

# Rhabdomyolysis: A Historical Review with Two Illustrative Cases

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**Learning Objectives:** 1) To identify the indicators of rhabdomyolysis, 2) to review the options for the management of patients with rhabdomyolysis, and 3) to appreciate the need for clinical vigilance and repeated examinations.

## Abstract

Rhabdomyolysis is not an uncommon occurrence; it has been observed from antiquity. The etiology of this long-standing condition is diverse. We report two classic cases that were managed successfully.

Rhabdomyolysis refers to disintegration of striated muscle.<sup>1</sup> The rhabdomyolysis syndrome was initially observed in the 13th century<sup>2,3</sup> BCE<sup>4</sup> and was presumed to be caused by the human ingestion of migratory quail that had eaten hemlock seeds.<sup>5,6</sup> In 1884, the first report of a presumptive metabolic disorder was reported in which horses developed weakness, bilateral paresis, and muscular tremors, and then myoglobinuria.<sup>7</sup> The first cases of crush syndrome and acute renal failure (ARF) were reported during the Sicilian earthquake in Messina<sup>8</sup> in 1908, and in the German medical literature during World War I.<sup>9</sup> In 1910, the classic trial of symptoms consisting of muscle pain, weakness, and brown urine was reported by Meyer-Betz.<sup>10,11</sup>

In 1924, physicians near Könisberger Haff shores along the Baltic coast recognized an outbreak of an illness manifested by sudden, severe muscular rigidity.<sup>12-15</sup> Other outbreaks resembling Haff disease were reported from Sweden and the Soviet Union from 1934 until 1984.<sup>16-19</sup> Similar outbreaks occurred in the following 9 years and affected approximately 1,000 individuals. Recently, Buchholz and associates<sup>12</sup> described in detail six U.S. cases that occurred in two clusters and as one sporadic case in California and Missouri, respectively. Haff disease has been identified as being caused by persons eating Bigmouth Buffalo fish (*Ictiobus cyprinellus*), a bottom-feeding freshwater fish similar to carp.<sup>20</sup>

Bywaters and Beall<sup>21</sup> identified the first causative association between rhabdomyolysis and ARF during World War II, following the observation of victims of the bombing of

London during the Battle of Britain in 1940. Bywaters<sup>22</sup> later published an overview of this syndrome.

The term "coturnism" was coined in 1972 by Samuel Bessman for this dietary-toxicologic syndrome. The articles written by Grivetti<sup>23</sup> and by Poels and Gabreels<sup>24</sup> describe in detail the fascinating history of this disease.

We present two cases of rhabdomyolysis that show its successful management.

## Case Report 1

A 29-year-old man presented to the emergency department with the following history, which he reported was of an unknown period of time, and after heavy alcohol use the preceding day. He was noted to have a swollen, severely tender, firm right buttock that was nonerythematous with no drainage and no sensory deficits. He was unable to dorsiflex or plantar flex the right big toe. He had no significant medical or surgical histories. Initial laboratory values were Na, 128; K, 5.9; Cl, 87; BUN, 61; CR, 3.4; Ca, 7.0; glucose, 187; CK, 21,985, with elevated liver enzymes; Hgb, 19.8 g/dL; Hct, 58; WBC,  $17.3 \times 10^3/\mu\text{L}$ ; and platelets,  $224 \times 10^3/\mu\text{L}$ . The blood alcohol level was 29 mg/dL and he tested positive for cocaine. The urine was dark brown and positive for myoglobin. After hydration with approximately 4 liters of crystalloid, a repeat set of laboratory determination showed Na, 128; K, 5.9; BUN, 33; CR, 1.4; CK, 41,779; Hgb, 7.4 g/dL; Hct, 21; and platelets  $92 \times 10^3/\mu\text{L}$ . At this time, arterial blood gas analyses showed a pH of 7.3,  $\text{paCO}_2$  of 33 mm Hg,  $\text{paO}_2$  of 92.4 mm Hg,  $\text{HCO}_3^-$  of 15.2 mEq/L, base deficit of -9.3 mEq/L, and  $\text{O}_2$  saturation of 96% on room air.

A diagnosis of compartment syndrome was made and the anesthesia department was notified. Aggressive fluid resuscitation was initiated after a large-bore intravenous (IV) and an arterial line were placed with approximately 6 liters of crystalloid being administered to this acidotic patient. He was transferred to the operating room for a surgical decompression fasciotomy under general anesthesia. A rapid-sequence induction technique was performed using fentanyl, midazolam, etomidate, and rocuronium with isoflurane for maintenance. Surgery lasted 40 minutes. Intraoperatively, the patient received 3,500 mL of lactated Ringer's solution/normal saline. The gluteus maximus was exposed and normal tissue with no evidence of necrosis was noted. The wound was packed and the patient was brought to the postanesthesia care unit and kept intubated for further resuscitation.

