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AN OVERVIEW OF RHABDOMYOLYSIS

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ABSTRACT: A clinical condition known as rhabdomyolysis involves the breakdown of skeletal muscle tissue and intracellular muscle fluid being released into the bloodstream. An overview of rhabdomyolysis is the aim of this thorough analysis of the literature. When there is a history of rhabdomyolysis, it is a dangerous illness that can pose a life-threatening threat. Although there are no universally accepted diagnostic criteria for rhabdomyolysis, it is appropriate to define it as an increase in a minimum 10-fold increase in serum creatine kinase activity, the maximum permitted by normal, after which a sharp drop in sCK levels to (or close to) normal levels. Myalgia, weakness, and pigmenturia are traditional aspects of the clinical presentation, which might vary greatly. Rhabdomyolysis treatment is dependent on an early diagnosis. Maintaining renal function, treating compartment syndrome, addressing metabolic imbalances, and fluid replacement should be the main goals of treatment throughout the acute period. Most individuals only have one rhabdomyolysis episode, which is typically brought on by drug addiction, prescription side effects, trauma, or epileptic seizures.

Keywords: **- Rhabdomyolysis, Myalgia, Creatinine kinase, Pigmenturia, Skeletal muscles.**

INTRODUCTION

Rapid disintegration of skeletal muscle that has been wounded or damaged is called rhabdomyolysis. Myoglobin, the amount of muscle cells, and rhabdomyolysis, or skeletal muscle disintegration, cause sarcoplasmic proteins (like aspartate aminotransferase, alanine, lactate dehydrogenase, and creatine kinase) and electrolyte leakage into the extracellular fluid and blood. The Greek terms mus (muscle), rhabdos (rod-like/striated), and Lucis are the source of the word rhabdomyolysis (breakdown).[1] Muscle weakness, discomfort, localized swelling, and myalgia are common symptoms and warning signs. Myoglobinuria, or dark red urine, may also be present. It might range from a minor elevation in creatinine phosphokinase to serious health issues such compartment syndrome, disseminated intravascular coagulation, intravascular fluid depletion, cardiac arrhythmias, pigment-induced acute kidney damage (AKI). There is no accepted blood level cut-off for the rhabdomyolysis diagnosis in the lab; however, elevated serum creatine phosphokinase (CPK) is indicative of the condition. For diagnosis, many doctors use values that are 3 to 5 times the typical upper limit range of 100–400 IU/L (about 1000 IU/litre). Rhabdomyolysis is one of the main causes of acute renal failure.[2] The prognosis

of acute renal damage with rhabdomyolysis is usually benign if detected early.[3] There are two different traumatic and nontraumatic rhabdomyolysis etiologies. Traumatic rhabdomyolysis is largely caused by crush syndrome, which can arise from earthquakes, accidents, and other man-made or natural disasters. Not every muscle injury leads to renal failure and rhabdomyolysis. Always take into account other possible causes of acute renal failure, such as medication use, infection, and dehydration. Frequent causes of nontraumatic rhabdomyolysis include convulsions, alcohol, drugs, and prolonged bed rest.[4] Rhabdomyolysis frequently results in acute renal failure, which is caused by the toxic effects of filtering excessive amounts of myoglobin in presence of hypovolemia.[5]

