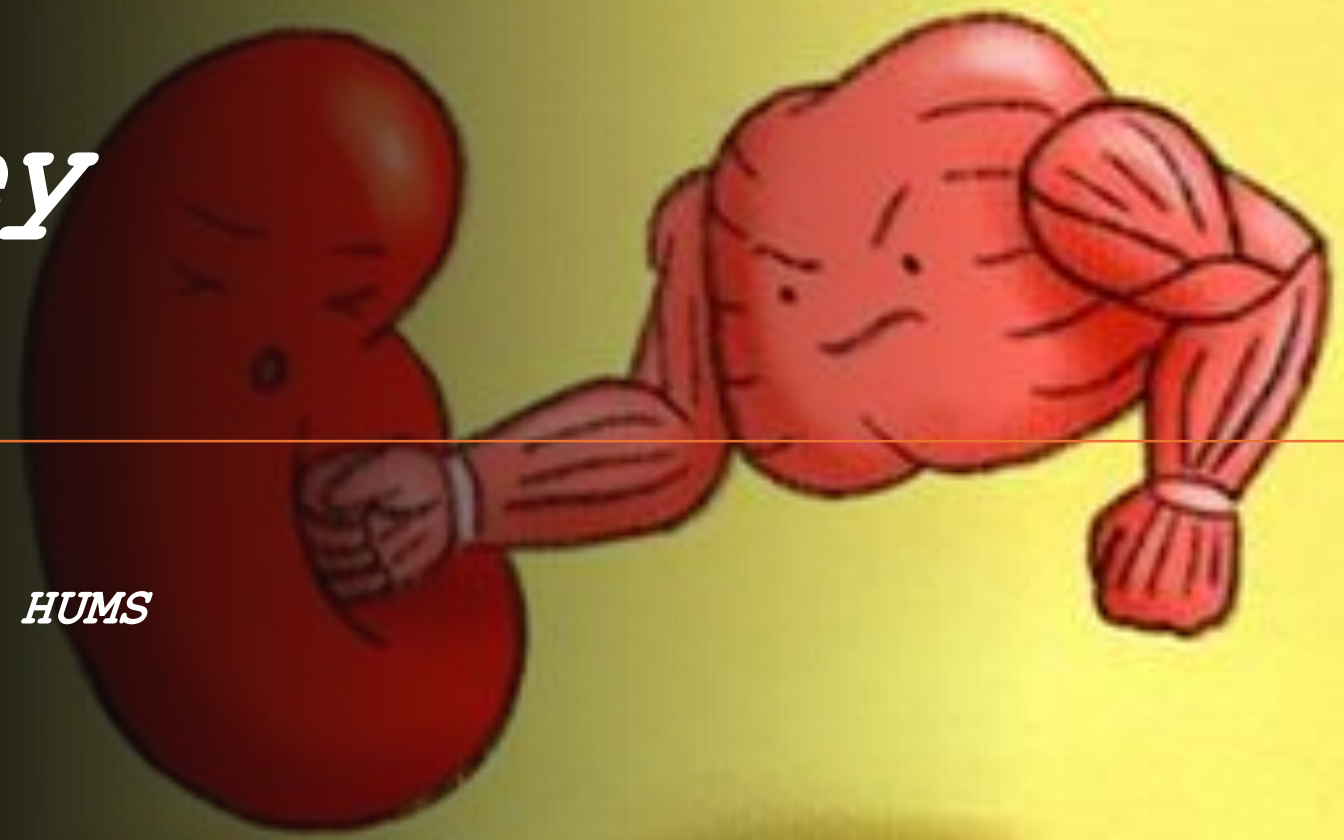
Rhabdomyolysis & Acute kidney Injury



Samimagham HR .MD

Professor of Nephrology Of HUMS

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 and Beall, as it alluded to the London bombing

Major Earthquakes in the Past 3 Decades [7]

Location and Year	Deaths	Overall Number of Crush Victims	Dialysis
Spitak, Armenia, 1988[8]	25,000	600	225-385
Northern Iran, 1990[9]	>40,000	?	156
Kobe, Japan, 1995[10]	5,000	372	123
Marmara Region, Turkey, 1999[11]	>17,000	639	477
Chi-Chi, Taiwan, 1999[12]	2,405	52	32
Gujarat, India, 2001[13]	20,023	35	33
Boumerdes, Algeria, 2003[14]	2,266	20?	15?
Bam, Iran, 2003[15]	26,000	124	96
Kashmir, Pakistan, 2005[16]	>80,000	118	65
Total	>217000	>1900	>1200

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%.

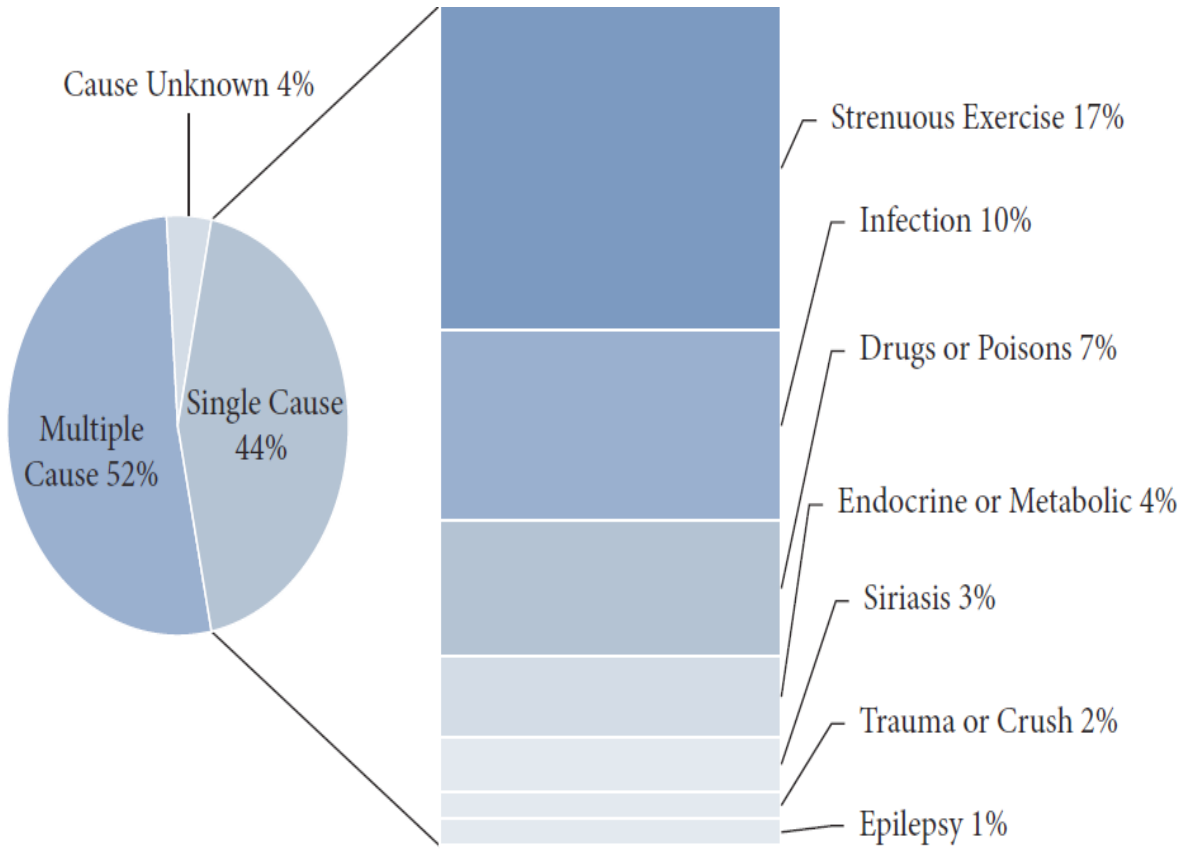
The incidence of RIAKI has increased 10-fold in the last decade, fueled in part by popular interest in studio fitness training, such as CrossFit.

