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An Aspirin a Day Keeps the Intensivist Away?

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In 2016 the Society of Critical Care Medicine and the European Society of Intensive Care Medicine convened a consensus panel that redefined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection(1). This definition moved past the previous definition of sepsis centered on the systemic inflammatory response syndrome(2). This new definition reflects advancement in the understanding of the pathophysiology of sepsis, recognizing the dysfunction of the immune system in sepsis that leaves patients unable to clear their primary infections and susceptible to secondary infection. This definition serves as the foundation for the development of the next generation immunoadjuvant therapies for sepsis targeted at restoring immunocompetency. In this issue of Critical Care Medicine, Leijte et al describe results that move this effort forward, and have taken a new path toward an old goal.

Aspirin is one of the most common medications used in the US, with up to 52% of US adults ages 45–75 reporting daily prophylactic use of aspirin(3). The high incidence of use in the US population has facilitated several large observational studies that have demonstrated that aspirin use is associated with improved outcomes from sepsis, and these results provided the impetus to expand a large randomized controlled trial of prophylactic aspirin(4) to prospectively measure the effect of aspirin on the incidence and outcome of sepsis (Aspirin To Inhibit SEPSIS, ANTISEPSIS)(5). These efforts inform the work of Leijte et al (6). In prior work, this group has demonstrated that aspirin can function as an immunomodulator, potentiating in-vivo and ex-vivo cytokine production in response to endotoxin, and have tied this effect to platelet production of PGE₂. In the current study, these authors measure the effect of aspirin on endotoxin tolerance in-vivo and demonstrate that treatment with aspirin initiated after an initial inflammatory stimulation restore the response to a secondary challenge. Importantly, they also find that platelets isolated from aspirin treated subjects are co-incubated with monocytes from septic patients, these monocytes are restored to an immunocompetent phenotype, with improved TNF-alpha production and attenuation of IL-10 production. These results demonstrate a potential mechanism for improved sepsis

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survival in patients taking prophylactic aspirin and suggest that aspirin may be effective as immunomodulatory treatment for septic patients.

For this study, the authors repurpose endotoxin tolerance as a model for sepsis-induced immune dysfunction. Endotoxin tolerance was first described in the 1960–70s, when it was recognized that animals treated with a low dose of bacterial endotoxin had reduced mortality when challenged with a second higher dose of endotoxin(7). Subsequent studies identified the mechanisms of endotoxin tolerance, culminating in a detailed molecular understanding of the genetic, epigenetic and cell-signalling mechanisms underpinning this process(8). Clinical studies of septic patients demonstrate significant parallels between the molecular- and cell-biology of sepsis induced immune-dysfunction and that of endotoxin tolerance(9). Unfortunately, endotoxemia has a checkered past as a model for clinical sepsis. In the 1980–90s inflammatory cytokines such as TNF-alpha and IL-1 were discovered to be the primary drivers of endotoxin-induced shock. Subsequent clinical studies found high levels of these inflammatory mediators in septic patients, and inspired a generation of failed clinical trials of anti-inflammatory strategies to treat sepsis(10,11).

Fortunately, this research team is well versed in the history of sepsis(12,13), and their current study epitomizes the bedside-to-bench reverse translational research approach that will be required to develop the next generation of sepsis therapies (14). Strong epidemiologic and population-based studies demonstrate that aspirin effectively improves outcomes from sepsis--we know it works for the “average” patient. This study takes these finding back to the bench and begins to explain why aspirin works in sepsis. Understanding the mechanisms of aspirin as a sepsis therapy will set the stage for the next iteration of clinical studies to identify the septic patients that will benefit most from treatment with aspirin.

In conclusion, this study provides a critical advance in the understanding of the role of aspirin as an immunomodulator for sepsis. They demonstrate that treatment with aspirin can reverse endotoxin tolerance in-vivo in human subjects, and that ex-vivo incubation with platelets from aspirin-treated subjects can restore an immunocompetent phenotype to monocytes isolated from septic patients. Establishing these mechanisms of action of aspirin in sepsis moves aspirin treatment toward the long-term goal of a precision therapy for sepsis.

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