Section 2. TREATMENT OF ACUTE KIDNEY INJURY

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GUIDELINES

1. Fluids

a. In the absence of haemorrhagic shock, we suggest using isotonic crystalloids rather than colloids for volume resuscitation. (2B)

b. We recommend against using hydroxyethyl starch (HES) solutions for volume resuscitation. (1B)

2. Protocolised haemodynamic management

a. We suggest using protocol-based management of haemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting (2C) or in patients with septic shock (2C).

3. Glycaemic control in critical illness: renal effects and outcomes

a. We recommend against using insulin to target a plasma glucose of less than 6.1 mmol/l (1B)

b. We suggest using insulin to treat hyperglycemia if the plasma glucose is more than 10.0 mmol/l (2C)

c. Once treatment has started we suggest targeting a plasma glucose between 8.0 and 10.0 mmol/L. (2C)

d. We recommend ensuring micronutrient intake is adequate and losses caused by RRT are replaced. (1C)

IMPLEMENTATION AND AUDIT

Implementation and audit of the guideline recommendations for fluid use and glycaemic control is relatively straightforward and a periodic audit of compliance at an individual unit level is recommended. Until further research is completed to inform which haemodynamic protocols should be used it is difficult to describe an implementation strategy, beyond recommending that a haemodynamic management protocol is used.
SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 21 in the Appendix of the KDIGO guideline) (Kidney International Supplements 2 (2012); 2: 102-113). Additional key papers have been identified by the authors that were published after the KHA-CARI update search.

**Databases searched:** Medline, Central, Cochrane database of systematic reviews

**Date of searches:** June 2012

ADEQUACY OF KDIGO SEARCH STRATEGY

The search strategy and evidence provided by KDIGO was comprehensive and included some important randomised controlled trials (RCTs). A number of systematic reviews and RCTs have subsequently been identified in the updated search by KHA-CARI and included in this update.

APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

There has been some significant new evidence in the field of fluid therapy since the KDIGO guidelines were released and this is reflected in the recommendations of the KHA-CARI guidelines. Of note, several of the landmark studies in fluid therapy and glycaemic control were conducted in Australia and New Zealand thus the findings are highly applicable. The recommendation for the use of protocols in the haemodynamic management of patients although not based on strong evidence is consistent with best practice in Australia and New Zealand. One of the 3 ongoing major trials in this area is being conducted in Australia and New Zealand and the results will help guide practice.
1. FLUIDS

BACKGROUND

Despite the recognition of volume depletion as an important risk factor for acute kidney injury (AKI), there are no RCTs that have directly evaluated the role of fluids vs. placebo in the prevention of AKI, except in the field of contrast-induced acute kidney injury (CI-AKI) (see KDIGO Clinical practice guideline for acute kidney injury Chapter 4.4). It is accepted that optimisation of the haemodynamic status and correction of any volume deficit will have a salutary effect on kidney function, will help minimise further extension of the kidney injury, and will potentially facilitate recovery from AKI with minimisation of any residual functional impairment. AKI is characterised by a continuum of volume responsiveness through unresponsiveness (Figure 8, KDIGO Clinical practice guideline for acute kidney injury), [1, 2] and large multicenter studies have shown that a positive fluid balance is an important factor associated with increased 60-day mortality [1, 3, 4].

Despite the fact that the administration of intravenous fluid is one of the most common performed medical interventions, the timing of administration, amount and selection of the type of fluid that should be used in the resuscitation of patients is still controversial. Early fluid resuscitation is recommended as a standard of care, and the evidence supporting this is discussed in KDIGO Clinical practice guideline for acute kidney injury section 3.1.3 however there is little current evidence to guide the amount of fluid given. This guideline focuses on the selection of the type of fluid given and on the evidence of the effects of different fluids on renal function.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified by the update searches conducted by KHA-CARI as part of the adaptation process.

