Sepsis-associated acute kidney injury (s-AKI) is frequent in critical illness and associated with important morbidity and mortality. Reactive oxygen species-mediated tubular injury appears to play an important role in its pathogenesis. Possible explanations for this include proteinuria and labile iron in the urine, both of which increase oxidative stress on renal tubular cells. Sodium bicarbonate directly scavenges peroxynitrite as well as other reactive species generated from nitric oxide, and attenuates proteinuria-associated oxidative damage or free iron renal toxicity. Thus, attenuating oxidative stress through urine alkalinisation with sodium bicarbonate may attenuate s-AKI.

Sodium bicarbonate has been used successfully in other conditions where oxidative stress is considered important. For example, sodium bicarbonate helped prevent AKI in animal models of ischaemia and doxorubicin toxicity. Although controversial, the use of sodium bicarbonate may provide protection against contrast-induced nephropathy and, in our recent clinical trial, it attenuated postoperative AKI in cardiac surgery patients. Thus, we hypothesised that sodium bicarbonate might also provide renal protection in critically ill patients at risk of s-AKI.

The benefit of any intervention in s-AKI is likely to be maximised by its commencement as early as possible. Biomarkers of tubular injury such as serum neutrophil gelatinase-associated lipocalin (sNGAL) now enable earlier diagnosis of AKI than traditional indices of renal function, such as serum creatinine. Hence, we hypothesised that

**ABSTRACT**

**Background:** Urine alkalinisation with sodium bicarbonate decreases renal oxidative stress and might attenuate sepsis-associated acute kidney injury (s-AKI). The safety and feasibility of urine alkalinisation in patients at risk of s-AKI has never been tested.

**Methods:** We randomly assigned patients at risk of s-AKI (those with systemic inflammatory response syndrome [SIRS], oliguria and elevated serum neutrophil gelatinase-associated lipocalin [sNGAL] concentration) to receive sodium bicarbonate (treatment group) or sodium chloride (placebo group) in a 0.5 mmol/kg bolus followed by an infusion of 0.2 mmol/kg/hour.

**Results:** Among 50 patients with SIRS and oliguria, 25 (50%) had an elevated sNGAL concentration. Of these, 13 were randomised to receive sodium bicarbonate and 12 to receive sodium chloride infusion. Study drugs were infused for a mean period of 25.9 hours (SD, 10 hours). Severe electrolyte abnormalities occurred in seven patients (28%) (four [30.8%] in the treatment group and three [25%] in the placebo group). These abnormalities resulted in early protocol cessation in six patients (24%) and study drug suspension in one patient (4%). This adverse event rate was judged to be unacceptable and the study was terminated early. There was no difference between the two groups in sNGAL or urinary NGAL concentrations over time, occurrence of acute kidney injury, requirement for renal replacement therapy, hospital length-of-stay or mortality.

**Conclusion:** Administration of sodium bicarbonate and sodium chloride solutions to patients at risk of s-AKI was associated with frequent major electrolyte abnormalities and early protocol cessation. The tested protocol does not appear safe or feasible.

Biomarkers of tubular injury such as serum neutrophil gelatinase-associated lipocalin (sNGAL) now enable earlier diagnosis of AKI than traditional indices of renal function, such as serum creatinine. Hence, we hypothesised that

**Abbreviations**

AKI Acute kidney injury
ANOVA Analysis of variance
APACHE Acute Physiological and Chronic Health Evaluation
ICU Intensive care unit
IQR Interquartile range
LOS Length of stay
NGAL Neutrophil gelatinase-associated lipocalin
RCT Randomised controlled trial
RIFLE Risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, end-stage renal failure
RRT Renal replacement therapy
s-AKI Sepsis-associated acute kidney injury
SIRS Systemic inflammatory response syndrome
an NGAL-directed early intervention would maximise any effect of possible protective therapy.