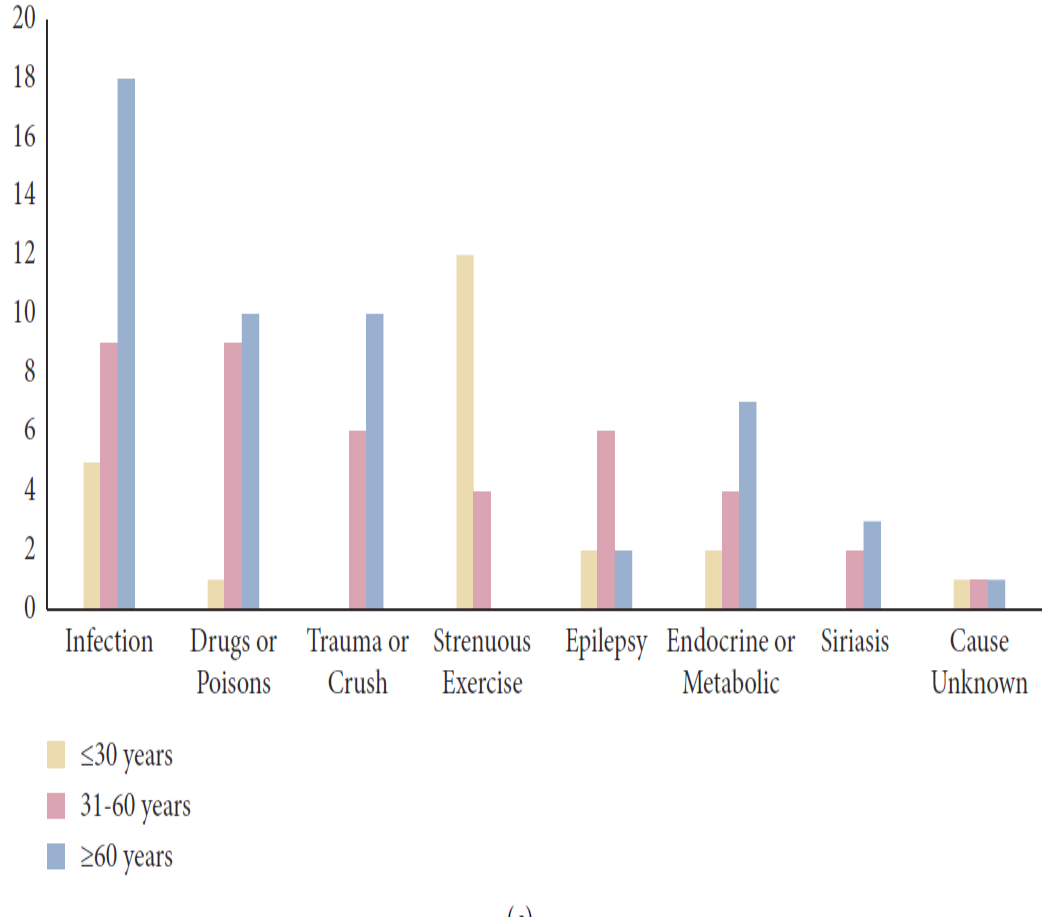
RIAKI is a significant comorbidity for injured soldiers who are 3 to 4

times more likely to develop rhabdomyolysis than civilians

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


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
18
16
14
12
10
8
6
4
2
0
Infection
Drugs or Poisons
Trauma or Crush
Strenuous Exercise
Epilepsy
Endocrine or Metabolic
Siriasis
Cause Unknown
≤30 years
31-60 years
≥60 years