Albumin vs. saline

The role of albumin physiology in critically ill patients, and the pros and cons for administering albumin to hypoalbuminemic patients, have recently been discussed [5]. Results of the Saline vs. Albumin Fluid Evaluation (SAFE) study, a RCT of 6997 ICU patients comparing 4% human albumin in 0.9% saline with isotonic saline as the sole resuscitation fluid demonstrated that albumin was no more effective than saline for either mortality, the development of AKI or the requirement for renal replacement therapy (RRT) [6]. Post-hoc analysis demonstrated a trend towards higher mortality in patients with traumatic brain injury who received albumin and a trend towards lower mortality with albumin in a subgroup of patients with sepsis. A large study of the use of albumin in septic patients has recently completed recruitment and the results once published may help to answer the question of beneficial effects of albumin in this patient group (ALBIOS Study).
http://clinicaltrials.gov/show/NCT00707122), however given the current evidence the routine use of albumin as a resuscitation fluid cannot be recommended.

**Hydroxyethylstarch vs. saline**

Hydroxyethylstarch (HES) is a widely used, relatively inexpensive alternative to human albumin for correcting hypovolemia. Different HES preparations are available that vary with regard to concentration, mean molecular weight (MW), molar substitution, and substitution of hydroxyethyl for hydroxyl groups. The mean MW of the different HES preparations ranges between 70,000 and 670,000 Da. The colloid osmotic pressure effect is strongly dependent upon the concentration of colloid in the solution; e.g., 6% HES is iso-oncotic, whereas 10% HES is hyperoncotic. The number of hydroxyethyl groups per glucose molecule is specified by the molar substitution, ranging between 0.4 (tetrastarch), 0.5 (pentastarch), 0.6 (hexastarch) and 0.7 (heptastarch).

The introduction of tetrastarches (HES 130/0.4 and HES 130/0.42) was in response to concerns that high molecular substitution HES solutions may be associated with impaired coagulation and the development of renal dysfunction. Multiple mostly small single centre studies have given conflicting results, which has not been helped by the retraction of several studies suggesting that the newer formulations are safe. It has been recommended that “HES should be avoided in ICUs and during the perioperative period” (for a summary, see de Saint-Aurin et al. [7] and Vincent [8]).

The first major randomised trial in patients with sepsis compared HES 200/0.60 to 0.66 with gelatin and showed a greater incidence of AKI in the HES group, but no effect on survival [9]. Criticisms of this study include a higher baseline SCr level in the HES group, small sample size, and short follow-up duration of 34 days. In the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study [10], patients with severe sepsis were randomly assigned to receive a hypertonic (10%) solution of low MW HES (HES 200/0.5), or an isotonic modified Ringer’s lactate solution. Patients in the HES group received a median cumulative dose of 70.4 ml per kilogram of body weight. The mortality was not significantly different, although showing a trend toward greater mortality at 90 days. However, the hypertonic HES group had a significantly higher rate of AKI (34.9% vs. 22.8%) and more days on which RRT was required (KDIGO Suppl Table 1). Also, this study has been criticized for: i) using a hyperoncotic colloid solution with potentially harmful renal effects as shown in experimental research [11]; ii) markedly exceeding the pharmaceutically recommended daily dose limit for 10% HES 200/0.5 by more than 10% in >38% of patients; and iii) pre-existing renal dysfunction in 10% of study patients, which represents a contra-indication for infusion of 10% HES 200/0.5 [12]. Posthoc analyses of the VISEP study showed the cumulative dose of HES to be a significant independent predictor for both mortality and RRT at 90 days. The median cumulative dose of HES in
the VISEP Study was 70 ml/kg compared to 31 ml/kg in the study by Schortgen et al [9].

A systematic review of RCTs on the use of HES for fluid management in patients with sepsis totaling 1062 patients, including 537 patients from the VISEP study, showed an almost two-fold increased risk of AKI with HES compared to crystalloids [13]. Given these limitations, the results of these studies should be interpreted with caution. Furthermore, a large, prospective observational study found that HES infusion of any type (median volume 555 ml/d; interquartile range 500–1000) did not represent an independent risk factor for renal impairment [14]; however, recently in a large cohort of critically ill patients (approximately 8000 subjects), infusion of 10% HES 200/0.5 instead of HES 130/0.4 appeared to be an independent risk factor for RRT [15].

Finally, a recent comprehensive Cochrane review [16] concluded that there is no evidence from RCTs that resuscitation with colloids, instead of crystalloids, reduces the risk of death in patients with trauma, burns, or following surgery.