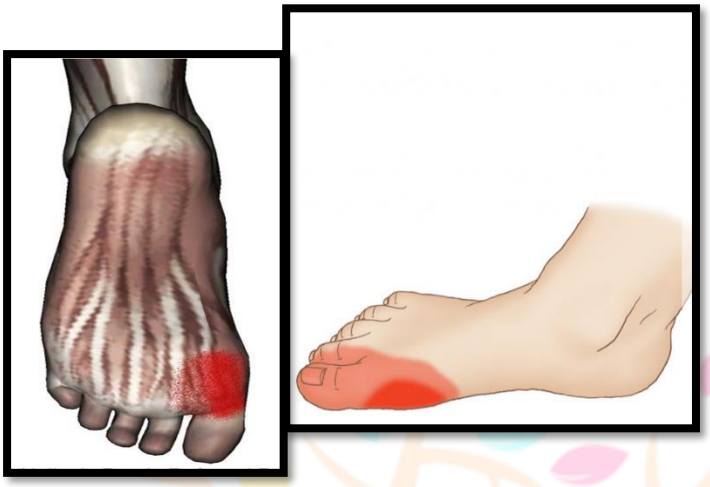

Figure 1.1: - Breakdown of Flexor Hallucis Brevis Muscle

HISTORY

The first case of rhabdomyolysis was documented in Germany in 1881;[6] following the London Battle in the Second World War, more information was provided. [7] Rapid skeletal muscle fiber breakdowns, or rhabdomyolysis, results in the discharge of potentially hazardous substances into the cellular contents of the bloodstream. [8&9] The activity of serum creatine kinase (sCK) is increased to at least 10 times the maximum permitted by normal in the condition, following a quick decline. The definition of rhabdomyolysis is controversial. Others believe that a smaller rise in sCK elevation (more than 5) is adequate for the diagnosis of rhabdomyolysis, whereas some stick to the previously described increase. [9&10] Clinical advice on the application and security of statins from the National Heart, Lung, and Blood Institute, the American College of Cardiology, and the American Heart Association on sCK elevations larger than ten times the maximum level of normal was used to diagnose statin-induced rhabdomyolysis. [10&11] Aside from people with muscle dystrophies, myositis, or a problem with glycogen metabolism, most patients' sCK levels are normal, except for those with particularly violent rhabdomyolysis. Due to increased myoglobin levels in urine, which manifest as urine that is dark tea or Coca-Cola-colored, rhabdomyolysis may be accompanied by myoglobinuria. [12]

EPIDEMIOLOGY

A thorough analysis of rhabdomyolysis with a focus on bicarbonates and mannitol appears to be underdiagnosed, and its incidence is not fully understood worldwide. There are no extensive epidemiologic studies on rhabdomyolysis or current registrations. However, American sources claim that 26,000 cases occur annually throughout the world. Due to differing definitions of kidney injury and the etiological and demographic heterogeneity reported in these studies, it is unclear how common AKI is among rhabdomyolysis patients. Rhabdomyolysis is thought to be the root cause of 7%–10% of AKI occurrences annually in the US, according to recent reports. Accordingly, according to estimates, AKI occurs in 4% to 33% of rhabdomyolysis patients. [13] In the USA, rhabdomyolysis cases are estimated to be 25,000 a year. Around 5 to 30% of those with rhabdomyolysis have acute renal damage. Due to the various definitions of kidney injury (KI), the incidence of AKI varies significantly throughout rhabdomyolysis scenarios. And with rhabdomyolysis of a varied degree. Rhabdomyolysis-related acute renal damage accounts for 15% of all

instances of AKI. [14] There are several factors to consider, making it difficult to pinpoint the exact number of cases of rhabdomyolysis. Hospital systems in the USA recorded 26,000 instances of rhabdomyolysis in 1995. Rhabdomyolysis affects about 85% of people who suffer severe trauma. [15] 10–50% of patients suffering from rhabdomyolysis experience acute renal damage. [16] When compared to muscle diseases, those who have previously abused alcohol, illegal substances, or experienced trauma are more at risk. It is also especially high if several risk factors coexist. In the USA, 7–10% of all instances of acute renal damage are caused by rhabdomyolysis. [14]

