

## REVIEW ARTICLE

# Prevention of rhabdomyolysis-induced acute kidney injury – A DASAIM/DSIT clinical practice guideline

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**Background:** Rhabdomyolysis-induced acute kidney injury (AKI) is a common and serious condition. We aimed to summarise the available evidence on this topic and provide recommendations according to current standards for trustworthy guidelines.

**Methods:** This guideline was developed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The following preventive interventions were assessed: (a) fluids, (b) diuretics, (c) alkalinisation, (d) antioxidants, and (e) renal replacement therapy. Exclusively patient-important outcomes were assessed.

**Results:** We suggest using early rather than late fluid resuscitation (weak recommendation, very low quality of evidence). We suggest using crystalloids rather than colloids (weak recommendation, low quality of evidence). We suggest against routine use of loop diuretics as compared to none (weak recommendation, very low quality of evidence). We suggest against use of mannitol as compared to none (weak recommendation, very low quality of evidence). We suggest against routine use of any diuretic as compared to none (weak recommendation, very low quality of evidence). We suggest against routine use of alkalinisation with sodium bicarbonate as compared to none (weak recommendation, low quality of evidence). We suggest against the routine use of any alkalinisation as compared to none (weak recommendation, low quality of evidence). We suggest against routine use of renal replacement therapy as compared to none (weak recommendation, low quality of evidence). For the remaining PICO questions, no recommendations were issued.

**Conclusion:** The quantity and quality of evidence supporting preventive interventions for rhabdomyolysis-induced AKI is low/very low. We were able to issue eight weak recommendations and no strong recommendations.

## 1 | INTRODUCTION

Rhabdomyolysis was first described when Bywaters and Beall observed severe renal failure in crush injured victims excavated from the rubble during the London Blitz in 1941.<sup>1</sup> Postmortem examination of the kidneys showed eosinophilic casts in the loops of Henle and collecting tubules, which were later identified as myoglobin. The incidence of rhabdomyolysis is not known, but is estimated to account for 7% of all cases of AKI in the United States.<sup>2</sup> In the

intensive care unit (ICU) population, mortality varies from 22% when AKI is not present to 59% when it is, indicating that AKI is a serious condition associated with increased mortality.<sup>2</sup> Rhabdomyolysis has been defined in various ways in the literature.<sup>2</sup> Elevated creatine kinase (CK) concentration in plasma is perhaps the most commonly used diagnostic criterion, yet a firm cut-off value has not been established.<sup>3</sup> CK levels of 1000 U/L, exceeding five times the upper limit of normal, is often used for diagnosing rhabdomyolysis.<sup>4</sup> A level of 5000 U/L or greater is likely related to acute kidney injury (AKI),<sup>5</sup>

and need of renal replacement therapy (RRT) is rarely seen with CK levels below 40 000 U/L on admission.<sup>6,7</sup> Rhabdomyolysis can occur secondary to traumatic crush lesions, but also due to a wide spectrum of non-traumatic circumstances such as exertion, muscle hypoxia, genetic defects, infection, changes in body temperature, drugs, toxins, and idiopathic.<sup>2</sup> The pathogenesis of rhabdomyolysis-induced kidney injury is unknown, however deposition of myoglobin in the renal tubules and ischemic injury has been proposed.<sup>2</sup>

It has been suggested that early fluid resuscitation with restoration of the intravascular volume may prevent AKI.<sup>8</sup> Other supportive strategies, including diuretics, alkalisation, antioxidants, and renal replacement therapy have also been proposed.<sup>2</sup> Reviews and expert opinions on the topic are available<sup>4,9,10</sup> and treatment algorithms have been suggested.<sup>2,11</sup> However, treatment varies, clinical equipoise exists, and there is a lack of clinical practice guidelines.<sup>4</sup> Consequently, we aimed to summarise the available evidence on the prevention of rhabdomyolysis-induced AKI and to provide recommendations according to standards for trustworthy guidelines.<sup>12</sup>

## 2 | METHODS

### 2.1 | Process

In 2015, the Danish Society of Intensive Care Medicine (DSIT) and the Danish Society of Anesthesia and Intensive Care Medicine (DASAIM) established a working group which aimed to provide a trustworthy clinical practice guideline on the prevention of rhabdomyolysis-induced AKI in adult patients. The group included critical care specialists, nephrologists, and methodologists.

### 2.2 | Clinical research question

“How can rhabdomyolysis-induced AKI be prevented?”

### 2.3 | Population

The population of interest was adult patients with rhabdomyolysis (as defined in the original trials) in any in-hospital setting. We aimed to differentiate between trauma patients and non-trauma patients with rhabdomyolysis; however, due to the paucity of data, this was not possible.

### 2.4 | Interventions and comparators

We assessed the following interventions and comparators, as defined by the included trials (Table 1):

1. Fluid therapy
  - a early vs late
  - b liberal vs conservative
  - c crystalloids vs colloids
  - d balanced crystalloids vs isotonic saline
2. Diuretics
  - a loop-diuretics vs none
  - b mannitol vs none

- c any diuretics vs none
  - d mannitol vs loop-diuretics
3. Alkalisation
  - a sodium bicarbonate vs none
  - b acetazolamide vs none
  - c any alkalisation vs none
4. Antioxidants
  - a antioxidants vs none
5. Renal replacement therapy
  - a preventive renal replacement therapy (RRT) vs none
  - b intermittent hemodialysis (IHD) vs continuous renal replacement therapy (CRRT)
  - c filtration vs diffusion
  - d high cut-off membranes vs low cut-off membranes
  - e high flow RRT vs low flow RRT

## 2.5 | Outcomes

The following patient-important outcomes<sup>13</sup> were assessed at the time of longest follow-up: (a) Short-term mortality (0-90 days, including in-ICU and in-hospital), (b) Long-term mortality (>90 days), (c) Quality of life (as defined in the included trials), (d) Acute kidney injury (as defined in the included trials), (e) Use of RRT, (f) End stage renal disease (ESRD) or dialysis dependence, (g) Use of mechanical ventilation, (h) Hospital length of stay (LOS).