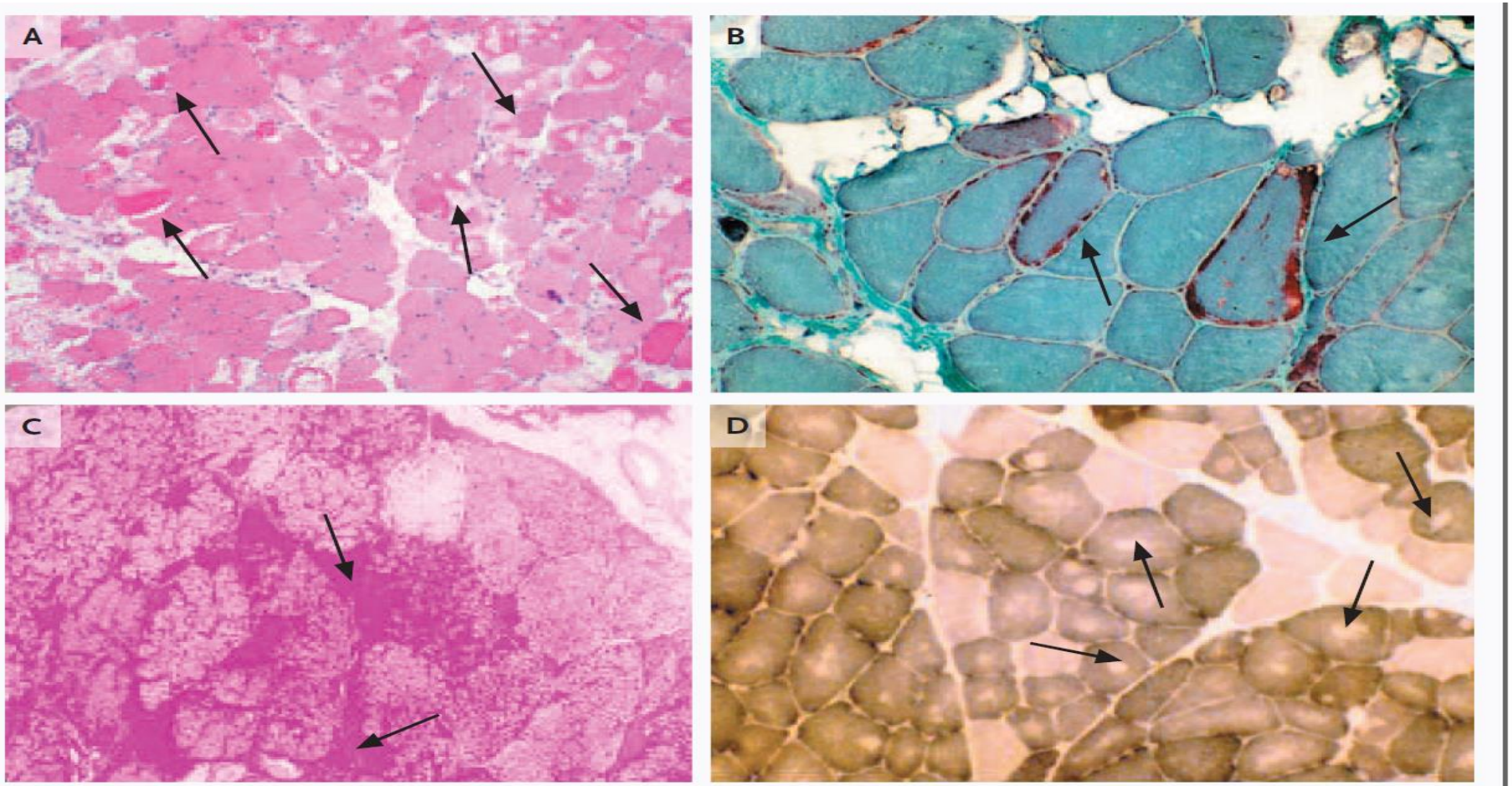
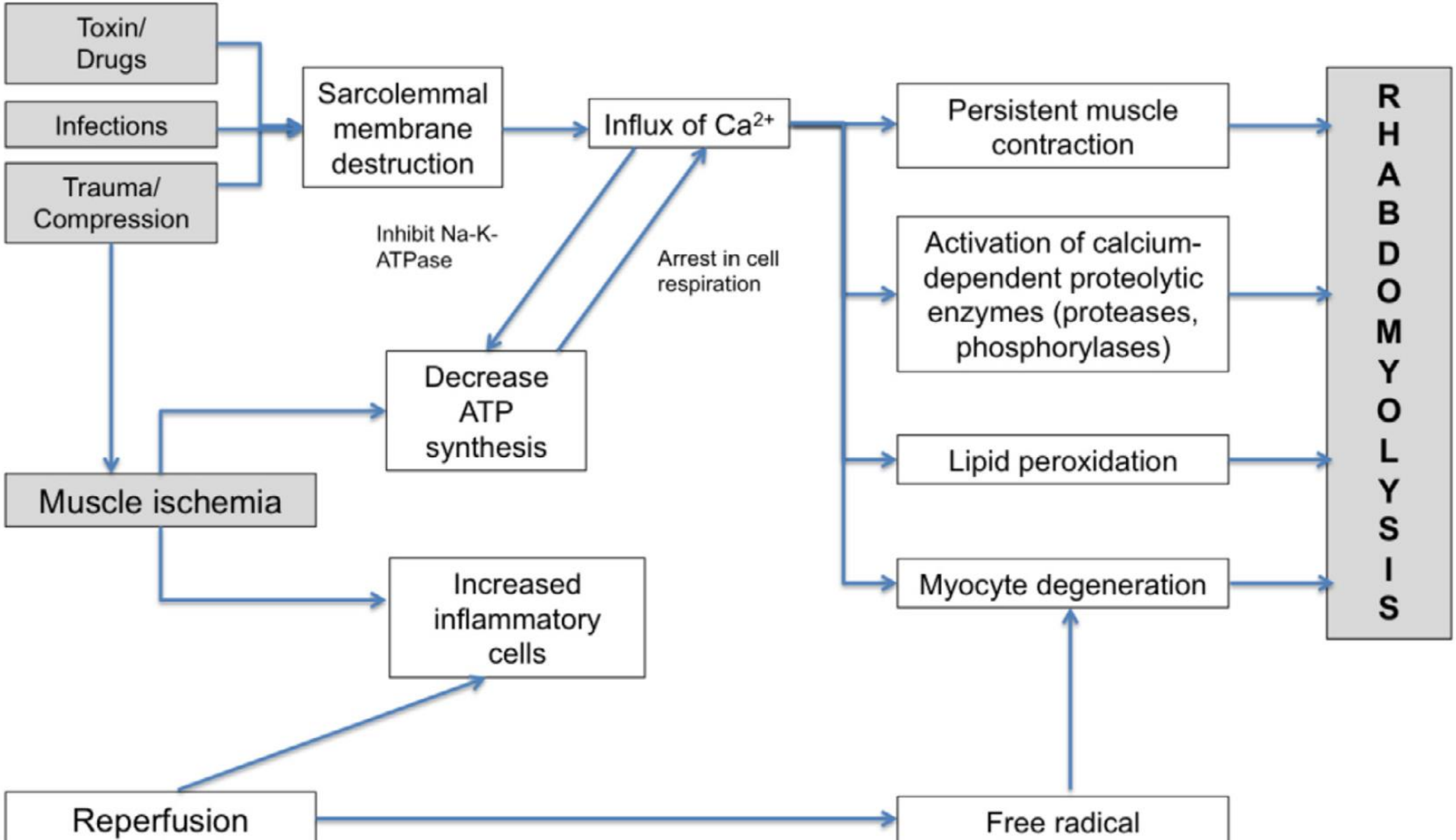
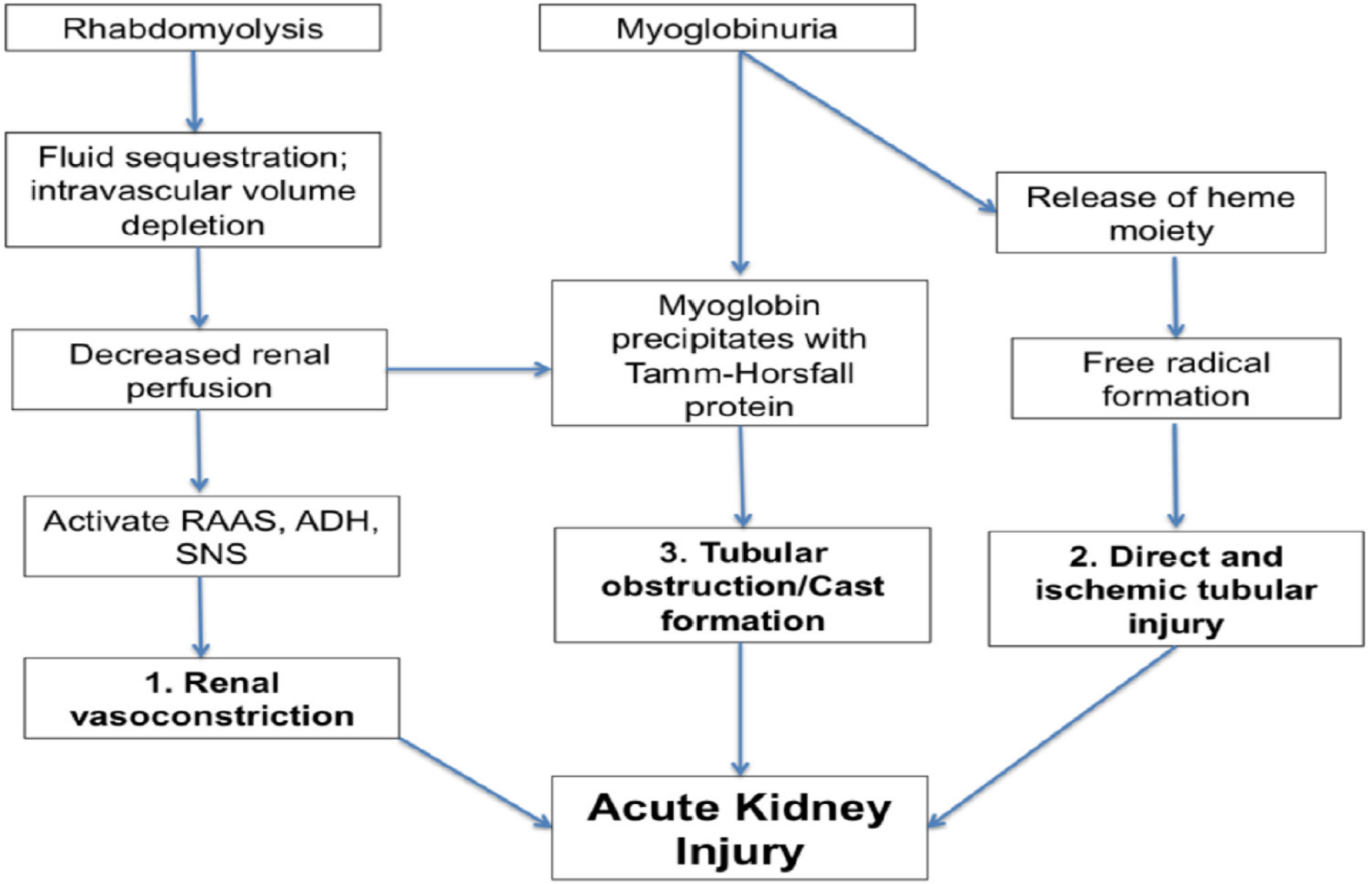


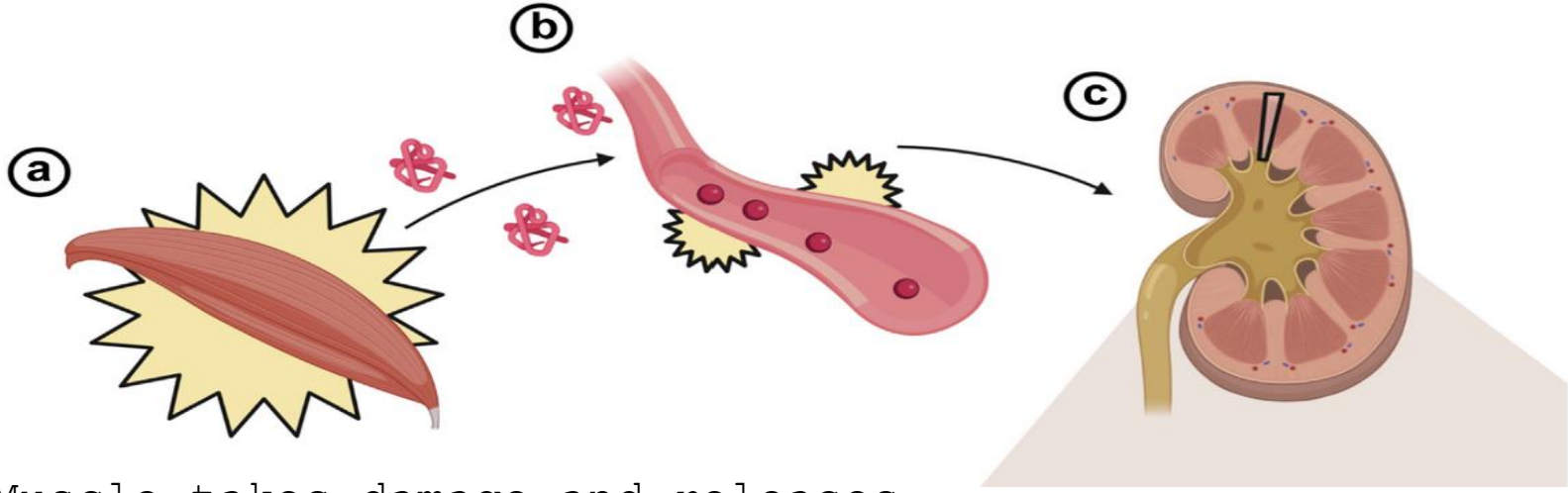
Figure 1. Histopathological Findings in Frozen Muscle-Tissue Specimens from Patients with Rhabdomyolysis.
Panel A shows massive muscle necrosis (arrows) in a patient with statin-related rhabdomyolysis (hematoxylin and eosin). This histologic feature would be similar in every case of rhabdomyolysis, irrespective 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

