Editorial on low-dose acetylsalicylic acid treatment and impact on short-term mortality in *Staphylococcus aureus* bloodstream infection: a propensity score-matched cohort study

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Abstract: The manuscript "Low-Dose Acetylsalicylic Acid Treatment and Impact on Short-Term Mortality in *Staphylococcus aureus* (*S. aureus*) Bloodstream Infection: A propensity Score-Matched Cohort Study" published in *Critical Care Medicine* by Osthoff *et al.* reported an association of aspirin intake with a reduced short-term mortality. Direct anti-microbial effects of aspirin and its metabolite salicylate were suggested in preclinical studies. Especially intriguing is the inclusion of a control group with *Escherichia coli* (*E. coli*) blood stream infections in this study, in which aspirin was not associated with an improved outcome. However, as other observational studies also reported benefits of aspirin in critically ill patients, randomized trials are needed to confirm the effects of low-dose aspirin.

Keywords: Aspirin; *Staphylococcus aureus* (*S. aureus*); mortality; *Escherichia coli* (*E. coli*)

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Acetylsalicylic acid (ASA) at low doses is usually regarded as an anti-platelet substance. The mode of action is an irreversible inhibition of the enzyme cyclooxygenase (COX) by acetylation (1,2), which inhibits arachidonic acid induced platelet aggregation even after single oral doses of 162 mg of aspirin (3). This effect is limited to COX-1 within platelets at low doses. At higher doses ASA also inhibits COX-2, which explains its use as an anti-inflammatory and analgetic drug. The use of low-dose ASA in the prevention of thromboembolic events has remained essential up to now (4,5).

However, apart from these well-known effects other beneficial responses were assigned to ASA and subject to investigation. ASA-triggered lipoxins, like other lipid mediators regulated by prostaglandins and COX enzymes, are thought to play an important part in the resolution of inflammation (6,7). Interestingly, at higher doses ASA inhibits the NF-κB pathway (8).

Inhibition of platelets, nowadays identified as "immune" cells contributing to inflammation activation and regulation, may prove beneficial in severe systemic inflammatory responses as inhibition may reduce the platelets' contribution to such a disease state (8,9). Various observational studies were performed showing overall positive effects of low-dose ASA in community-acquired pneumonia, in critically ill patients or in acute respiratory distress syndrome (10-14). Moreover, a possible role of low-dose ASA in prevention of cancer was suggested (15).

Finally, ASA was demonstrated to exert direct, antimicrobial effects. In a rabbit model of *Staphylococcus aureus* (*S. aureus*) endocarditis ASA at 8 mg/kg/day reduced vegetation weight, growth, bacterial density and embolic lesions (16). These observed benefits were at least partially diminished when other doses (4 and 12 mg/kg) were used. It's important to note that salicylate levels at the dose of 8 mg/kg were ranging between 47 and 53 μg/mL over a period of 12 hours, which is much higher than peak levels measured in healthy volunteers after a single dose of 162 mg of ASA, which were approximately 7.6±1.4 μg/mL (3). After intake of 800 mg of different NO-aspirin formulations mean peak plasma levels ranged between 10 and 21 μg/mL (17).

Considering these data from healthy volunteers, rather high doses of aspirin would be necessary to achieve the proposed doses. On the other hand, the interspecies differences have to be considered. Beneficial effects of ASA in combination with ticlopidine were also found in a rat endocarditis model caused by *Enterococcus faecalis* and *Streptococcus gallolyticus* (18). Salicylic acid, the main metabolite of ASA, affected the virulence of *S. aureus in-vitro* by activating a stress response regulon *sigma factor β.* This stress response *reduces α-hemolysin* (*hla*) and *fibronectin-binding protein A* (*fnbA*) gene expression (19,20). These results were confirmed in a study investigating not just the adhesive potential of *S. aureus* but also its invasiveness using human vascular endothelial cells. ASA reduced the virulence of *S. aureus* in this *in vitro* model (21). Again doses of 30 and 50 µg/mL were used. However, using a distinct, encapsulated *S. aureus* strain, ASA enhanced invasiveness in an *in vitro* model using bovine mammarian endothelial cells (MAC-T) (22). This suggests that the effects of ASA may differ between strains of *S. aureus* and more data are needed to better define the antimicrobial effects of ASA (22). Interestingly platelets were demonstrated to contribute to biofilm formation and inhibition of platelets by low-dose ASA may reduce biofilm formation and its resistance to antimicrobial substances (23).

In their manuscript Osthoff *et al.* investigated effects of low-dose ASA in *S. aureus* bloodstream infection (BSI) (24). Low-dose ASA was associated with a reduced mortality in this propensity score-matched cohort study. Of note, beside ASA intake another difference was evident between groups: in the ASA group significantly more patients were treated with statins compared to the non-ASA group. The intake of statins alongside the intake of low-dose ASA is not merely surprising taking the overlapping indications into account. Although statins were associated with reductions in mortality in other non-interventional studies (25), in the multivariate analysis of this study statins were not associated with an improved clinical outcome. Thus, although it cannot entirely be excluded, statin use should not interfere with the study's endpoints.

