity score matched 1445 pairs of ASA users and non-users	Association of ASA administration at the time of SIRS/sepsis and mortality	Reduced mortality in ASA group	Treatment bias of ASA at the time of enrollment
O'Neal et al. [8]	Cross-sectional analysis of prospective cohort	ASA, statins	2006–2008	575 medical or surgical ICU patients	Association of prehospital statin, APT, or combination with risk of sepsis, ARDS, and mortality	Reduced risk of ARDS and severe sepsis for prehospital statin user, but not ASA user. No significant benefit on mortality rate	Uncontrolled administration of statins and aspirin
Valerio-Rojas et al. [8]	Retrospective cohort	ASA, clopidogrel	2007–2009	651 ICU patients with sepsis; 272 on APT; propensity matched 180 pairs of users and non-users	Association of APT before development of severe sepsis and outcome	No association between prehospital ASA use and mortality. Reduce incidence of ARDS/ALI and the need of mechanical ventilation	Inadequate patient number and power
Winning et al. [13]	Retrospective cohort	ASA, clopidogrel	2010	615 ICU patients; 179 received prehospital APT	Association of prehospital APT and mortality in critically ill patients	Reduction in mortality in APT group	Including non-sepsis critical patient
Losche et al. [14]	Retrospective cohort	ASA	2011	834 ICU patients presenting severe sepsis or septic shock. 187 receiving ASA	Effect of ASA use during ICU stay on outcomes of severe sepsis patients	Reduce ICU mortality in ASA group	Unequal distribution of each cohort
Chen et al. [15]	Secondary analysis of prospective cohort	ASA	2006–2012	1149 ICU patients; 725 patients with sepsis; 287 on prehospital ASA treatment	Effect of prehospital ASA use on the risk of ARDS and outcomes in critical patients including sepsis subgroup	Reduce the risk of ARDS. No significant association with mortality	Inaccurate ASA prescription; underpowered
Otto et al. [6]	Retrospective cohort	ASA, clopidogrel	2013	886 ICU patients with sepsis	Association of APT during ICU stay on outcome of patients with sepsis	Reduction in mortality in ASA and clopidogrel groups, but not in ASA + clopidogrel group	Surgical ICU patients
Tsai et al. [3]	Observational cohort	ASA, clopidogrel, ticlopidine	2000–2010	683,421 patients with sepsis; 117,447 prehospital APT users; propensity score matched 186,374 pairs of users and non-users	Association of prehospital APT and mortality of sepsis	Reduction in mortality in prehospital APT user. Survival benefit was inversely proportional to the interval between drug discontinuation and sepsis onset	Claims database

ASA aspirin, *APT* antiplatelet therapy, *ARDS* acute respiratory distress syndrome, *ALI* acute lung injury, *ICU* intensive care unit, *SIRS* systemic inflammatory response syndrome

the authors to address the effect of these potential confounding variables on the outcomes. As we know, the inhibitory effect of aspirin or clopidogrel on platelet activation could last for about 1 week despite discontinuing these agents [12, 11]. Our previous registry study also found that the benefit of prehospital use of antiplatelet drugs on sepsis outcomes was strongest in current users followed by recent users [3]. However, in the current study, the use of antiplatelet agents before enrollment was not clear. Besides, possible receipt of antiplatelet agents after ICU admission in non-antiplatelet users wound tend to bias the results to the null. Furthermore, only less than 50 % of patients still had the antiplatelet drugs in the first 2 days of ICU admission. Therefore, early discontinuation of antiplatelet drugs prior to sepsis onset could also partially explain the neutral association in this study.

Although there are some limitations, this prospective observational cohort study introduced by Dr. Wiewel and colleagues is still very valuable. It is the first prospective study in this field and enrolled sepsis patients according to well-defined clinical evidence rather than database or chart review. It also performed meticulous propensity matching, including disease severity by APACHE score, SOFA score, organ failure, and shock, which is lacking in most previous investigations and may causing significant confounding.

Given the conflicting results and inherent limitations from observational studies, only randomized controlled trials aimed at exploring the potential roles of antiplatelet agents as adjuvant treatment in sepsis or preventive agents to reduce disease severity will integrate the best evidence into clinical care of sepsis patients. There are currently at least two ongoing relevant clinical trials. The first trial is "Aspirin for the Treatment of Sepsis" (NCT01784159) which will investigate the beneficial effect of aspirin treatment for 7 days on organ dysfunction and duration of ventilation in severe sepsis patients. Another one is "Aspirin to Inhibit Sepsis" (ANTISEPSIS, ACTRN12613000349741) which will assess the effect of daily aspirin treatment on the mortality and admission to ICU for sepsis. Overall, we suggest that clinicians must be cautious in prescribing routine prophylactic antiplatelet drugs for sepsis prevention of treatment in view of further cost-effectiveness and harm–benefit analyses with hard evidence.

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Compliance with ethical standards

Conflicts of interest
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