time, leading to muscle hypoxia.[3] Conditions leading to skeletal muscle ischemia, such as direct compression or compartment syndrome, may lead to irreversible damage to the muscle; much of the injury may actually occur with reperfusion, in addition to injury sustained during the period of ischemia.[7] Trauma is a common cause of rhabdomyolysis, but less than 20% of all cases of rhabdomyolysis are thought to be related to direct injury; metabolic or medical causes of rhabdomyolysis are more common.[8]

Metabolic etiologies

Recommendation

Rhabdomyolysis should be suspected in any patient with a medical condition causing increased metabolic demands on myocytes in excess of the available supply of ATP. This may result from extreme exertional demands on skeletal muscle from exercise, exogenous agents such as drugs or toxins, genetic defects or myopathies affecting the muscle cell, and infections.

Discussion

Any process that impairs ATP production by skeletal muscle and any state where skeletal muscle energy requirements exceed the available ATP may lead to rhabdomyolysis.[3] With ATP depletion, active transport pumps are no longer able to maintain low levels of intracellular calcium; unregulated increases in intracellular calcium lead to activation of calcium-dependent enzymes with eventual breakdown of the muscle cell.[1] Exertional causes of rhabdomyolysis may include extreme and prolonged exercise or seizure activity such as status epilepticus.[9] Most commonly, drugs and toxins lead to rhabdomyolysis. Alcohol abuse or dependence may actually be the most common risk factor for rhabdomyolysis; ethanol has direct adverse effects on muscle tissue metabolism and cellular integrity including inhibition of active transport pumps.[3 8] Other illicit substances such as cocaine, heroin, and phencyclidine may also be implicated in cases of rhabdomyolysis. Lipid-lowering agents, especially statins, are a common cause of rhabdomyolysis, particularly in patients with concomitant renal or liver insufficiency.[10] Infections such as influenza, Epstein-Barr virus, *Streptococcus pyogenes*, or *Staphylococcus aureus* may rarely lead to rhabdomyolysis.[1] Genetic diseases including disorders of glycolysis or glycogenolysis, lipid metabolism defects, or mitochondrial disorders are rare causes of rhabdomyolysis.[1] Finally, rhabdomyolysis may be seen in patients with extreme alterations in body temperature due to conditions such as malignant hyperthermia, heat stroke, or neuroleptic malignant syndrome.[11] Metabolic etiology for rhabdomyolysis is very broad and a number of different risk factors may need to be considered in this population.

CLINICAL MANIFESTATIONS

What clinical findings are expected with rhabdomyolysis?

Recommendation

Rhabdomyolysis presentation may vary from asymptomatic to commonly implicated clinical features, including acute muscle weakness, pain/tenderness, and swelling (dolor, tumor) of the affected extremity or body region.[12] Darkened (tea-colored) urine may be an additional common finding. A low threshold of clinical suspicion in the proper laboratory and historical context is warranted to initiate appropriate therapy.

Discussion

Rhabdomyolysis is a clinical syndrome consequent to skeletal muscle cell death with release of intracellular contents (described in next section) into the circulation.[12] Resultant organ dysfunction may include renal (AKI), cardiac (arrhythmia), and coagulopathy. Despite this cluster of findings, there is no formally held definition for rhabdomyolysis and clinical presentations may vary greatly. Commonly implicated muscle groups are the extremities and the lower back. Superficial pressure ulceration or blistering may suggest the diagnosis, but is not a reliable finding. At the extremes of pathology, compartment syndromes of affected muscle groups lead to increased morbidity and potential need for decompression.[13]

What laboratory findings aid in the diagnosis of rhabdomyolysis?

Recommendation

The most commonly implicated variables include elevated serum concentrations of CK (>5× the upper limit of normal or >1000 IU/L), myoglobin, lactate dehydrogenase (LDH), potassium, creatinine, and aspartate aminotransferase (AST). Elevated urine myoglobin provides additional evidence. A low threshold of suspicion in the proper clinical context is warranted to initiate appropriate therapy. A strategy for disease monitoring with serial CK measurement should be additionally undertaken. Interval CK values should be followed until a peak concentration is identified (typically at 24–72 hours), discontinued once the CK is reliably downtrending.

Discussion

Traumatic or non-traumatic injury to the skeletal muscle cellular membrane leads to an influx of calcium into the cytoplasm, disrupting cellular homeostasis and leading to cell death. Injury may be exacerbated by the generation of reactive oxygen species after restoration of blood flood to the affected tissue (reperfusion injury). The resulting effect is the accumulation of CK, myoglobin, LDH, and potassium in the circulation.[2] In a recent systematic review, the laboratory definition of rhabdomyolysis varied to include an elevated CK level >5× the upper limit of normal or >1000 IU/L, with the CK-MM subtype being the most reflective of skeletal muscle injury.[1 2] CK values may become elevated within 12 hours of injury, peak at 24 to 72 hours, and return to normal in roughly 5 days, depending on the degree of injury and appropriate therapy.

Myoglobin becomes elevated in the circulation once intrinsic binding proteins are overwhelmed. Given a shorter half-life (1–3 hours) versus CK, myoglobin may elevate and resolve prior to CK depreciating its clinical utility. Myoglobin may also be evident in the urine and, although the sensitivity has been reported up to 100%, the specificity varies widely from 15% to 88%.[5] Although a causal relationship may exist between rhabdomyolysis and elevations in hepatic aminotransferases (AST, ALT: alanine transaminase), this is of unclear value as both enzymes exist within skeletal muscle and may become elevated as a result of primary muscle injury.[7 8 14 15]

MANAGEMENT

What is the optimal crystalloid type, rate of administration, and urine output goals to prevent AKI in rhabdomyolysis?

Recommendation

Either lactated Ringer's solution or saline (0.9% or 0.45%) is an acceptable fluid for resuscitation in rhabdomyolysis. A starting rate of 400 mL/hour can be initiated, with goal-directed therapy of urine output of 1 mL/kg/hour to 3 mL/kg/hour, and up to 300 cc/hour.