## 2.6 | Definitions

We defined rhabdomyolysis and rhabdomyolysis-induced acute kidney injury according to the included trials.

## 2.7 | Search strategy

We systematically searched PubMed (January 1966 to June 13th, 2018), Cochrane Library (Issue 6, June 2018), and Epistemonikos. We gave priority to systematic reviews of randomised clinical trials (RCTs) and RCTs, but no study designs were per se excluded. The search was updated June 13th, 2018. No language restriction was employed. We used the following search strategies:

1. PubMed: ‘rhabdomyolysis or crush syndrome’.
2. Cochrane Library: ‘rhabdomyolysis’ and ‘crush syndrome’ using the ‘Cochrane Review’ filter.
3. Epistemonikos: same search as for PubMed adapted and without filters.

## 2.8 | Statistics and GRADE

Specific clinical questions were formulated using the relevant patient population and/or clinical problem (P), the intervention (I) under scrutiny, the comparator (C), and patient-important outcomes (O) – PICO questions<sup>14</sup> (Table 1).

We were not able to summarise data quantitatively, due to the lack of data and clinical heterogeneity. We were, however, for some PICOs able to extrapolate from other relevant patient populations.

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for formulating clinical questions, assessing the quality of evidence, generating anticipated absolute effects and for moving from evidence to recommendations.<sup>12,15</sup> In brief, we downgraded the quality of evidence (our confidence in the effect-estimates) for an intervention for identified risks of bias (including lack of blinding, or early termination of studies), inconsistency (unexplained heterogeneity), indirectness (including other patient populations or use of surrogate outcomes), imprecision (wide confidence interval around the effect estimate) or publication bias. Accordingly, the quality of evidence was rated from “high” to “very low”. We used GradePro v. 3.5 to prepare summary of finding tables with anticipated relative and absolute effects for

the outcomes, together with our confidence in the effect-estimates (Appendix S1).

When moving from evidence to recommendations, four factors were considered and integrated: (a) benefits and harms, (b) quality of evidence, (c) values and preferences (of patients or their proxies), and (d) cost considerations. Strong recommendations were issued when almost all patients would choose the intervention, and weak recommendations were proposed when fully informed patients would choose different management strategies, and reflect a close call between benefits and harms, uncertainty regarding treatment effects, questionable cost-effectiveness, or variability in values and preferences.<sup>12</sup>

The wording “we recommend” was used if strong recommendations were made, and “we suggest” was used when weak recommendations were made.

All members of the working group agreed on the recommendations in this guideline.

**TABLE 1** Clinical research questions and PICO questions

Clinical question	PICO question		
	Population (P)	Intervention (I) and Comparator (C)	Outcomes (O)
How can rhabdomyolysis-induced AKI be prevented?	Adult patients with rhabdomyolysis	1. Fluid therapy	(1) Short term mortality (0-90 d, including in-ICU and in-hospital)
		(a) early vs late	(2) Long-term mortality (>90 d)
		(b) liberal vs conservative	(3) Quality of life (as defined in the included trials)
		(c) crystalloid vs colloid	(4) Acute renal injury (as defined in the included trials)
		(d) balanced crystalloids vs normal saline	(5) Use of renal replacement therapy (RRT)
		2. Diuretics	(6) End stage renal disease (ESRD) or dialysis dependence
		(a) loop-diuretics vs none	(7) Use of mechanical ventilation
		(b) mannitol vs none	(8) Hospital length of stay (LOS)
		(c) any diuretics vs none	
		(d) mannitol vs loop-diuretics	
		3. Alkalinisation	
		(a) sodium bicarbonate vs none	
		(b) acetazolamide vs none	
		(c) any alkalinisation vs none	
		4. Antioxidants	
		(a) antioxidants vs none	
		5. Renal replacement therapy	
		(a) preventive RRT vs none	
		(b) IHD vs CRRT	
		(c) hemofiltration vs diffusion	
(d) low vs high cut-off membranes			
(e) high vs low-flow dialysis			