Heme pigment may injure the kidney in three ways:

- Tubular obstruction, possibly in association with uric acid
- Direct proximal tubular epithelial cell injury
- Vasoconstriction, which results in a reduction in blood flow in the outer medulla


Rhabdomyolysis
Myoglobinuria
Fluid sequestration; intravascular volume depletion
Release of heme moiety
Decreased renal perfusion
Myoglobin precipitates with Tamm-Horsfall protein
Free radical formation
Activate RAAS, ADH, SNS
3. Tubular obstruction/Cast formation
2. Direct and ischemic tubular injury
1. Renal vasoconstriction
Acute Kidney Injury

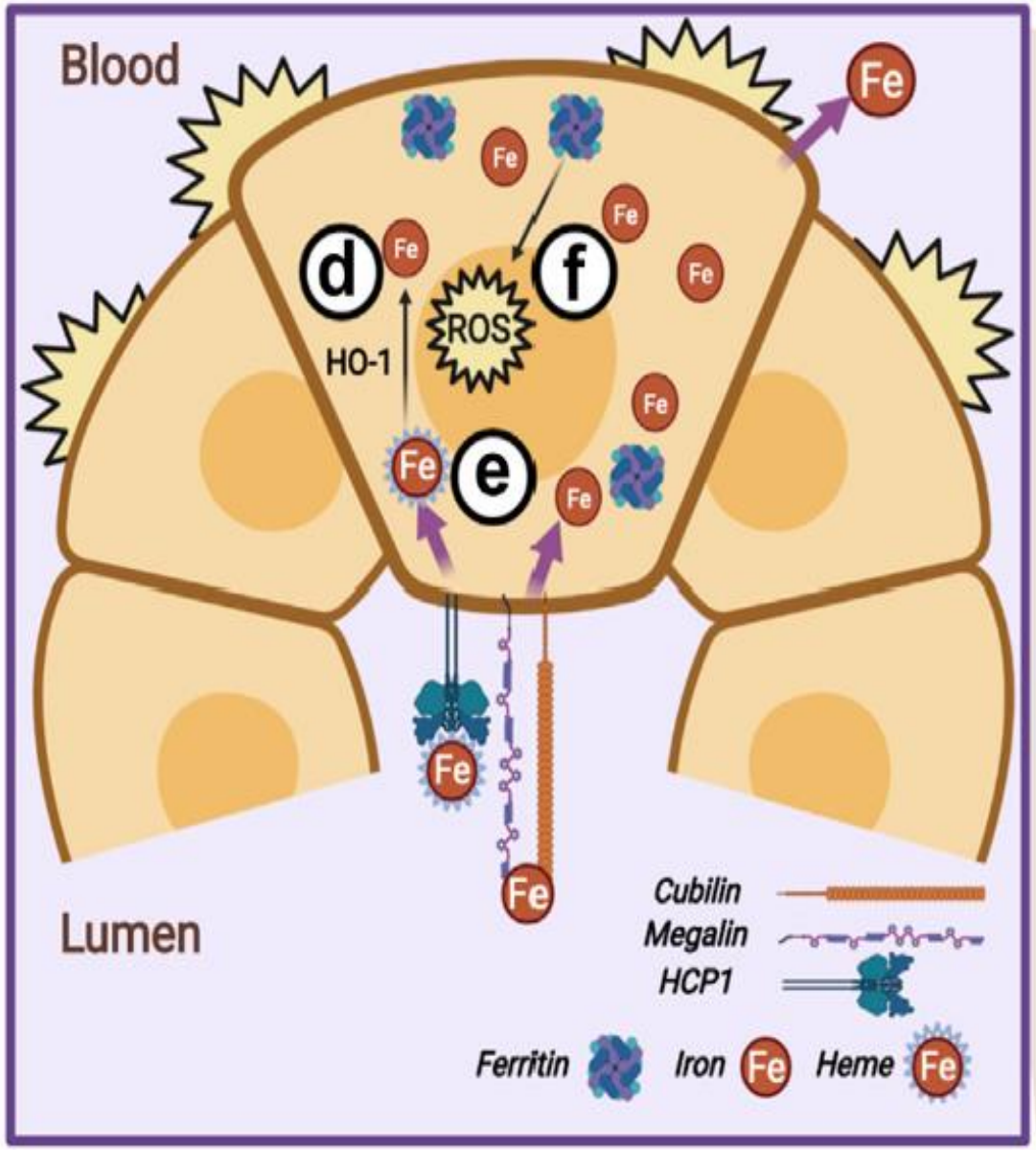


(a) Muscle takes damage and releases myoglobin and other metabolites into circulation.

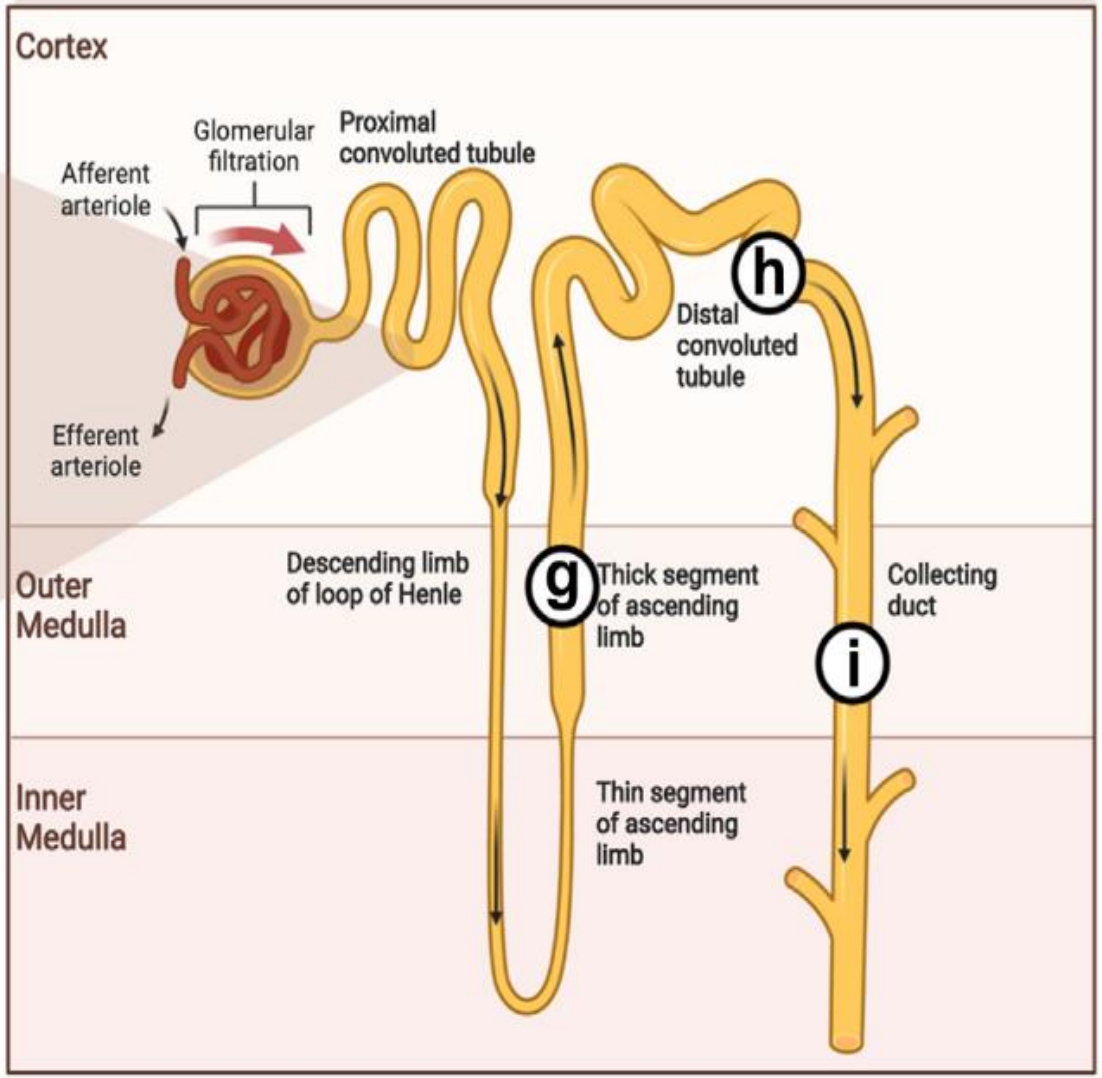
(b) Myoglobin is circulated to the kidney for filtration, causing capillary damage and hypovolemia en route

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

Kidney International Reports (2023) 8, 17–29



- (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)



(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.

