Intensive Care Medicine Update

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Two important studies of transfusion practice have been influential. TRICS III (*NEJM* 2017, 377(22):2133-2144) randomised 5243 adults at moderate to high risk undergoing cardiac surgery to a restrictive (<75g/L) or liberal (<9.5 g/L in OR or ICU, <8.5 g/L in the ward) transfusion strategy. The composite primary outcome of death, myocardial infarction, stroke or new dialysis requirement to day 28 (censored at hospital discharge) occurred in 11.4% of the restrictive group and 12.5% of the liberal group (P<0.001 for non-inferiority). Red cell transfusion was less common in the restrictive group, and there were no differences in the individual components of the composite outcome (half of the events were new MI) or secondary outcomes between the groups. In the TRANSFUSE study (*NEJM* 2017; 377(19):1858-1867) 4994 patients undergoing first transfusion in intensive care were randomly assigned to receive either the freshest available compatible red cells or the standard issue of oldest compatible red cells for that and subsequent transfusions. In the freshest available group, mean storage duration was 11.8 days compared to 22.4 days in the standard group. Transfusion volume was a median of 2 units (IQR 1 – 4) in both groups. All-cause mortality after 90 days was 24.8% in the freshest available group and 24.1% in the standard group (P=0.57). New bloodstream infections were more common with the freshest-available transfusion (5.0% vs 3.6%). In sub-group analysis treatment effect varied by severity of illness (P=0.03 for heterogeneity) with significantly lower mortality transfusing older red cells in patients with higher than median APACHE III scores (OR 1.18, P=0.05). Following this and earlier studies confirming the safety of older red-cell transfusion (ABLE, RECESS and INFORM), the New Zealand Blood Service is currently consulting on a change to their Fresh Blood policy to not provide red cells with <14 days storage for adult patients undergoing cardiac surgery with cardiopulmonary bypass.

The use of steroids in sepsis, and septic shock in particular, has long been an area of controversy. Two recent trials have sought to provide clarity on the issue. In the "ADRENAL" study (*NEJM* 2018; 378(9):797-808), undertaken by the ANZICS CTG, 3800 patients with septic shock receiving mechanical ventilation were randomised to receive 200mg/day of hydrocortisone or blinded placebo for up to 7 days while in ICU. The primary outcome of all-cause mortality at 90 days was 27.9% in the hydrocortisone group and 28.8% in the placebo group (OR 0.90, 95% CI 0.82 – 1.10, P=0.50). However, there were significant differences in secondary outcomes: with hydrocortisone the initial period of mechanical ventilation was shorter (median 6 vs 7 days, P<0.001), duration of ICU stay was shorter (median 10 vs 12 days, P<0.001), fewer patients received a blood transfusion (37.0% vs 41.7%, P=0.004) and, in keeping with several prior studies, resolution of shock was quicker (median 3 vs 4 days, P<0.001). The second trial (*NEJM* 2018; 378:809-818) was conducted by the CRICS-TRIGGERSEP Network in Europe and randomised 1241 patients with moderate or severe septic shock to receive either hydrocortisone 200mg/day plus fludrocortisone 50µg/day or matching placebos. Mechanical ventilation was not required but was present at baseline in 92% of participants. Mortality at 90 days was also the primary outcome in this study and occurred in 43.0% of patients in the hydrocortisone + fludrocortisone group and 49.1% of patients in the placebo group (RR 0.88, 95% CI 0.78 – 0.99, P=0.03). Similar to ADRENAL, the hydrocortisone + fludrocortisone group had significantly more vasopressor-free days (mean 17 vs 15, P<0.001) and ventilator-free days (mean 11 vs 10, P=0.07) to day 28. Of the potential complications of steroid treatment, only hyperglycaemia was more common in the hydrocortisone + fludrocortisone group; no significant differences were found in the incidence of new infections, gastro-intestinal bleeding or neurologic sequelae. Although some have expressed concerns that there was an unmeasured hazard in the ADRENAL study to explain why mortality was no different when the secondary outcomes found benefit, the combination of these 2 studies has consolidated the use of low-dose hydrocortisone in patients with "significant" septic shock, especially if receiving mechanical ventilation. Outside of Europe, few intensivists consider that fludrocortisone is important, given the mixed glucocorticoid and mineralocorticoid effects of hydrocortisone.

The treatment of ICU patients with severe metabolic acidaemia with sodium bicarbonate has been suggested to improve the metabolic environment, in particular the expectation of improved cardiovascular responsiveness to vasoactive therapies. However, in current practice this has generally been considered inappropriate due to concerns about paradoxical intracellular acidification, conflicting results in physiological and observational studies and the

lack of evidence of impact on clinical outcomes. Treatment for such patients has focused on addressing the underlying disease processes and support with renal replacement therapy if required. However, the first major randomised trial to report effect of sodium bicarbonate on clinical outcomes in the critically ill has recently been published. The BICAR-ICU trial (*Lancet* 2018; 392:31-40) was an open-label randomised trial which assigned 389 ICU patients in 26 ICUs with severe metabolic acidaemia (pH<7.2, P_aCO_2 <45mmHg, bicarbonate <20mmol/L) to receive no sodium bicarbonate or 4.2% sodium bicarbonate to maintain pH>7.3, using aliquots of 125 – 250ml with a maximum of 1L in the first 24h. Randomisation was stratified by site, age, sepsis and significant acute kidney injury (AKIN grades 2 or 3). The primary composite outcome in all patients (death by day 28 or at least one organ failure at day 7) occurred in 71% of the control group and 66% of the sodium bicarbonate group (absolute difference -5.5%, 95% CI -15.2 to +4.2, P=0.24). However, in the acute kidney injury stratum (189 patients), there was a significant difference in 28 day mortality (63% vs 46%, P=0.017), organ failure at day 7 (82% vs 66%, P=0.014) and the composite of the two (82% vs 70%, P=0.04). Renal replacement therapy was required in significantly fewer patients in the bicarbonate group (52% vs 35%, P<0.001), and ICU stay was shorter (median 4 vs 7 days, P=0.06). Metabolic alkalosis, hypernatraemia and hypocalcaemia were more frequent in the sodium bicarbonate group, but with no life-threatening complications reported. This is the first trial to demonstrate significant clinical benefit of bicarbonate therapy in the critically ill and should be considered for patients with acidaemia in the presence of acute kidney injury.