

An age-of-blood transfusion trial in the trauma setting is crucial and animal models may help inform trial design

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TO THE EDITOR: We read with interest the recent editorial by Aubron et al.¹ It highlighted the difficulty of an age-of-blood trial in trauma patients, given their lower preventable mortality compared with the general population of patients with critical illness. Alternative outcomes such as long-term quality of life were discussed; however, acute outcomes such as tissue oxygenation and utilisation, coagulopathy and cardiac dysfunction were not considered. It is entirely feasible that aged packed red blood cells (PRBCs) could have significant detrimental effects in the acute resuscitation phase. Despite this, the study of early resuscitation outcomes has been largely neglected with only one study examining tissue oxygenation effects during human trauma resuscitation.² Of the 12 published human trauma studies included in Lelubre and Vincent's review, eight excluded patients who died within either 24 or 48 hours of admission, also introducing a survivor bias.³

Currently, 91% of studies that have investigated PRBC transfusions in trauma patients have suggested an association of aged PRBCs with harm, compared with 45% of studies in cardiac surgery patients and 36% in intensive care patients.³ Many trauma systems (for example, the United States Army Joint Trauma System) have responded to this suggested association by allocating the freshest PRBCs available to these patients. However, not every patient can receive the freshest PRBCs in the hospital. It will be difficult to justify continuing trauma resuscitation with the freshest available PRBC if the TRANSFUSE (ACTRN12612000453886) and ABLE (ISRCTN44878718) trials (which largely exclude trauma patients) indicate a benefit with fresher PRBCs in other forms of critical illness. Therefore, an unintended consequence of TRANSFUSE and ABLE may be to deprive trauma patients of the freshest possible PRBCs, as they will no longer be the priority, despite the plausible hypothesis that they stand to gain the greatest benefit.

Arresting metabolism by cryopreserving fresh PRBCs could, theoretically, deliver a storage lesion-free product. From their limited use,⁴ we know that cryopreserved PRBCs do not cause severe transfusion reactions, but there is very little evidence of their efficacy as a resuscitation therapy. If cryopreserved PRBCs can be shown to be equal to fresh PRBCs and superior to aged PRBCs, they may be a solution to the problem of transfusing aged PRBCs.

Our research group is developing an ovine model of severe trauma, building on previous haemorrhage-only⁵ and other models of critical illness.^{6,7} We have characterised ovine neutrophil function⁸ and coagulation,⁵ validated a method for storing liquid ovine PRBCs for transfusion,⁹ and characterised the ovine PRBC storage lesion.¹⁰ We are in the process of characterising ovine immunomodulation and coagulopathy in trauma, and perfecting a method for cryopreserving ovine PRBCs for transfusion. Our large animal model will allow for invasive organ monitoring and will provide controlled, standardised experimental conditions to test the effects of various resuscitation fluids — including fresh, aged and cryopreserved PRBCs — on the early resuscitation phase of severe trauma. We believe our trauma model will provide valuable data to inform the design of an age-of-blood clinical trial in the trauma setting which, of necessity, may need to use similar surrogate end points. Failure to undertake such a trial may leave trauma patients, who have the potential to benefit most from the transfusion of fresh PRBCs, with inferior treatment and outcomes.

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“Being a doctor” — and some further pedantry

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TO THE EDITOR: I would like to make two points in the letters section (regrettably, too lightly used) of *Critical Care and Resuscitation*. The first is to recommend to the Journal's readers, and particularly to trainees of the College of Intensive Care Medicine (CICM) of Australia and New Zealand, a recently published book, *Being a doctor: understanding medical practice*.¹ It comes from two senior lecturers in general practice at the University of Otago, with a foreword by doctor-poet Glenn Coulquhoun. I found it a totally absorbing read, lucidly presented, and it made me uncomfortably aware of my deficiencies in such topics as curing versus healing, the culture of medicine, somatisation, the meaning response (ie, the placebo effect), the patient's world, and thoughtful listening. I was reminded that our relationships with the relatives of patients may become close, but our patients in an intensive care unit may be unconscious or sedated and therefore inaccessible for consultation for much of their stay. This can lead us too readily into a formulaic approach, at times with tunnel-vision concentration on a disorder and its rectification. As I read on in this book, I was pulled up with a jerk on many occasions and given cause to reflect. I can see benefit in every CICM trainee reading the book, but perhaps there is less need in these enlightened days, with improved curricula? I am sorry such a book was not on the reading list at my medical school and during later learning, when it was all “head down”, acquiring the facts. Perhaps the new curriculum for CICM trainees may include some of the medical issues raised.

I will not review the book here (some more competent soul should) but I dispute² one unfortunate aspect of a comment on the National Women's Hospital in Auckland, at the top of page 53.

My second point arises from this sentence on page 49: “Science is empirical, meaning that all knowledge is derived from experience”. My reaction was that surely they had the meaning of “empirical” wrong, so I checked the trusty *Shorter Oxford English Dictionary* (SOED).³ It appears that “empirical” can have meanings which are somewhat contrary in meaning. So do I have to rely on the context to know which meaning the writer intends? The SOED definitions given are:

1. Based on, guided by, or employing observation and experiment rather than theory (of a remedy, rule, etc.); used because it works or is believed to [I had always understood that it meant solely the latter] [an additional meaning is obsolete: practises medicine without scientific knowledge].
2. Derived from or verifiable by experience, esp. sense-experience.³

My simple reaction to all this now is never to use the word “empirical” (I do not think I have ever written it).

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- 3 Hughes AM, Sykes J, Brown L, editors. *Shorter Oxford English Dictionary*. Oxford: Oxford University Press, 1993. □