PREVENTION OF ACUTE KIDNEY INJURY AND PROTECTION OF RENAL FUNCTION IN THE INTENSIVE CARE UNIT: UPDATE 2017

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INTRODUCTION

1

AKI affects up to 50% of critically ill patients and is independently associated with both short and long-term morbidity and mortality.

2

The recent AKI-EPI study demonstrates that the most frequent causes of AKI in the critically ill are sepsis and hypovolemia followed by nephrotoxic agents.

METHODOLOGY: SYSTEMATIC REVIEW USING THE FOLLOWING DATABASES

- 1.MEDLINE (1966 through March 2017)
- 2.EMBASE (1980 through March 2017)
- 3.CINAHL (1982 through March 2017)
- 4.Web of Science (1955 through March 2017)
- 5.PubMed/ PubMed CENTRAL to identify key studies, preferably randomized (placebo) controlled trials (RCT) and meta-analyses, addressing strategies to prevent AKI in adult critically ill patients.

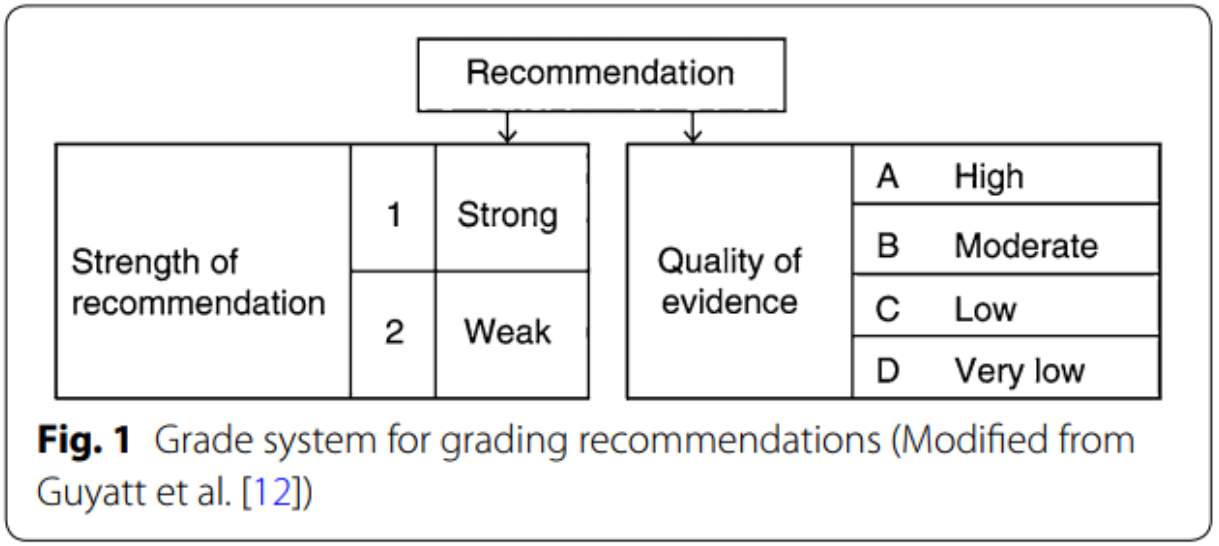

Fig. 1 Grade system for grading recommendations (Modified from Guyatt et al. [12])

Table 1 Criteria for best practice statements (Modified from Guyatt et al. [14])

	Criteria for best practice statements
1	Is the statement clear and actionable?
2	Is the message necessary?
3	Is the net benefit (or harm) unequivocal?
4	Is the evidence difficult to collect and summarize?
5	Is the rationale explicit?
6	Is this better to be formally GRADEd?

GRADE Gradings of Recommendations, Assessment, Development, and Evaluation

VOLUME EXPANSION

VOLUME EXPANSION RECOMMENDATION

1. We recommend controlled fluid resuscitation in volume depletion, while, however, avoiding volume overload (***Grade 1C***).
2. We recommend against the use of starches (***Grade 1A***) as harm has been shown and suggest not using Gelatine or Dextrans for fluid resuscitation (Grade 2C).
3. We recommend correction of hypovolemia/dehydration using isotonic crystalloids in patients receiving intravascular contrast media (***Grade 1B***).