How should the findings of the study be interpreted and integrated into the growing body of evidence that there may be more to ASA than inhibiting platelet aggregation? This retrospective study was well-designed with a large propensity score-matched cohort, groups were well-balanced, except for the statin use, and existing standard practices for treatment and diagnosis of BSI within the hospital improve the quality of data. There is one particular strength, which adds much to the validity of the results: the inclusion of the *Escherichia coli* (*E. coli*) BSI control group. Thus, it is tempting to assume that direct antimicrobial effects of ASA against *S. aureus* cause this benefit. Furthermore it suggests that platelet inhibition in BSI caused by *E. coli* does not improve survival. After all, it has to be emphasized that although this study certainly adds important information still many questions remain. Observational studies, no matter how well designed and performed, are prone to bias and confounders. To confirm the reported, potentially beneficial effects of treating patients with *S. aureus* BSI with low-dose ASA, or other reported positive effects of ASA in critical illness, randomized trials are necessary. As the number of observational studies suggesting positive effects of ASA increase the call for such studies becomes louder. It seems likely that realization of such a trial is subject to academic research, as ASA use does not offer enough financial incentives for industrial sponsoring. Until randomized trials are performed, it remains unknown whether the observed effects are true or subject to bias.

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Footnote

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References

1. Born G, Patrono C. Antiplatelet drugs. Br J Pharmacol 2006;147 Suppl 1:S241-51.
2. Gaglia MA Jr, Clavijo L. Cardiovascular pharmacology core reviews: aspirin. J Cardiovasc Pharmacol Ther 2013;18:505-13.

3. Hobl EL, Schmid RW, Stimpfl T, et al. Absorption kinetics of low-dose chewable aspirin--implications for acute coronary syndromes. Eur J Clin Invest 2015;45:13-7.
4. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-619.
5. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457-507.
6. Romano M, Cianci E, Simiele F, et al. Lipoxins and aspirin-triggered lipoxins in resolution of inflammation. Eur J Pharmacol 2015;760:49-63.
7. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature 2014;510:92-101.
8. Eisen DP. Manifold beneficial effects of acetyl salicylic acid and nonsteroidal anti-inflammatory drugs on sepsis. Intensive Care Med 2012;38:1249-57.
9. Akinosoglou K, Alexopoulos D. Use of antiplatelet agents in sepsis: a glimpse into the future. Thromb Res 2014;133:131-8.
10. Lösche W, Boettel J, Kabisch B, et al. Do aspirin and other antiplatelet drugs reduce the mortality in critically ill patients? Thrombosis 2012;2012:720254.
11. Erlich JM, Talmor DS, Cartin-Ceba R, et al. Prehospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: a population-based cohort study. Chest 2011;139:289-95.
12. Boyle AJ, Di Gangi S, Hamid UI, et al. Aspirin therapy in patients with acute respiratory distress syndrome (ARDS) is associated with reduced intensive care unit mortality: a prospective analysis. Crit Care 2015;19:109.
13. Chen W, Janz DR, Bastarache JA, et al. Prehospital aspirin use is associated with reduced risk of acute respiratory distress syndrome in critically ill patients: a propensity-adjusted analysis. Crit Care Med 2015;43:801-7.
14. Kor DJ, Erlich J, Gong MN, et al. Association of prehospitalization aspirin therapy and acute lung injury: results of a multicenter international observational study of at-risk patients. Crit Care Med 2011;39:2393-400.
15. Chubak J, Kamineni A, Buist DS, et al. Aspirin Use for the Prevention of Colorectal Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality (US), 2015.
16. Kupferwasser LI, Yeaman MR, Shapiro SM, et al. Acetylsalicylic acid reduces vegetation bacterial density, hematogenous bacterial dissemination, and frequency of embolic events in experimental Staphylococcus aureus endocarditis through antiplatelet and antibacterial effects. Circulation 1999;99:2791-7.
17. Derhaschnig U, Schweeger-Exeli I, Marsik C, et al. Effects of aspirin and NO-aspirin (NCX 4016) on platelet function and coagulation in human endotoxemia. Platelets 2010;21:320-8.
18. Veloso TR, Oechslin F, Que YA, et al. Aspirin plus ticlopidine prevented experimental endocarditis due to Enterococcus faecalis and Streptococcus gallolyticus. Pathog Dis 2015;73:ftv060.
19. Palma M, Bayer A, Kupferwasser LI, et al. Salicylic acid activates sigma factor B by rsbU-dependent and -independent mechanisms. J Bacteriol 2006;188:5896-903.
20. Kupferwasser LI, Yeaman MR, Nast CC, et al. Salicylic acid attenuates virulence in endovascular infections by targeting global regulatory pathways in Staphylococcus aureus. J Clin Invest 2003;112:222-33.
21. Park WB, Kim SH, Cho JH, et al. Effect of salicylic acid on invasion of human vascular endothelial cells by Staphylococcus aureus. FEMS Immunol Med Microbiol 2007;49:56-61.
22. Alvarez LP, Barbagelata MS, Gordiola M, et al. Salicylic acid diminishes Staphylococcus aureus capsular polysaccharide type 5 expression. Infect Immun 2010;78:1339-44.
23. Jung CJ, Yeh CY, Shun CT, et al. Platelets enhance biofilm formation and resistance of endocarditis-inducing streptococci on the injured heart valve. J Infect Dis 2012;205:1066-75.
24. Osthoff M, Sidler JA, Lakatos B, et al. Low-Dose Acetylsalicylic Acid Treatment and Impact on Short-Term Mortality in Staphylococcus aureus Bloodstream Infection: A Propensity Score-Matched Cohort Study. Crit Care Med 2016;44:773-81.
25. Kopterides P, Falagas ME. Statins for sepsis: a critical and updated review. Clin Microbiol Infect 2009;15:325-34.

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