In 2012 two landmark clinical trials studying the effects of tetrastarch use were published. The Scandinavian Starch for Severe Sepsis/Septic Shock Study (6S study) [17] randomised patients with defined severe sepsis or septic shock to receive either HES 140/0.42 (Tetraspan) or Ringer’s acetate as their resuscitation fluid. At day 90 after randomisation, 201 of 398 patients (51%) assigned to HES 130/0.42 had died, as compared with 172 of 400 patients (43%) assigned to Ringer’s acetate (RR 1.17; 95% CI, 1.01 to 1.36; P=0.03). In the 90-day period, 87 patients (22%) assigned to HES 130/0.42 were treated with RRT versus 65 patients (16%) assigned to Ringer’s acetate (RR 1.35; 95% CI, 1.01 to 1.80; P=0.04), and 38 patients (10%) and 25 patients (6%), respectively, had severe bleeding (RR 1.52; 95% CI, 0.94 to 2.48; P=0.09).

Following this the CHEST study, comparing 0.9% sodium chloride with 140/0.4 HES (Voluvén) as the primary resuscitation fluid for patients in intensive care was published. This study had a very similar design to the SAFE study and included 7000 patients. Overall mortality was 18.0% in the HES group and 17.0% in the saline group (RR 1.06; 95% CI 0.96–1.18; P=0.26) with RRT used in 7.0% of the HES group and 5.8% of the HES group (RR 1.21; 95% CI 1.00–1.45; P=0.04). As defined by RIFLE, renal injury occurred in 34.6% of the HES group and 38.0% of the saline group (P=0.005) and renal failure in 10.4% and 9.2% respectively (P=0.12). HES use was associated with significantly more adverse events (especially itching) – 5.3% vs. 2.8%). Post hoc analysis demonstrated that treatment with HES was associated with increased urine output but conversely higher serum creatinine, which may explain the diverging results when RIFLE criteria are used.

A recently updated analysis by Gattas and the CHEST management committee that included the results of both the 6S and CHEST studies (Gattas ICM – in press) included 35 trials enrolling 10391 patients has recently been published. Death occurred in 19.8% of patients in the HES group and 18.5%
of patients in the control fluid groups, including both saline and balanced salt solutions (RR 1.08; 95% CI 1.00-1.17). RRT was required in 8.9% of the HES group and 7.2% of the control groups (RR 1.25; 95% CI 1.08-1.44).

The recommendation for the use of isotonic crystalloids rather than colloids is based upon lack of evidence of improved outcomes with colloids in studies reported to date, although the outcome of ongoing studies of the use of albumin in specific patient groups is awaited. We recommend against using HES solutions as there is no evidence of improved outcomes and recent large RCTs have shown harm particularly an increase in significant AKI requiring RRT.

**Isotonic saline vs. balanced crystalloid solutions**

One of the concerns with isotonic saline is that this solution contains 154 mmol/l chloride and that administration in large volumes will result in relative or absolute hyperchloremia (for a review, see Kaplan et al [18].). A recent single centre prospective open label study [19] of 1533 patients admitted to the intensive care unit who received either standard care or a fluid regime designed to minimise chloride administration (primarily through the use of a balanced salt solution) demonstrated a decrease in chloride administration from 694 to 496 mmol/patients and this was associated with a significant decrease in AKI and the use of RRT. Although direct proof of harm arising from saline-induced hyperchloremia is lacking, buffered salt solutions approximate physiological chloride concentrations and their administration is less likely to cause acid-base disturbances. Whether use of buffered solutions results in better outcomes is, however, uncertain and will require large RCTs.
2. PROTOCOLISED HAEMODYNAMIC MANAGEMENT

BACKGROUND

A resuscitation strategy devised for patients with hypotension from septic shock that is based upon achieving specific physiologic end-points within 6 hours of hospital admission has been termed Early Goal-Directed Therapy (EGDT). This approach has been endorsed by the “Surviving Sepsis Campaign” [20] and has gained considerable acceptance despite only one, single-center, RCT evaluating its effectiveness. This protocolised strategy, consisting of fluids, vasoactive medication, and blood transfusions targeting physiological parameters, is recommended by many experts for the prevention of organ injury in septic-shock patients.