Postoperative laboratory values revealed progressive renal failure with BUN of 73, CR of 3.2, and hypocalcemia. The patient later became anuric and developed renal failure and atrial fibrillation. He was treated with diltiazem HCl by IV drip and then transferred to the intensive care unit and hemodialyzed. After 30 days, he was discharged home with resolved renal failure (BUN, 18; CR, 1.1; K, 3.9; Na, 140) and medicated with diltiazem HCl and vitamins.

## Case Report 2

A 21-year-old man was brought into the emergency department on 8/13/2002 with fracture of the left femur following a motor vehicle crash. He was noted to have a medical history of hip screws at age 7 and 15 for slipped femoral growth plates. Physical examination at time of presentation revealed broken glass shards over the head and neck, slurred speech, and the smell of ethanol on his breath.

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Vital signs were a blood pressure of 130/80 mm Hg, pulse rate of 113 beats per minute, respiratory rate of 26 per minute, and a temperature of 98.7°F. Examination of the cranial nerves revealed no deficit. The chest was clear to auscultation bilaterally. Examination of the cardiovascular system was normal with a regular rate and rhythm and heart sounds S<sub>1</sub> and S<sub>2</sub> only; there were no murmurs. The abdomen was obese, soft, nontender; bowel sounds were normal and there was no organomegaly. Rectal examination was within normal limits.

Examination of the extremities revealed a comminuted fracture of the left femur, comminuted fractures of the distal third of the left fibula and tibia, and a right midshaft fracture of the tibia and fracture, which were all painful and tender to palpitation. The dorsalis pedis was 2+ on the left and positive using a Doppler signal on the right. Computerized tomography studies of the abdomen, pelvis, cervical spine, and head were all within normal limits. Initial laboratory determinations were Na, 139; K, 3.5; CR, 102; HCO<sub>3</sub>, 26; BUN, 14; CR, 1.4; glucose, 126; Ca, 9.6; Hb, 15.1; Hct, 43.4; WBC, 13.3 x 10<sup>3</sup>/mL; platelets, 307 x 10<sup>3</sup>/μL. The ECG showed normal sinus rhythm. At the preoperative anesthesia visit, the patient was scheduled for open reduction and internal fixation of the left femur and intramedullary rodding of the left and right tibia under general anesthesia.

Preinduction vital sign values were blood pressure of 129/65 mm Hg, pulse rate of 129 beats per minute, respiratory rate of 20 per minute, and temperature of 99.1°F. Induction was with etomidate and fentanyl; suxamethonium was used to facilitate endotracheal intubation with a size 8.0 cuffed tube under direct vision. Rocuronium was used to facilitate ventilation. Anesthesia was maintained with oxygen in nitrous oxide 50% with desflurane and intermittent doses of fentanyl. Standard and invasive monitoring devices were placed. The patient was positioned on an Amsco-OrthoVision orthopaedic and fracture table (Steris Corp., Mentor, Ohio) for the surgery. Vital signs ranged from 80–140, 40–80, and 90–130 mm Hg. Normal saline, 9,500 mL, was infused. The surgery lasted 7 hours and 10 minutes. Blood loss was estimated to be 2,000 mL and the patient was transfused with 4 units of packed red blood cells. The patient was transferred, intubated, to the postanesthetic recovery room.

At 03:30 on 8/16/02, the patient was noted to have the following vital signs: blood pressure, 124/72 mm Hg; pulse rate of 155 beats per minute, respiration of 12 on ventilator settings of A/C RR 12, V<sub>T</sub> 800, F<sub>I</sub>O<sub>2</sub> 1.0, and PEEP of 5 cm H<sub>2</sub>O. The arterial blood gas values were pH, 7.33; PaCO<sub>2</sub>, 51 mm Hg; and PaO<sub>2</sub>, 249 mm Hg. The laboratory determination revealed Na, 138; K, 4.5; Cl, 110; HCO<sub>3</sub>, 23; BUN, 17; CR, 1.8; glucose, 105; AST, 765; ALT, 185; bilirubin, 1.1; alkaline phosphatase, 28; CPK, 78,000; WBC, 10.4 x 10<sup>3</sup>/μL; Hgb 7.9, g/dL; Hct, 27.3; platelets, 110 x 10<sup>3</sup>/mL; PT/PTT, 13.4/36.9; and INR, 1.6. Examination of the extremities revealed that the left lower extremity was warm, with a palpable dorsalis pedis; the extremity was edematous, with a capillary refill >2 seconds. The right lower extremity was cold from the middle lower leg to the foot, with no pulses noted. The urine was dark. A diagnosis of right anterior compartment syndrome was made and the surgeon was notified. The patient was resuscitated with hydration and prepared for fasciotomy under general anesthesia, and a four-compartment fasciotomy was performed in the postanesthetic recovery room. The surgical findings were muscles under tension with evidence of unhealthy muscle within the compartments.