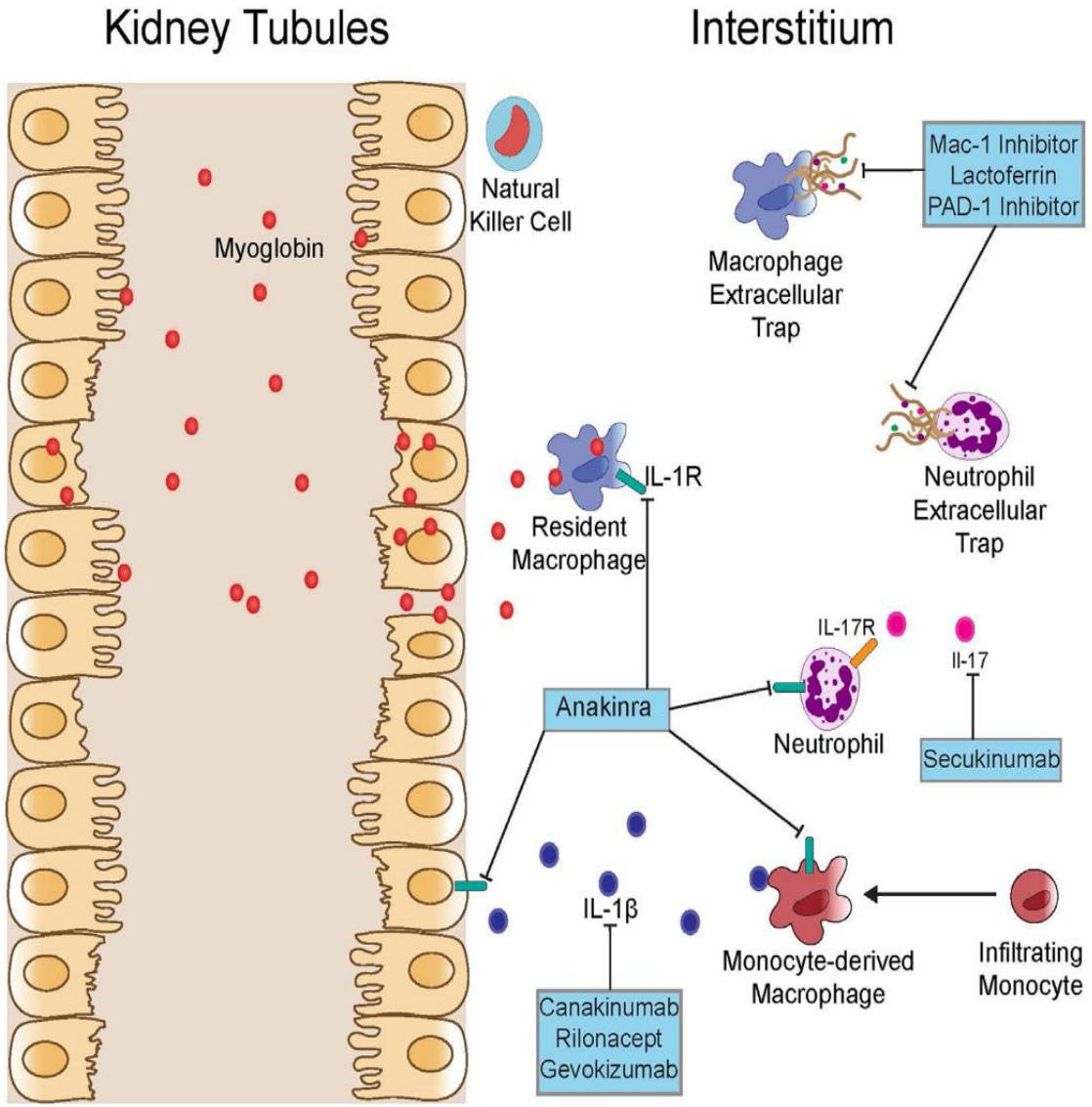
(i) Urine output decreases, resulting in reduced potassium excretion and perturbation of water, pH, and sodium balances, putting further pressure on the vascular system. ROS, reactive oxygen species

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 yet been investigated in

VASOCONSTRICTION

- High myoglobin level increasing F2-isoprostane quantity.
- Fluid sequestration and afterward increasing renal blood flow, activate RAAS.
- ROS production leads to endothelial dysfunction and then to an imbalance between vasoconstrictors and vasodilators substances.
- All these factors promote vessel spasm and its consequences

Rhabdomyolysis- Induced Acute Kidney Injury. Kidney Blood Press Res 2015;40:507-532

Pathogenesis and treatment of renal dysfunction in rhabdomyolysis.

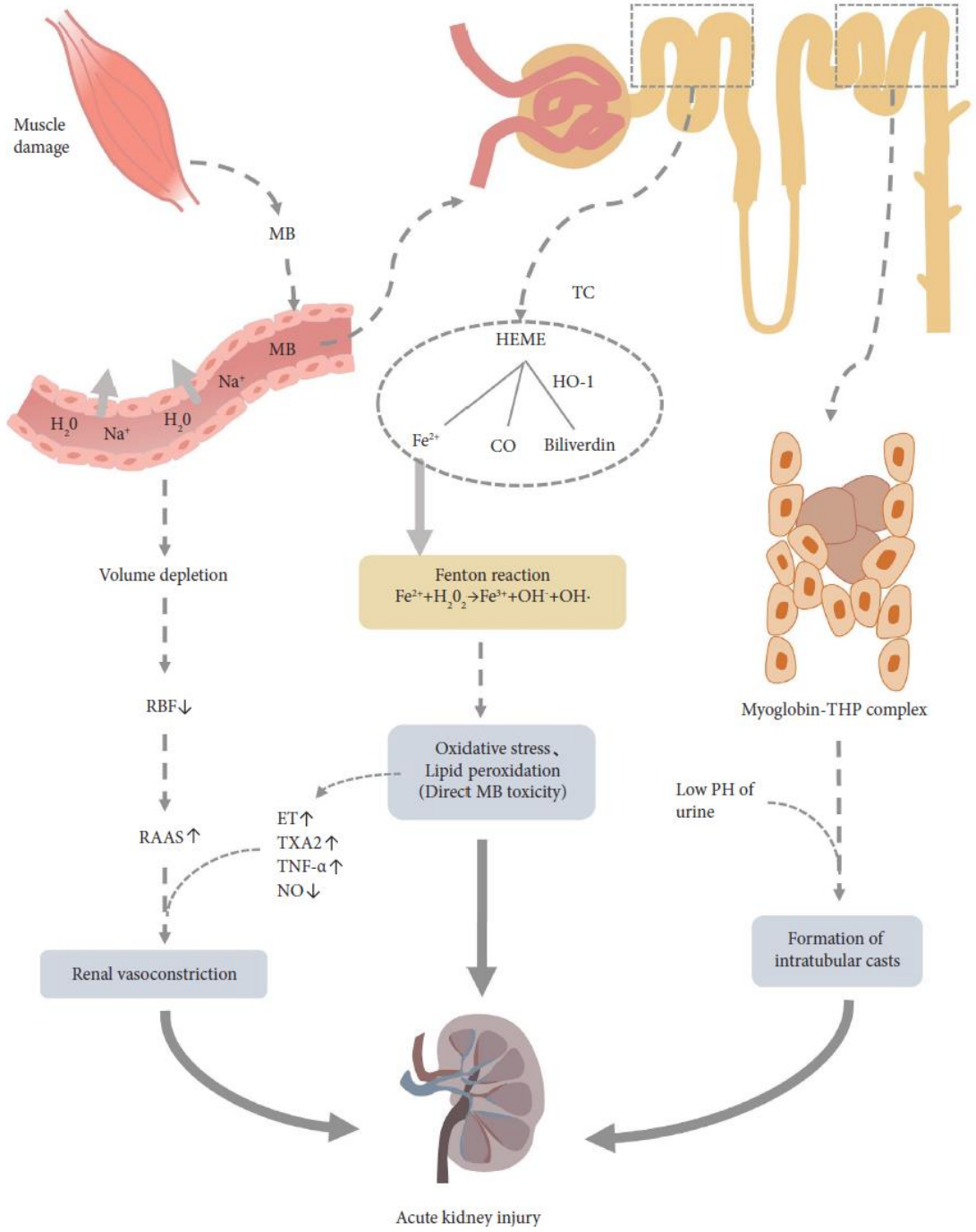
Intensive Care Med 2001;27:803-811.