Similarly, protocolised care strategies in surgical patients at high risk for postoperative AKI have been extensively studied in an effort to provide optimal oxygen delivery to tissues in the perioperative period. In these patients, goal directed therapy is defined as haemodynamic monitoring with defined target values and with a time limit to reach these stated goals. Together these protocols with bundled, haemodynamic, and tissue-support measures have the potential to reduce the risk of AKI following major surgical procedures in high-risk patients (e.g., age >60 years, emergent surgery, elevated American Society of Anesthesiologists score, preoperative comorbid illnesses).

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified by the update searches conducted by KHA-CARI as part of the adaptation process.

 Protocolised haemodynamic management strategies in septic shock

Early fluid resuscitation in the management of hypotensive patients with septic shock has been a standard treatment paradigm for decades [10, 20, 21]. What has not been clear, however, is how much fluid to give, for how long, or what type of fluid therapy is optimal in the physiologic support of septic shock [10, 20, 21]. In 2001, Rivers et al. [22] published the results of a small (n=263), open-label, single-center study that compared a treatment protocol that the authors referred to as EGDT in the emergency management of septic shock. EGDT is predicated upon the premise that an early, protocolised resuscitation program with predefined physiologic end-points will prevent organ failure and improve the outcome of patients presenting with septic shock.

Hypotensive patients with severe infection are rapidly assessed for evidence of tissue hypoperfusion and microcirculatory dysfunction by mean arterial blood pressure measurement and plasma lactate levels [22]. Blood lactate levels are neither sensitive nor specific but are readily available measures of
tissue hypoperfusion and do correlate with adverse outcomes in sepsis [23, 24]. Early recognition of septic shock then initiates a protocol of resuscitation with the goal of re-establishing tissue perfusion in patients within 6 hours of diagnosis. The physiologic goals are: i) return of mean arterial blood pressure to ≥ 65 mmHg; ii) central venous pressure between 8–12 mmHg; iii) improvement in blood lactate levels; iv) central venous oxygen saturation (ScvO2) >70%; and v) a urine output of ≥0.5 ml/kg/h.

In the study by Rivers et al. [22] the protocol-driven process resulted in more rapid use of fluids, more blood transfusions, and in a small number of patients, earlier use of dobutamine over the 6-hour time period than standard emergency care. The in-hospital mortality rate in the control group was 46.5% vs. 30.5% in the EGDT group (P=0.01) [23]. Follow-up, predominantly observational studies, have found less dramatic but generally similar effects [25-29], though not without exception [30].

The Rivers study did not specifically look at AKI outcomes, but multiple-organ function-scoring systems (i.e., APACHE II and SAPS 2) both showed significant improvements with EGDT. In a subsequent study, prevention of AKI was significantly improved in patients randomised to a modified EGDT strategy (without measurement of ScvO2) compared to a standard-care group [26]. Criticisms of the Rivers study include: i) a complex, multistep protocol for which individual interventions have not been validated; ii) the use of a treatment team in the active-therapy arm, thus risking a Hawthorne effect; iii) high mortality in the standard care arm; and iv) the study was a small single-center study. Three large multicenter clinical trials in the USA, UK, and Australia are currently underway to definitively evaluate this therapy.

**Goal-directed therapy for haemodynamic support during the perioperative period in high-risk surgical patients**

Efforts to improve tissue oxygen delivery by optimizing haemodynamic support in high-risk surgical patients to prevent AKI and other adverse patient outcomes have been investigated for many years [31-33]. A recent meta-analysis of these studies by Briana et al [34] concluded that protocolised therapies (regardless of the protocol) with specific physiological goals can significantly reduce postoperative AKI.

