Rhabdomyolysis & Acute kidney Injury

Samimagham HR .MD

Professor of Nephrology Of Hormozgan University of Medical Sciences

What is Rhabdomyolysis?

Rhabdomyolysis (rhabd/o, my/o, -lysis) literally means dissolution of striated muscle.

It is caused by the breakdown and necrosis of muscle tissue and the release of intracellular content into the blood stream.

It usually results from traumatic or non-traumatic injury to skeletal muscle.

Since skeletal muscle comprises about 40% of body mass, such an insult can result in the accumulation of cellular contents that could eventually overwhelm the underlying elimination mechanism

History

- The first ever description of rhabdomyolysis can be seen in some chapters of the Bible, more specifically in the Book of Exodus, when a population of Jews was exposed to certain toxic substances like hemlock herbs during their migration from Egypt.
- The classic description and the identification of the pathophysiological mechanism of myoglobinuric

AKI is based on the 1941 publication of Bywaters

Clinical Chemistry and Laboratory Medicine

during World War II

Etiology

Etiology of Rhabdomyolysis

Acquired	Genetic
Traumatic • Crush injuries • Compression • Electrical injury • Vascular or orthopedic surgery Coma/Prolonged immobilization Non-traumaticExertional • Strenuous activities • Seizures • Sickle cell trait • Exposure to extreme heat • Malignant hyperthermia • Neuroleptic Malignant Syndrome (NMS) Non-exertional • Alcohol • Drugs/Toxin • Infections • Electrolyte imbalance	Disorders of lipid metabolismDisorders of carbohydrate metabolism • McArdle's disease • Tarui's disease Mitochondrial disordersPentose phosphate pathwayPurine nucleoside cycleMyositis

Most Commonly Reported Drugs Causing Rhabdomyolysis

Medications	Illicit Drugs
• Lipid-lowering agents (statins, fibrates)	• Cocaine
• Psychiatric medications (antipsychotics like haloperidol, SSRIs, lithium, valproic acid)	• Amphetamines/Methamphetamines
• Antimicrobials (protease inhibitors, TMP-SMX, quinolones, amphotericin B)	• Hallucinogens
• Anesthetics/Paralytics (succinylcholine, propofol)	• Heroin
• Antihistamines	• LSD
• Others (sunitinib, erlotinib, narcotics, vasopressin, colchicine, glucocorticoids, aminocaproic acid)	

Note: list is not exhaustive

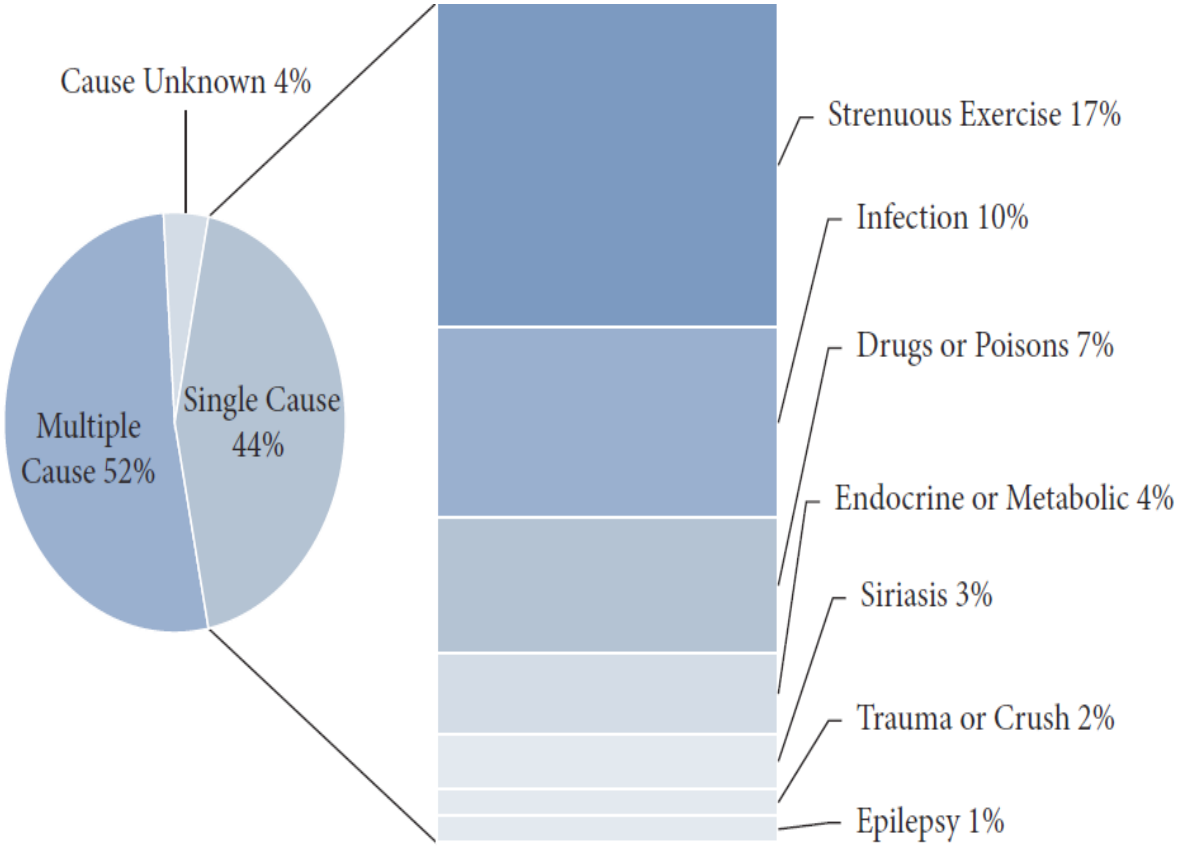
RIAKI

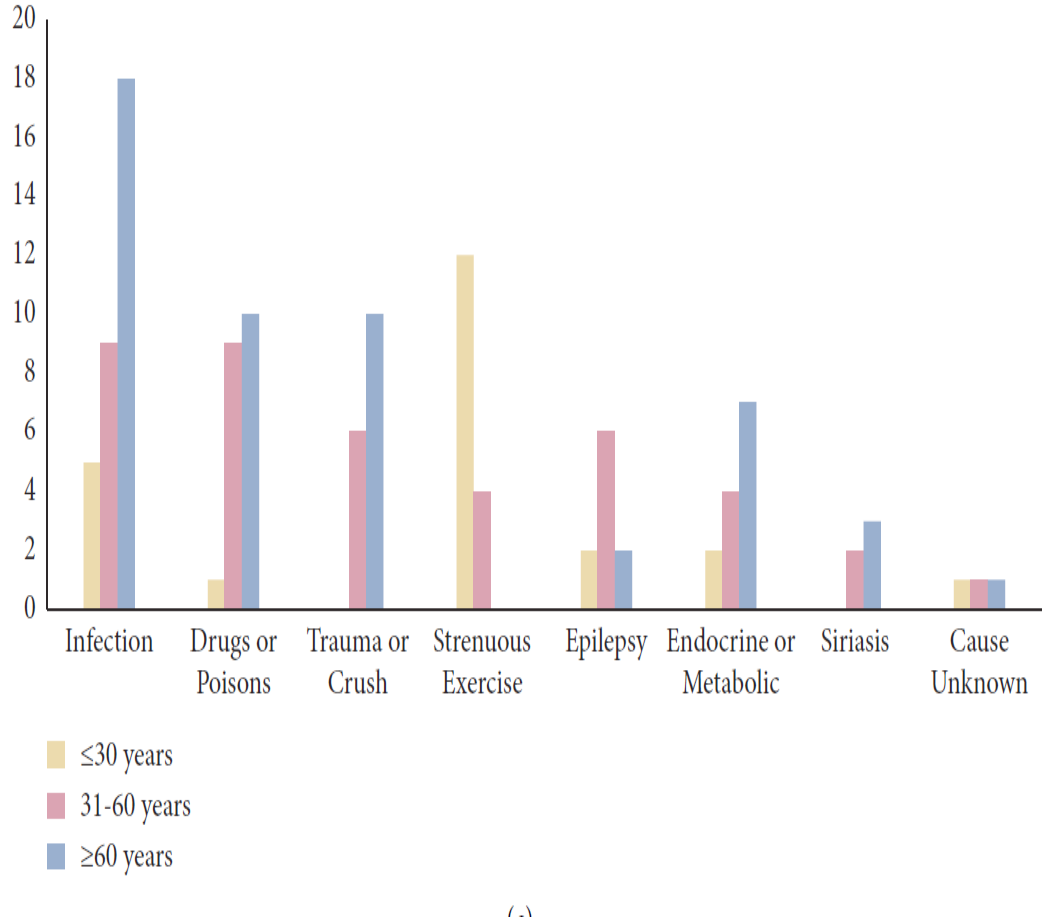
RIAKI, is a common complication affecting up to 46% of patients hospitalized and 80% of those requiring intensive care unit for rhabdomyolysis.

Even with excellent care, mortality is greater than15%.

The incidence of RIAKI has increased 10-fold in the last decade, fueled in part by popular interest in studio fitness training, such as CrossFit.