The postfasciotomy results revealed that the posterior tibial artery was positive with Doppler but the dorsalis pedis was absent. Postoperatively, the patient was maintained on the ventilator (paralyzed). His right lower limb compartment syndrome worsened and he underwent above-knee amputation on the right leg on 8/24/02. He subsequently developed respiratory insufficiency, as characterized by increased airway pressures and hypoxemia. The arterial blood gas values on 100% O<sub>2</sub> were 7.309, 49, 55, 24.7, -1.2, and 86.8%.

The patient's respiratory failure worsened and he developed clinical features of adult respiratory distress syndrome. He was maintained on ventilator support. There was worsening of renal failure, with oliguria (160 mL over 24 hours) and BUN of 79 and CR of 5.5. Dialysis was started on 8/26/02. Following a tracheostomy under general anesthesia on 9/17/02, the patient gradually improved and was transferred for further rehabilitation.

## Etiology

Rhabdomyolysis is not an uncommon disorder and its etiology may be diverse.<sup>24</sup> Rhabdomyolysis may be inherited (Table 1) or acquired. The most common hereditary cause of rhabdomyolysis is McArdle disease, which is related to myophosphorylase deficiency. If rhabdomyolysis is acquired, it may be subdivided with some overlap into the groups shown in Table 2. Table 3 shows some causes primarily related to drugs and toxins. As can be seen from these tables, a multitude of factors may cause this condition; almost anything may produce rhabdomyolysis!

Crush injuries following earthquakes are a major cause of rhabdomyolysis. An average of 1,000 earthquakes with intensities of 5.0 or greater on the Richter scale are recorded each year.<sup>25</sup> With wars and an increase in terrorist activities, one may expect further instances of rhabdomyolysis, which will overwhelm presently available resources of personnel and equipment (e.g., dialysis equipment) for treating the injured.

**Table 1. Inherited Causes of Rhabdomyolysis**

### *Deficiencies of Glyco(Geno)Lytic Enzymes*

- Myophosphorylase (McArdle disease)
- Phosphorylase kinase
- Phosphofructokinase (Tarui's disease)
- Phosphoglycerate mutase
- Phosphoglycerate kinase
- Lactate dehydrogenase

### *Abnormal Lipid Metabolism*

- Carnitine palmitoyltransferase deficiency I and II
- Carnitine deficiency

### *Other Genetic Disorders*

- Idiopathic rhabdomyolysis
- Myoadenylate deaminase deficiency
- Malignant hyperthermia
- Neuroleptic malignant syndrome

**Table 2. Acquired Causes of Rhabdomyolysis**

<i>Traumatic: Direct Muscle Injury</i>	
Crush	
Burning, freezing	
Electric shock, lightning stroke	
<i>Ischemic Injury</i>	
Compression	
Vascular occlusion	
Sickle cell trait	
<i>Metabolic/Metabolic Disorders</i>	
Diabetic ketoacidosis	
Nonketotic hyperosmolar coma	
Hypothyroidism	
Hypophosphatemia	
Hyponatremia	
Hypokalemia	
<i>Infectious/Infections</i>	
Bacterial	
Viral	
<i>Inflammatory</i>	
Polymyositis	
Dermatomyositis	
<i>Exercise/Excessive Muscle Exercise</i>	
Sports and military training	
Status epilepticus	
Status asthmaticus	
Convulsions	
Prolonged myoclonus, acute dystonia	
<i>Heat-related Syndromes</i>	
Toxic shock syndrome	
Heat stroke	

Under ischemic injury, we may consider compartment syndrome. This condition results from a confined swelling within a muscular compartment, which, if untreated, may result in a cessation of capillary circulation, ischemia, and necrosis of muscle and nerves. Tiwari et al<sup>26</sup> recently published a detailed review of acute compartment syndrome with reference to the abdominal compartment syndrome and the limb compartment syndrome, describing the etiology, treatment, and outcome of each of these syndromes.