A major problem in interpreting these studies is the lack of standardised haemodynamic and tissue oxygenation targets and management strategies used to verify the efficacy of these measures over standard perioperative care. A heterogeneous collection of study populations, types of surgical procedures, monitoring methods, and treatment strategies comprise this recent meta-analysis [34]. The basic strategy of goal-directed therapy to prevent AKI in the perioperative period is based on protocols that avoid hypotension, optimise oxygen delivery, and include careful fluid management, vasopressors when indicated, and inotropic agents and blood products if needed [34].
The relative merits and risk: benefit ratio of each discrete element of EGDT in the successful resuscitation of patients with septic shock requires further study. Given the limitations of the current studies and lack of comparative effectiveness studies comparing individual protocols, we can only conclude that protocols for resuscitation in the setting of septic shock and high-risk surgery appear to be superior to no protocol.
3. GLYCEMIC CONTROL IN CRITICAL ILLNESS: RENAL EFFECTS AND OUTCOMES

BACKGROUND

As outlined in a recent review [37] stress hyperglycemia is a distinctive clinical feature of critical illness. Stress mediators, and central and peripheral insulin resistance appears pivotal to the occurrence of stress hyperglycemia. Inflammatory mediators and counter-regulatory hormones have been shown to impede crucial elements of the insulin-signaling pathway. Still, exogenous insulin administration normalises blood glucose levels in this setting. Insulin treatment may counteract hepatic insulin resistance during acute critical illness. Extensive observational data have shown a consistent, almost linear, relationship between blood glucose levels in patients hospitalized with myocardial infarction and adverse clinical outcomes, even in patients without established diabetes [38, 39].

It has never been entirely clear, however, whether glycaemia serves as a mediator of these outcomes or merely as a marker of the sickest patients, who present with the well-known counter-regulatory stress response to illness [40]. Interestingly, Kosiborod et al. [38] recently showed, in a population with myocardial infarction, that while hypoglycemia was associated with increased mortality, this risk was confined to patients who developed spontaneous hypoglycemia. In contrast, iatrogenic hypoglycemia after insulin therapy was not associated with higher mortality risk.

Tight glycemic control is frequently used in patients at risk of AKI, and in the management of those who develop AKI. It has been proposed that tight glycemic control can reduce the incidence and severity of AKI. Since the landmark trial of Van den Berghe et al. [41], additional studies provided initial confirmation of the benefits (reduced morbidity and mortality), and some additional mechanistic insights of tight glycemic control in critically ill patients [42].

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified by the update searches conducted by KHA-CARI as part of the adaptation process.

Further secondary analysis of the original trial, which was conducted in 1548 mechanically ventilated surgical ICU patients, found that intensive insulin therapy (IIT) target plasma glucose 80–110 mg/dl (4.44–6.11 mmol/l) was associated with substantial cost savings compared to conventional insulin therapy (CIT) targeting plasma glucose 180–200 mg/dl (9.99–11.1 mmol/l) [43]. However, when Van den Berghe et al. repeated their original study in a different population of critically ill patients (medical rather than surgical ICU patients), the primary end-point of in-hospital mortality did not differ between groups (40% CIT group vs. 37.3% IIT group; P=0.33) [44]. As in the original surgical ICU study, varieties of secondary end-points were improved in this...
study, including a lower incidence of AKI and need for RRT. In the original surgical ICU study, severe AKI (peak SCr>2.5 mg/dl [>221 µmol/l]) developed in 7.2% of the IIT group, compared to 11.2% of the CIT group (P=0.04); the incidence of RRT was also lower in the IIT group than the CIT group (4.8% vs. 8.2%, respectively; P=0.007) [41]. In the medical ICU study, the IIT group similarly had a significantly lower rate of AKI (doubling of SCr, 5.4%) than the CIT group (8.9%, P=0.04), although RRT incidence was not decreased [44]. In a recent analysis, Schetz et al. [45] combined the renal end-points of both of these trials and used a modified version of the RIFLE classification of AKI to demonstrate that tight glycemic control reduced the incidence of severe AKI (peak SCr increments two- or three-fold increased from baseline) from 7.6% to 4.5% (P=0.0006) in a combined patient population of 2707. The need for RRT was not decreased in the overall population or the medical ICU population, but was significantly lower in the surgical ICU patients managed with IIT (4% vs. 7.4%, P=0.008).