RIAKI is a significant comorbidity for injured soldiers who are 3 to 4


Cause Unknown 4%
Multiple Cause 52%
Single Cause 44%
Strenuous Exercise 17%
Infection 10%
Drugs or Poisons 7%
Endocrine or Metabolic 4%
Siriasis 3%
Trauma or Crush 2%
Epilepsy 1%


20
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Trauma or Crush
Strenuous Exercise
Epilepsy
Endocrine or Metabolic
Siriasis
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≤30 years
31-60 years
≥60 years

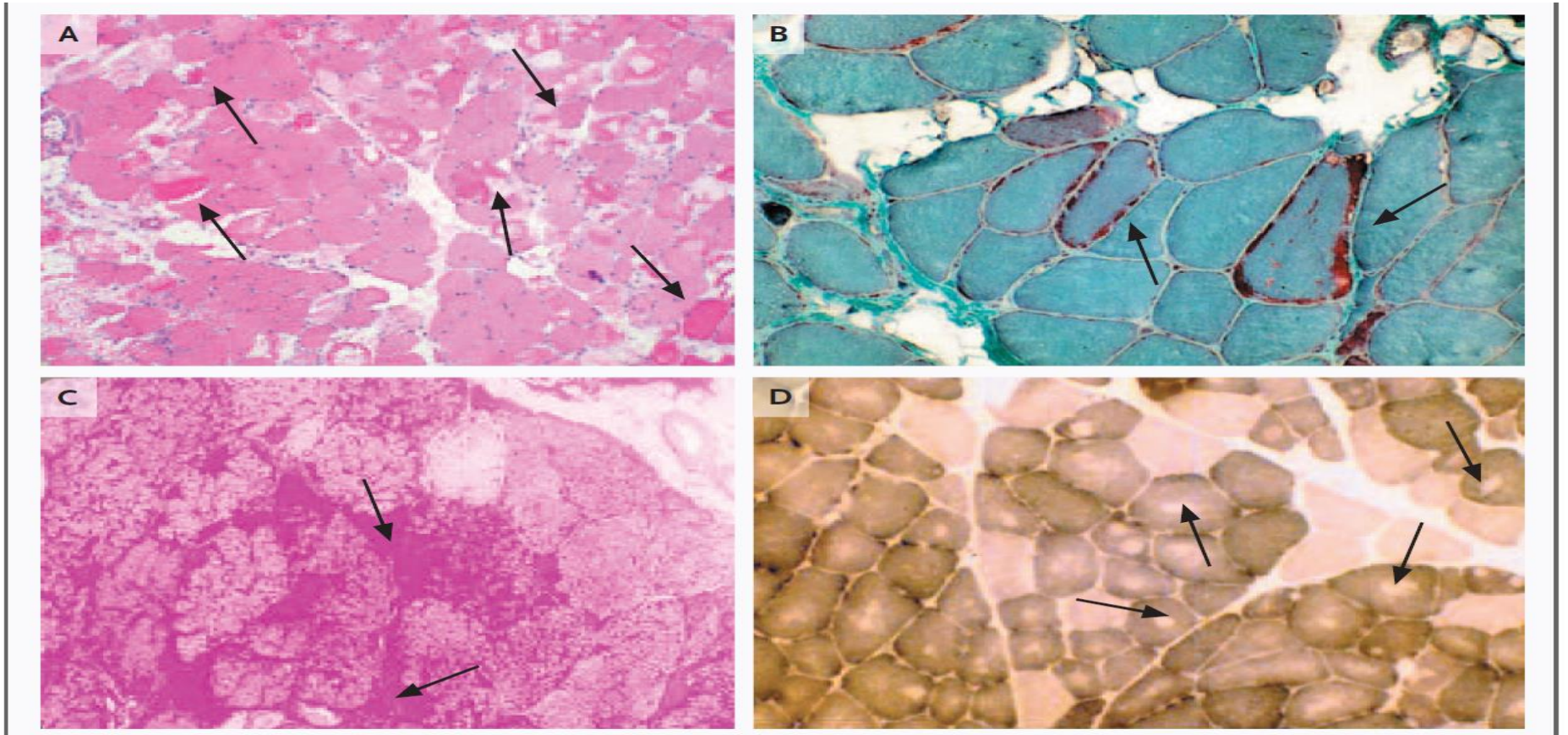
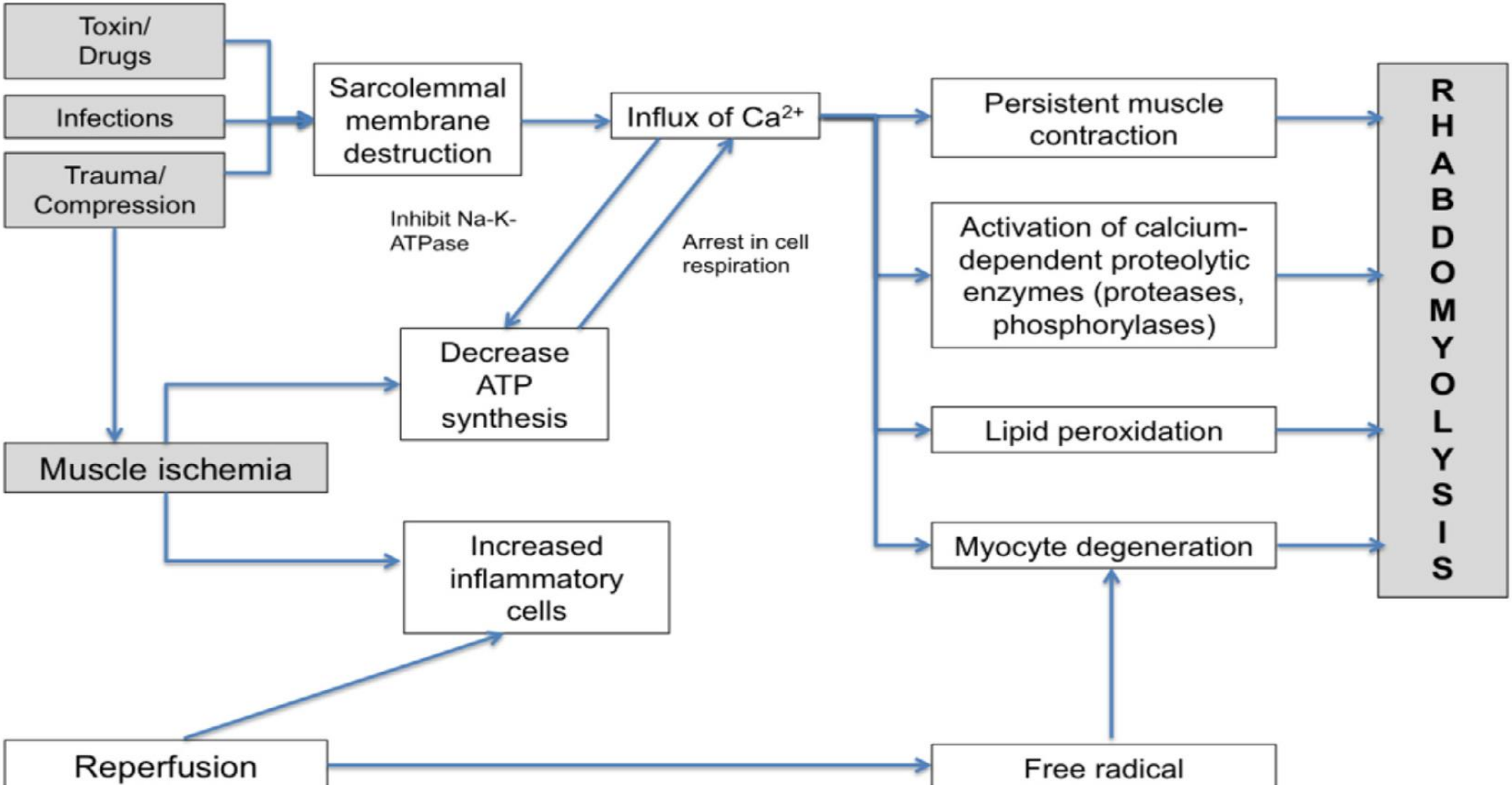
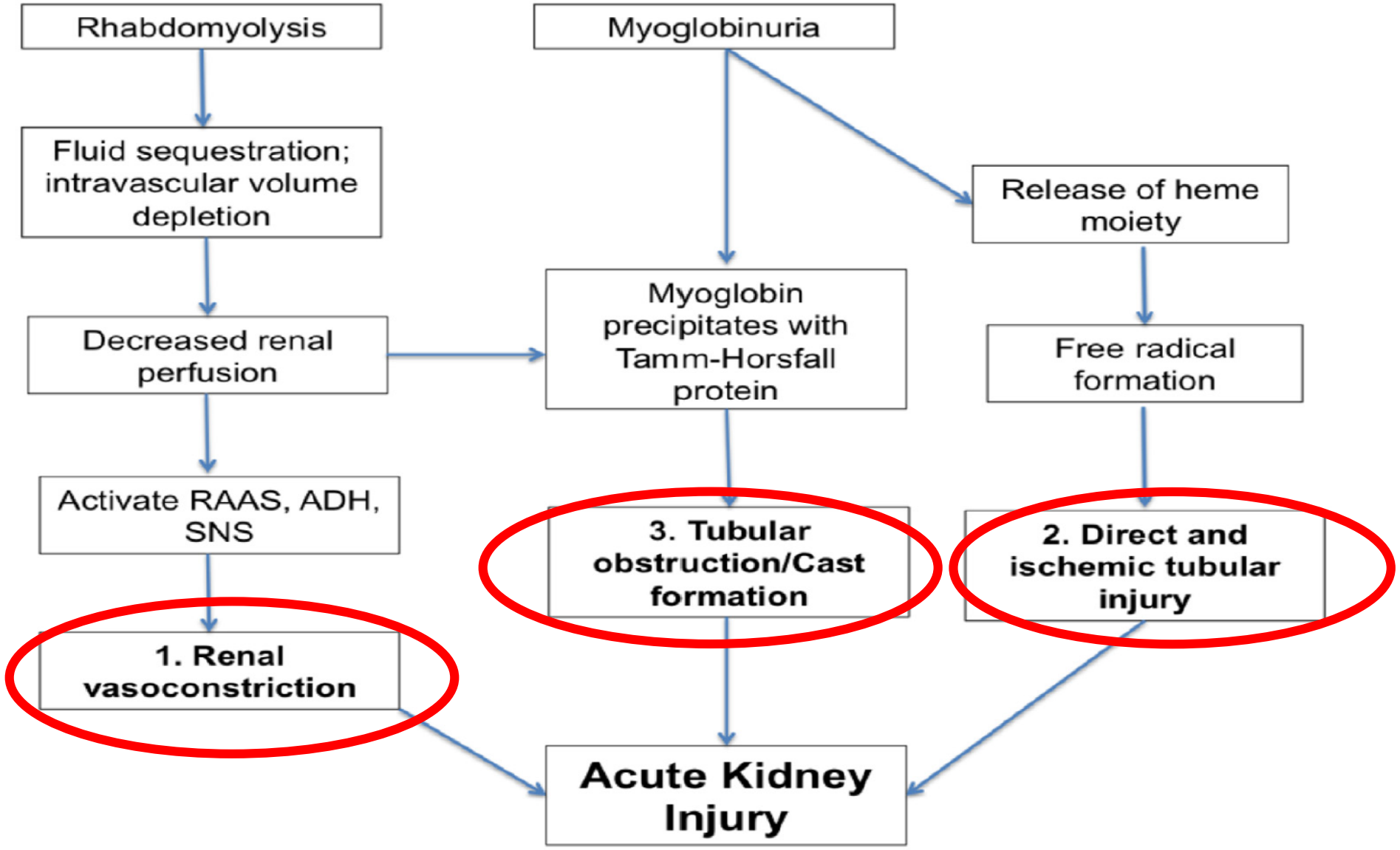