**TABLE 2** Key recommendations and quality of evidence

Recommendations	Strength of the recommendation	Benefits and harms	Quality of evidence and reason for downgrading	Comments
<b>1. Fluid resuscitation in the prevention of rhabdomyolysis-induced AKI</b>				
We suggest using early rather than late fluid resuscitation	Weak	Possible reduced risk of mortality, AKI and use of RRT with early treatment	Very low due to risk of bias and imprecision	Fluid overload may be deleterious and should be avoided
Liberal vs conservative fluid administration	None			Hypovolemia as well as fluid overload may be deleterious and should be avoided
We suggest using crystalloids rather than colloids	Weak	The harm associated with some colloids in general ICU patients, cautions use in other patients, including patients at risk of rhabdomyolysis-induced renal injury	Low due to indirectness	No data available for this population; data extrapolated from general ICU patients
Balanced crystalloids vs normal saline	None			No data available for this population; no difference in AKI between groups in general ICU patients
<b>2. Diuretics in the prevention of rhabdomyolysis-induced AKI</b>				
We suggest against routine use of loop diuretics as compared to none	Weak	No difference in outcomes in the relevant population. Possible increased risk of ototoxicity in critically ill patients in general	Low due to risk of indirectness	Loop-diuretics may be considered in fluid resuscitated patients to prevent overhydration, especially in patients with ARDS
We suggest against the use of mannitol as compared to none	Weak	No difference in the predefined outcomes, however the risk of electrolyte disorders, osmotic diuresis causing hypovolemia, and osmotic nephrosis warrants caution	Very low due to risk of indirectness	Studies in rhabdomyolysis patients used a combination of balanced salt solution, mannitol and bicarbonate
We suggest against the use of any diuretics as compared to none	Weak		Low due to risk of indirectness	Any diuretics may be considered in fluid resuscitated patients to prevent overhydration, especially in patients with ARDS
Mannitol vs loop diuretics	None			No relevant data in the population of interest available
<b>3. Alkalinisation in the prevention of rhabdomyolysis-induced AKI</b>				
We suggest against the routine use of alkalinisation with sodium bicarbonate as compared to none	Weak	No difference in the predefined outcomes, however, the risk of intracellular acidosis and hypernatremia warrants caution	Low due to indirectness	Alkalinization may be considered in patients with severe metabolic acidosis. Studies used a combination of balanced salt solution, mannitol and bicarbonate
Acetazolamide vs none	None			No relevant data in the population of interest available
We suggest against the routine use of any alkalinisation as compared to none to prevent rhabdomyolysis-induced AKI	Weak		Low due to indirectness	Alkalinization may be considered in patients with severe metabolic acidosis

(Continues)

TABLE 2 (Continued)

Recommendations	Strength of the recommendation	Benefits and harms	Quality of evidence and reason for downgrading	Comments
4. Antioxidant therapy in the prevention of rhabdomyolysis-induced AKI				
We suggest against the routine use of antioxidants as compared to none	Weak		Low due to indirectness	No relevant data in the population of interest available; no difference in patient-important outcome measures in general ICU patients
5. Dialysis in the prevention of rhabdomyolysis-induced AKI				
We suggest against the routine use of renal replacement therapy as compared to none	Weak	No difference in patient-important outcomes, however, the risk of complications related to vascular access warrants caution. No established association between clearing of myoglobin and improved outcome have been found	Low due to risk of bias and imprecision	Renal replacement therapy may be considered in patients with life-threatening changes in fluid, electrolyte, or acid-base balance
CRRT vs IHD	None			No data available for this population; no difference in patient-important outcome measures in general ICU patients
Filtration vs Diffusion	None			No relevant data in the population of interest available
Low vs high cut-off membranes	None			No relevant data in the population of interest available
High vs low flow dialysis	None			No relevant data in the population of interest available

We followed the standards for preparing and reporting trustworthy clinical practice guidelines through use of the GRADE system, management of intellectual and financial conflicts of interest on a recommendation per recommendation basis, a peer review process, and a plan for updating of recommendations. We did not include patient representatives or nurses in the guideline process.

### 3 | RESULTS

The results and recommendations based on the PICOs are presented in Table 2 and in the summary of findings tables (Appendix S1).

#### 3.1 | Fluid resuscitation in the prevention of rhabdomyolysis-induced AKI

1. We suggest using early rather than late fluid resuscitation to prevent rhabdomyolysis-induced AKI (weak recommendation, very low quality of evidence).

No RCTs or systematic reviews reporting patient-important outcome measures were available in our predefined population. Three observational studies found lower short-term mortality in the group receiving early fluids,<sup>16-18</sup> and four studies found a lower incidence of AKI and/or need of RRT.<sup>16-19</sup> No other outcome measures of interest have been assessed.

The quality of evidence was downgraded due to risk of bias and imprecision.

2. Liberal vs conservative fluid administration to prevent rhabdomyolysis-induced AKI: no suggestion/recommendation.

No RCTs or systematic reviews reporting patient-important outcomes were available in our predefined population. Two observational studies found a lower incidence of AKI in the group treated with liberal fluid resuscitation,<sup>20,21</sup> whereas one observational study found a higher incidence of AKI in the group treated with liberal fluid resuscitation.<sup>22</sup> No other outcome measures of interest have been assessed. Due to lack of data, conflicting results, and equipoise in critically ill patients in general, we refrain from any recommendation/suggestion.

3. We suggest using crystalloids rather than colloids to prevent rhabdomyolysis-induced AKI (weak recommendation, low quality of evidence).

No RCTs, systematic reviews, or observational studies on the use of colloids vs crystalloids in patients with rhabdomyolysis were available in our predefined population. A recent systematic review in critically ill patients in general found increased risk of mortality, acute kidney injury, and bleeding from hydroxyethyl starch (HES) vs crystalloids, and no benefit from other colloids vs crystalloids (moderate quality of evidence).<sup>23</sup>

The quality of evidence was downgraded due to indirectness (extrapolation from critically ill patients in general).