Accordingly, we designed a two-centre randomised controlled trial (RCT) to test the efficacy of sodium bicarbonate administration in patients with systemic inflammatory response syndrome (SIRS) at risk of s-AKI, as demonstrated by oliguria and an elevated sNGAL level. We hypothesised that we would identify patients at high risk of AKI stage 2; that the treatment would be easy to administer and well tolerated; and that sodium bicarbonate would reduce the risk of developing s-AKI by 20%. Our main feasibility outcomes were time to randomisation, the screened:recruited patient ratio and weekly recruitment rate. Our main safety outcomes were occurrence of severe electrolyte abnormalities, protocol suspension and the rate of protocol cessation.

Methods
Design and patients
The Bicarbonate and Lipocalin in Systemic Inflammatory Response Syndrome Study (BLISS) was a prospective, Phase I, double-blinded, feasibility and safety pilot RCT (NCT00706771). It was conducted in two intensive care units in Australia. Institutional human research and ethics committees at both participating sites approved the study with prospective informed consent from patients or their next of kin (approval number H2009/03583).

Within the study period, all patients admitted to participating ICUs were screened for the following clinical eligibility criteria:
- aged > 18 years
- ≥ two SIRS criteria
- oliguria (urine output < 0.5 mL/kg for 2 hours).

Clinically eligible patients were then screened for their sNGAL level and those with an sNGAL concentration > 150 μL were included in the study. The sNGAL level was chosen as an inclusion criterion because it can be measured rapidly at the bedside (see below).

Exclusion criteria were:
- inability to provide or obtain consent
- absence of central venous access
- expected duration of ICU stay < 48 hours
- enrolment in a conflicting study
- moribund patient with expected death within 24 hours
- known chronic kidney disease (defined as baseline serum creatinine level > 350 μmol/L or chronic hemodialysis requirement)
- any of the following serum electrolyte abnormalities at the time of randomisation:
  - chloride level > 110 mmol/L
  - bicarbonate level > 35 mmol/L
  - sodium level > 150 mmol/L
  - confirmed or suspected acute glomerulonephritis
  - acute interstitial nephritis, renal vasculitis or urinary tract obstruction
  - patient already receiving (or about to start) renal replacement therapy (RRT) for acute renal failure
  - known or documented allergy to sodium bicarbonate
  - participating doctor’s belief that the study drug could not be administered for the expected study duration.

Randomisation
Patients were randomly assigned to sodium bicarbonate or sodium chloride infusion by permuted blocks of random sizes (2–6) in a 1:1 ratio.

Study solutions and allocation concealment
Patients allocated to the treatment group were administered sodium bicarbonate 0.5 mmol/kg diluted in 5% dextrose 250 mL over 1 hour, followed by an infusion of sodium bicarbonate 0.2 mmol/kg/hour diluted in 5% dextrose 1000 mL over 47 hours (total administered dose 9.9 mmol/kg).

Patients allocated to the placebo group were administered sodium chloride 0.5 mmol/kg diluted in 5% dextrose 250 mL over 1 hour, followed by an infusion of sodium chloride 0.2 mmol/kg/hour diluted in 5% dextrose 1000 mL over 47 hours (total administered dose 9.9 mmol/kg). The goal was to ensure that the intervention and control groups would receive the same amount of sodium. Both these solutions were hypertonic (equivalent to sodium chloride 3%).

Study solutions were prepared by research nurses after randomisation. Patients, clinical staff and research staff responsible for data collection were all blinded to study group. To enable allocation concealment, both types of infusion were reconstituted in identical bags labelled “study drug” and infused at an identical rate. Both study solutions were infused into a central venous catheter via a computerised syringe pump or volumetric infusion pump.

In-study protocol modification
After the first six patients were enrolled, three had early protocol cessation (one for an elevated serum bicarbonate level and two for logistical reasons). Thus, the study protocol was revised and the duration of the study drug infusion was decreased from 48 to 24 hours. The total administered dose was therefore decreased from 9.9 mmol/kg to 5.3 mmol/kg for both solutions.