Figure 1. Histopathological Findings in Frozen Muscle-Tissue Specimens from Patients with Rhabdomyolysis.

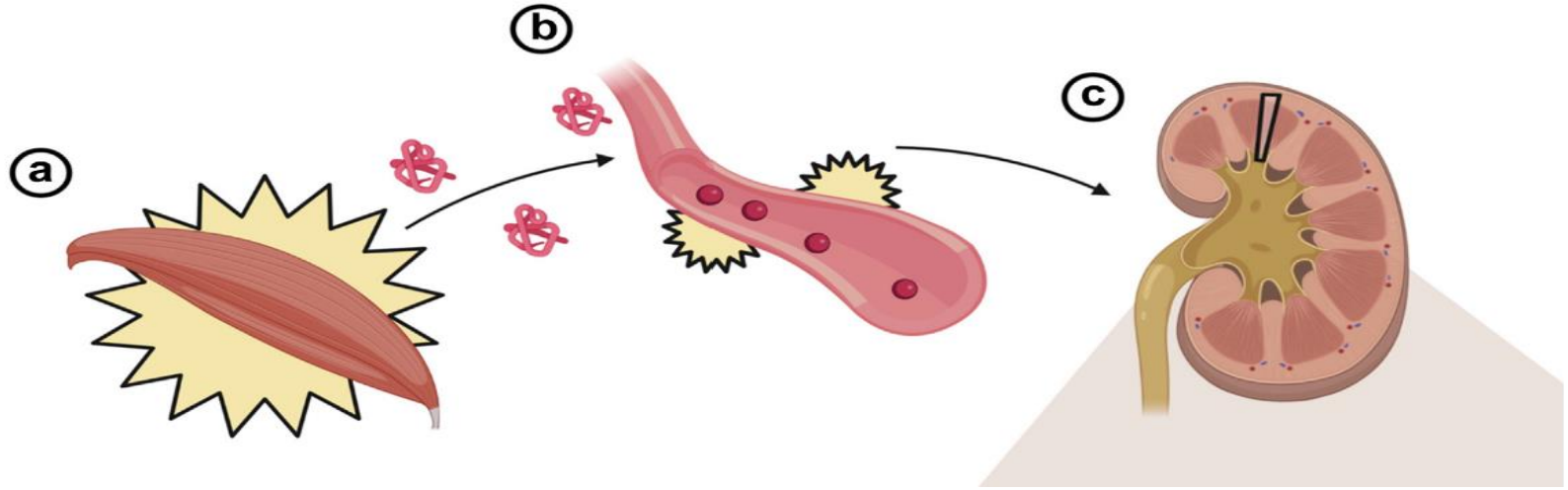
Panel A shows massive muscle necrosis (arrows) in a patient with statin-related rhabdomyolysis (hematoxylin and eosin). This histologic feature would be similar in every case of rhabdomyolysis, irrespective of the cause. Panel B shows the typical ragged-red fibers (arrows) in a muscle-biopsy specimen from a patient with mitochondrial myopathy that was obtained 3 months after an episode of severe rhabdomyolysis. The mitochondrial dysfunction was confirmed by a mitochondrial respiratory chain–based assay (Gomori's trichrome). Panel C shows periodic acid–Schiff (PAS)–positive material (arrows) in some muscle fibers in a case of McArdle's disease. The biopsy was performed a few months after the patient's recovery from recurrent rhabdomyolysis (PAS stain). Panel D shows a muscle-biopsy specimen from a patient with central core disease. The specimen was obtained after the patient's recovery from malignant hyperthermia. Abundant central cores can be seen (arrows) (NADH–tetrazolium reductase stain).


Toxin/ Drugs
Infections
Trauma/ Compression
Sarcolemmal membrane destruction
Influx of Ca^{2+}
Inhibit Na-K-ATPase
Arrest in cell respiration
Decrease ATP synthesis
Muscle ischemia
Increased inflammatory cells
Reperfusion
Free radical
Persistent muscle contraction
Activation of calcium-dependent proteolytic enzymes (proteases, phosphorylases)
Lipid peroxidation
Myocyte degeneration
RHABDOMYOLYSIS

PATHOGENESIS



PATHOGENESIS



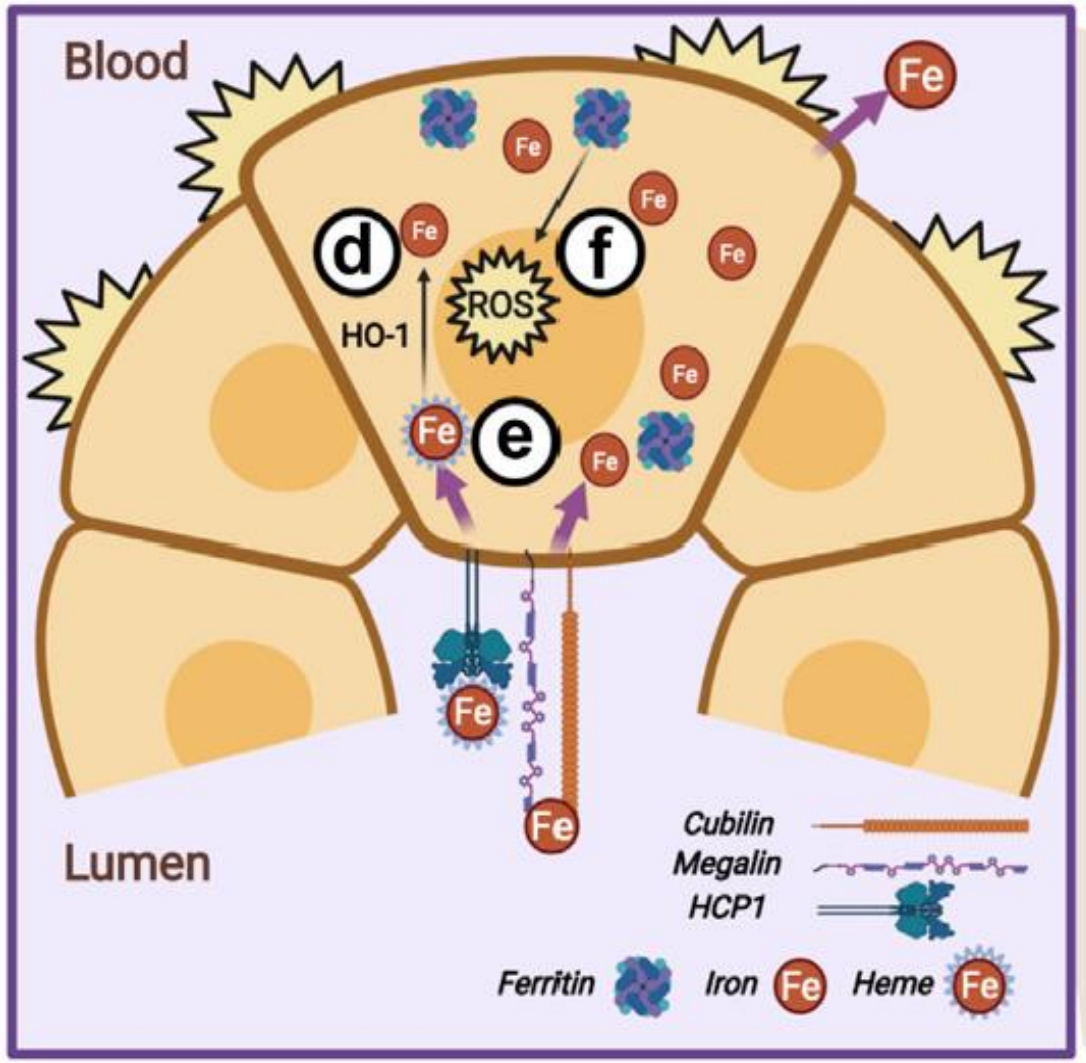
(a) Muscle takes damage and releases myoglobin and other metabolites into circulation.