Several newer studies have provided additional insight concerning the efficacy and safety of tight glycemic control in critically ill patients [10, 12, 46-49]. Thomas et al. [48] conducted a systematic review of randomised trials of tight glycemic control in 2864 critically ill patients, and found a 38% risk reduction of AKI with IIT, and a non-significant trend towards less acute dialysis requirement. However, IIT was also associated with a greater than four-fold increase in the risk of hypoglycemia. A body of literature demonstrating that uncontrolled hyperglycemia was associated with increased AKI following cardiac surgery led to the conduct of a 400- patient, single-center RCT of tight vs. conventional intraoperative glucose control [46, 47]. The investigators found that this approach did not decrease perioperative morbidity or mortality (included in a composite end-point that included AKI within 30 days of surgery): the composite end-point occurred in 44% of the IIT group vs. 46% of the CIT group. Although the incidence of hypoglycemia was similar in the groups, there was a significantly higher incidence of stroke in the IIT group (4.3%) compared to the CIT group (0.54%), as well as trends towards higher mortality and more postoperative heart block in the IIT group, raising concerns about the safety of this approach.

Further prospective comparison of IIT vs. CIT in critically ill septic patients was provided in the VISEP trial, which also incorporated a comparison on crystalloid vs. colloid infusions in a 2 X 2 factorial design [10]. Patients with severe sepsis or septic shock in 18 ICUs were randomised to IIT (target glycaemia 80–110 mg/dl [4.44–6.11mmol/l]; n=247) or CIT (target glycaemia 180–200 mg/dl [9.99–11.1mmol/l]; n=290) (Suppl Tables 2 and 3). There were no significant differences in 28-day or 90-day mortality, sequential organ failure assessment scores, or AKI rates between the groups. However, hypoglycemia (blood glucose level <40 mg/dl [<2.22 mmol/l]) was more frequent in the IIT group (12% vs. 2%; P<0.001) and led to early termination of the IIT study arm. Following publication of this study, Thomas et al. updated the meta-analysis (discussed above) to include these data, and reported that, with the addition of the VISEP data, the analysis of a 3397-patient group found a 36% risk reduction of AKI with IIT, but this pooled estimate was no longer
statistically significant (relative risk [RR] 0.74; 95% CI 0.47–1.17) [12]. In a detailed review of the VISEP trial, Thomas et al. also noted that another multicenter mixed ICU trial of IIT (the GLUCOCONTROL Study: Comparing the effects of two glucose control regimens by insulin in intensive care unit patients; available at: http://www.clinicaltrials.gov/ct/show/NCT00107601) was stopped after 1101 patients were enrolled because of greater rates of hypoglycemia with IIT [12]. Such data have raised significant concerns regarding the effectiveness and safety of using IIT with tight glycemic control to prevent or ameliorate morbidity and mortality in patients at high risk of AKI and other forms of organ injury.

The recent meta-analysis of IIT vs. CIT by Wiener et al. [49] continued to find a greater incidence of hypoglycemia with IIT, but the balance of evidence now suggests no improvement in survival with this approach. Twenty-nine RCTs totaling 8432 patients contributed data for this meta-analysis. Twenty-seven studies reported no difference in hospital mortality (21.6% in IIT vs. 23.3% in CIT) with a pooled RR of 0.93 (95% CI 0.85–1.03; P=NS). Nine studies reported no difference in incidence of new RRT. There was a significant benefit of tight glycemic control in reducing the incidence of septicemia but this was associated with a significantly increased risk of hypoglycemia (blood glucose <40 mg/dl [<2.22 mmol/l]) in patients randomised to IIT with a pooled RR of 5.13 (95% CI 4.09–6.43; P<0.05).