4. Balanced crystalloids vs isotonic saline to prevent rhabdomyolysis-induced AKI: no recommendation/suggestion.

No RCTs, systematic reviews, or observational studies reporting patient-important outcome measures were available in our predefined population. A recent large cluster-randomised controlled trial on buffered crystalloid solutions vs saline in critically ill patients (SPLIT trial) showed no reduction in the risk of AKI between treatment groups.<sup>24</sup> In the SMART trial, critically ill adults randomised to balanced crystalloids as compared to normal saline resulted in a lower rate of the composite outcome of death from any cause, renal-replacement therapy, or persistent renal dysfunction.<sup>25</sup> In the SALT-ED trial, non-critically ill adults in the emergency department treated with balanced crystalloids experienced fewer major adverse kidney events within 30 days, as compared to patients treated with normal saline.<sup>26</sup> There was however no difference in the primary outcome measure hospital-free days.<sup>26</sup> Due to conflicting results and equipoise, we refrain from any recommendation/suggestion.

#### 3.2 | Diuretics in the prevention of rhabdomyolysis-induced renal injury

1. We suggest against routine use of loop diuretics as compared to none to prevent rhabdomyolysis-induced AKI (weak recommendation, low quality of evidence).

No RCTs or systematic reviews reporting patient-important outcomes were identified in our predefined population. One observational study in earthquake victims with rhabdomyolysis (n = 495), found no difference in short-term mortality or acute kidney injury.<sup>27</sup> Furthermore, two systematic reviews of RCTs in patients with acute kidney injury of any cause, did not find any beneficial effect of treatment or prevention with loop-diuretics, but they found increased risk of harm, including ototoxicity (moderate quality of evidence).<sup>28,29</sup> This warrants caution in other patient populations, including patients with rhabdomyolysis.

The quality of evidence was downgraded due to indirectness (extrapolation from critically ill patients in general).

2. We suggest against the use of mannitol as compared to none to prevent rhabdomyolysis-induced AKI (weak recommendation, very low quality of evidence).

No RCTs or systematic reviews reporting patient-important outcomes were identified in our predefined population. Observational studies on the use of mannitol (often concomitant with alkalinisation) were identified, but differentiation of treatment groups regarding mannitol or not, and interpretation of exact relevant outcome data was not possible.<sup>30-36</sup> Importantly, a systematic review of RCTs suggests increased risk of AKI in patients undergoing contrast-induced

nephropathy receiving mannitol (low quality of evidence).<sup>37</sup> This warrants caution in other patient populations, including patients with rhabdomyolysis.

The quality of evidence was downgraded due to indirectness (extrapolation from patients at risk of contrast-induced nephropathy).

3. We suggest against the use of any diuretics as compared to none to prevent rhabdomyolysis-induced AKI (weak recommendation, low quality of evidence).

No RCTs, systematic reviews, or observational studies on any diuretics vs none were identified in our predefined population. Two systematic reviews of RCTs in patients with acute kidney injury of any cause, did not find any beneficial effect of treatment or prevention with loop-diuretics, but they found increased risk of harm, including ototoxicity (moderate quality of evidence).<sup>28,29</sup> This warrants caution in other patient populations, including patients with rhabdomyolysis.

The quality of evidence was downgraded due to indirectness (extrapolation from critically ill patients in general).

4. Mannitol vs loop diuretics to prevent rhabdomyolysis-induced AKI: no recommendation/suggestion.

No RCTs, systematic reviews, or observational studies on mannitol vs loop diuretics were identified in our predefined population. We did not identify other relevant patient populations to extrapolate from.

### 3.3 | Alkalinisation in the prevention of rhabdomyolysis-induced renal injury

1. We suggest against the routine use of alkalinisation with sodium bicarbonate as compared to none to prevent rhabdomyolysis-induced AKI (weak recommendation, low quality of evidence).

No RCTs, systematic reviews, or observational studies on alkalinisation compared to none were identified in our predefined population. A French multicenter RCT assessed sodium bicarbonate vs saline in the prevention of contrast-induced AKI in critically ill patients in general and found no difference in patient-important outcomes.<sup>38</sup> In the PRESERVE trial 5177 high-risk patients bound for angiography were randomised to 5 days of oral acetylcysteine and iv saline or intravenous bicarbonate using a 2-by-2 factorial design.<sup>39</sup> No difference in mortality, need for renal replacement therapy, or persistent decline in kidney function was found (moderate quality of evidence).

The quality of evidence was downgraded due to indirectness (extrapolation from another relevant patient population).

2. Acetazolamide vs none to prevent rhabdomyolysis-induced AKI: no recommendation/suggestion.

No RCTs, systematic reviews or observational studies on acetazolamide vs no acetazolamide in rhabdomyolysis-induced AKI reporting patient-important outcomes were identified in our predefined population. We did not identify other relevant patient populations to extrapolate from.

3. We suggest against the routine use of any alkalinisation as compared to none to prevent rhabdomyolysis-induced AKI (weak recommendation, low quality of evidence).

No RCTs, systematic reviews or observational studies on any alkalinisation vs none in rhabdomyolysis-induced AKI reporting patient-important outcomes were identified in our predefined population.

In the PRESERVE trial 5177 high-risk patients bound for angiography were randomised to 5 days of oral acetylcysteine and iv saline or intravenous bicarbonate using a 2-by-2 factorial design.<sup>39</sup> No difference in mortality, need for renal replacement therapy, or persistent decline in kidney function was found (moderate quality of evidence).

The quality of evidence was downgraded due to indirectness (extrapolation from another relevant patient population).

### 3.4 | Antioxidant therapy in the prevention of rhabdomyolysis-induced renal injury

1. We suggest against the use of antioxidants as compared to none to prevent rhabdomyolysis-induced AKI (weak recommendation, low quality of evidence).