(b) Myoglobin is circulated to the kidney for filtration, causing capillary damage and hypovolemia en route

(c) Myoglobin reaches the kidney and is filtered by the glomerulus.

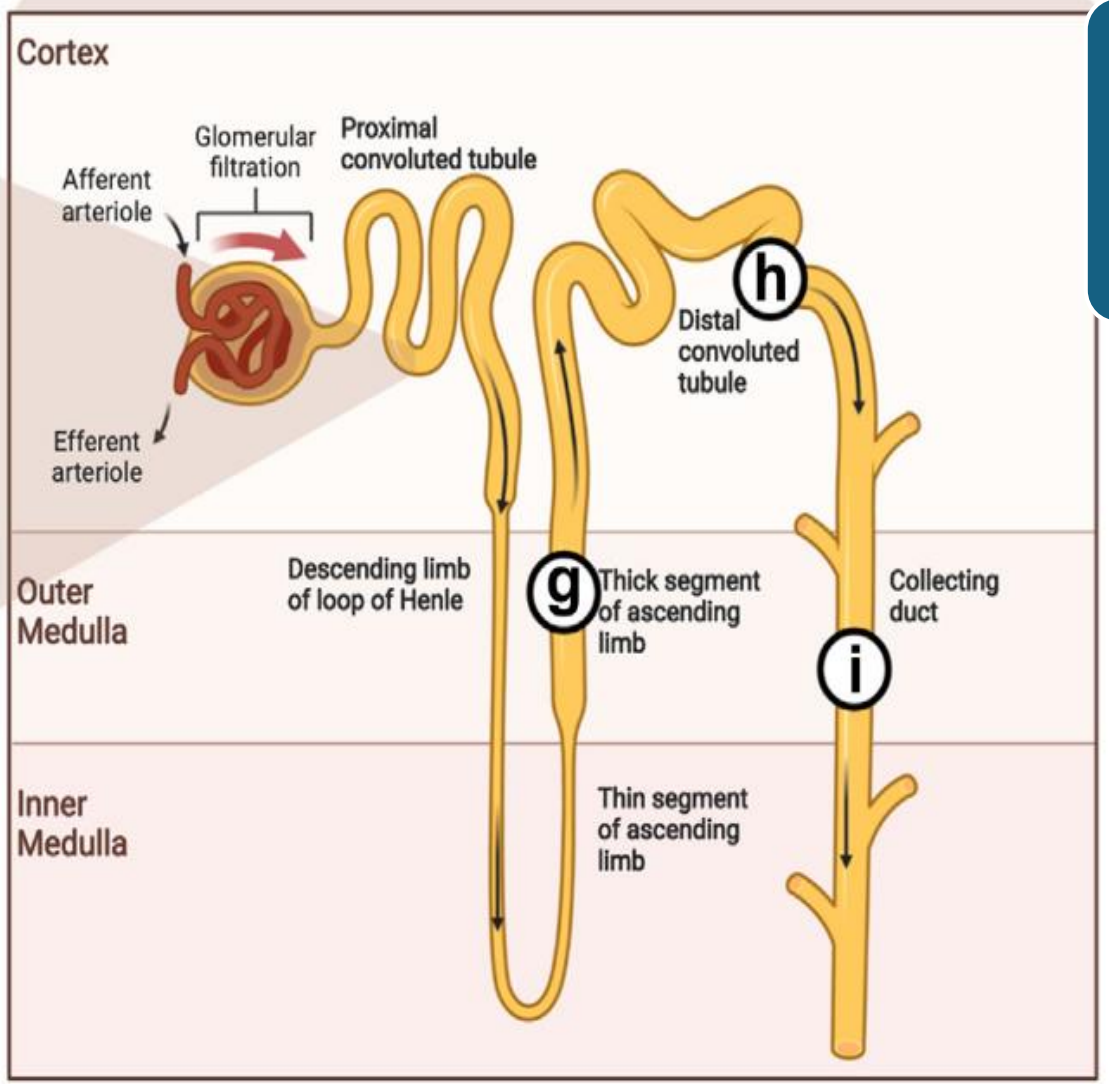
Kidney International Reports (2023) 8, 17–29

PATHOGENESIS



- (d)Heme oxygenase-1 degrades heme transported into the proximal tubule by Heme carrier protein 1 to release free ferrous iron.
- (e) Iron bound to substrates, including myoglobin, is transported into the proximal kidney tubule by megalin and cubilin, further increasing the concentration of free ferrous iron.
- (F)Ferritin, which oxidizes Fe(2+) to Fe(3+) and stores it, fails to keep up with incoming free ferrous. Fe(2+) reacts with hydrogen peroxide in the Fenton reaction, producing hydroxyl radicals, lipid peroxidation, and overwhelming superoxide dismutase activity, resulting in the formation of damaging reactive oxygen species (ROS)

PATHOGENESIS



(g) Myoglobin combines with Tamm-Horsfall protein (THP), found in the thick segment of the ascending limb, forming a precipitate.

(h) THP-Myoglobin precipitate forms obstructive tubular casts in the distal convoluted tubule.

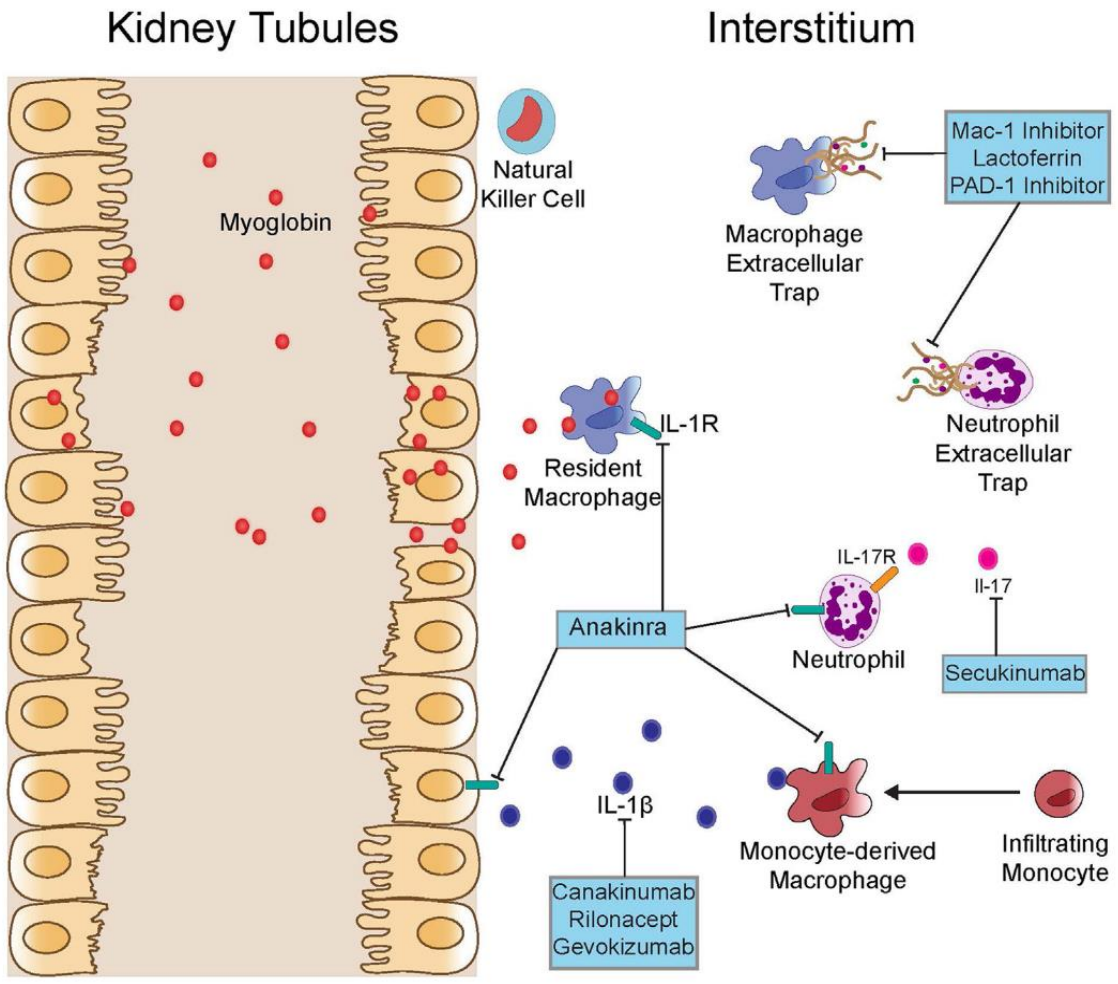
(i) Urine output decreases, resulting in reduced potassium excretion and perturbation of water, pH, and sodium balances, putting further pressure on the vascular system. ROS, reactive oxygen species

Kidney International Reports (2023) 8, 17–29

Immune-Mediated Mechanisms

In addition to processes directly related to myoglobin toxicity, products released from skeletal muscle and TEC damage act as immunogenic damage-associated molecular patterns, activating resident macrophages and recruiting circulating immune cells into the kidney interstitium.

Kidney inflammation during RIAKI and associated molecular targets



Myoglobin from the tubular system infiltrates into the interstitial space, resulting in immune activation.

Studies thus far demonstrate that primarily innate immune cells are involved in kidney inflammation

during RIAKI.

These cells include monocytes, macrophages, natural killer cells, and neutrophils.