VOLUME EXPANSION RECOMMENDATION

4. We recommend regular monitoring of chloride levels and acid–base status in situations where chloride rich solutions are used (BPS).

5. We suggest the use of balanced crystalloids for large volume resuscitation (Grade 2C).

6. We suggest using human serum albumin if a colloid is deemed necessary for the treatment of patients with septic shock (Grade 2C).

VOLUME EXPANSION RECOMMENDATION

7. We suggest prophylactic volume expansion with crystalloids to prevent AKI by certain drugs (specified below) (BPS).

8. We suggest not delaying urgent contrast-enhanced investigations or interventions for potential preventative measures (BPS).

RATIONALE

- Volume replacement should be performed in a controlled, monitored fashion.
- Injudicious use of fluids carries its own inherent risks and may even contribute to AKI by increasing renal interstitial edema and renal parenchymal pressure.
- Goal-directed therapy including the use of central venous pressure (CVP) as a resuscitation target has not been shown to prevent AKI in sepsis.

*Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, Yearly DM, Huang DT, Angus DC, ProCESS and ProGReSS-AKI Investigators (**2016**) The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. **Am J Respir Crit Care Med** 193:281–287*

RATIONALE

- Isotonic crystalloids represent the mainstay for correcting extracellular volume depletion with the caveat that hyperchloremia is prevented to reduce potential renal vasoconstriction.
- Compared to crystalloids, colloids theoretically result in a greater plasma expansion.

*Chowdhury AH, Cox EF, Francis ST, Lobo DN (**2012**) A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. **Ann Surg** 256:18–24*

RATIONALE

- Large volume replacement with colloids alone risks hyper-oncotic impairment of glomerular filtration and osmotic tubular damage.
- Human albumin is the only naturally occurring colloid and may appear attractive in hypo-oncotic hypovolemia. It does increase the response to diuretics in patients with hypoalbuminemia, has no negative effects on kidney function, is safe but can be costly.

1. *Wiedermann CJ, Dunzendorfer S, Gaioni LU, Zaraca F, Joannidis M (**2010**) Hyperoncotic colloids and acute kidney injury: a meta-analysis of randomized trials. **Crit Care** 14:R191*
2. *Wiedermann CJ, Joannidis M (**2015**) Nephroprotective potential of human albumin infusion: a narrative review. **Gastroenterol Res Pract** 2015:912839*

CLINICAL STUDIES

- Pre-operative volume expansion failed to reduce the incidence of post-operative AKI in 328 patients undergoing cardiac surgery.

*Serrano AB, Candela-Toha AM, Zamora J, Vera J, Muriel A, Del Rey JM, Liano F (**2016**) Preoperative hydration with 0.9% normal saline to prevent acute kidney injury after major elective open abdominal surgery: a randomized controlled trial. **Eur J Anaesthesiol** 33:436–443*

- A recent pilot RCT in sepsis could demonstrate that a volume-restrictive fluid protocol can reduced the incidence of AKI (RR 0.32; 95% CI 0.32–0.96).

*Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettila V, Aaen A, Lodahl D, Berthelsen RE, Christensen H, Madsen MB, Winkel P, Wetterslev J, Perner A, **CLASSIC Trial Group**; Scandinavian Critical Care Trials Group (**2016**) Restricting volumes of resuscitation fuid in adults with septic shock after initial management: the CLASSIC randomized, parallel-group, multicenter feasibility trial. **Intensive Care Med** 42:1695–1705*

CLINICAL STUDIES

- Observational studies suggest an increased risk of AKI, RRT and mortality associated with the use of large volumes of 0.9% NaCl as compared to so-called balanced solutions where chloride is partially replaced by another metabolizable anion.

1. *Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M (**2012**) Associa- tion between a chloride-liberal vs chloride-restrictive intravenous fuid administration strategy and kidney injury in critically ill adults. **JAMA** 308:1566–1572*
2. *Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR (**2014**) Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. **Intensive Care Med** 40:1897–1905*
3. *Kellum JA, Lameire N, **KDIGO AKI Guideline** Work Group (**2013**) Diag- nosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). **Crit Care** 17:204*

CLINICAL STUDIES

- An RCT comparing saline to a balanced solution (Plasmalyte®) in 2278 patients treated in four ICUs failed to show any superiority of balanced crystalloids regarding renal outcomes. *(multiple limitation in data studied)*
- Multiple-crossover ***SALT trial*** comparing saline to a balanced solution in 974 critically ill adults, only modest volumes were used, but increased rates of AKI were found in the normal saline group if larger volumes were administered.

*Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED, Wang L, Byrne DW, Shaw AD, Bernard GR, Rice TW, SALT Investigators and the Pragmatic Critical Care Research Group (**2017**) Balanced crystal- loids versus saline in the intensive care unit: **the SALT randomized trial**. **Am J Respir Crit Care Med**.*

CLINICAL STUDIES

- Large RCTs have substantiated the increased risk of AKI and RRT with use of starches particularly in sepsis, where they also lead to increased mortality.

1. *Myburgh JA, et.al, CHEST Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group (**2012**) Hydroxyethyl starch or saline for fluid resuscitation in intensive care. **N Engl J Med** 367:1901–1911*
2. *Brunkhorst FM, et.al, German Competence Net- work Sepsis (SepNet) (**2008**) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. **N Engl J Med** 358:125–139*
3. *Perner A, et.al, 6S Trial Group, Scandinavian Critical Care Trials Group (**2012**) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. **N Engl J Med** 367:124–134*

CLINICAL STUDIES

- In contrast to artificial colloids, the administration of albumin appears to be safe for the kidney.
- In **the ALBIOS trial** the use of hyper-oncotic (20%) albumin showed no effect on AKI or need for RRT in severe sepsis.
- A post hoc analysis of the ALBIOS trial showed survival benefit in septic shock confirmed by meta-analyses.

Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L, ***ALBIOS Study*** *Investigators (****2014****) Albumin replacement in patients with severe sepsis or septic shock.* ***N Engl J Med*** *370:1412–1421*

CLINICAL STUDIES

- Prophylactic volume expansion is the mainstay of all recommendations to prevent contrast-associated AKI and is based on several randomized controlled studies performed in non-critically ill patient. *(traditional)*
- In the most recent propensity-matched cohort study, IV contrast was not associated with an increased risk of AKI or dialysis, but a subgroup with pre-CT eGFR of at most 45 ml/min/1.73 m2 showed an increased risk of dialysis.

*Ehrmann S, Quartin A, Hobbs BP, Robert-Edan V, Cely C, Bell C, Lyons G, Pham T, Schein R, Geng Y, Lakhal K, Ng CS (**2017**) Contrast-associated acute kidney injury in the critically ill: systematic review and Bayesian meta-analysis. **Intensive Care Med**.*

DIURETICS RECOMMENDATIONS

1. We recommend against loop diuretics given solely for the prevention of acute kidney injury (***Grade 1B***).
2. We suggest using diuretics to control or avoid fluid overload in patients that are diuretic-responsive (Grade 2D).

CLINICAL STUDIES

- To date 4 RCTs have examined the role of diuretics in established renal failure in the ICU and showed no demonstrable improvements in clinically relevant outcomes, such as recovery of renal function or mortality.
- 3 meta-analyses confirmed that the use of diuretics in established AKI did not alter outcome but carried a significant risk of side effects such as hearing loss.

OTHERS RECOMMENDATION

VASOPRESSORS RECOMMENDATIONS

- We recommend titrating vasopressors to a mean arterial pressure (MAP) of 65–70 mmHg (***Grade 1B***) rather than a higher MAP target (80–85 mmHg) in patients with septic shock.
- However, for patients with chronic hypertension we recommend aiming for a higher target (80–85 mmHg) for renal protection in septic shock (***Grade 1C***).

VASOPRESSORS RECOMMENDATIONS

- We recommend lowering systolic pressure to 140–190 mmHg rather than to 110-139 mmHg in patients with acute cerebral hemorrhage with severe admission hypertension (***Grade 1C***).
- If vasopressors are needed for treatment of hypotension, we recommend norepinephrine (along with correction of hypovolemia) as the first-choice vasopressor to protect kidney function (Grade 1B) and suggest vasopressin in patients with vasoplegic shock after cardiac surgery (Grade 2C).