INTRATUBULAR OBSTRUCTION AND APOPTOSIS

Characteristic manifestation in the tubular lumen is pigment

deposits after muscle cell disintegration, myoglobin and the Tamm-Horsfall protein, precipitate and forming tubular casts.

Volume depletion and acidic urine Ph promoting this process.


Muscle damage
MB
MB
Na+
H20
Na+
H20
TC
HEME
HO-1
Fe2+
CO
Biliverdin
Volume depletion
Fenton reaction
Fe2++H202→Fe3++OH-+OH·
Myoglobin-THP complex
RBF↓
Oxidative stress、
Lipid peroxidation
(Direct MB toxicity)
Low PH of urine
ET↑
TXA2↑
TNF-α↑
NO↓
RAAS↑
Renal vasoconstriction
Formation of intratubular casts
Acute kidney injury

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 urine (classically described as “tea colored”), and oligo-anuria.

Ortner 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 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.

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.
- 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

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

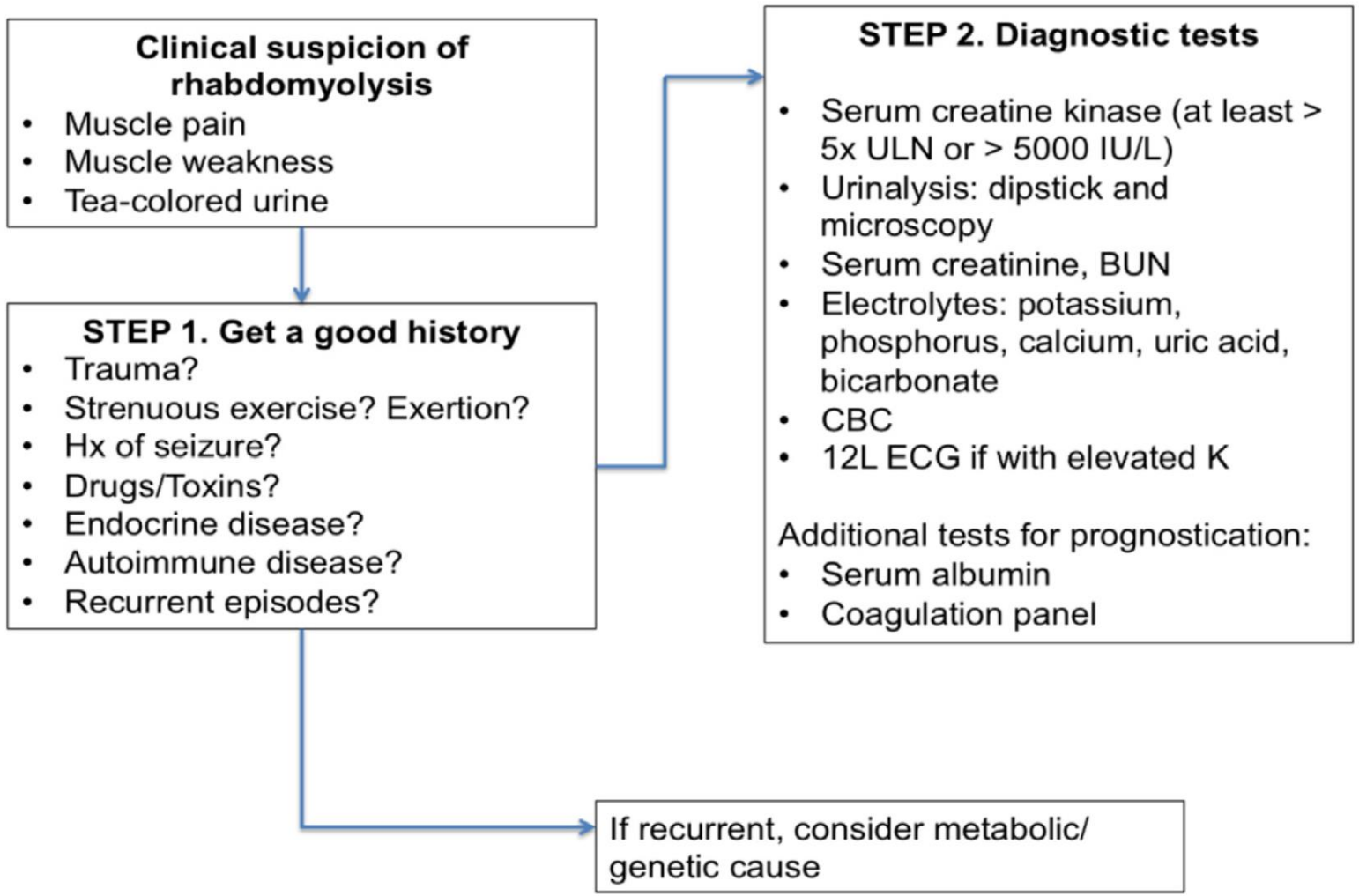
.

A McMahon score < 5 indicates a 2-3% risk of either need for RRT or death, whereas a score

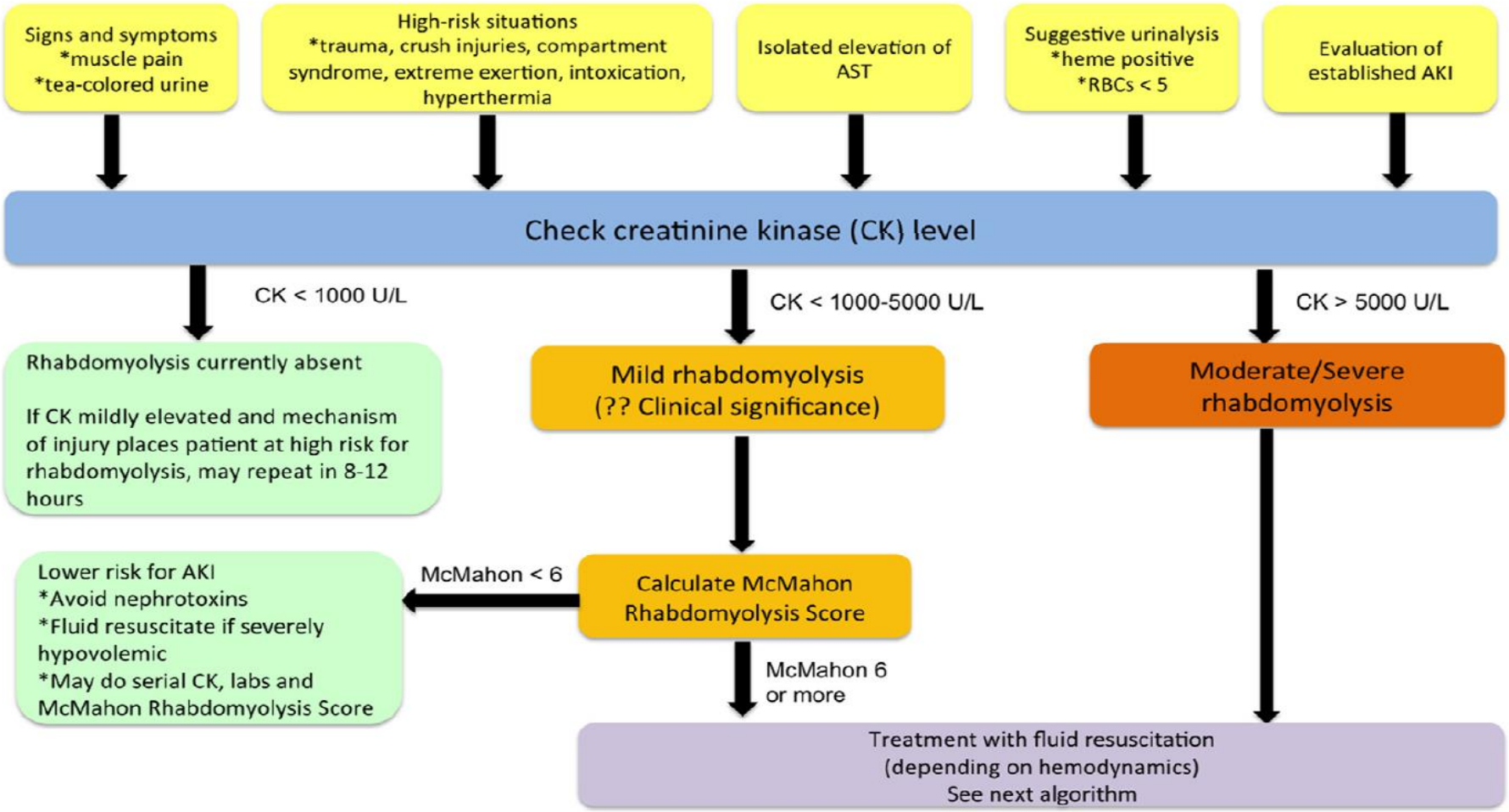
> 10 indicates a 52-61.2% risk of RRT or death.