No RCTs, systematic reviews or observational studies on antioxidant therapy vs none to prevent rhabdomyolysis-induced AKI reporting patient important outcomes were identified in our predefined population. Antioxidant therapy in the general ICU population is controversial with systematic reviews showing conflicting results.<sup>40,41</sup> In the PRESERVE trial 5177 high-risk patients bound for angiography were randomised to 5 days of oral acetylcysteine and iv saline or intravenous bicarbonate using a 2-by-2 factorial design.<sup>39</sup> No difference in mortality, need for renal replacement therapy, or persistent decline in kidney function was found (moderate quality of evidence).

The quality of evidence was downgraded due to indirectness (extrapolation from another relevant patient population).

### 3.5 | Renal replacement therapy in the prevention of rhabdomyolysis-induced renal injury

1. We suggest against the routine use of renal replacement therapy as compared to none to prevent rhabdomyolysis-induced AKI (weak recommendation and low quality of evidence).

A Cochrane review from 2014 evaluating the efficacy of CRRT for rhabdomyolysis (3 RCTs, 101 patients) assessed mortality, renal outcome, and hospital length of stay.<sup>10,42-44</sup> No statistically difference in mortality or adverse events was found, whereas a shorter hospital length of stay was suggested in the patients who received preventive CRRT.

The quality of evidence was downgraded due to risk of bias and imprecision.

2. CRRT vs IHD to prevent rhabdomyolysis-induced AKI: no recommendations/suggestion.

We found no RCTs, systematic reviews or observational studies with relevant outcomes that compared CRRT vs IHD to prevent rhabdomyolysis-induced AKI.

A systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in ICU patients in general did not find a definitive advantage for any RRT modality on short-term patient survival or dialysis dependence.<sup>45</sup> Consequently, we refrain from giving any recommendation/suggestion.

3. Filtration vs diffusion to prevent rhabdomyolysis-induced AKI: no recommendations/suggestion.

We found no RCTs, systematic reviews or observational studies with relevant outcomes that compared filtration vs diffusion to prevent rhabdomyolysis-induced AKI.

In a systematic review and meta-analysis of 19 RCTs (n = 540), there was no difference in clinical outcomes between patients undergoing hemofiltration vs hemodialysis.<sup>46</sup> Consequently, we refrain from giving any recommendation/suggestion.

4. Low vs high cut-off membranes to prevent rhabdomyolysis-induced AKI: no recommendations/suggestion.

We found no RCTs, systematic reviews or observational studies with relevant outcomes that compared filter types to prevent rhabdomyolysis-induced AKI. We did not identify studies with patient important outcomes from critically ill patients in general to extrapolate from.

5. High vs low flow dialysis to prevent rhabdomyolysis-induced AKI: no recommendations/suggestion.

We found no RCTs, systematic reviews or observational studies with relevant outcomes comparing intensity of dialysis to prevent rhabdomyolysis-induced AKI.

A recent Cochrane systematic review assessed the effect of different intensities of CRRT on mortality, kidney recovery, function, and adverse events among 3185 critically ill patients with AKI. No beneficial effect with intensive CRRT flows compared with less intensive therapy was found.<sup>47</sup> Two systematic reviews evaluating the effects of high volume hemofiltration (HVHF, effluent >50 mL/kg/h) compared with standard volume hemofiltration found insufficient evidence for a therapeutic benefit with routine use of

HVHF for septic AKI.<sup>48</sup> Consequently, we refrain from giving any recommendation/suggestion.

## 4 | DISCUSSION

This clinical practice guideline on prevention of rhabdomyolysis-induced AKI in adult patients has been prepared in accordance with GRADE<sup>12</sup> to inform readers about clinically relevant issues based on current best evidence, and to avoid advice based solely on expert opinion.

Providing evidence-based clinical practice recommendations for the prevention of rhabdomyolysis-induced AKI is challenging. First, there is no established definition of rhabdomyolysis, and the precise pathophysiology may differ depending on the cause of the condition.<sup>2</sup> Second, the vast majority of evidence on the prevention of rhabdomyolysis-induced AKI derives from animal studies. Third, the few human studies, which have been conducted, suffer from high risk of bias, and assess several interventions at the same time,<sup>17,27</sup> making it difficult to discern treatment effects of a single intervention. Fourth, many of the studies assessed non-patient centered outcomes (surrogate outcomes), including myoglobin clearance or change in creatinine, which inherently results in inflated estimates.<sup>49</sup> Fifth, the definition of AKI was not uniform, ie based on the KDIGO (Kidney Disease: Improving Global Outcomes) criteria.<sup>3,50</sup> Finally, rhabdomyolysis in the critically ill population is often part of very complicated disease processes like trauma, sepsis, intoxications or cardiac failure.<sup>2</sup> Since the significance of clearing the bloodstream of myoglobin on patient-important outcomes, such as mortality or renal failure, is uncertain, it may well be that the treatment of the competing disease processes in the critically ill patient, is far more important than treating rhabdomyolysis in itself. Some patients with rhabdomyolysis may already have established renal failure on presentation, which make the effectiveness of clearance of myoglobin questionable—a challenge which has not been extensively discussed to date.