NGAL measurements
sNGAL and urinary NGAL (uNGAL) levels were obtained at randomisation as well as on Days 2 and 3 after randomisation. sNGAL levels were measured at the point of care using...
a Triage device (Alere). uNGAL levels were measured at the central laboratories of both hospitals using the Abbott Architect platform (Abbott). uNGAL was not used as a criterion for randomisation.

**Monitoring**
During the infusion period, the serum bicarbonate, sodium and chloride levels of included patients were monitored with routine point-of-care arterial blood gas analyses at least every 6 hours, and with venous blood chemistry by the pathology laboratory as requested at least once a day by the treating clinician.

**Outcomes measures**

**Feasibility outcomes**
We recorded the ratio of patients randomised to patients screened, the time from ICU admission to randomisation, the time from randomisation to the start of administration of the study drug, and the duration of the study drug infusion. The duration of recruitment was also reported, and the average number of patients randomised per week.

**Safety outcomes**
Severe electrolyte abnormalities were defined as serum concentrations of bicarbonate > 35 mmol/L, sodium > 150 mmol/L and chloride > 110 mmol/L. If any of these abnormalities was detected during the study period, administration of the study drug infusion was suspended for 6 hours. Serum electrolyte levels were then retested, and if the abnormality had corrected, the study drug was resumed at half strength. The infusion protocol was discontinued if the electrolyte abnormality was still present. No additional time was allowed to make up for the duration of the stopped infusion.

**Clinical outcomes**
We collected ICU length-of-stay (LOS), hospital LOS and vital status at discharge. We calculated peak:baseline creatinine ratio to classify patients according to the risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, or end-stage renal failure (RIFLE) classification.25,26 The need for and duration of RRT was recorded.

**Statistical analysis**
All data were assessed qualitatively for normality using histograms or box-plots. Normally or near normally continuous data are reported as means with SDs, and compared using the student t test or analysis of variance (ANOVA). Non-normally distributed continuous data are reported as medians with interquartile ranges and were compared using the Mann–Whitney U test or Kruskall–Wallis ANOVA.

Categorical data are reported as numbers and percentages and were compared using the χ2 or Fisher exact test where indicated. Significance was set at 0.05 for all comparisons unless otherwise stated. On the basis of our previous trial in cardiac surgery patients, we set the target enrolment at 170 patients (75 in each treatment arm), which provided 80% power to detect a 20% risk reduction in the incidence of RIFLE I AKI with a baseline of 50% (α < 0.05). On the basis of our previous experience with clinical pilot studies, we estimated a sample size of 25 patients for this pilot study to allow meaningful assessment of safety and feasibility. Data were analysed using PASW Statistics version 20 (IBM, Chicago, IL).

**Results**

**Population**
Among the 50 patients (Figure 1) who fulfilled the clinical eligibility criteria during the study period, 25 had an elevated sNGAL concentration and were included in the study. Informed consent was obtained for all patients; 13 were randomly allocated to the treatment group (sodium bicarbonate) and 12 to the placebo group.
When compared with patients in the placebo group, those randomised to the treatment group had a higher uNGAL concentration (548.5 μg/L versus 87.0 μg/L, \( P = 0.03 \)) at the time of randomisation, and tended to be older, have a higher APACHE (Acute Physiology and Chronic Health Evaluation) III score, a higher white cell count and higher sNGAL and serum creatinine and lactate concentrations (Table 1).

### Recruitment and randomisation times

The 25 participating patients were recruited over a period of 69 weeks (a mean of 0.4 patients per week); 21 were recruited at the main study centre and four at the secondary centre.

The median time between ICU admission and randomisation was 16.9 hours (interquartile range [IQR], 14.5–23.7 hours). There was no difference in this time between the placebo group (median time, 18 hours; IQR, 16–29.4 hours) and the treatment group (median time, 16.8 hours; IQR, 11.3–23.7 hours) (\( P = 0.32 \)) (Table 2).