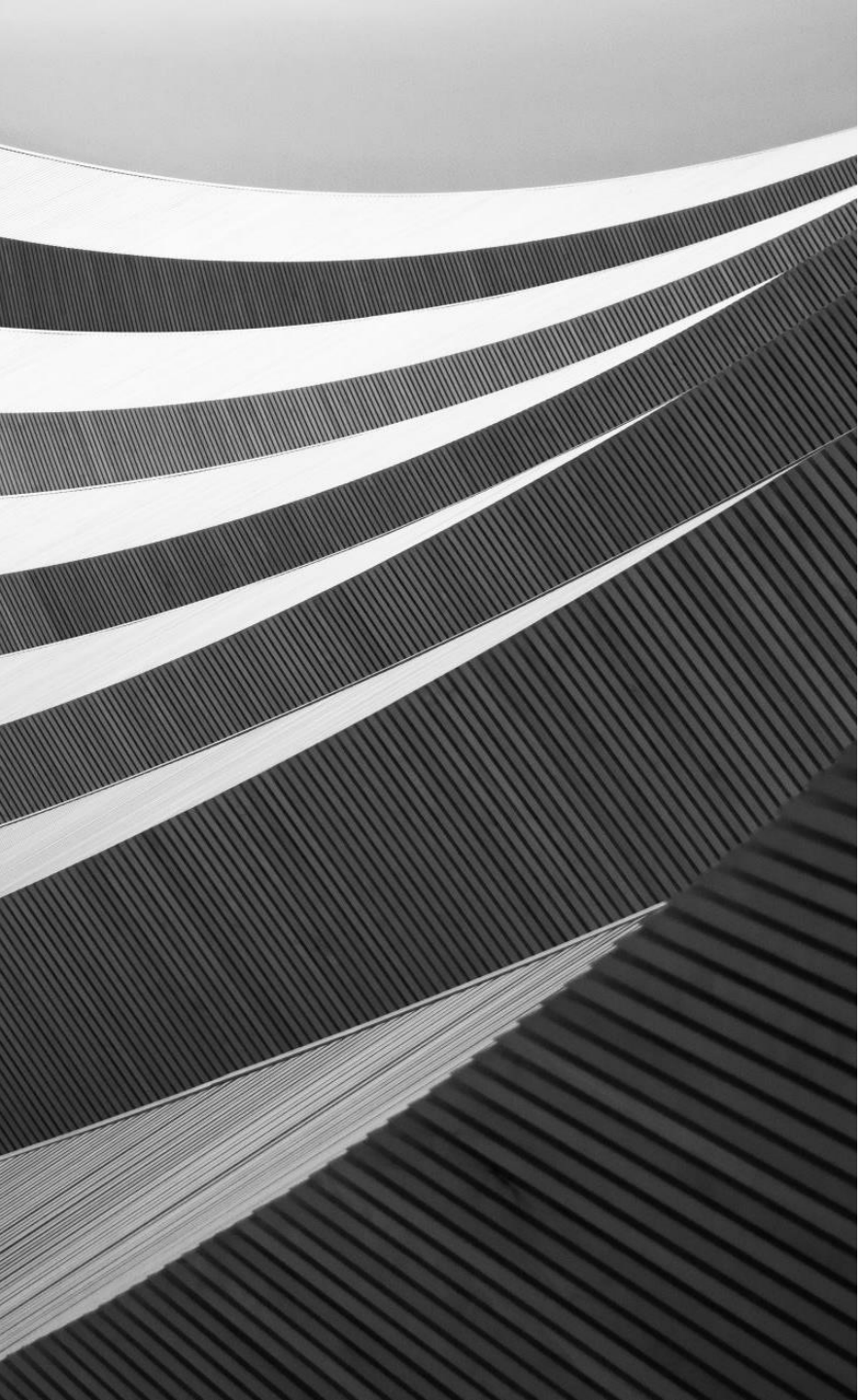
A score of 6 or greater indicates risk of acute kidney injury or dialysis, hence renal protective therapies should be considered in all patients with this score.

Intern Med . 2013 October 28;173(19):1821-1828


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





Who needs prevention

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, suggested 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.

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
- Prevention of intratubular cast formation

Volume Replacement

- 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.

Emerg Med J 2007;24:276–280

- 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 300 mL/hour

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)

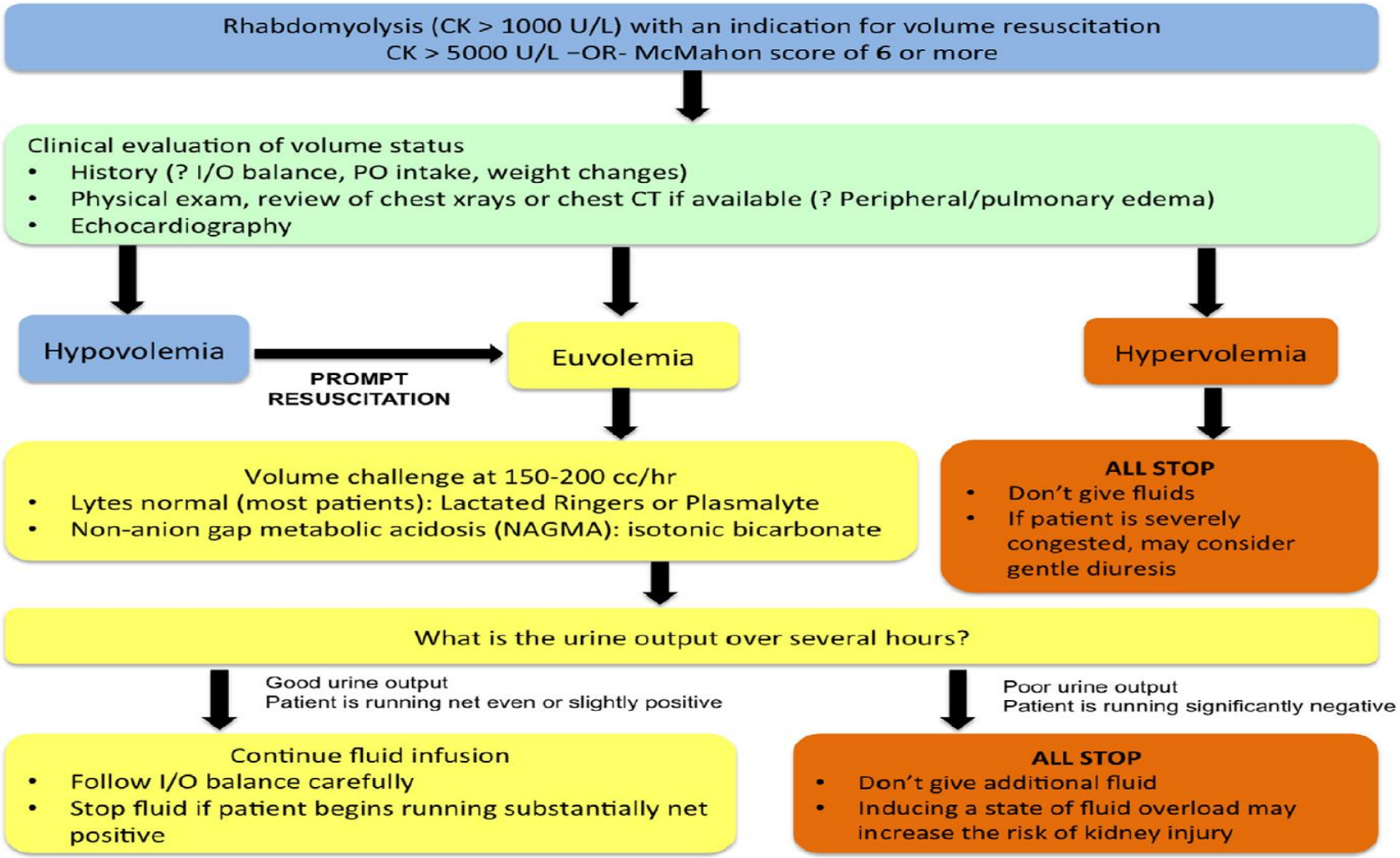
Recommendation is decreasing intravenous fluids to a rate sufficient only to maintain circulatory support.

