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EDITORIAL

The Janus faces of bicarbonate therapy in the ICU: not sure!

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Metabolic acidosis often complicates critical illness and is associated with poor outcomes [1]. However, there is often a failure to differentiate between cause of the acidosis and/or the effect of the metabolic disturbance and the mechanism(s) by which acidosis may cause such consequences are often unexplored [2]. Indeed, it is of fundamental importance that biochemical correction of any observed acidosis by whatever means must be coupled with correction of the underlying physiological disturbance. If one considers diabetic ketoacidosis for example, simple manipulation of the arterial pH will not address the underlying disturbance in glucose metabolism and indeed guidelines for the management do not support the use of alkali therapy. However, in the heterogenous critically ill population untangling the effects of the acidosis from those that arise because of the underlying condition is often a sisyphean task. Many clinical consequences of metabolic acidosis have been described, particularly with regard to the cardiovascular effects of severe metabolic acidaemia including myocardial dysfunction and vasopressor resistance [3–5]. The cardiovascular dysfunction observed appears to be pH dependent with an inevitable fall in cardiac output seen when the pH falls below 7.1–7.2 as well as a predisposition to ventricular arrhythmias. Correction of metabolic acidosis *may* have an observved positive inotropic effect which even extends to pH values above the normal physiological pH range although this will depend, in part, on the aetiology of the acidosis [6, 7]. Altered mental state is often observed clinically in patients with acute metabolic acidosis, this is despite only minor changes in cerebrospinal and brain pH [8]. Of note, despite such clinical presentations, many of the observations are experimental with much of the quoted literature from animal studies, often non-mammalian, performed at 25–28 °C and at extremes of pH (often 6.8 or lower) [2]. Clinical studies focus solely on extracellular acidosis as it is easily measured and can be manipulated through exogenous means. Intracellular acidosis, on the other hand, is difficult to measure but of paramount importance to cellular function, particularly cardiac muscle cells [9].

Most discussions regarding metabolic acidosis focus on such negative effects. However, there are some that propose that the generation of an acidosis may have beneficial effects and confer a teleological advantage. Perhaps the most important observation supporting this view is the effect of acidosis on the oxyhaemoglobin dissociation curve of erythrocytes, first described by Bohr [10]. The oxyhaemoglobin dissociation curve is influenced by the local pH as well as CO_2 levels. In areas of high O_2 tension, O_2 uptake is little affected by pH and the bound CO_2 is readily off loaded. In areas of lower O_2 tension the curve is "shifted to the right" in the presence of acidaemia increasing O_2 extraction. This allows increased O_2 delivery in areas where it is needed thereby matching local demand. This is observed in exercising muscle where local lactate and CO_2 levels rise in concert with a lowering of pH, thereby promoting O_2 delivery and maintaining more efficient aerobic metabolism. Indeed, such effects on O_2 delivery may be much more pronounced than any effects on cardiac output. For example, a decrease in pH from 7.4 to 7.2 that equates to an increase in hydrogen ion concentration of just 23 nmol/l, results in an increase in O_2 delivery that would otherwise require a 20% increase in cardiac output [2]. It could be argued therefore that we are adapted to survive physiological acidosis; hence intervening in a patient with metabolic acidosis without thought as to the potential physiological

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consequences may potentially be inappropriate. For these reasons, the use of bicarbonate therapy in treating metabolic acidosis remains controversial. There are clinicians who are bicarbonate protagonists, supportive of its use and those who feel that bicarbonate therapy is of little benefit, being no more than a temporising action and at worst potentially harmful.

The principal objections to correcting acute metabolic acidosis with bicarbonate therapy include an increase in $PaCO_2$ and hence increasing intracellular acidosis (so-called paradoxical acidosis), potential hypernatraemia and resulting hyperosmolar states, hypokalaemia and impairment in oxygen delivery. With regard to paradoxical acidosis, we appreciate that when sodium bicarbonate is added to a weakly acidic solution this generates CO_2. Given there is no significant gradient between intracellular and extracellular CO_2, the former rises in parallel and this results *potentially* in an intracellular acidosis. This has been demonstrated experimentally but in conditions so far removed from human physiology as to make the results inapplicable to clinical medicine [11]. However, if the in vitro experiments are repeated under conditions designed to simulate clinical practice, progressive intracellular alkalinisation rather than acidosis is observed [12]. Similarly, studies involving intact animals with imposed predetermined ventilatory restraints also differ significantly from the clinical situation with either a spontaneously breathing patient or one being mechanically ventilated with monitoring of the arterial blood gases and appropriate changes in ventilator settings [13]. Experimental studies have used a bicarbonate buffering system that approximates the 'closed' state, whereas in clinical practice it is almost fully 'open'. Under such conditions paradoxical acidosis is much less likely to occur, if at all.