The median time from randomisation to study drug administration was 40 minutes (IQR, 30–60 minutes). Similarly, there was no difference in this time between the placebo group (median time, 45 minutes; IQR, 30–60 minutes) and the treatment group (median time, 30 minutes; IQR, 30–61 minutes) (\( P = 0.47 \)).

### Study drug delivery

The study drug was delivered for a mean duration of 25.9 hours (SD, 10 hours). For the treatment group, the study drug mean delivery duration was 26.8 hours (SD, 8.6 hours), versus a mean delivery duration of 25 hours (SD, 11.6 hours) in the placebo group. This duration was 38.1 hours (SD, 13.3 hours) in the first six patients (study protocol duration, 48 hours) and 22 hours (SD, 4.2 hours) in the following 19 patients (study protocol duration, 24 hours).

### Adverse events

The study drug infusions were suspended or stopped in 11 patients. For four patients, treatment was ceased for logistical reasons (one patient was transferred to the operating theatre and three were discharged to the ward), and in six patients, treatment was ceased because of severe electrolyte abnormalities (serum bicarbonate > 30 mmol/L in four patients in the treatment group and serum chloride > 110 mmol/L in two patients in the control group). In one patient in the placebo group, the study protocol was only resumed after temporary suspension resolved a severe electrolyte abnormality. The rate of protocol cessation for severe electrolyte disturbances did not decrease after the change in study drug infusion (one patient was discontinuous).

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### Table 1. Patients’ characteristics at time of randomisation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment ((n = 13))</th>
<th>Control ((n = 12))</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>70.3 (11.1)</td>
<td>65.8 (9.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>Sex (% male) (SD)</td>
<td>9 (69.2%)</td>
<td>7 (58.3%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Mean weight (kg) (SD)</td>
<td>91.5 (21.1)</td>
<td>78.2 (16.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>APACHE III score (SD)</td>
<td>73.6 (18.0)</td>
<td>69 (24.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Patients who had vasoconstrictor administered (% of patients)</td>
<td>11 (84.6%)</td>
<td>10 (83.3%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean heart rate (beats/min) (SD)</td>
<td>81.8 (20.3)</td>
<td>89.3 (10.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean central venous pressure (mmHg) (SD)</td>
<td>10.3 (4.4)</td>
<td>11.2 (4.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>Patients who had frusemide administered in previous 6 hours (% of patients)</td>
<td>2 (18.2%)</td>
<td>2 (16.7%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean arterial pH (SD)</td>
<td>7.39 (0.08)</td>
<td>7.38 (0.06)</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean arterial base excess (SD)</td>
<td>–1.96 (3.0)</td>
<td>–1.4 (3.5)</td>
<td>0.68</td>
</tr>
<tr>
<td>Mean PaCO(_2) (mmHg) (SD)</td>
<td>38.8 (6.8)</td>
<td>40.0 (8.1)</td>
<td>0.68</td>
</tr>
<tr>
<td>Mean bicarbonate (mmol/L) (SD)</td>
<td>22.5 (2.0)</td>
<td>22.8 (3.5)</td>
<td>0.79</td>
</tr>
<tr>
<td>Mean chloride (mmol/L) (SD)</td>
<td>103.7 (4.9)</td>
<td>105.0 (4.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean lactate (mmol/L) (SD)</td>
<td>2.5 (1.6)</td>
<td>1.9 (0.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean white cell count (SD)</td>
<td>16.3 (7.81)</td>
<td>11.9 (5.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean sNGAL (μg/L) (SD)</td>
<td>429.1 (168.8)</td>
<td>323.1 (89.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median uNGAL (μg/L) (IQR)</td>
<td>548.5 (282.6–1427.6)</td>
<td>87.0 (54.4–478.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean serum creatinine (mmol/L) (SD)</td>
<td>18.0 (84.7)</td>
<td>133.0 (44.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean serum urea (mmol/L) (SD)</td>
<td>12.3 (6.8)</td>
<td>10.7 (4.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Patients with AKI RIFLE R, I or F</td>
<td>6 (113.2%)</td>
<td>8 (100%)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

\(APACHE = \) Acute Physiological and Chronic Health Evaluation.

