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What's old is new again: acetaminophen as a novel approach to treating sepsis

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Sepsis is among the most common conditions encountered in adult critical care, occurring in approximately 2% of all hospitalizations and in some hospitals occurring in more than 50% of all ICU admissions.^{1,2} The past three decades have seen tremendous advances in understanding the pathophysiology of sepsis. However, some core elements of sepsis pathophysiology that remain unchanged include the general processes of oxidative stress, inflammation, endothelial dysfunction, among other factors that advance along a common pathway towards multiple organ dysfunction.³ These contributors are most apparent in critically ill patients with severe sepsis and septic shock, where multiple organ dysfunction is the major cause of death.^{4,5} The underlying instigators of reactive oxygen species and endothelial injury are myriad and unlikely to be from a single cause in all patients.

Hemolysis occurs in many diseases, producing cell-free hemoglobin (CFH) as a result. Increased quantities of circulating CFH have been reported in a variety of diseases, including sickle cell disease, blood transfusion, malaria and sepsis, among other conditions. Two of the predominant effects of CFH are depletion of nitric oxide (NO) and generation of reactive oxygen species (ROS).⁶ A primary effector for NO is reduced oxyhemoglobin that rapidly reacts with it to form methemoglobin and nitrate. This reaction accounts for the vasoconstrictor response known to occur with CFH and hemoglobin-based oxygen carriers (i.e. one class of artificial blood substitutes). In addition, oxidation reactions are catalyzed by hemoglobin, heme, and iron to generate ROS, subsequently leading to lipid peroxidation and cellular injury.⁷ While free heme can amplify some innate immune responses in sepsis, free iron can amplify a deleterious inflammatory response. Fortunately, there is an efficient biological system to scavenge hemoglobin and heme, using haptoglobin, CD163 and hemopexin, which effectively sequesters these redox-active molecules to prevent them from interacting with NO or generating ROS. However, in conditions such as sepsis the normal

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biological mechanisms are insufficient to prevent CFH from inciting at least a local if not a systemic inflammatory reaction.

It has been well established that patients with severe sepsis often have circulating CFH. Furthermore, acetaminophen has been shown to reduce the iron protoporphyrin radical in CFH and inhibit lipid peroxidation.⁸ In this study⁹, a group of clinical and translational scientists studied oral acetaminophen in patients with severe sepsis. They sought to replicate some of the beneficial effects of acetaminophen demonstrated in animal models (reducing oxidative stress and renal injury) and observational human studies (reduced markers of oxidative stress). In this randomized study of patients with severe sepsis and circulating CFH, 40 subjects completed the treatment protocol. Those who received acetaminophen had reduced levels of F2-isoprostanes on day 2, lower serum creatinine on day 3 (even after adjusting for imbalances in baseline creatinine) and lower maximum body temperature on day 3. However, there were no significant differences in day 3 F2-isoprostane levels, heart rate, blood pressure or measures of organ failure. Overall, there were no significant safety concerns with study drug administration in terms of hospital mortality and adverse effects.

The authors well described the limitations of this study: its small size, single center nature, surrogate endpoints, limited safety assessments and baseline imbalances between groups. These are real and valid concerns, and they restrict our ability to draw conclusions from the study. This is compounded by the few positive results that withstood statistical scrutiny, which ultimately becomes even fewer when the multiple comparisons are taken into consideration. However, this study stands as a significant achievement in testing a new therapeutic for a condition where no effective pharmacological therapy exists. Furthermore, the correlation of CFH and creatinine support an underlying mechanism thought to cause kidney injury and produced a similar response to acetaminophen in preclinical models.

This study sets the stage for further clinical trials in patients with severe sepsis. Larger trials are needed to better characterize the molecular and biochemical responses from acetaminophen therapy in these patients, and to further characterize the tissue responses and additional outcomes that predict clinical benefits. Subsequent studies would also need to consider the optimal dose for a given response, better define the patients most likely to respond, and consider sepsis subgroups that have not been studied as well (e.g. surgical patients). These subsequent trials will allow us to gain more confidence with potential adverse effects, particularly those that are less common and would not have been expected to occur in a small population.

Where do we go from here? This distinguished group deserves credit for considering the existing armamentarium of treatment possibilities rather than narrowly considering only the newly discovered pathways and novel targeted therapies that have become popular. It reminds us that much of the gains we have made in the past years improving the care of critically ill patients is from optimizing the utilization of existing therapies and redoubling our efforts to ensure timely, high quality care. This study proves once more, what's old is new again.

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