In summary, pooled analysis of early multicenter studies has failed to confirm the early observations of beneficial effects of IIT on renal function; the risks of hypoglycemia with this approach is significant, and even the survival benefits of IIT are in doubt. More recently, the international Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, with a targeted enrolment of 6100 patients, set out to definitively determine the risk-benefit comparison of tight glycemic control in critically ill patients (KDIGO Suppl Table 3) [50,51]. In this trial, adult patients were randomised within 24 hours after admission to an ICU to receive either intensive glucose control (target blood glucose range of 81–108 mg/dl [4.50–5.99 mmol/l]), or conventional glucose control (target of ≤180 mg/dl [≤9.99 mmol/l]) [51]. The primary outcome was mortality from any cause within 90 days after randomisation. The two groups had similar characteristics at baseline. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (OR for intensive control, 1.14; 95% CI 1.02–1.28; P=0.02). The treatment effect did not differ significantly between surgical patients and medical patients. There was no significant difference between the two treatment groups in incidence of new RRT (15.4% vs. 14.5%), respectively. Severe hypoglycemia (blood glucose level ≤40 mg/dl [≤2.22 mmol/l]) was reported in 6.8% in the intensive-control group and in 0.5% in the conventional-control group (P<0.001). In summary, the largest randomised trial of intensive vs. conventional insulin therapy found that intensive glucose control actually increased mortality among adults in the ICU: a blood glucose target of ≤180 mg/dl (≤9.99 mmol/l) resulted in lower mortality than did a target of 81–108 mg/dl (4.50–5.99 mmol/l). Furthermore, this trial confirmed the consistent finding of an increased incidence of hypoglycemia.
associated with IIT, without any proven benefit in reducing mortality, organ
dysfunction, or bacteremia.

There were some methodological differences between the Leuven and NICE-
SUGAR studies, possibly explaining the different outcomes [52]. These
comprised different target ranges for blood glucose in control and intervention
groups, different routes for insulin administration and types of infusion pumps,
different sampling sites, and different accuracies of glucometers, as well as
different nutritional strategies and varying levels of expertise. Finally,
Griesdale et al. [53] performed a meta-analysis of trials of intensive vs.
conventional glycemic control that included most of the studies in the Wiener
meta-analysis, in addition to some newer studies, including data supplied by
the NICE-SUGAR investigators. All 26 trials that reported mortality found a
pooled RR of death with IIT compared to CIT of 0.93 (95% CI 0.83–1.04).
Among the 14 trials reporting hypoglycemia, the pooled RR with IIT was 6.0
(95% CI 4.5–8.0). However, in subset analysis, patients in surgical ICUs
appeared to benefit from IIT while patients in the other ICU settings (medical
or mixed) did not. Although results from the early trials were better in studies
that included surgical rather than purely medical ICU patients [44], and this
latest meta-analysis appears to confirm that trend, it should be noted that no
such phenomenon was noted in the NICE-SUGAR trial.

Overall, the current evidence does not support the use of IIT aiming to control
plasma glucose below 110 mg/dl (6.11mmol/l) in critically ill patients, including
in subsets of surgical patients.

Considering the balance between potential benefits and harm (see KDIGO
Suppl Table 2), we recommend using insulin for preventing severe
hyperglycemia (blood glucose > 10mmol/l) in critically ill patients and targeting
a blood glucose level of between 8.0 and 10.0 mmol/l.
In view of the risk of potentially serious hypoglycemia and lack of convincing
evidence of benefit, we recommend against using insulin to target a plasma
glucose <6.1mmol/l.

Ungraded suggestions for clinical care

We suggest ensuring micronutrient intake is adequate and losses
cased by RRT replaced. (Ungraded)

AKI patients are at risk of depletion of minerals (including trace elements) and
water-soluble vitamins. The cause is multifactorial, including acute phase
reaction to critical illness, acute losses of biological fluids, suboptimal
nutritional intake, oxidative stress caused by critical illness and removal by
RRT [54]

Due to their continuous nature and the high filtration rates, CRRT techniques
can better control azotaemia and fluid overload associated with nutritional
support but may also result in additional losses of water-soluble, low-
molecular weight substances, including nutrients. Those reported to be depleted are vitamin C, thiamin, folic acid, copper, selenium, and zinc [55-59].

In addition, stores of most water soluble vitamins and some minerals are relatively low in critical illness, so supplementation should be considered in this group even when RRT is not required [57,58]. In the critically ill, supplementation with high dose trace elements and vitamins may improve mortality rates, and has shown a trend to decrease infections. Selenium, in particular, has been identified as being associated with decreased mortality [64, 66].

Levels of potassium, magnesium and phosphate should be monitored. These are lost during dialysis, but high levels are also detrimental and provision of high levels of protein may cause excessive intake [60-63]. Metabolic balance studies have shown that absence of any one of potassium, phosphorus or magnesium results in negative nitrogen balance in the critically ill [65].

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative (2013): [67]

KDOQI commentary on KDIGO Acute Kidney Injury Prevention and Treatment section, agrees with all 7 level 1 recommendations, viewing them as applicable in the United States of America.