\(sNGAL = \) serum neutrophil gelatinase-associated lipocalin.

\(uNGAL = \) urinary neutrophil gelatinase-associated lipocalin.

\(IQR = \) interquartile range. AKI = acute kidney injury. RIFLE = risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, end-stage renal failure. \(P^*\) calculated using student \(t\) test or \(\chi^2\), as appropriate.
ued from the protocol while infusion duration was 48 hours, and five patients were discontinued from the protocol while infusion duration was 24 hours). Due to these safety concerns, study recruitment was ceased.

Clinical outcomes

Electrolyte changes

During the study period (Table 3), patients in the sodium bicarbonate group had an increase in their mean bicarbonate serum concentration from 22.5 mmol/L to 33 mmol/L ($P<0.001$), but there were no clinically relevant changes in their mean chloride and sodium serum concentrations. Similarly, there were no statistically or clinically relevant changes in the mean serum electrolyte concentrations of the patients in the placebo group.

Serum and urinary NGAL levels

The sNGAL and uNGAL levels for the two groups are shown in Table 3. During the study period, the sNGAL concentration decreased in both sodium bicarbonate and control groups ($P<0.001$ for both groups). As previously stated, the uNGAL concentration at the time of randomisation was higher in the sodium bicarbonate group compared with the placebo group, but that difference disappeared in the following two days ($P = 0.37$ and 0.67, respectively).

Acute kidney injury

Within the treatment group, 11 patients fulfilled the RIFLE criteria for AKI at some stage during their hospital stay, versus 10 patients in the placebo group ($P = 0.93$) (Table 4). Of these, three patients in each group were classified as “failure” (RIFE F) ($P = 0.75$). Two patients in the sodium bicarbonate group required RRT, versus none in the placebo group ($P = 0.26$). All patients were RRT-free on discharge from ICU.

Length of stay

Median ICU LOS for the sodium bicarbonate group was 4.1 days (IQR, 2.4–14.9 days) versus 4.4 days (IQR, 2.2–6.4 days) for the placebo group ($P = 0.34$). Median hospital LOS for the treatment group was 18.2 days (IQR, 14.4–32.1 days) compared with 26.8 days (IQR, 9.8–46.9 days) in the placebo group ($P = 0.27$).

Mortality

ICU mortality was zero patients in the sodium bicarbonate group versus one patient in the placebo group ($P = 0.48$). In-hospital mortality was three patients in the sodium bicarbonate group compared with three patients in the placebo group ($P = 0.64$).

Discussion

Key findings

We performed a double-blinded RCT comparing sodium bicarbonate infusion to sodium chloride infusion in critically ill patients at risk of s-AKI, as defined by the presence of SIRS, oliguria and elevated sNGAL. We found that patient recruitment, enrolment, and randomisation were all feasible within practical timelines, and that using our inclusion criteria, we were able to identify a population with an 85% chance of developing AKI according to the RIFLE classification. However, we also found that the administration of sodium bicarbonate and sodium chloride solutions at the concentrations used for the trial were both associated with severe electrolyte abnormalities resulting in early cessation of the protocol in close to one in four patients. The study was terminated early for safety concerns. Finally, on intention-to-treat analysis, we did not find any significant difference or trend in the incidence of AKI, sNGAL or uNGAL levels, the need for RRT, hospital LOS or hospital mortality between the groups.

Comparison with previous studies

Experimental evidence suggests that urinary alkalisation could protect the kidney from oxidative injury. In particular, sodium bicarbonate appears to limit the generation of reactive oxygen species and lipid peroxidation, especially...
when triggered by proteinuria, labile iron (via the Haber–Weiss and Fenton reactions) or ischaemia. Similarly, urinary alkalinisation decreased the severity of haemoglobinuria-associated AKI in two animal models. Sodium bicarbonate’s potential nephroprotective effect has also been extensively studied in the context of contrast-induced nephropathy. Importantly, and of direct relevance to the current study, no safety concern was raised among these studies other than the theoretical risk associated with dosing errors during drug reconstitution.

