Treating critically ill anaemic patients with erythropoietin - less is more

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Dear editor,

We read with interest the letter by Lasocki et al. [1] We agree with many of the authors' points including their call for further research to understand the clinical effects of erythropoietin (EPO) in critically ill patients as this remains a promising therapy. However, the Task Force stands by its "less is more" approach and weak recommendation against widespread use of EPO in anemic critically ill patients [2].

Firstly, as per GRADE methodology, a conditional (weak) recommendation against EPO means that there are some circumstances where patients or clinicians may still choose to use a therapy [3]. A conditional recommendation is used when: (i) the benefits and risks of an intervention are closely balanced; (ii) the evidence provides us with a low certainty of a treatments' effect; (iii) patient values and preferences may vary in important ways; (iv) cost and cost-effectiveness may be prohibitive; (v) or a treatments' widespread acceptability or feasibility may make it impracticable to implement. In this instance, the ESICM task force reviewed the evidence for EPO to reduce transfusion in critically ill patients with anemia. While we identified a possible reduction in mortality (Relative Risk (RR) 0.80, 95% CI 0.61 to 1.05, absolute risk reduction 3.1%) this seemed disproportionate to its effects upon transfusion, which were more modest (RR 0.89, 95%CI -9.1 to -2.7, absolute risk reduction 5.9%, a mean of 0.65 units of blood fewer per patient). Any such benefit is likely to be even lower now that more transfusion practice is increasingly restrictive [4], largely driven by randomized controlled trials (e.g. TRISS [5]), and in the future likely to be more driven by transfusion triggers other than hemoglobin.

Secondly, data from the TRACE survey [4] indicates that use of EPO is uncommon (but not rare). A recommendation for use of EPO would represent a shift in practice for many clinicians. Taking a "less is more" approach, we judged that the burden of proof is on the intervention to demonstrate its worth before widespread adoption. A "why not" approach can result in widespread adoption of questionable therapies with the potential for harm and detracting from high-quality, evidence-based practice (consider the rise and fall of hydroxychloroquine in COVID-19). The Task Force judged that in the absence of a clear mechanism, target patient population, and safety profile, EPO has not yet met the high standard of proof to recommend a change in practice which would impact the majority of critically ill patients. The Task Force also judged that in those centres where EPO use is already well-established, the current evidence base is unlikely to support widespread de-adoption. More evidence for EPO is necessary, before recommending its routine use in critically patients.

Thirdly, while the costs of EPO may have decreased, they remain variable between regions and may as of yet not be cost-effective (assuming our estimates of its effect on mortality are true). Cost-utility analyses from the UK have shown that EPO was not cost-effective in reducing transfusion requirements, with very high incremental cost-effectiveness ratios ranging from £1,020,000 per quality adjusted life year (QALY) and £21,193,000 per QALY [6]

Fourthly, we would like to emphasize that a conditional recommendation against EPO does not mean it should never be used. The Task Force indicated there may be patients or ICUs where EPO could reasonably be implemented to reduce transfusion (e.g. areas with low blood bank stores, Jehovah's witnesses). On the basis of current

evidence, widespread use of EPO to reduce transfusion does not appear warranted and might be harmful. Use of EPO as a mortality-reducing agent in and of itself is a different question, and one which requires more evidence from a well powered and designed randomized controlled trial to demonstrate the risk and benefits of EPO in this patient population before widespread use

Lastly, the difference in the recommendation regarding the use of EPO between the Task Force and by Lasocki et al. highlights some of the limitations when addressing the role of guidelines. The development of guidelines on the same topic by different organizations can leave the front-end user confused, particularly if there are different recommendations based on the same primary evidence, such as in this instance. One solution could be for international societies to develop collaborative models, where a single, diverse, multi-disciplinary group takes ownership to develop guidelines using standardised processes and promote transparency.

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