Resident macrophages express IL-1b receptor, activation of which promotes production of inflammatory cytokines and cytotoxic macrophage extracellular traps, similar to neutrophil

extracellular traps.

Depicted in this figure are several potential molecular targets that have not yet been investigated in RIAKI. IL-b, interleukin 1beta; IL-R, interleukin receptor.

Kidney International Reports (2023) 8, 17-29

History

The classic triad of rhabdomyolysis comprises the following:

1. Myalgias
2. Generalized weakness
3. Darkened urine

The classic triad is actually seen in only about 50% of adult patients, and it may be even less common in children.

Diagnosing rhabdomyolysis

While a thorough medical history and examination may raise suspicion of rhabdomyolysis, the diagnosis is usually confirmed by the finding of an elevated creatinine kinase (CK).

Features suggestive of rhabdomyolysis in the history include an episode of limb ischemia, a fall followed by an extended period of immobility, and concomitant drug use.

Clinical features suggestive of rhabdomyolysis include aching muscles, an unusual color to the ... and

Ochsner Journal 2015; 15(1): 58–69.

Diagnosing rhabdomyolysis

- Presenting patients may have a tachycardia secondary to pain, dehydration or fluid shifts into the muscles.
- Muscle swelling can be present on admission or become apparent after the patient has received fluid resuscitation.
- Skin changes such as bruising, and evidence of pressure necrosis can point to a compression injury.
- In critically ill patients, clinical signs may be masked or blunted, and therefore a high clinical index of suspicion is warranted.
- A rare, but important cause of rhabdomyolysis in critical illness is propofol infusion syndrome (PRIS)

Diagnosing rhabdomyolysis

Various criteria have been used for diagnosing rhabdomyolysis, but the commonest recommended criterion in use is that a CK >1000 or 5 times the upper limit of normal is considered diagnostic of rhabdomyolysis.

The plasma CK concentration correlates with the severity of muscle injury, and concentrations >5000 units/L identify patients with rhabdomyolysis who are at risk for the development of AKI

CK typically continues to rise for the first 12–24 h following injury before beginning to decline.

Serial CK measurement at 12 hourly intervals until it begins to fall is useful for prognostication in terms of renal dysfunction

J Neurol 2020; 267:877–882

Dipstick urinalysis may show positive for blood, but urine

microscopy typically reveals tubular casts (from the precipitation of myoglobin with Tamm-Horsfall protein in the urine), but no blood.

Epidemiology

- Approximately 25,000 cases of rhabdomyolysis are reported each year in the USA.
- The prevalence of acute kidney injury in rhabdomyolysis is about 5 to 30%.
- There is a large variation in the incidence of acute kidney injury (AKI) in rhabdomyolysis settings because of multiple definitions of KI And with varying severity of rhabdomyolysis.

Medicine (Baltimore). 2005 Nov;84(6):377-385

Epidemiology

6 to 10% of patients with crush syndrome with acute kidney injury in survivors of the Bam earthquake in Iran required hemodialysis, and there is a correlation between the severity and duration of crush injury and the need for hemodialysis

Kidney Dis. 2006 Mar;47(3):428-38

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Acute kidney injury following traumatic rhabdomyolysis in Kermanshah earthquake victims; A cross-sectional study

Hamidreza Omrani [a], Iraj Najafi [b], Kiomars Bahrami [a], Farid Najafi [a], Saeed Safari [c,d,*]

Data from 370 patients who were victims of an earthquake in Iran in 2017 were analyzed.

Of these, 31.2 % had moderate to severe RML, and 2.7 % developed AKI.

Even with a low incidence, this complication should be considered due to the unfavorable outcome

Incidence. Intensive Care Network Audit and Research Centre (ICNARC) report

- 733 admissions to critical care where rhabdomyolysis was reported as the primary diagnosis in the time period 2006-2010.
- This constituted 0.2% of all admissions to nonspecialized adult critical care units.
- 75% of patients were male and the median age was 54.5 y.
- The in-hospital mortality was 31.1%.

- However, ICNARC only requires the reporting of the primary diagnosis, and given that rhabdomyolysis frequently complicates other disease states, this is likely to be an underestimate of the true incidence on the intensive care unit

Epidemiology

RIAKI takes on greater importance as the leading cause of death in immediate survivors of earthquakes.

Nearly 400 million people live in cities in earthquake prone areas, a number that is projected to double by 2050, making RIAKI treatment strategies an essential part of any disaster relief plan.

RIAKI Diagnosis

Cr ?

RIAKI Diagnosis &Diagnostic Criteria

The most used clinical test for rhabdomyolysis is the

measurement of plasma creatine kinase.

Typically, a level greater than 10,000 IU/l is considered diagnostic

confirmation of severe rhabdomyolysis and an increased risk for RIAKI.

Serum CK levels gradually increase during the first

12 h. with a peak of 3–5 days

Intensive Care Med. 2003;29: 1121–1125.

Classification of Rhabdomyolysis based on CK level

Diagnosis	CK level	Clinical Significance	Treatment Needed
Normal CK level	~40-200 U/L		
Mild rhabdomyolysis	1,000-5,000 U/L	Low risk for kidney injury	Possible Depends on context
Moderate rhabdomyolysis	5,0000-15,000 U/L	Increased risk of renal injury	Yes
Severe rhabdomyolysis	>15,000 U/L	Increased risk of dialysis	Yes

Am J Med . 20 06;119:40 0-409

General Urinalysis	
Dipstick	
Heme/blood	Positive (3+ or 4+)
pH	Acidic (5-6)
Proteins	Positive
Color	Reddish-brown
Microscopic analysis	Absent or few red blood cells
Urine sediment	Myoglobin casts, dead epithelial cells

Urine Findings in Rhabdomyolysis

Arterial blood gas	Evaluate acid-base balance
ECG	Evaluate cardiac dysrhythmias related to hyperkalemia and hypocalcemia
CBC	Check for signs of hemolysis, infection
PT, aPTT, D-dimer, fibrinogen	DIC can ensue secondary to release of thromboplastin
Serum albumin	Hypoalbuminemia = poor prognostic sign; represents capillary rupture with leakage
Toxicological screen	If drugs are the suspected causal agents

Other Important Diagnostic Tests

Summary of Biochemical Changes in Rhabdomyolysis

Creatine Kinase (CK)	↑
Myoglobin	↑
Creatinine	↑
Potassium	↑
Phosphorus	↑
Calcium	Initially ↓, then ↑
Uric Acid	↑
pH	↓
LDH, SGOT, Aldolase	↑
Albumin	↓
Anion Gap	↑
Hematocrit	↓
Intravascular volume	↓
Platelets	↓
Fibrinogen Degradation Products (FDP)	↑
Prothrombin Time	↑