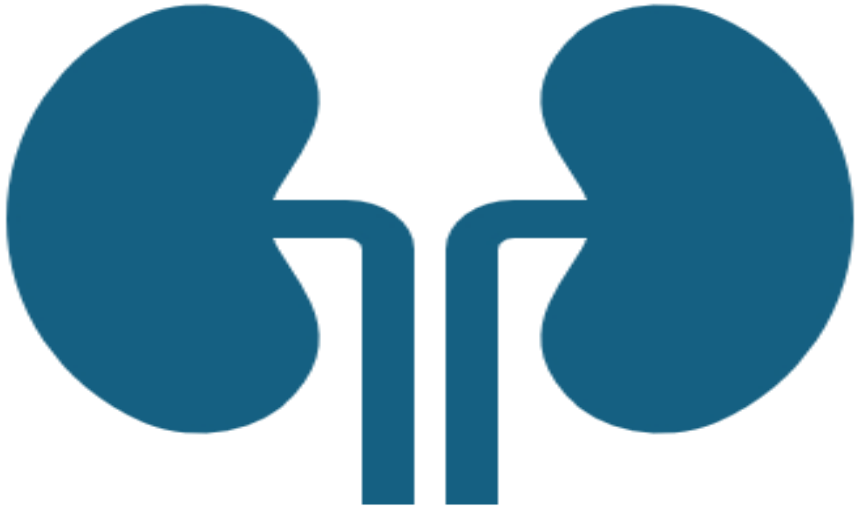
Fluid administration totals may need to be adjusted in patients with heart failure, and signs and symptoms of volume overload should be assessed frequently in such patients

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

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 mEq/L

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, hypocalcemia, or symptomatic fluid overload

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

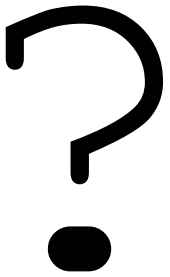
Hypocalcemia To minimize the late occurrence of hypercalcemia in rhabdomyolysis as well as the risk of calcium-phosphate precipitation, calcium supplementation for hypocalcemia should be avoided unless significant signs and symptoms of hypocalcemia develop or calcium administration is required for the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

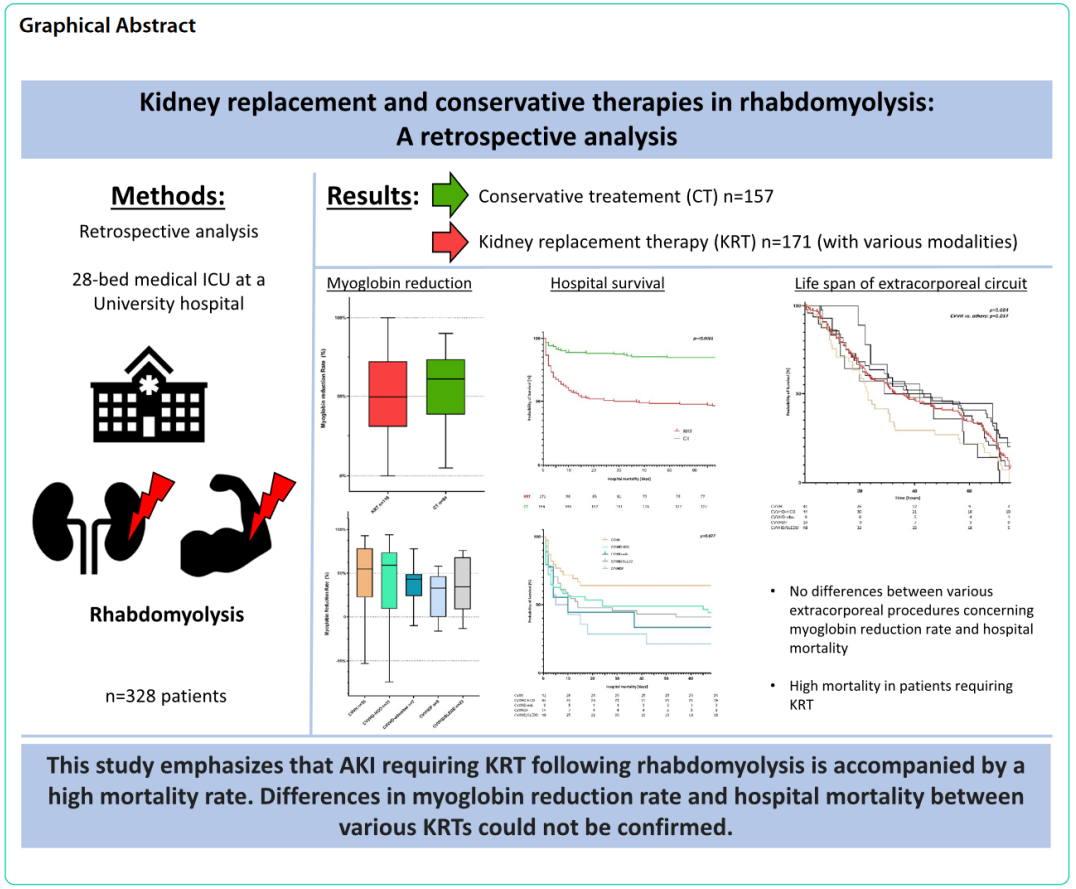
BMC Nephrology

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

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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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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

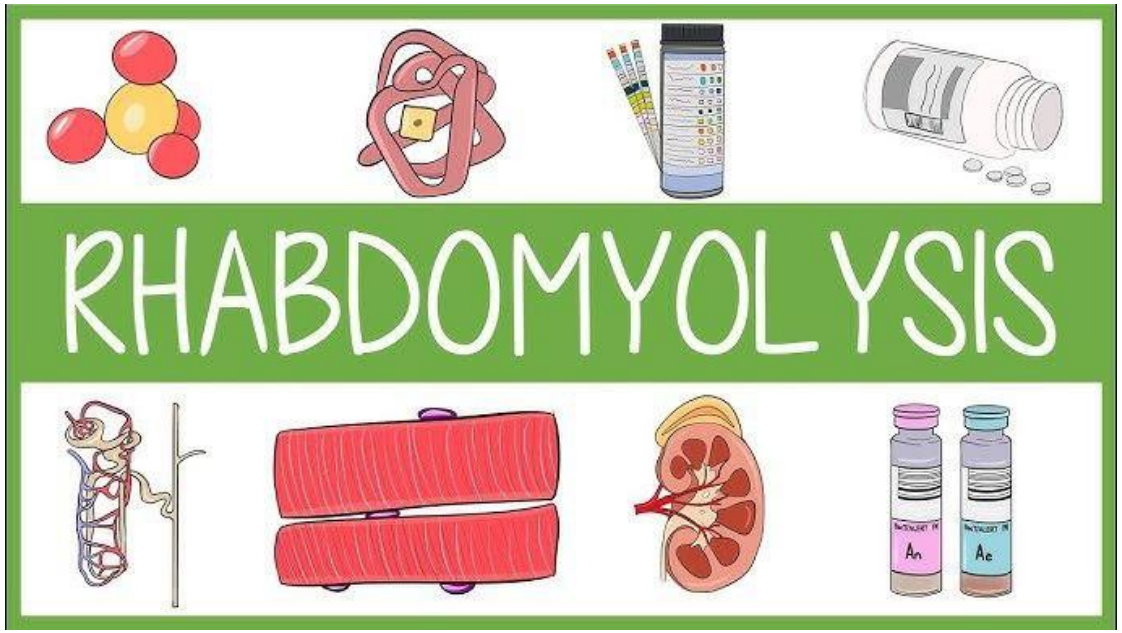
- N Engl J Med2006 Mar 9;354(10):1052-63

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


Thank You
For Your
Attention


RHABDOMYOLYSIS
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