Open access • Journal Article • DOI:10.1111/AAS.13308

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Published on: 01 May 2019 - Acta Anaesthesiologica Scandinavica (Wiley-Blackwell)

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Published in:
Acta Anaesthesiologica Scandinavica

DOI:
10.1111/aas.13308

Publication date:
2019

Document version:
Accepted manuscript

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Article type : Review

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

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/AAS.13308

Conflict of interest

Please see supplementary material 2

Funding

This guideline was not funded.

Running head

Prevention of rhabdomyolysis-induced acute kidney injury – a clinical practice guideline

Word count

Abstract

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: 1) fluids, 2) diuretics, 3) alkalinisation, 4) antioxidants, and 5) 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.

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. (1) 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. (2) 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 (2). Rhabdomyolysis has been defined in various ways in the literature. (2) 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. (3) CK levels of 1000 U/L, exceeding five times the upper limit of normal, is often used for diagnosing rhabdomyolysis. (4) A level of 5000 U/L or greater is likely related to acute kidney injury (AKI) (5), and need of renal replacement therapy (RRT) is rarely seen with CK levels below 40,000 U/L on admission. (6, 7) 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. (2) The pathogenesis of rhabdomyolysis-induced kidney injury is unknown, however deposition of myoglobin in the renal tubules and ischemic injury have been proposed. (2)

It has been suggested that early fluid resuscitation with restoration of the intravascular volume may prevent AKI. (8) Other supportive strategies, including diuretics, alkalinisation, antioxidants and renal replacement therapy have also been proposed. (2) Reviews and expert opinions on the topic are available (4, 9, 10) and treatment algorithms have been suggested. (2, 11) However, treatment varies, clinical equipoise exists, and there is a lack of clinical practice guidelines. (4) 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. (12)

Methods

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.

Clinical research question

"How can rhabdomyolysis-induced AKI be prevented?"

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.

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) 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 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

Outcomes

The following patient-important outcomes (13) were assessed at the time of longest follow-up: 1) Short term mortality (0-90 days, including in-ICU and in-hospital), 2) Long-term mortality (> 90 days), 3) Quality of life (as defined in the included trials), 4) Acute kidney injury (as defined in the included trials), 5) Use of RRT, 6) End stage renal disease (ESRD) or dialysis dependence, 7) Use of mechanical ventilation, 8) Hospital length of stay (LOS).

Definitions

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

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.

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 (14) (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. (12, 15) 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 (supplementary material 1).

When moving from evidence to recommendations, four factors were considered and integrated: 1) benefits and harms, 2) quality of evidence, 3) values and preferences (of patients or their proxies), and 4) 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 reflects a close call between benefits and harms, uncertainty regarding treatment effects, questionable cost-effectiveness, or variability in values and preferences. (12)

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.

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.

Results

The results and recommendations based on the PICOs are presented in Table 2 and in the summary of findings tables (Supplementary Material 1).

1. Fluid resuscitation in the prevention of rhabdomyolysis-induced AKI.

A) 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 (16-18), and four studies found a lower incidence of AKI and/or need of RRT. (16-19) No other outcome measures of interest have been assessed.

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

B) 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 (20, 21), whereas one observational study found a higher incidence of AKI in the group treated with liberal fluid resuscitation. (22) 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.

C) 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). (23)

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

D) 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-randomized 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. (24) 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. (25) 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. (26) There was however no difference in the primary outcome measure hospital-free days. (26) Due to conflicting results and equipoise, we refrain from any recommendation/suggestion.

2. Diuretics in the prevention of rhabdomyolysis-induced renal injury.

A) 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. (27) 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). (28, 29) 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).

B) 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. (30-36) Importantly, a systematic review of RCTs suggests increased risk of AKI in patients undergoing contrast-induced nephropathy receiving mannitol (low quality of evidence) . (37) 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)

C) 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). [28, 29] 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).

D) 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. Alkalinisation in the prevention of rhabdomyolysis-induced renal injury.

A) 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. (38) 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. (39) 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).

B) 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.

C) 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. (39) 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).

4. Antioxidant therapy in the prevention of rhabdomyolysis-induced renal injury.

A) 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. (40, 41) 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. (39) 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).

5. Renal replacement therapy in the prevention of rhabdomyolysis-induced renal injury.

A) 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. (10, 42-44) 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.

B) 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. (45) Consequently, we refrain from giving any recommendation/suggestion.

C) 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. (46) Consequently, we refrain from giving any recommendation/suggestion.

D) 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.

E) 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. (47) Two systematic reviews evaluating the effects of high volume hemofiltration (HVHF, effluent > 50 ml/kg/hour) compared with standard volume hemofiltration found insufficient evidence for a therapeutic benefit with routine use of HVHF for septic AKI. (48) Consequently, we refrain from giving any recommendation/suggestion.

Discussion

This clinical practice guideline on prevention of rhabdomyolysis-induced AKI in adult patients has been prepared in accordance with GRADE (12) 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. (2) 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, (17, 27) 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. (49) Fifth, the definition of AKI was not uniform, i.e. based on the KDIGO (Kidney Disease: Improving Global Outcomes) criteria. (3, 50) Finally, rhabdomyolysis in the critically ill population is often part of very complicated disease processes like trauma, sepsis, intoxications or cardiac failure. (2) 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. (2) This is however based on pathophysiological principles, experimental studies, and clinical experience with treatment of primarily trauma-induced rhabdomyolysis, including casualties from earthquakes. (21, 30, 51) 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. (16) 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. (52) Overt hypovolemia and dehydration is likely harmful, (16, 21, 31) and should probably be avoided, but recent evidence suggests that fluid overload may be equally or even more detrimental to organ perfusion than hypovolemia. (53, 54) 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. (2, 9) Normal saline may worsen acidosis because of the high chloride content, (55) but balanced fluids may be inappropriate in hyperkalemic patients. (11) The choice of fluid has been far more thoroughly investigated in other patient populations (24, 25, 56) and should probably be based on the clinical context, i.e. 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, (57) 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. (57)

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. (58) 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. (17, 27) Since two systematic reviews of patients with AKI treated with diuretics failed to show any benefit and suggested potential harm, (28, 29) we suggest against the routine use of diuretics to prevent rhabdomyolysis. However, it seems reasonable to administer diuretics in patients were fluid resuscitation has resulted in fluid overload, as tissue oedema may contribute to organ dysfunction and may be detrimental. (53, 54)

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

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. (40, 41) Recently a non-randomized 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, (62) 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. (2) 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. (63-65) RCTs in patients with cast nephropathy with multiple myeloma have not found any effect on dialysis-dependence, (66, 67) but the difference in patient populations makes extrapolation to rhabdomyolysis difficult. A Cochrane review by Zeng and co-workers, was unable to make firm conclusions owing to the poor methodological quality of the included studies. (10) 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. [5,22,34,38] 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. (12) We proposed eight weak recommendations, no strong recommendations, and for 11 questions we refrained from giving any recommendations, due to the lack of data.

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