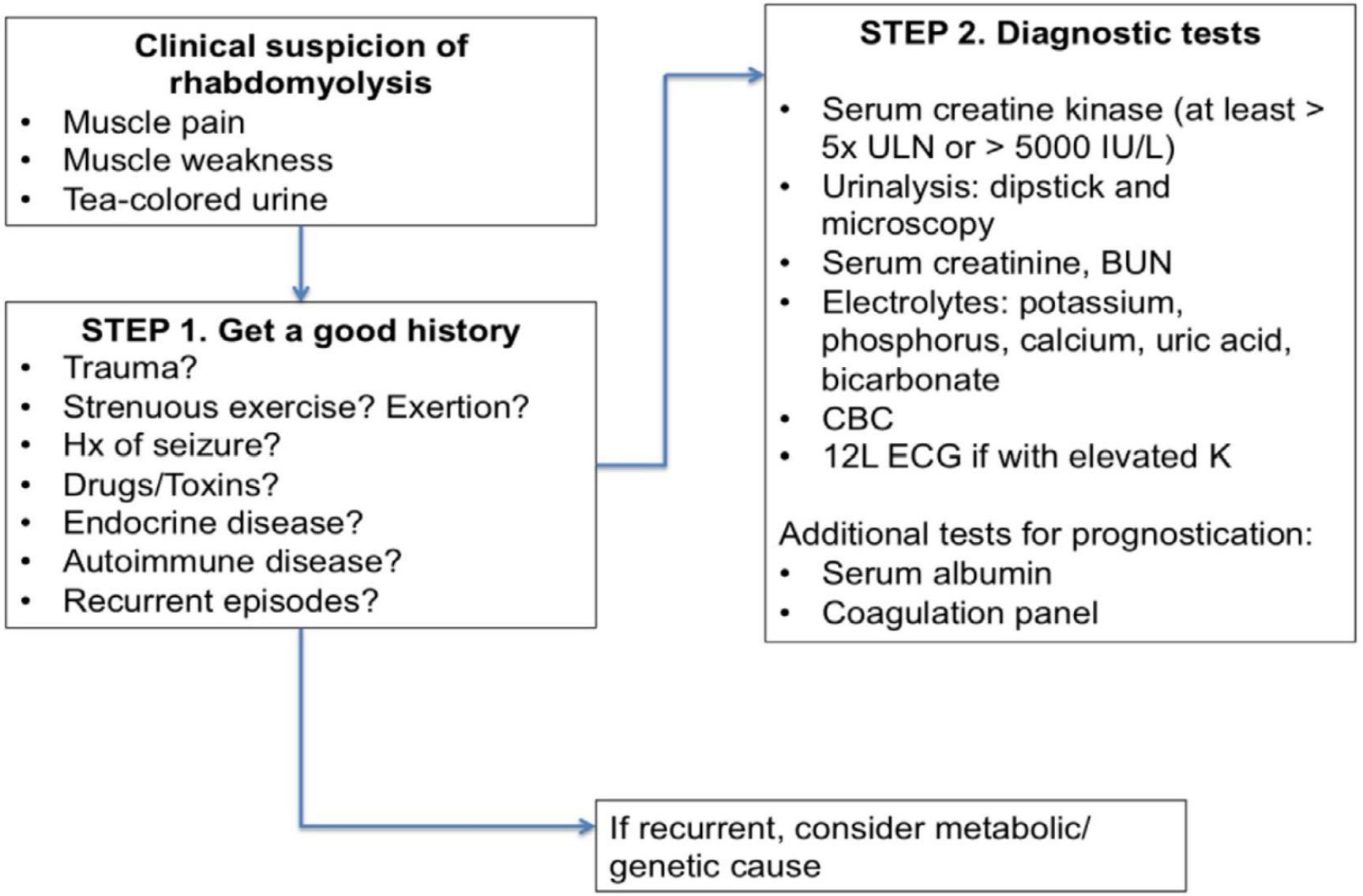
Calculation of the McMahon Risk Score

Variable	Points	
Age, years	≤50	0
	51-70	1.5
	71-80	2.5
	>80	3
Sex	Male	0
	Female	1
Initial Creatinine	<1.4 mg/dL (<124 μmol/L)	0
	1.4-2.2 mg/dL (124-195 μmol/L)	1.5
	>2.2 mg/dL (>195 μmol/L)	3
Initial Calcium <7.5 mg/dL (1.88 mmol/L)	No	0
Initial CK > 40000 U/L	Yes	2
	No	0
	Yes	2
Rhabdo secondary to seizures, syncope, exercise, statins or myositis	Yes	0
	No	3
Initial Phosphate	<4.0 mg/dL (<1.0 mmol/L)	0
	<4.0-5.4 mg/dL (1.0-1.4 mmol/L)	1.5
	>5.4 mg/dL (>1.4 mmol/L)	3
Initial Bicarbonate <19 mEq/L (19 mmol/L)	No	0
	Yes	2

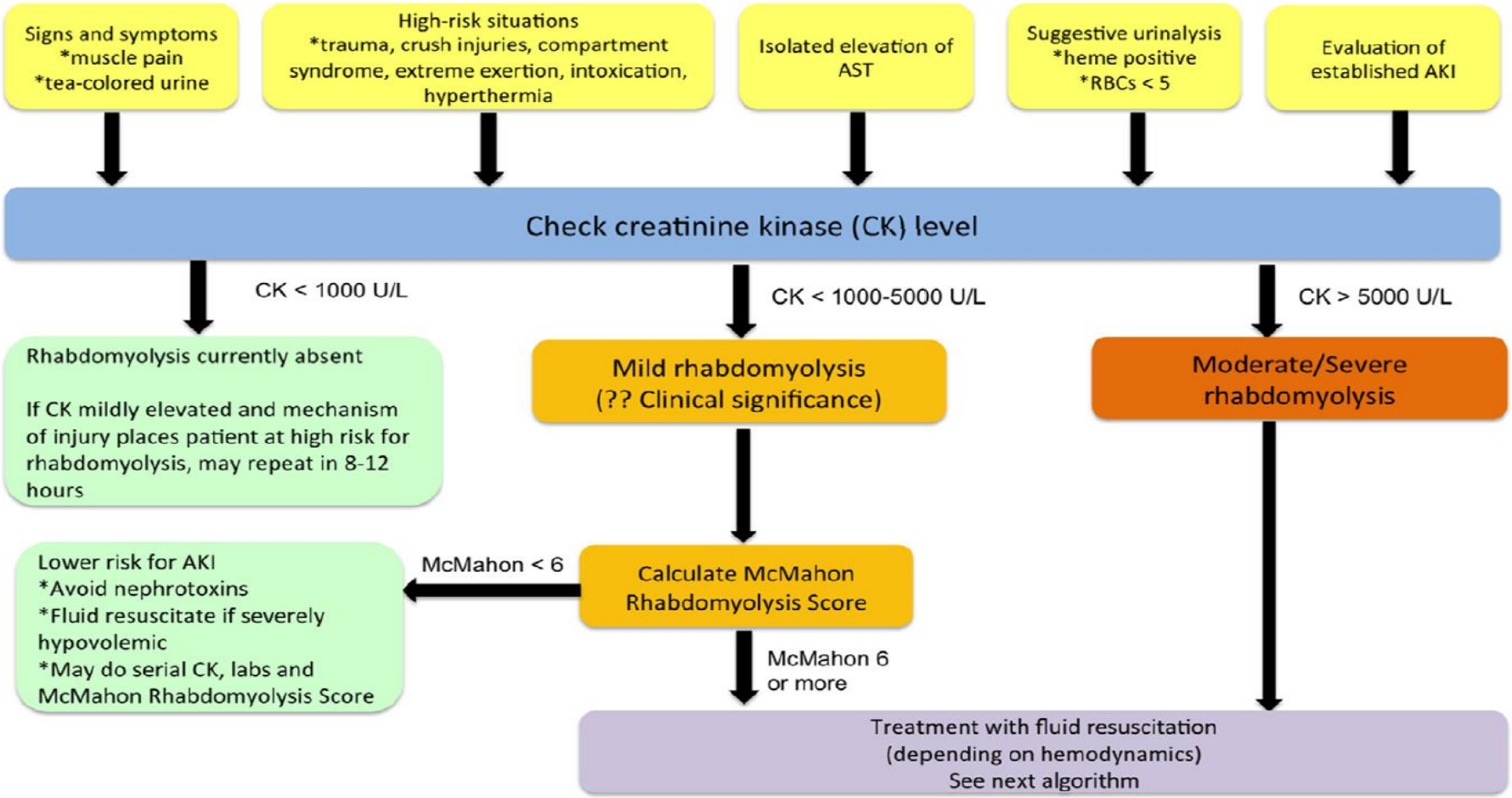
McMahon score

specificity

vs 55%, respectively) than CK level > 50 0 0 U/L in predicting risk of RRT
.
A McMahon score < 5 indicates a 2-3% risk of either need for RRT or death, whereas a score
> 10 indicates a 52-61.2% risk of RRT or death.
A score of 6 or greater indicates risk of acute kidney injury or dialysis, hence renal protective therapies should be considered in all patients with this


Clinical suspicion of rhabdomyolysis
• Muscle pain
• Muscle weakness
• Tea-colored urine
STEP 1. Get a good history
• Trauma?
• Strenuous exercise? Exertion?
• Hx of seizure?
• Drugs/Toxins?
• Endocrine disease?
• Autoimmune disease?
• Recurrent episodes?
STEP 2. Diagnostic tests
• Serum creatine kinase (at least > 5x ULN or > 5000 IU/L)
• Urinalysis: dipstick and microscopy
• Serum creatinine, BUN
• Electrolytes: potassium, phosphorus, calcium, uric acid, bicarbonate
• CBC
• 12L ECG if with elevated K
Additional tests for prognostication:
• Serum albumin
• Coagulation panel
If recurrent, consider metabolic/ genetic cause

Approach to Diagnosing and Stratifying Rhabdomyolysis using the McMahon Scoring System



Prevention&treatment

For patients with rhabdomyolysis who have plasma creatine kinase (CK) values >5000 units/L and those who have CK values that are increasing regardless of baseline value, we suggest the administration of intravenous (IV) fluid.

IV fluids to prevent AKI should be administered until it is clear from sequential laboratory values that the plasma CK level is ≤5000 units/L and not increasing.

- Correction of volume depletion if present

Choice of IV fluids : the optimal type of fluid in this setting is not established

- Most recommendations are based on observational or retrospective studies, case reports, and case series, which describe diverse and often simultaneous medical treatments for this syndrome.
- A study by Cho et al. compared the effects of Lactated Ringer's (LR) vs normal saline (NS) in patients diagnosed with rhabdomyolysis secondary to doxylamine overdose.
- Serum and urine pH were higher in the LR group 12 hours after infusion.
- Large amounts of NS infusion induced mild metabolic acidosis in contrast with mild metabolic alkalosis induced by LR infusion.
- The acidosis may cause impaired cardiac performance, decreased responsiveness to cardiac inotropic drugs and decreased renal perfusion

Volume Replacement

- Initial fluid resuscitation may be given at a rate of 1 to 2 L/hour. Normally, hydration is maintained
- Serial CK measurements are helpful in adjusting therapeutic hydration parameters.
- The volume status should be carefully assessed and urine output monitored.
- Fluid rates should be adjusted as necessary, paying particular attention to any signs of volume overload.
- If adequate diuresis is established, fluids are titrated to maintain a urine output of 200 to

Titrating fluids

The initial fluid rate should be titrated according to the patient's

volume status

urine output

parameters which must be carefully monitored during treatment

Volume replete with oligoanuria

For patients with rhabdomyolysis who are volume replete but remain oligoanuric after an aggressive course of initial IV fluid administration ,(6 liters)