Fluid resuscitation has been recommended as perhaps the most important intervention in the prevention of AKI and RRT in patients with severe rhabdomyolysis.<sup>2</sup> This is, however, based on pathophysiological principles, experimental studies, and clinical experience with treatment of primarily trauma-induced rhabdomyolysis, including casualties from earthquakes.<sup>21,30,51</sup> This makes it difficult to make firm conclusions on timing and the required amount of fluids needed. Heterogeneous definitions of “early” vs “late” or “liberal” vs “conservative” and the use of co-interventions also challenges interpretation.<sup>16</sup> Furthermore, several of the studies have been performed in low income countries during natural disasters with a massive number of casualties, making translation to more modern high-income countries difficult.<sup>52</sup> Overt hypovolemia and dehydration is likely harmful,<sup>16,21,31</sup> and should probably be avoided, but recent evidence suggests that fluid overload may be equally or even more detrimental to organ perfusion than hypovolemia.<sup>53,54</sup> Bearing this in mind, initiation of fluid therapy as early as possible with the

goal of restoring normovolemia, yet not overhydrating the patient, seems reasonable.

The composition of the fluid used for repletion remains controversial.<sup>2,9</sup> Normal saline may worsen acidosis because of the high chloride content,<sup>55</sup> but balanced fluids may be inappropriate in hyperkalemic patients.<sup>11</sup> The choice of fluid has been far more thoroughly investigated in other patient populations<sup>24,25,56</sup> and should probably be based on the clinical context, ie sepsis, ongoing bleeding, traumatic brain injury, severe acidosis or hyperkalemia, rather than on the presence of rhabdomyolysis. Hydroxy-ethyl starch containing solutions have been shown to harm critically ill patients in general,<sup>57</sup> and it is therefore highly unlikely to be of any benefit in patients with rhabdomyolysis, and colloids have not been shown to be superior to crystalloids.<sup>57</sup>

The use of diuretics in fluid resuscitated patients is based on the hypothesis that increasing urinary output will reduce the risk of precipitation of myoglobin in the tubules.<sup>58</sup> However, this has not been confirmed in human studies/trials with assessment of patient-important outcomes. As with fluid treatment, a recurring challenge is that diuretics are often administered as part of a "bundle" and not protocolised as a single intervention.<sup>17,27</sup> Since two systematic reviews of patients with AKI treated with diuretics failed to show any benefit and suggested potential harm,<sup>28,29</sup> we suggest against the routine use of diuretics to prevent rhabdomyolysis. However, it seems reasonable to administer diuretics in patients where fluid resuscitation has resulted in fluid overload, as tissue oedema may contribute to organ dysfunction and may be detrimental.<sup>53,54</sup>

Alkalinisation therapy has been shown to have protective properties in animal models of rhabdomyolysis,<sup>59,60</sup> but human studies have failed to demonstrate its effectiveness in combination with mannitol and fluid resuscitation.<sup>5,61</sup> Furthermore, a large randomised trial failed to show any benefit in contrast-induced AKI.<sup>39</sup>

We found no studies on antioxidant therapy for patient with rhabdomyolysis looking at patient-important outcomes. Antioxidant therapy in the general ICU population is controversial with systematic reviews showing conflicting results.<sup>40,41</sup> Recently a non-randomised before and after study found an impressive reduction in hospital mortality from 40.4% to 8.5% using vitamin C, thiamine, and steroids in patients with sepsis,<sup>62</sup> but while these results are interesting, RCTs are necessary to confirm the results.

Extracorporeal removal of myoglobin by RRTs has been proposed as an effective preventive therapy for rhabdomyolysis-induced AKI.<sup>2</sup> Several studies have reported on myoglobin removal by different dialysis modalities, filters, and flow types, but whether this has any effect on mortality, ESRD, or any other patient important outcome is uncertain.<sup>63-65</sup> RCTs in patients with cast nephropathy with multiple myeloma have not found any effect on dialysis-dependence,<sup>67</sup> but the difference in patient populations makes extrapolation to rhabdomyolysis difficult. A Cochrane review by Zeng et al,<sup>10</sup> was unable to make firm conclusions owing to the poor methodological quality of the included studies. Due to the low quantity and quality of evidence on this question, we recommend against the routine use of RRT (a highly invasive

intervention) as preventive therapy in rhabdomyolysis-induced AKI.

The strengths of this guideline include use of the GRADE methodology to create a systematic, transparent, and trustworthy set of recommendations. Also, we were not able to identify other trustworthy clinical practice guidelines on the topic. Our guideline holds limitations too: Our guideline is based on a very limited number of human observational studies of poor methodological quality, often with the use of "bundle-therapies" including concomitant use of alkalinisation and mannitol, other diuretics or fluids.<sup>5,22,34,38</sup> This made it difficult to discern treatment effects of individual therapies. Of note, none of the combination-therapies were found to have any beneficial effect on any of the predefined patient-important outcomes. The poor quality of the existing evidence has forced us to extrapolate findings from other critically ill patient populations with different etiologies of renal failure. This should be taken into account when interpreting and reading the guideline. Furthermore, because of the paucity of data, we were not able to differentiate between traumatic or non-traumatic causes of rhabdomyolysis. This lack of evidence is striking, since rhabdomyolysis is not a rare occurrence. High quality RCTs, a uniform definition of rhabdomyolysis, and tools that predict the risk of developing AKI are highly needed. Finally, our guideline group did not include critical care nurses or other relevant stakeholders, including patient-groups, relatives, and representatives of regulatory bodies and hospital owners.

In conclusion, this clinical practice guideline provides transparent recommendations on the prevention of rhabdomyolysis-induced AKI in adult patients according to current standards for trustworthy guidelines.<sup>12</sup> We proposed eight weak recommendations, no strong recommendations, and for 11 questions we refrained from giving any recommendations, due to the lack of data.

## CONFLICT OF INTEREST

None.