UK Renal Association (2011): [68]

3.1 We recommend that patients at risk of AKI should be identified and appropriate preventative measures should be instituted as early as possible. (1B)

3.2 We recommend that prescription of appropriate intravenous fluid should be carefully considered following assessment of the patient's volume status. Thereafter the patient's clinical response should be monitored closely. (1B)

3.3 We recommend that patients identified as being at risk of contrast induced-AKI (CI-AKI) should have a careful assessment of volume status and receive pre-procedure volume expansion with 0.9% sodium chloride or isotonic sodium bicarbonate if clinically indicated. (1A)

Canadian Society of Nephrology (2013): [69]

Canadian Society of Nephrology commentary supports the recommendations from 2012 KDIGO AKI Clinical Practice Guidelines on Haemodynamic Monitoring and Support of AKI.

It also recognises that there are some specific subgroups of patients who often receive albumin solutions and in whom their use may be rational.
3.1.1 In the absence of haemorrhagic shock, we recommend using isotonic crystalloids rather than colloids (albumin or starches) as initial management for expansion of intravascular volume in patients at risk for AKI. (1B)

3.1.2 We recommend the use of vasopressors to maintain perfusion pressure in volume-resuscitated patients with vasomotor shock with, or at risk for, AKI. (1C)

3.1.3 We suggest using protocol-based management of haemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients. (2C)

3.3. Glycaemic control and nutritional support

3.3.1 In critically ill patients, we suggest using insulin therapy to maintain plasma glucose levels between 110 and 180 mg/dL (6.1–8.3 mmol/L) (2C). We recommend implementing this strict glycaemic control only as part of a good functioning glycaemic control protocol, including close monitoring of glycaemia to avoid hypoglycaemia, and the use of flow charts of action. (1A)

**SUGGESTIONS FOR FUTURE RESEARCH**

- Randomised trials of isotonic crystalloid vs. colloid therapy for intravascular volume expansion to prevent or treat AKI should be conducted in a variety of settings (critical illness, high-risk surgery, sepsis), including patient subsets.

- Comparisons of specific crystalloid solutions for effectiveness in preventing AKI should be conducted. Specifically, there is a need to examine physiologic electrolyte solutions vs. saline.

- Studies are needed that compare different types of vasopressors for prevention and treatment of AKI in haemodynamically unstable patients. Some evidence suggests that certain vasopressors may preserve renal function better than others (e.g., vasopressin analogues vs. catecholamines) and studies are needed to compare them in this setting.

- The choice of a target mean arterial perfusion pressure range of 65–90mm Hg as a component of resuscitation (perhaps in the context of age, chronic blood pressure, or other comorbidities) also needs further study.

- The specific components of goal-directed therapy that accrue benefits for patients at risk for AKI need to be determined. Is it the timing of
protocolised haemodynamic management that is beneficial: prophylactically in high-risk surgical patients, or early in the course of severe sepsis? In contrast to the benefits of prophylactic or EGDT, protocolised use of inotropes to normalise mixed venous oxygen saturation or supranormalise oxygen delivery in “late” critical illness did not result in decreased AKI or improved outcomes [35, 36]. Alternatively, is it attention to haemodynamic monitoring, the protocol itself that standardizes supportive care to achieve the stated goals, or a single or combination of the multiple possible interventions that improves outcome? Thus, further research is required to determine the specific components of goal directed therapy that accrues benefits for patients at risk for AKI, if such benefits actually occur.

- The extent and effect of electrolyte, trace element and vitamin abnormalities in AKI should be investigated, and the most appropriate means of management of these to aid recovery determined.

**CONFLICT OF INTEREST**

S McGunniess received financial support from Fresenius for CHEST study and financial support from Baxter for the SPLIT and Supplement PN studies.

R Bellomo has received consultancy fees from Gambro Pty Ltd & Baxter Pty Ltd, for consultation regarding acute dialysis and fluid market. An Honorarium has been provided by BBraun Pty Ltd for consultation regarding fluid management, Gambro Pty Ltd additionally paid for R Bellomo travel to a dialysis meeting.

K. Salamon has no financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

J. Woods has no financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
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