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# Aspirin for Sepsis Prophylaxis: An Ounce of Prevention?

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Sepsis remains a scourge of modern medicine. With more than 750,000 cases annually in the United States alone, sepsis causes 10% of all ICU admissions and nearly one-half of all inpatient deaths (1–3). In recent decades, our understanding of sepsis pathophysiology has progressed significantly, but this knowledge has not translated into effective disease-modifying therapies, despite more than 80 Phase II or III randomized clinical trials of sepsis treatment (4, 5). The recurrent failure of novel therapies to translate from preclinical studies into successful sepsis treatment trials has led investigators to [1] search for new tools to more accurately identify promising candidate therapies in non-randomized data and [2] shift focus toward a new target: sepsis prevention.

In this issue of *Critical Care Medicine*, Trauer and colleagues [*draft reference,* (6)] apply a novel methodologic approach, meta-analysis of propensity-matched individual patient level data, to explore whether pre-admission acetyl-salicylic acid (aspirin) use prevents mortality among patients hospitalized with sepsis. The authors obtained individual patient data from all completed observational cohort studies examining sepsis, mortality, and the pre-hospitalization use of aspirin; no small feat. This allowed the authors to develop a propensity score for the likelihood of receiving pre-admission aspirin within each cohort. A meta-analysis of these propensity score analyses demonstrated that sepsis patients receiving pre-admission aspirin experienced a mortality rate between 2% and 12% lower than those not receiving aspirin.

Propensity score matching within a meta-analysis is a relatively new statistical tool for evaluating the effect of an intervention on an outcome in pooled observational data. First, available baseline characteristics are used to generate a model predicting each patient's likelihood of receiving the intervention of interest (the propensity score). Second, patients who received the intervention are matched with patients with a similar likelihood of receiving the intervention who, for whatever reason, did not receive it (propensity matching). The goal of this matching is to account for the patient factors that drove providers choice to administer or withhold the therapy of interest, differences which might otherwise make the two groups too dissimilar for fair comparison (indication bias). Third, clinical outcomes are compared between the matched patients who did and did not receive the intervention.

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Finally, in the step unique to this technique, the comparisons of clinical outcomes between matched patients in each individual cohort study are combined into a traditional meta-analysis, producing greater power than each individual cohort study and estimating the consistency of the results across studies. A Meta-analyses of propensity-matched individual patient level data share the basic limitations of both propensity score analyses and meta-analyses. Most notably, propensity score matching remains susceptible to bias from unmeasured confounders and neglects patients who “always” or “never” receive a given intervention (because they cannot be matched with patients in the opposing arm). Despite these limitations, meta-analysis of propensity-matched individual patient level data may prove superior to traditional multivariate analyses in predicting the outcome of randomized controlled trials…and the current study of pre-admission aspirin use and sepsis mortality may have the opportunity to serve as the test case.

Whether pre-illness aspirin receipt prevents sepsis or improves sepsis outcomes is the subject of the ongoing ANTISEPSIS trial (11), a sub-study of the ASPREE trial (12), a double-blinded, randomized, placebo-controlled trial of daily low dose aspirin to extend disability-free longevity in 19,000 healthy elderly adults. The ANTISEPSIS trial will collect additional information on the development and outcome of sepsis from 16,703 participants with 4.75 years average follow-up time. The primary endpoint will be sepsis-related mortality, and the secondary endpoints will be sepsis-related hospital and ICU admission.

A biologic rationale exists by which pre-illness aspirin use could impact sepsis at a number of points along the disease continuum: preventing infection, preventing infection from progressing to sepsis, or preventing organ dysfunction and subsequent morbidity and mortality. Pre-clinical studies have demonstrated that aspirin has multiple biologic effects that may be important in mitigating the effects of sepsis. By irreversibly inhibiting COX I and COX II enzymes and reducing activation of platelets, aspirin decreases prostaglandins, including $PGE_2$, which is required both for the production of pro-inflammatory cytokines and increased microvascular permeability in sepsis (8). In human umbilical vein endothelial cells stimulated by tumor necrosis factor, aspirin inhibits nuclear localization of transcription factor NFκB, decreasing production of pro-inflammatory cytokines and prostaglandins thereby attenuating monocyte adhesion (9). Finally, aspirin increases the production of anti-inflammatory lipoxins, including 15-epi-lipoxin A4 which promotes apoptosis of human neutrophils, an essential step in resolution of inflammation (10).

Confirmation of the current findings of Trauer et al in the ongoing ANTISEPSIS trial would both [1] lend credibility to the use of meta-analysis of propensity-matched individual patient level data to predict the results of randomized trials and [2] produce a seismic shift in sepsis management and research. Aspirin would represent a cheap, low-risk intervention to prevent sepsis, which could easily be delivered to patients at high risk of severe infection in the healthcare system or community. Basic and translational research could define which of aspirin’s anti-inflammatory, anti-platelet, or anti-coagulant effects mediated the clinical benefit, allowing the development of tailored therapy.

Sepsis prevention warrants enthusiasm…but tempered by the lessons learned from sepsis treatment. Identifying sepsis patients has been challenging enough, sepsis prevention trials

will need to accurately identify patients likely to develop sepsis in the future! Even in populations “enriched” for the development of sepsis, the majority of patients will not experience sepsis (13), requiring potentially massive trials. Similar to preventing acute respiratory distress syndrome (14), preventing sepsis may not be viewed as a patient-centered outcome, and sepsis prevention trials may require power to examine clinical outcomes. The heterogeneity of sepsis as an illness has confounded sepsis treatment trials and may be even more challenging in prevention trials in which the intervention must be implemented before the phenotype of the illness is even present. Finally, the gap between pre-clinical and observation data and clinical trial results may be as hard to close for sepsis prevention as it has been for sepsis treatment, even with new methods like meta-analysis of propensity-matched individual patient level data.

In summary, we applaud Trauer and colleagues for using a novel methodologic approach to highlight aspirin as a promising candidate in the expanding field of sepsis prevention research. We eagerly await the results of the ongoing ANTISEPSIS trial. The last two decades of sepsis research have tested “a pound of cure,” perhaps aspirin will be the much-needed “ounce of prevention”.

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