

## Commentary

# Erythropoietin in the critically ill – is it more than just blood?

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### Abstract

Erythropoietin (EPO) has been in clinical use for the treatment of anemia for over 15 years. Recently it has been demonstrated that EPO has actions other than stimulating the bone marrow. It has been suggested that due to its tissue protecting effect, EPO may be effective in improving outcome in the critically ill.

**Keywords** apoptosis, erythropoietin, sepsis

Recombinant human erythropoietin (EPO) has been in widespread clinical use for over 15 years. Initially employed for the treatment of anemia associated chronic renal failure, it has now been demonstrated to be effective in treating anemia in a variety of other clinical settings, including HIV, cancer, surgery, and most recently critical illness [1]. Over the past several years it has become apparent that EPO has actions other than 'just' stimulating bone marrow to produce mature erythrocytes. EPO is also a cytokine with important antiapoptotic activity [2]. In this latter role, EPO has been demonstrated to confer important tissue protection in preclinical and some clinical studies [3–6].

In their excellent review in this issue of *Critical Care*, Coleman and Brines [7] provide a succinct discussion of the 'nonhematologic' actions of EPO in protecting tissues and raise the intriguing possibility of clinical use of EPO to 'protect' tissues in the critically ill. Apoptosis is important in the pathogenesis of many critical illnesses such as sepsis and multiorgan failure. Experimental studies have also suggested that blocking apoptosis may be of benefit. Therefore, if pharmacologic doses of EPO were administered to critically ill patients, would the antiapoptotic activity EPO result in improved clinical outcomes?

Some data bearing on this question are currently available. Two prospective randomized clinical trials examined the

efficacy of EPO administration in reducing red blood cell (RBC) transfusion in the critically ill [8,9]. Both studies demonstrated a significant reduction in the number of RBC transfusions with EPO administration; however, no clinical outcome benefits were observed to be associated with this reduction in RBC transfusion. It is important to note that these studies were only designed to look at RBC transfusion and were not powered to look at clinical outcome differences. On the other hand, even if a clinical outcome benefit were observed, it would be very difficult to separate nontransfusion-related effects of EPO in any clinical study. Any clinical benefit observed could be a result of a higher hemoglobin level, the avoidance of RBC transfusions, a direct effect of EPO, or some combination of these factors.

Although the possibility of tissue protective benefit with EPO administration in the critically ill is clearly of interest, the difficulties involved in conducting clinical studies to test the hypothesis should not be underestimated. The studies to date that suggested a protective role of EPO have been conducted in clinical settings, such as neurologic injury, in which the populations studied were well defined and in which the timing of injury and the initiation of therapy could be defined [4]. This is clearly not the case in the critically ill population, in which patients are a heterogeneous group, there may be multiple insults, and the time from initiation of 'disease' to presentation can be highly variable and often

difficult to determine. More importantly, the pathophysiology of tissue injury in the critically ill can be quite complex, involving many interacting factors [10,11]. The history of clinical trials in sepsis should stand as an example of the challenges in performing such studies [12].

The recent appreciation of the importance of the nonhematologic activities of EPO is providing exciting new avenues for study. Despite the inherent difficulties in performing these studies in the critically ill, the potential for EPO to be of benefit in the critically ill is an important issue. At a minimum, EPO is clearly effective in reducing the number of RBC units transfused in patients with the anemia of critical illness, similar to the effect of EPO in patients with anemia associated with other clinical conditions. However, it remains to be seen whether any outcome benefits are associated with EPO administration, either related to transfusion effects or, in some patients, a direct effect of EPO.

### Competing interests

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