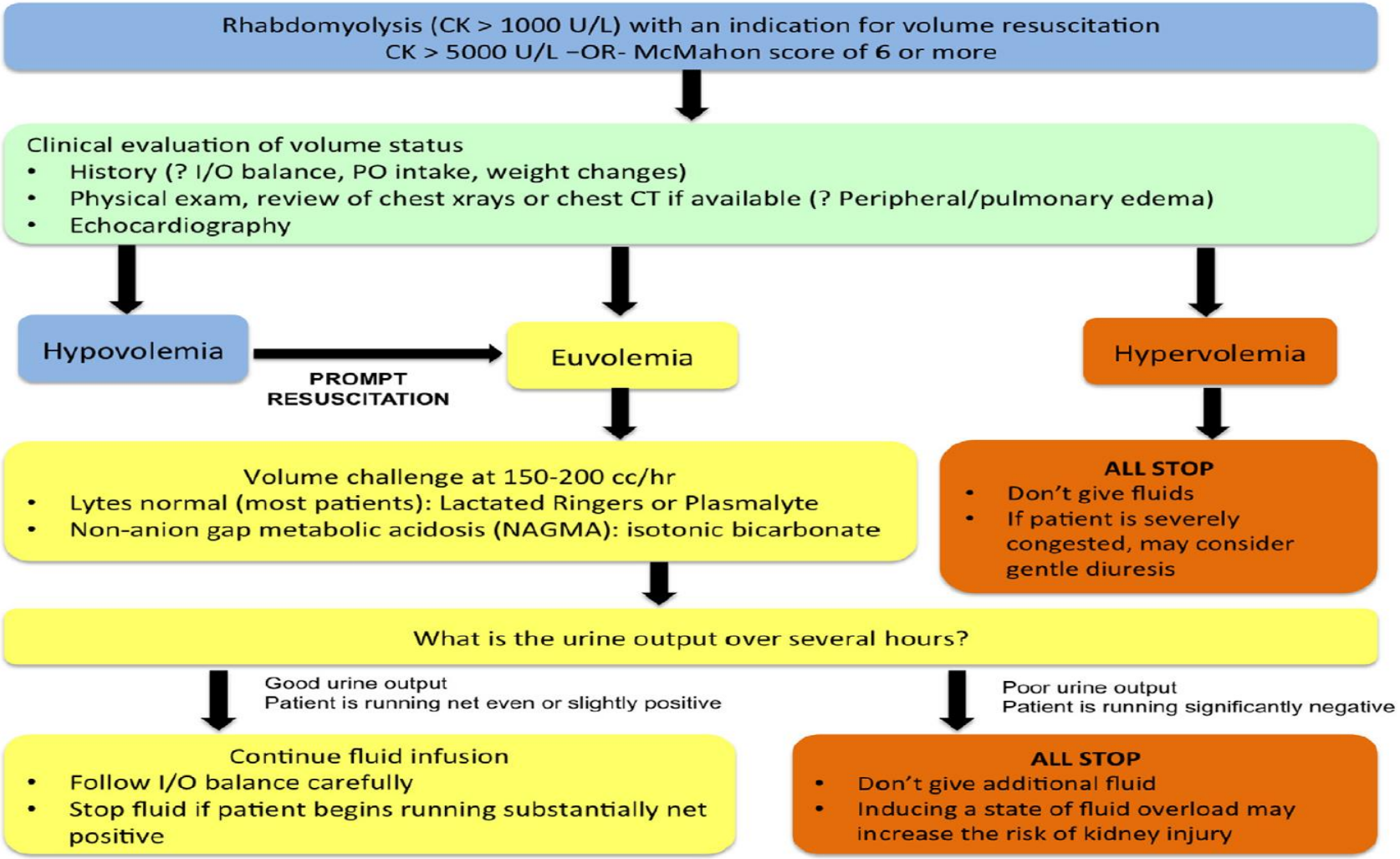
Recommendation is decreasing intravenous fluids to a rate sufficient only to maintain circulatory support.

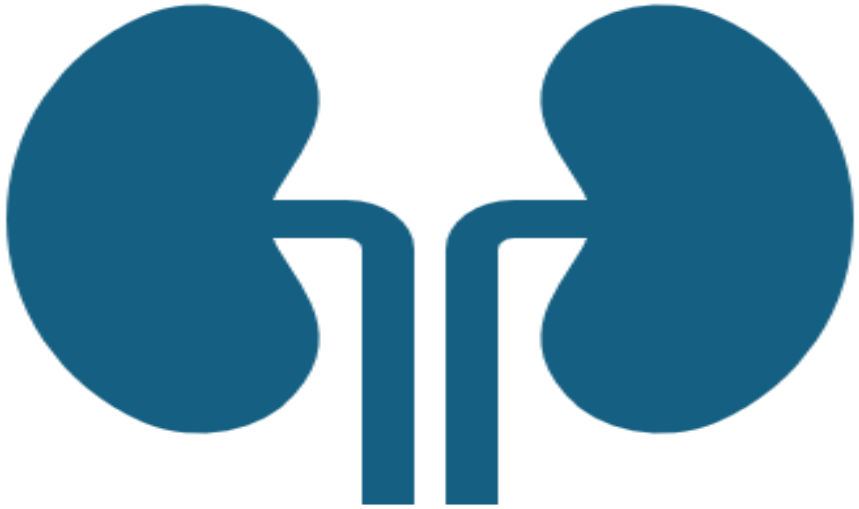
Fluid administration totals may need to be adjusted in patients with heart failure, and signs and symptoms of volume overload should be assessed frequently in such patients

Patients who are volume replete but do not produce urine after an adequate volume challenge should be considered to have established acute kidney injury.

These patients should be closely followed for indications to initiate dialysis

Suggested Algorithm for Fluid Resuscitation





Bicarbonate in selected patients

(Grade 2C)

After an ***adequate diuresis*** has been established with isotonic saline

Generally, administer a bicarbonate infusion to patients who have severe rhabdomyolysis, such as those with :

- Serum CK level above 5000 units/L
- Clinical evidence of severe muscle injury (eg, crush injury)
- Rising serum CK level, regardless of the initial value

➢Hypocalcemia is not present

➢ Arterial pH is less than 7.5

➢Serum bicarbonate is less than 30

Administration

- Among patients with rhabdomyolysis, infuse isotonic sodium bicarbonate (150 mEq of sodium bicarbonate added to 1 L of 5 percent dextrose or water) via an intravenous line separate from that used for the isotonic saline infusion.

The initial rate of infusion is 200 mL/hour; the rate is adjusted to achieve a urine pH of >6.5.

Continue bicarbonate therapy until the plasma CK level decreases to less than 5000 units/L or until the development of alkalemia

Monitoring

IF BICARBONATE IS GIVEN, THE ARTERIAL PH AND SERUM CALCIUM SHOULD BE MONITORED EVERY TWO HOURS DURING THE INFUSION.

THE BICARBONATE INFUSION SHOULD BE DISCONTINUED IF THE URINE PH DOES NOT RISE ABOVE 6.5 AFTER THREE TO FOUR HOURS, IF THE PATIENT DEVELOPS SYMPTOMATIC HYPOCALCEMIA, IF THE ARTERIAL PH EXCEEDS 7.5, OR IF THE SERUM BICARBONATE EXCEEDS 30 MEQ/L.

Rhabdomyolysis -- an overview for clinicians. Crit Care 2005; 9:158.

Metabolic abnormalities

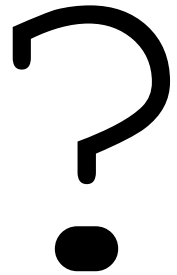
Hypocalcemia To minimize the late occurrence of hypercalcemia in rhabdomyolysis as well as the risk of calcium-phosphate precipitation, calcium supplementation for hypocalcemia should be avoided unless significant signs and symptoms of hypocalcemia develop or calcium administration is required for the management of hyperkalemia.

Hyperkalemia Hyperkalemia should be anticipated and may occur even in the absence of severe AKI. Hyperkalemia should be aggressively treated with standard medical management. Dialysis may be required to treat severe hyperkalemia.

Hyperuricemia – Patients who develop hyperuricemia should be treated with allopurinol. Allopurinol should be given orally at 300 mg if uric acid levels are >8 mg/dL (476 micromol/L) or if there is a 25 percent increase from baseline. Allopurinol is not indicated in the treatment of hemolysis in the absence of hyperuricemia.

Dialysis

- The use of dialysis to remove myoglobin, hemoglobin, or uric acid to prevent the development of kidney injury has not been demonstrated



- Acta Anaesthesiol Scand 2005; 49:859
- Exp Nephrol 2000;8:72.

de Fallois *et al. BMC Nephrology* (2024) 25:96
https://doi.org/10.1186/s12882-024-03536-8