In the leg, the anterior compartment is commonly affected and "the commonest fractures in limb compartment syndrome are those of the tibial shaft."<sup>27</sup> Comminuted fractures are most prone to compartment syndrome and may reflect the high energy required to cause this type of fracture; operative treatment of fractures with intramedullary nailing can lead to limb compartment syndrome.<sup>26,27</sup> This situation occurred in the second case report presented here, and was diagnosed by clinical vigilance and repeated examinations.

Alcoholism is a common cause of rhabdomyolysis. This may be secondary to alcohol-related trauma, seizures, or coma or may be due to the direct effect of ethanol on skeletal

**Table 3. Drugs and Toxins Known To Cause Rhabdomyolysis**

Alcohol (ethanol)	Loxapine
Amoxapines	LSD (lysergic acid diethylamide)
Amphetamines	
Amphotericin B	
Anticholinergic syndrome	Malignant hyperthermia
Antihistamines	Mercuric chloride
	Methadone
Barbiturates	Morphine
Benzene	
Bezafibrate	Neuroleptics
Carbenoxolone	Oxprenolol
Carbon monoxide	
Chloralose	Paracetamol
Chlorpromazine	Paraphenyl diamine
Clofibrate	Pentamidine
Copper sulfate	Phencyclidine
	Phenformin
Diazepam	Phenylpropanolamine
Dihydrocodeine	Phenylzene
Diuretics	
L-Dopa withdrawal	Quail ingestion
	Haff disease
Ethylene glycol	Brown spider bite
	Snake bite
Fenfluramine	Hornet/wasp sting
Fluphenazine	
	Rohypnol
Gasoline sniffing	
Glutethimide	Salicylates
	Stelazine
Haloperidol	Strychnine
Heroin	Suxamethonium
Isoniazid	Theophylline
Isopropyl alcohol	Toluene (paint sniffing)
Lindane	Vasopressin
Lithium	
Liquorice	Zinc phosphide

muscle, resulting in both chronic myopathy and acute rhabdomyolysis. It is believed that ethanol causes direct sarcolemmal injury, leading to increased sodium permeability and subsequent accumulation of calcium. Hypophosphatemia may also be an important precipitant because the ability of muscle cells is reduced.

There are many reports on rhabdomyolysis following propofol use by children and adults, but the authors question a direct cause-and-effect relationship (not having observed or heard of same from colleagues). Drugs such as lipid-lowering agents and antibiotics have been implicated as etiologic agents in statin-associated rhabdomyolysis,<sup>28,29</sup> which may occur in patients with normal creatine levels.<sup>30</sup> Prolonged immobilization, as for a patient in the lithotomy position<sup>31-33</sup> or the Lloyd-Davies position,<sup>34,35</sup> may result in a compartment syndrome.

## Complications

Complications are due to the local effects of muscle injury and the systemic effects of released muscle components. These complications include 1) hypovolemia from hemorrhage and influx of fluid to necrotic muscle, 2) cardiac arrest and arrhythmia (due to hyperkalemia, which is potentiated by hypocalcemia resulting from calcium deposition in necrotic muscle), 3) compartment syndrome, 4) disseminated intravascular coagulation, and 5) ARF.

## Treatment

As indicated by Dhawan et al,<sup>36</sup> treatment consists of the following six steps: 1) hydration, in order to maintain adequate hydration and urinary output, 2) alkalinization of the urine to prevent dissociation of myoglobin to its nephrotoxic metabolites, 3) diuretic therapy to dilute the nephrotoxic metabolites, 4) normalization of electrolyte disturbances (e.g., hyperkalemia [when >6.5 mEq/L] by the administration of glucose and insulin, hyperphosphatemia by oral administration of  $\text{CaCO}_3$  or  $\text{Ca}[\text{OH}]_2$ ), 5) dialysis, if indicated (e.g., in uncontrolled hyperkalemia, acidosis, uremic encephalopathy), and 6) supportive therapy (e.g., fresh-frozen plasma is indicated in the event of disseminated intravascular coagulation when associated with bleeding, and decompressive fasciotomy, in the case of a compartment syndrome to prevent further local tissue necrosis).

## Discussion

Myoglobin, a 17,000 molecular weight oxygen-binding protein, is present in skeletal muscle at a concentration of 1 g/kg. Upon skeletal muscle damage, myoglobin is released into the bloodstream and filtered therefrom by the kidneys. The visible discoloration of urine by myoglobin indicates both massive and acute muscle destruction (rhabdomyolysis). The kidneys may be occluded, with resultant damage (e.g., tubular necrosis or kidney failure). Myoglobinuric renal failure occurs within the clinical scenario of rhabdomyolysis in about 30% of patients.