There is evidence that prophylactic sodium bicarbonate administration may attenuate cardiac surgery-associated AKI. In a single-centre pilot RCT of patients selected for their high risk of developing AKI, sodium bicarbonate infusion was associated with a lower incidence of AKI when compared with sodium chloride. In this trial, in which a regimen similar to the one used in our study was used (4 mmol/kg versus 5.3 mmol/kg in our study after in-study modification), only two out of 100 patients had the intervention discontinued, and none were discontinued for reasons of electrolyte disturbances. No significant side effects were found.

### Study significance

To the best of our knowledge, this study is the first to test administration of hypertonic solutions (sodium bicarbonate or sodium chloride) in patients at high risk of s-AKI. In our pilot RCT, we have shown that such patients appear unable to tolerate a chloride or a bicarbonate load similar in amount to what had been well tolerated in a previous trial of patients receiving cardiac surgery. Tolerance was not improved by a decrease in infusion duration or pauses in the administration. These findings indicate that future studies on fluid-based interventions in patients with rapidly developing renal injury must consider the possibility of impaired chloride and bicarbonate excretion.

Given that a very similar load was well tolerated in patients undergoing cardiac surgery, our observations raise the question of why septic patients were unable to receive such treatment safely. Most of the cardiac surgery patients started the operation with normal renal function, but the septic patients in our study had rapidly evolving renal injury, as shown by the elevated NGAL levels. Our

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### Table 3. Changes in serum electrolytes and biomarkers in 72 hours following randomisation

<table>
<thead>
<tr>
<th>Electrolytes and biomarkers</th>
<th>Treatment (n = 13)</th>
<th>Placebo (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean sNGAL (µg/L) (SD)</td>
<td>418.7 (159.6)</td>
<td>349.3 (76.8)</td>
</tr>
<tr>
<td>Median uNGAL (µg/L) (IQR)</td>
<td>548.5 (282.6–1427.6)</td>
<td>87.0 (14.4–32.1)</td>
</tr>
<tr>
<td>Mean bicarbonate (mmol/L) (SD)</td>
<td>22.5 (2.1)</td>
<td>22.5 (3.9)</td>
</tr>
<tr>
<td>Mean chloride (mmol/L) (SD)</td>
<td>103.7 (5.4)</td>
<td>105.4 (4.9)</td>
</tr>
<tr>
<td>Mean sodium (mmol/L) (SD)</td>
<td>135.3 (5.4)</td>
<td>138.2 (4.7)</td>
</tr>
</tbody>
</table>


---

### Table 4. Patient outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment (n = 13)</th>
<th>Control (n = 12)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean peak sNGAL (µg/L) (SD)</td>
<td>455.8 (193)</td>
<td>333.7 (97)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median peak uNGAL (µg/L) (IQR)</td>
<td>764.4 (282.6–1427.6)</td>
<td>193.6 (78.4–644.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with AKI (RIFLE F, I or F) (% of patients)</td>
<td>11 (84.6%)</td>
<td>10 (83.3%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Patients with severe AKI (RIFLE F) (% of patients)</td>
<td>4 (30.8%)</td>
<td>3 (25%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Patients undergoing RRT (% of patients)</td>
<td>2 (15.4%)</td>
<td>0 (0%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Median ICU length of stay (days) (IQR)</td>
<td>4.1 (2.4–14.9)</td>
<td>4.4 (2.2–6.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Median hospital length of stay (days) (IQR)</td>
<td>18.2 (14.4–32.1)</td>
<td>26.8 (9.8–46.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>ICU deaths (% of patients)</td>
<td>0 (0%)</td>
<td>1 (8.3%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hospital deaths (% of patients)</td>
<td>3 (23.1%)</td>
<td>3 (25%)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