The recent multicentre randomized trial, BICAR-ICU has reignited this debate about bicarbonate therapy [14]. No significant reduction in the primary composite outcome was observed, unsurprising given the study was powered to detect a 15% reduction in mortality. However, both a delay in the commencement of RRT as well as a reduction in the need for RRT was observed in patients with AKI (52–35%, absolute difference estimate − 16·7 (95% CI − 26.4 to − 7.0), $P = 0.0009$), with a number needed to treat of only six. Such a meaningful patient centred outcome with significant health economic repercussions is of great interest. Moreover, a recent study using the MIMIC-III database reinforced this observation showing that the treatment of acute metabolic acidosis with sodium bicarbonate in patients with sepsis had no impact on the overall mortality but seems beneficial for those with coexistent AKI [15]. A recent scoping review highlighted the lack of data on the effects of intravenous sodium bicarbonate and called for further studies [16]. Before widespread adoption of alkali therapy in such patients it is worth considering that there are some significant limitations. The study was unblinded with 24% of patients in the control group receiving bicarbonate therapy, although blinding in this study would have been difficult given the regularity in which blood gases are drawn in ICU patients. Furthermore, all patients with metabolic acidosis were considered, without reference to different underlying aetiologies and as outlined, it is possible that potential benefit from bicarbonate replacement may be related to the cause of the metabolic disturbance.

So, what does this study tell us? Little with regard to further mechanistic insights as to the effects of acidosis, which is no surprise given the complex interactions involved within the patient as a whole. But it is hypothesis generating in that patients with metabolic acidosis and moderate to severe AKI, bicarbonate therapy may improve outcomes and reduce the requirement for RRT. This observation may reflect a reduction in the incidence of hyperkalaemia as well as other predefined indications for RRT through bicarbonate therapy. This does beg the question that RRT may not be necessary in some of these individuals as it may be viewed as little more than a mechanism by which bicarbonate is given in a controlled fashion. Furthermore, the results may identify individuals who can accommodate the higher osmolality and electrolyte swings associated with bicarbonate therapy an effect negated by renal replacement therapy (RRT).

At present, no robust recommendations can be given regarding the use of sodium bicarbonate to correct metabolic acidosis. The basic tenant remains that the underlying cause of the acidosis must be addressed. Clearly this rekindled interest in the use of alkali therapy is intriguing and further studies will be needed to confirm these findings. Particular interest should be focussed on patients with acute kidney injury and metabolic acidosis with stricter adherence to treatment protocols where possible (Table 1). Outcomes should include rates of RRT as well as mortality as outlined in the Table. Until these questions are answered then Janus will keep the doors open for bicarbonate therapy. For now.

Table 1 PICOR design

PICOT parameter	Description of parameter	Rationale
Patient/population	Eligibility: (1) Adult, (2) AKI KIDIGO stage 2/3, (3) Metabolic acidosis (pH < 7.25, $PaCO_2$ < 6.0 kPa and $HCO_3 \leq 20$ mmol/l), (4) < 48 h of ICU admission Exclusions: single respiratory disorder, acute diarrhoea, ileostomy or biliary drainage, stage 4 CKD or chronic dialysis, known RTA, DKA, high anion gap acids poisoning (e.g. aspirin, methanol), pregnancy, hypocalcaemia, clinical decision in place to start RRT, death perceived as imminent	Jaber (2018) and Zhang (2018) both suggested benefit in patients with metabolic acidosis and AKI (with no benefit seen in all-comers)
Intervention	IV $NaHCO_3$ titrated to achieve serum pH > 7.3	Routinely used formulation in clinical practice to replace HCO_3 replicating a target pH used in the Jaber study; represents a physiologically plausible target in patients presenting with metabolic acidosis and AKI, in which renal dysfunction may be a significant contributor to the acid–base derangement
Compare	Usual care including standard indications for RRT	Usual care will include predetermined criteria for commencing RRT
Outcome	Primary outcome 90-day mortality	A primary outcome of mortality is patient centred in a high risk group; Secondary outcomes would include need for RRT due to cost, resources
RCT design	Superiority	Secondary outcomes—If non-inferior HCO_3 would be represent cheaper and less resource intensive

CKD chronic kidney disease stage 4 (eGFR < 30), *DKA* diabetic ketoacidosis, *IV* intravenous, *KDIGO (kidney disease improving global outcomes) stage 2* doubling baseline serum creatinine or urine output < 0.5 ml/kg for ≥ 12 h, *$NaHCO_3$* sodium bicarbonate, *RRT* renal replacement therapy, *RTA* renal tubular acidosis

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Compliance with Ethical Statement

Conflict of interest
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