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## REFERENCES

1. Bywaters EG, Beall D. Crush injuries with impairment of renal function. *Br Med J*. 1941;1(4185):427-432.
2. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med*. 2009;361(1):62-72.
3. Safari S, Yousefifard M, Hashemi B, et al. The value of serum creatine kinase in predicting the risk of rhabdomyolysis-induced acute kidney injury: a systematic review and meta-analysis. *Clin Exp Nephrol*. 2016;20(2):153-161.
4. Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. *Crit Care*. 2016;20(1):135.

5. Brown C, Rhee P, Chan L, Evans K, Demetriades D, Velmahos GC. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? *J Trauma*. 2004;56(6):1191-1196.
6. de Meijer AR, Fikkers BG, de Keijzer MH, van Engelen BG, Drenth JP. Serum creatine kinase as predictor of clinical course in rhabdomyolysis: a 5-year intensive care survey. *Intensive Care Med*. 2003;29(7):1121-1125.
7. McMahon GM, Zeng X, Waikar SS. A risk prediction score for kidney failure or mortality in rhabdomyolysis. *JAMA Intern Med*. 2013;173(19):1821-1828.
8. Chatzizisis YS, Misirli G, Hatzitolios AI, Giannoglou GD. The syndrome of rhabdomyolysis: complications and treatment. *Eur J Intern Med*. 2008;19(8):568-574.
9. Scharman EJ, Troutman WG. Prevention of kidney injury following rhabdomyolysis: a systematic review. *Ann Pharmacother*. 2013;47(1):90-105.
10. Zeng X, Zhang L, Wu T, Fu P. Continuous renal replacement therapy (CRRT) for rhabdomyolysis. *Cochrane Database Syst Rev*. 2014;6:CD008566.
11. Sever MS, Vanholder R. Disasters RoWGoRftMoCViM. Recommendation for the management of crush victims in mass disasters. *Nephrol Dial Transplant*. 2012;27(Suppl 1):i1-67.
12. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
13. Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *Eur J Anaesthesiol*. 2015;32(2):88-105.
14. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64(4):395-400.
15. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
16. Reis ND, Michaelson M. Crush injury to the lower limbs. Treatment of the local injury. *J Bone Joint Surg Am*. 1986;68(3):414-418.
17. Knottenbelt JD. Traumatic rhabdomyolysis from severe beating—experience of volume diuresis in 200 patients. *J Trauma*. 1994;37(2):214-219.
18. Donmez O, Meral A, Yavuz M, Durmaz O. Crush syndrome of children in the Marmara Earthquake, Turkey. *Pediatr Int*. 2001;43(6):678-682.
19. Zepeda-Orozco D, Ault BH, Jones DP. Factors associated with acute renal failure in children with rhabdomyolysis. *Pediatr Nephrol*. 2008;23(12):2281-2284.
20. Shimazu T, Yoshioka T, Nakata Y, et al. Fluid resuscitation and systemic complications in crush syndrome: 14 Hanshin-Awaji earthquake patients. *J Trauma*. 1997;42(4):641-646.
21. Oda J, Tanaka H, Yoshioka T, et al. Analysis of 372 patients with Crush syndrome caused by the Hanshin-Awaji earthquake. *J Trauma*. 1997;42(3):470-475; discussion 5-6.
22. Ward MM. Factors predictive of acute renal failure in rhabdomyolysis. *Arch Intern Med*. 1988;148(7):1553-1557.
23. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. 2013;2:CD000567.
24. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the Intensive Care Unit: the SPLIT randomized clinical trial. *JAMA*. 2015;314(16):1701-1710.
25. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378(9):829-839.
26. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med*. 2018;378(9):819-828.
27. Atef MR, Nadjafji I, Boroumand B, Rastegar A. Acute renal failure in earthquake victims in Iran: epidemiology and management. *Q J Med*. 1994;87(1):35-40.
28. Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. *BMJ*. 2006;333(7565):420.
29. Ho KM, Power BM. Benefits and risks of furosemide in acute kidney injury. *Anaesthesia*. 2010;65(3):283-293.
30. Gunal AI. Early and vigorous fluid resuscitation prevents acute renal failure in the crush victims of catastrophic earthquakes. *J Am Soc Nephrol*. 2004;15(7):1862-1867.
31. Michaelson M, Taitelman U, Bursztein S. Management of crush syndrome. *Resuscitation*. 1984;12(2):141-146.
32. Eneas JF, Schoenfeld PY, Humphreys MH. The effect of infusion of mannitol-sodium bicarbonate on the clinical course of myoglobinuria. *Arch Intern Med*. 1979;139(7):801-805.
33. Michaelson M, Taitelman U, Bshouty Z, Bar-Joseph G, Bursztein S. Crush syndrome: experience from the Lebanon War, 1982. *Isr J Med Sci*. 1984;20(4):305-307.
34. Ron D, Taitelman U, Michaelson M, Bar-Joseph G, Bursztein S, Better OS. Prevention of acute renal failure in traumatic rhabdomyolysis. *Arch Intern Med*. 1984;144(2):277-280.
35. Homsí E, Barreiro MF, Orlando JM, Higa EM. Prophylaxis of acute renal failure in patients with rhabdomyolysis. *Ren Fail*. 1997;19(2):283-288.
36. Altintepe L, Guney I, Tonbul Z, et al. Early and intensive fluid replacement prevents acute renal failure in the crush cases associated with spontaneous collapse of an apartment in Konya. *Ren Fail*. 2007;29(6):737-741.
37. Yang B, Xu J, Xu F, et al. Intravascular administration of mannitol for acute kidney injury prevention: a systematic review and meta-analysis. *PLoS ONE*. 2014;9(1):e85029.
38. Valette X, Desmeulles I, Savary B, et al. Sodium bicarbonate versus sodium chloride for preventing contrast-associated acute kidney injury in critically ill patients: a randomized controlled trial. *Crit Care Med*. 2017;45(4):637-644.
39. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med*. 2017;378:603-614.
40. Szakmany T, Hauser B, Radermacher P. N-acetylcysteine for sepsis and systemic inflammatory response in adults. *Cochrane Database Syst Rev*. 2012;9:CD006616.
41. Manzanares W, Dhaliwal R, Jiang X, Murch L, Heyland DK. Antioxidant micronutrients in the critically ill: a systematic review and meta-analysis. *Crit Care*. 2012;16(2):R66.
42. Dong W. The treatment effect of continuous venovenous hemofiltration on crush syndrome. *Lin Chuang Yi Xue [Clin Med]*. 2005;25:14-16.
43. Wang Z, Liu J. The efficacy of CAVHD for crush syndrome. *Hei Long Jiang Yi Yao Ke Xue [Heilongjiang Med Pharm]*. 2008;31(85).
44. Zeng L, Mi X, Zhang J, Li C. The efficacy of CVVH for acute kidney injury induced by rhabdomyolysis. *Si Chuan Yi Xue [Sichuan Med J]*. 2008;29:307-308.
45. Nash DM, Przech S, Wald R, O'Reilly D. Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. *J Crit Care*. 2017;41:138-144.
46. Friedrich JO, Wald R, Bagshaw SM, Burns KE, Adhikari NK. Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis. *Crit Care*. 2012;16(4):R146.