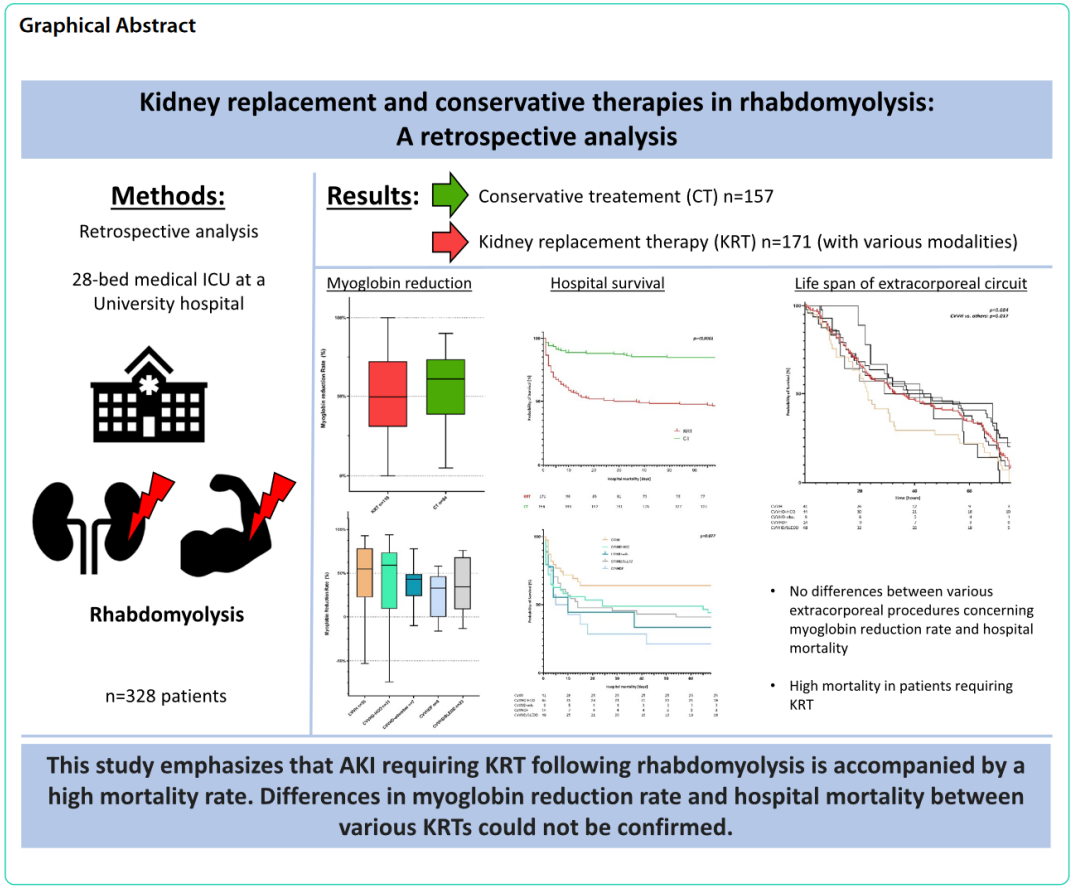
BMC Nephrology

RESEARCH Open Access

Kidney replacement and conservative therapies in rhabdomyolysis: a retrospective analysis

Jonathan de Fallois[1†], Robert Scharm[2†], Tom H. Lindner[1], Christina Scharf[3], Sirak Petros[2] and Lorenz Weidhase[2*]

Graphical Abstract



Blood Purification

Critical Care Nephrology – Research Article

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Extracorporeal Removal of Myoglobin in Patients with Rhabdomyolysis and Acute Kidney Injury: Comparison of High and Medium Cut-Off Membrane and an Adsorber Cartridge

Alexander Jerman[a] Milena Andonova[a, b] Vanja Persic[a, b] Jakob Gubensek[a, b]

[a]Department of Nephrology, Center for Acute and Complicated Dialysis, University Medical Center Ljubljana, Ljubljana, Slovenia; [b]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Table 2. Operational parameters of dialysis procedures and laboratory results for all three groups

Parameter	HCO	MCO	Adsorber	*p* value
N	13	9	6	–
Treatment duration, h	8 [6–8]	5 [4–6]	11 [10–12]	<0.001
Blood flow, mL/min	300 [300–300]	250 [250–250]	250 [250–250]	<0.001
Dialysis modality	HDF 13 (100)	HD 9 (100)	CVVHD 1 (17) HD 5 (83)	–
Pre-procedure s-myoglobin, µmol/L	65,320 [54,931–143,999]	99,379 [36,624–128,491]	53,646 [32,731–137,828]	0.82
Post-procedure s-myoglobin, µmol/L	42,849 [30,163–62,600]	47,034 [23,010–69,639]	27,583 [22,550–31,491]	0.49
Before/after comparison	$p = 0.03$	$p = 0.004$	$p = 0.06$	–
Myoglobin decrease, µmol/L	42,959 [6,539–10,6734]	56,226 [24,638–68,096]	32,554 [12,268–70,962]	0.80
Myoglobin reduction rate	0.64 [0.13–0.72]	0.54 [0.51–0.61]	0.50 [0.37–0.62]	0.83
Albumin before, g/L	31±3	27±3	28±3	0.03
Albumin after, g/L	32±3	28±33	28±5	0.03
Before/after comparison	$p = 0.56$	$p = 0.41$	$p = 0.81$	–

Data are presented as frequency (percentage), mean ± standard deviation or median [inter-quartile range]. HDF, hemodiafiltration; HD, hemodialysis; CVVHD, continuous hemodialysis.

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Extracorporeal Removal of Myoglobin in Patients with Rhabdomyolysis and Acute Kidney Injury: Comparison of High and Medium Cut-Off Membrane and an Adsorber Cartridge

Alexander Jerman[a] Milena Andonova[a, b] Vanja Persic[a, b] Jakob Gubensek[a, b]

[a]Department of Nephrology, Center for Acute and Complicated Dialysis, University Medical Center Ljubljana, Ljubljana, Slovenia; [b]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Results from a small cohort of patients show that the MCO membrane, as a novel approach, seems to allow for efficient removal of myoglobin from the circulation, comparable to the HCO membrane, but associated with much lower costs and no need for albumin supplementation.

Therefore, MCO dialysis might be the optimal mode of treatment of severe rhabdomyolysis-associated AKI.

Calcium

- Calcium supplementation should be given only for symptomatic hypocalcemia or severe hyperkalemia because early deposition of calcium in muscle is followed by hypercalcemia later in the injury process.

loop diuretics

- In the context of rhabdomyolysis, loop diuretics may worsen the already existing trend for hypocalcemia since they induce calcinuria and may increase the risk of cast formation.
- Despite these concerns, however, judicious use of loop diuretics may be justified in older patients, especially if volume overloaded

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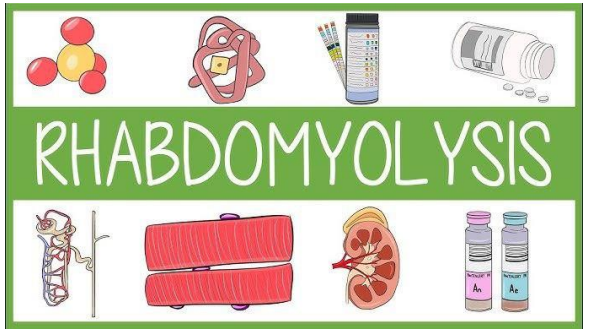
Substance	Category	Description	Evidence
Desferrioxamine	**IC**	lipid peroxidation inhibitor – reducing myoglobin to its ferrous form; hydrophilic – requires a lipophilic form to reduce nephrotoxicity [23] alternative: *deferiprone* – the oral form used for ferrous overload by repeated blood transfusions	animal studies, no data about human trials no data available
Vitamin E	**AO**	the major lipophilic antioxidants present in cellular membranes and protecting them against lipid peroxidation – theoretically could prevent myoglobin tubular toxicity – impediment: liposolubility implies a low ability to prevent myoglobin oxidation in the urine	animal studies with some efficiency to decrease toxicity [24-26], no animal/ human clinical trials
Vitamin C	**AO**	water-soluble; reduce oxidative stress and inflammation by (theoretically) blocking the oxidation of myoglobin in urine and antiinflammatory role by inhibiting MCP-1 production [27] synergic effects: *polyphenols* lipid-soluble	animal (murine) studies with some efficiency to decrease toxicity [24-26], no animal/ human clinical trials
Acetaminophen	**AO**	inhibits lipid peroxidation by reducing ferryl myoglobin and urinary level of F2-isoprostanes some studies have shown benefits not only in prophylaxis but in treatment [28]	mostly murine or rat studies, no clinical data for benefits in human
NAC	**AO**	preventing cellular apoptosis by decrease in urinary thiobarbituric acid reactive substances (TBARS) concentrations, a lipid peroxidation marker, and inducing extracellular-signal-regulated kinase (ERK)pathway [31]	lots of research available, but proven efficacy only in animal models [29-30]
Flavonoids	**AO**	Probably electron donors with B-ring conjugated chemical structures rich in hydroxyl groups, which have potent antioxidant actions by reacting with and inactivating superoxide anions, oxygen lipid peroxide radicals, and/or stabilizing free radicals [32]	animal studies – largely concentrated on the influence on nerve cells, little data on the effect in people suffering from kidney damage from RM

AO – antioxidants and IC – iron chelators in RM-AKI treatment, NAC – N-acetylcysteine, ROS – reactive oxygen species MCP-1 – monocytechemoattractant protein-1

RIAKI treatments (current and proposed) and their molecular targets

Current therapies

Treatment	Molecular target	Investigated in RIAKI?	Investigation stage
Intravenous fluid	Tubular flow	Y	Current recommended treatment
Sodium bicarbonate	Tubular pH, myoglobin precipitation	Y	Current treatment at some centers
Mannitol	Tubular flow, ROS	Y	Current treatment at some centers
Proposed therapies			
Treatment	Molecular target	Investigated in RIAKI?	Investigation stage
Cilastatin	Megalin/tubular endocytosis	Y	Preclinical
High flux dialysis	Myoglobin	Y	Phase I - NCT01467180
N Acetylcystine	Reactive oxygen species	Y	Phase II - NCT00391911
CytoSorb device	Myoglobin	Y	Phase II - NCT02111018
Peptidyl arginine deaminase	NET/MET formation	N-lupus	Preclinical
Brensocatib	Dipeptidyl peptidase-1	N- brochiectasis	Phase II - NCT03218917
Secukinumab	IL-17A	N-rheumatoid diseases	FDA approved for rheumatoid diseases
Lactoferrin	MET formation	Y	Preclinical
Anti-Mac-1 antibody	Mac-1	Y	Preclinical
Canakinumab	IL-1B	N-CKD	Phase III - NCT01327846
Anakinra	IL-1B	N-inflammation in CKD	Phase II - NCT00420290, Phase II - NCT02278562
Rilonacept	IL-1B	N-inflammation in CKD	Phase II - NCT00897715
Gevokizumab	IL-1B	N-Type 2 diabetic kidney disease	Phase II - EudraCT2013–003610–41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