sNGAL = serum neutrophil gelatinase-associated lipocalin. uNGAL = urinary neutrophil gelatinase-associated lipocalin. IQR = interquartile range. AKI = acute kidney injury. RIFLE = risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, end-stage renal failure. RRT = renal replacement therapy. ICU = intensive care unit. *P calculated using the student t test or χ², as appropriate.
findings suggest that in this setting, tolerance of bicarbonate and chloride loading is impaired. Unfortunately, little is known about the kidney’s ability to adjust chloride and/or bicarbonate excretion in the context of early renal dysfunction with SIRS and an elevated sNGAL level. Only a small study (15 patients) has reported data in similar patients.32 In that study, in which not all patients had s-AKI, a highly variable fractional excretion of chloride was reported.33 This suggests that impaired chloride handling might have played a role in our findings. On the other hand, chloride administration itself may have affected renal function, as suggested by a recent study.34 This effect might depend on the tubuloglomerular feedback mechanism triggering vasoconstriction of the afferent arteriole.32 To the best of our knowledge, there are no data describing the capacity of the kidney to modulate bicarbonate reabsorption during s-AKI.

Despite the fact that we were unable to achieve the necessary safety and feasibility profile, our study proved we had been correct in our choice of NGAL as an identifier of patients at high risk of AKI when associated with oliguria and two SIRS criteria, because 85% of patients went on to fulfil the RIFLE criteria for AKI. Not only was NGAL measurement useful in the identification of a high-risk cohort, but it also enabled randomisation and intervention earlier in the disease process than would otherwise have been the case. To our knowledge, these findings represent the first attempt to use a novel biomarker to guide an experimental intervention. Our study is thus the first to simultaneously test an experimental diagnostic strategy and an unproven intervention.

Strength and limitations
This study has several strengths. It is the first to test such a protocol of hyperosmolar bicarbonate or sodium chloride in patients at risk of s-AKI. The intervention was administered in a strict double-blinded fashion. Patients were identified based on SIRS criteria, oliguria and elevated NGAL, which enabled early identification of a population with an 85% risk of developing AKI, and allowed early intervention. Time to randomisation and rate of recruitment were satisfactory. This study was initially planned to include 170 patients but was stopped for safety reasons after 25. It is therefore grossly underpowered to detect differences between the two groups in clinical outcomes. However, the important safety issues associated with a protocol such as this in patients at risk of AKI precluded further enrolment.

There is no real evidence that the cut-offs for electrolyte abnormalities we defined as unsafe in our study would have been associated with a higher incidence of adverse clinical outcomes. However, these limits were agreed to by the treating clinicians as suitable for the identification of safety risks in a Phase I pilot study and appear to be physiologically and biochemically justified.

Conclusions
Administration of hypertonic solutions of sodium bicarbonate or sodium chloride to patients at risk for s-AKI was associated with a high rate of severe electrolyte abnormalities and early protocol cessation. In these patients, although early correct identification and intervention were possible with a good degree of accuracy by means of sNGAL testing, the interventional protocol did not appear safe, and further studies are likely to be unsafe.

Competing interests
None declared.

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2 Himmelfarb J. Linking oxidative stress and inflammation in kidney disease: which is the chicken and which is the egg? Semin Dial 2004; 17: 449-54.


**Correction**

In “The HEAT trial: a protocol for a multicentre randomised placebo-controlled trial of IV paracetamol in ICU patients with fever and infection” in the December 2012 issue of the Journal (Crit Care Resusc 2012; 14: 290-296), the description of when to cease study medication on the basis of resolution of fever on page 293 is incorrect. The temperature at which medication should be restarted after being withheld should be > 38°C rather than ≥ 38°C. For example, the sentence: “If the patient does not develop a fever of ≥ 38°C within 48 hours from the time study treatment has been withheld, they will be deemed to have completed the course of study medication” should read “If the patient does not develop a fever of > 38°C within 48 hours from the time study treatment has been withheld, they will be deemed to have completed the course of study medication”. The process for determining resolution of fever is correctly described in Figure 1.