47. Fayad AI, Buamscha DG, Ciapponi A. Intensity of continuous renal replacement therapy for acute kidney injury. *Cochrane Database Syst Rev*. 2016;10:CD010613.
48. Lehner GF, Wiedermann CJ, Joannidis M. High-volume hemofiltration in critically ill patients: a systematic review and meta-analysis. *Minerva Anesthesiol*. 2014;80(5):595-609.
49. Ciani O, Buysse M, Garside R, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. *BMJ*. 2013;346:f457.
50. Ad-hoc working group of E, Fliser D, Laville M, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant*. 2012;27(12):4263-4272.
51. Iraj N, Saeed S, Mostafa H, et al. Prophylactic fluid therapy in crushed victims of Bam earthquake. *Am J Emerg Med*. 2011;29(7):738-742.
52. Schultz MJ, Dunser MW, Dondorp AM, et al. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. *Intensive Care Med*. 2017;43(5):612-624.
53. Hjortrup PB, Delaney A. Fluid management in the ICU: has the tide turned? *Intensive Care Med*. 2017;43(2):237-239.
54. Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or dereuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med*. 2017;43(2):155-170.
55. Cho YS, Lim H, Kim SH. Comparison of lactated Ringer's solution and 0.9% saline in the treatment of rhabdomyolysis induced by doxylamine intoxication. *Emerg Med J*. 2007;24(4):276-280.
56. Perner A, Juntila E, Haney M, et al. Scandinavian clinical practice guideline on choice of fluid in resuscitation of critically ill patients with acute circulatory failure. *Acta Anaesthesiol Scand*. 2015;59(3):274-285.
57. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev*. 2018;8:CD000567.
58. Oken DE, Arce ML, Wilson DR. Glycerol-induced hemoglobinuric acute renal failure in the rat. I. Micropuncture study of the development of oliguria. *J Clin Invest*. 1966;45(5):724-735.
59. Zager RA. Studies of mechanisms and protective maneuvers in myoglobinuric acute renal injury. *Lab Invest*. 1989;60(5):619-629.
60. Moore KP, Holt SG, Patel RP, et al. A causative role for redox cycling of myoglobin and its inhibition by alkalinization in the pathogenesis and treatment of rhabdomyolysis-induced renal failure. *J Biol Chem*. 1998;273(48):31731-31737.
61. Charra B, Hachimi A, Benslama A, Motaouakkil S. Does fluid resuscitation prevent acute renal failure in toxic rhabdomyolysis? *Ann Fr Anesth Reanim*. 2008;27(5):456-457.
62. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*. 2017;151(6):1229-1238.
63. Wakabayashi Y, Kikuno T, Ohwada T, Kikawada R. Rapid fall in blood myoglobin in massive rhabdomyolysis and acute renal failure. *Intensive Care Med*. 1994;20(2):109-112.
64. Peltonen S, Ahlstrom A, Kylavainio V, Honkanen E, Pettila V. The effect of combining intermittent hemodiafiltration with forced alkaline diuresis on plasma myoglobin in rhabdomyolysis. *Acta Anaesthesiol Scand*. 2007;51(5):553-558.
65. Mikkelsen TS, Toft P. Prognostic value, kinetics and effect of CVVHDF on serum of the myoglobin and creatine kinase in critically ill patients with rhabdomyolysis. *Acta Anaesthesiol Scand*. 2005;49(6):859-864.
66. Bridoux F, Carron PL, Pegourie B, et al. Effect of High-Cutoff Hemodialysis vs Conventional Hemodialysis on Hemodialysis Independence Among Patients With Myeloma Cast Nephropathy: A Randomized Clinical Trial. *JAMA*. 2017;318(21):2099-2110.
67. Hutchison CA, Cockwell P, Heyne N, et al. European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE); survival and renal outcomes. *J Am Soc Nephrol*. 2016;27. Abstract Edition (November 2016).

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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