At a urine pH less than 5.6, myoglobin is transformed to ferrihematin, which precipitates in the proximal tubule. Renal damage is facilitated by hypovolemia and acidic urine. Oligonuria is associated with hyperkalemia, hypocalcemia, anion-gap acidosis, and rapid azotemia because of the hypercatabolic state. Early and aggressive fluid hydration may prevent complications by rapidly eliminating the myoglobin from the kidneys. The hydration needs with muscle necrosis may approximate the massive fluid volume needs of a severely burned patient.

Evidence of rhabdomyolysis can range from a subclinical rise of creatine levels to a medical emergency comprising interstitial and muscle cell edema, contraction of intravascular volume, and pigment-induced ARF.

Serum creatine kinase  $\geq 5$  times the normal (reference ranges: males, 38-174  $\bar{U}$ ; females, 96-140  $\bar{U}$ ) is a primary diagnostic indication of rhabdomyolysis, as observed in both case reports presented here. This elevation is so great that other causes (e.g., myocardial infarction) may be excluded. In addition, the CK-MM isoenzymes constitute at least 98% of the total volume. Other significant biochemical findings are hyperkalemia, hypocalcemia, hyperphosphatemia, and

hyperuricemia. Metabolic acidosis may result from release of phosphate, sulfate, uric acid, and lactic acid from the muscle. The pathogenesis and management of rhabdomyolysis have been well described in detail by Dhawan et al<sup>36</sup>; the search for the toxic mechanisms has also been well described by Grivetti.<sup>23</sup>

## Conclusions

Rhabdomyolysis is not an uncommon event and may result from a variety of conditions. The complications thereof can be life-threatening. As Dhawan et al<sup>36</sup> determined, "The treatment in the acute phase consists of maintaining an adequate circulating volume and sufficient diuresis to prevent renal complications. The prognosis of adequately treated rhabdomyolysis is excellent."

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## Guidelines for Management of Mechanical Ventilation in Critically Injured Patients

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### Premise

Patients suffering severe trauma are at high risk of developing respiratory failure: both acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) (Appendix 1). Management strategies for these patients should begin upon arrival at the trauma center/emergency department by initially identifying who is most likely to develop severe respiratory insufficiency. The goal is to institute therapies early (e.g., “open lung” or “protective” lung ventilation) in the emergency department, operating room, and in the intensive care unit (ICU) in an effort to lessen the degree or to prevent the formation of atelectasis and/or parenchymal damage to the lung.

### Statement of the Issue

One of the most basic and paradoxically advanced clinical skills in the practice of anesthesiology and critical care medicine is the management of mechanical ventilation. Ideally,

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mechanical ventilation should potentiate alveolar recruitment, optimizing intrapulmonary gas distribution, and narrowing time-constant discrepancies. Ideal ventilator management should distribute pressure and volume to dependent and nondependent regions proportionally.

Recommendations for ventilator management from several randomized, prospective trials are suggested in Table 1. These recommendations refer to ALL locations where patients following injury may be located: the emergency department, operating theatre, and ICUs. For patients with respiratory failure who require surgery, *if the ventilator settings in the ICU exceed the capability of the operating room ventilator, then the patient should be taken to the operating room on the ICU ventilator, and remain on the ICU ventilator for the surgical procedure.* The goal, from admission onward in these high-risk patients, is to do no further harm.

**Table 1. Recommendations for Ventilator Settings**

- Tidal volumes 6–8 mL/kg
- PEEP higher than the lower inflection point
- Limit peak/plateau pressure to <35 cm H<sub>2</sub>O
- Adjust I:E ratio and respiratory rate as needed to achieve above
- Wean FiO<sub>2</sub> to obtain PaO<sub>2</sub> 80–100 mm Hg (or an oxygenation saturation of 93–97%)
- Early conversion to pressure-limited modes of ventilation

### Atelectasis

Recent studies provide data that support the use of positive pressure and low oxygen concentrations to minimize or reverse the formation of atelectasis during mechanical ventilation and general anesthesia. Atelectasis formation is also seen in the ICU in dependent lung zones.

Within 5 minutes of induction of general anesthesia, increased densities appear in the dependent regions of both lungs.<sup>1</sup> They develop with both intravenous and inhalational anesthesia and whether the patient is breathing spontaneously or is paralyzed and ventilated mechanically.<sup>2</sup> Although atelectasis may not appear to be severe on chest radiograph