CLINICAL STUDIES

- A large RCT in patients with acute cerebral hemorrhage with severe hypertension on admission, patients were randomized to SBP target of 110–139 or 140–179 mmHg.
- The primary endpoint (death or disability) was not different between groups.
- However, the rate of serious renal adverse events was higher in the lower target group (9% vs. 4%, p = 0.002)

*Qureshi AI, Palesch YY, Suarez JI (**2016**) Intensive blood-pressure lowering in cerebral hemorrhage. **N Eng J Med** 375:e48*

CLINICAL STUDIES

- A large RCT comparing dopamine to norepinephrine as initial vasopressor in patients with shock found no difference in mortality.
- However, norepinephrine was associated with less tachycardia and was superior regarding survival in cardiogenic shock patients.
- In addition, there was a trend towards more RRT-free days through day 28 in the norepinephrine group

*De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL, SOAP II Investigators (**2010**) Comparison of dopamine and norepinephrine in the treatment of shock. **N Engl J Med** 362:779–789*

USE OF VASODILATORS RECOMMENDATIONS

- We recommend against low-dose dopamine for protection against AKI (***Grade 1A***).
- We recommend not using levosimendan for renal protection in patients with sepsis (***Grade 1B***) and recommend against its use for renal protection in cardiac surgery patients with poor preoperative left ventricular function or needing postoperative hemodynamic support (***Grade 1B***).
- We suggest not using fenoldopam or natriuretic peptides for renal protection in critically ill or cardiovascular surgery patients at risk of AKI (Grade 2B).

CLINICAL STUDIES

- Low-dose or 'renal' dose dopamine has been advocated in the past to prevent selective renal vasoconstriction.
- Several meta-analyses have concluded that 'renal-dose' dopamine has no benefit in either preventing or ameliorating AKI in the critically ill.

1. *Friedrich JO, Adhikari N, Herridge MS, Beyene J (**2005**) **Meta-analysis**: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. **Ann Intern Med** 142:510–524*
2. *Karthik S, Lisbon A (**2006**) Low-dose dopamine in the intensive care unit. Semin Dial 19:465–471*
3. *Holmes CL, Walley KR (**2003**) Bad medicine: low-dose dopamine in the ICU. Chest 123:1266–1275*

HORMONAL MANIPULATION RECOMMENDATIONS

1. We suggest targeting a blood glucose level at least below 180 mg/dL (10 mmol/l) for the prevention of hyperglycemic kidney damage in the general ICU population (Grade 2B).
2. We suggest not using erythropoietin (Grade 2B) or steroids (Grade 2B) for prevention of acute kidney injury

CLINICAL STUDIES

- A large prospective RCT in 1548 surgical ICU patients compared tight glucose control with insulin (target blood glucose 80–110 mg/dL) to standard care (insulin when blood glucose is >200 mg/dL resulting in a mean blood glucose of 150–160 mg/dL) and showed not only an improved survival rate but also a 41% reduction in AKI requiring RRT.

*van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R (**2001**) Intensive insulin therapy in critically ill patients. **N Engl J Med** 345:1359–1367*

CLINICAL STUDIES

- Because of the risk of hypoglycemia, current guidelines suggest more moderate blood glucose targets (less than 180 mg/dL, less than 150 mg/dl, 140–180 mg/dL) in critically ill patients, although these targets have not been formally compared with tolerating hyperglycemia.

METABOLIC INTERVENTIONS RECOMMENDATIONS

- We recommend not using high-dose IV selenium for renal protection in critically ill patients (1B).
- We suggest not using N-acetylcysteine to prevent contrast-associated AKI in critically ill patients because of conflicting results and possible adverse effects (Grade 2B).
- We suggest that all patients with or at risk of acute kidney injury have adequate nutritional support preferably through the enteral route (BPS).

CLINICAL STUDIES

- The latest meta-analysis assessing the efficacy of intravenous NAC only showed no reduction of AKI or RRT.

*Sun Z, Fu Q, Cao L, Jin W, Cheng L, Li Z (**2013**) Intravenous N-acetyl- cysteine for prevention of contrast-induced nephropathy: a meta-analysis of randomized, controlled trials. **PLoS One** 8:e55124*

- The ACT trial, currently the largest RCT including 2308 patients undergoing coronary and peripheral vascular angiography, failed to demonstrate any beneficial effect of NAC.

***ACT Investigators (2011)** Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). **Circulation** 124:1250–1259*

THANK YOU FOR YOUR ATTENTION