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Erythropoietin in sepsis: a new use for a familiar drug?

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Despite significant advances in understanding the pathophysiology of sepsis (1), mortality from the disease remains unacceptably high (2). Management of sepsis is largely supportive, and outside of antibiotics, no therapy aimed at treating sepsis is universally accepted (3). There is a huge gap between rapid scientific advances at the bench and translating these advances into clinical practice. The literature is replete with therapies showing marked mortality benefits in animal trials. Unfortunately, when these same agents are tried in patients, the vast majority have turned out to be no better than placebo. While the reasons behind this are complex (4), it has proven much easier to cure sepsis in inbred rodents under controlled laboratory settings than genetically diverse humans with significant co-morbidities. Despite this frustrating reality, the search for novel therapies that can improve outcomes in septic shock remains of paramount importance.

Usually, a novel therapeutic comes in the form of a new agent that is previously unfamiliar to the medical community. However, sometimes it can proverbially be right under everyone's nose, in the form of a new indication for a widely-familiar drug already readily available. In this issue of *Critical Care Medicine*, Dr. Aoshiba and colleagues report that administration of erythropoietin improves survival in a murine model of sepsis (5). Erythropoietin acts as the primary regulator of erythropoiesis and is used clinically to treat anemia resulting from chronic kidney disease (6) or chemotherapy (7). Erythropoietin has previously been studied in two large-scale trials in critically ill patients. One showed a 19% decrease in blood transfusion with erythropoietin (8) while the other showed no impact on transfusion practices (9). Neither trial showed an overall benefit in mortality, although a similar trend toward improved survival was noted in both studies in trauma patients.

While erythropoietin is best known for its clinical efficacy in anemia, it has a number of effects outside of the hematopoietic system. Erythropoietin receptors have been identified in a variety of cells including neurons, endothelial cells, cardiocytes, muscle, and hair follicles, and erythropoietin has been demonstrated to play a role in protecting, and potentially reversing pathologic changes in response to stressors such as ischemia/reperfusion, hypoxia, or metabolic injury (10;11). In theory, these tissue protective properties could make erythropoietin an attractive agent for modulating the host response in sepsis.

To address this, Dr. Aoshiba and colleagues gave erythropoietin to inbred mice at varying timepoints after a lethal dose of lipopolysaccharide (LPS). Animals given erythropoietin 30

minutes, 1 or 2 hours after LPS had improved survival; however, the survival benefit was lost when erythropoietin was initiated 3 or more hours after LPS. Interestingly, pretreatment with erythropoietin also failed to confer a survival advantage. The survival benefit with erythropoietin administration 1 hour after LPS was associated with attenuated apoptosis in multiple organs, reduced nitric oxide production and tissue hypoxia. In contrast, it was not associated with inflammatory changes.

This study is exciting because it identifies a potential new therapy for treating sepsis. However, it has a number of limitations. First, erythropoietin was efficacious only in a very narrow time window. Sepsis usually presents over the course of a number of hours to a few days, and it is frequently difficult to pinpoint exactly when a patient gets septic. It would therefore be difficult to know when the drug could be started and expected to be useful, which minimizes its theoretical utility. Additionally erythropoietin's lack of efficacy in pretreatment argues against its usage as prophylaxis in patients at risk for developing sepsis (i.e. ventilated burn patients who may develop a secondary pneumonia).

The results are also limited by the model used. LPS does not accurately replicate the features seen in human sepsis. Endotoxemia causes a rapid, intense pro-inflammatory response with rapid death or recovery. In contrast, sepsis has a more indolent timecourse with a complicated, lower intensity, mixed inflammatory response with prolonged immunoparalysis (12). The marked difference in the immunopathologic response between LPS and more authentic models of sepsis such as cecal ligation and puncture (CLP) (13) has been proposed as one reason why positive animal studies using endotoxemia as a surrogate for sepsis have not translated into clinical benefit in human trials. Recognizing this shortcoming, the authors also gave erythropoietin beginning 1 hour after a lethal model of CLP. While erythropoietin extended survival by 12 hours, all animals died within three days. While it is possible that this modest prolongation in time until death could translate into a meaningful survival advantage if a less lethal sepsis model were used, this would have to be convincingly demonstrated prior to proceeding with clinical trials as there would be no utility to bringing an agent to the bedside if survival is extended by less than 1 day.

Another concern of this study was the high dose of erythropoietin used. Clinical trials of erythropoietin in critically ill patients with anemia used 40,000 units/week (600 IU/kg). In contrast, the authors used a dose of 1000 IU/kg/day. Since four doses of erythropoietin were given, mice received a total of 4000 IU/kg over the course of the study, a greater than 6-fold increase over doses used in ICU patients. A dose of 40,000 units/week has been associated with an increased incidence of thrombosis in critically ill patients, and it is unclear whether the higher dose used in this study would be associated with a further increase in the rate of clinically significant thrombosis. This risk as well as the fact that erythropoietin is associated with shorter time to death and more rapid tumor growth in patients with cancer suggests the risk/benefit ratio would have to be carefully considered in patients prone to thrombosis or those with cancer.

Despite these limitations, this study represents a triumph of imagination. It takes a common agent and looks at it in a new way, resulting in improved survival in experimental sepsis, accompanied by exciting mechanistic insights. However, multiple hurdles need to be overcome before erythropoietin could be considered for clinical trials. Erythropoietin thus represents a new member of the ever growing list of agents that improve survival in inbred rodents but whose utility is currently limited by the chasm between preclinical studies and the difficulties encountered when trying to translate these studies into effective therapeutics.

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