PATHOPHYSIOLOGY

Although there are several reasons why rhabdomyolysis occurs, direct myocyte damage, or a breakdown in the source of energy within the muscle cell, is the last prevalent mechanism that leads to muscle damage and necrosis. [17] The sodium-potassium pump and sodium-calcium exchanger located in the sarcoplasmic membrane maintain low intracellular and sarcoplasmic concentrations of Na+, Ca2+, and K+ in resting muscle. Sarcoplasmic reticulin is where calcium is deposited while at rest. During muscle contraction, excess calcium enters the sarcoplasm by an active mechanism that employs adenosine triphosphate (ATP) to form an actin-myosin bond. An injury that tampers with the plasma membrane, ATP, or ion channels leads to a loss of intracellular electrolyte equilibrium. There is an influx of calcium and sodium into cells when a muscle cell experiences either a lack of ATP (drugs, electrolytes, genetic and metabolic illnesses, ischemia, and intensive exercise) or a muscular injury (trauma, exercise, and temperature-dependent syndromes). Together with salt, water is pulled within the cell, leading to cell enlargement and the breakdown of membranous and intracellular structures. Excess intracellular calcium stimulates the formation of actin-myosin cross-linkage, myofibrillar contraction, and ATP depletion. Furthermore, excessive intracellular calcium stimulates proteases and phospholipases that are dependent on calcium, which leads to the disintegration of cell membranes and ion channel disruption (Na+K+ pumps and Na+Ca2+ exchangers). Leukocytes that have been injured during reperfusion go into the injured muscle and produce more prostaglandins, free radicals, and cytokines. This leads to further myolysis and the necrosis of muscle fibers, and it also releases products of muscle breakdown entering the blood, such as potassium, myoglobin, phosphate, creatine kinase, uric acid, and different organic acids. [18] The consequences of hyperphosphatemia and hyperkalemia result from this. The first signs of hypocalcemia in rhabdomyolysis are followed by hypercalcemia. The reason behind this is that, upon cell lysis, calcium seeps out into extracellular spaces after initially entering the myocyte during damage. Thromboplastin secreted It is believed that disseminated intravascular coagulation occurs during muscle damage (DIC).[19&20] Myoglobinuria is only linked to rhabdomyolysis. Myoglobin is freely filtered through the glomerulus and reabsorbed in the renal tubule by endocytosis when it is in a normal, healthy state. Myoglobin does not have a nephrotoxic effect on the tubules in alkaline urine. The kidney's proximal convoluted tubule (PCT) can only convert a certain amount of iron to ferritin. Ferrihemate accumulates as a result of excessive myoglobin transport to PCT and urine acidification in rhabdomyolysis. Myoglobin's ferrihemate portion, which contains iron, may be readily removed from the globin chain and promptly converted into ferritin. Oxygen-free radicals produced by ferritin cause excessive oxidative stress and damage to proximal convoluted tubular cells.[21] The distal convoluted tubule (DCT) can only reabsorb so much extra myoglobin before rhabdomyolysis sets in. Vasoconstriction, hypovolemia, and excessive water reabsorption cause myoglobin to be further concentrated in DCT, which in turn promotes cast formation and DCT obstruction.[10] Rhabdomyolysis-induced acute kidney damage (AKI) is complex. Muscle breakdown and water sequestration within the muscle are the causes of volume depletion, as well as the activation of the Renin-Angiotensin-Aldosterone and antidiuretic hormone production pathways. Strong intracellular antioxidants neutralize the hydroxyl free radicals produced by myoglobin, a heme protein that circulates ferrous oxide (Fe2+) when it oxidizes to ferric oxide (Fe3+) in a normal, healthy state. Lipids are oxidatively damaged when excess myoglobin is produced during rhabdomyolysis. Direct renal vasoconstriction is the result of it allowing the overproduction of endothelin, thromboxane A2, isoprostanes (vasoconstrictors), decreased nitric oxide (vasodilators), and necrotic tumor factor-alpha. Excess myoglobinuria that exceeds the renal metabolic threshold and manifests as myoglobinuria—brownish-reddish tea-colored urine—occurs when rhabdomyolysis occurs. Many variables, including volume depletion, ischemia, intrarenal vasoconstriction, direct cellular injury in PCT, and the formation of the Tamm-Horsfall protein-myoglobin complex blocking DCT, all have an impact on the development

of AKI. Muscle swelling from trauma affecting specific compartment-containing muscle groups increases the chance of developing compartment syndrome, which in turn leads to more pressure-related damage such as muscle necrosis and artery blockage. Irreversible peripheral nerve palsy may result from persistently elevated compartment pressure. Significant muscular ischemia is caused by compartmental pressure greater than 30 mmHg, and measuring compartmental pressure is useful when deciding whether to do a fasciotomy. Muscle ischemia is more likely in rhabdomyolysis patients with significant blood loss and hypotension, even in cases when compartment pressure is lower. [22]

HISTOPATHOLOGY

When there is a possibility of metabolic myopathies in rhabdomyolysis, a muscle biopsy is an essential diagnostic. [23] Muscle biopsy is not recommended until complete rhabdomyolysis recovery, according to the most recent study. Patients with muscle discomfort, weakness with a two- to three-fold increase in CPK, hypertrophic or atrophying muscles, myoglobinuria, and EMG indicative of myopathy can get, around the time of presentation, a muscle biopsy, according to the EFNS muscle panel specialists. [23] Multiple lesions can be seen on the results of a renal biopsy in people who have acute renal damage due to rhabdomyolysis. There is considerable necrosis, microvilli loss, and diminished basal infoldings in the proximal convoluted tubule. [23] Electron microscopy reveals that the whole distal tubular lumen is totally filled with castings that are electron dense.[24]

EVALUATION

Acute rhabdomyolysis is characterized by elevated CPK levels. In 50% of instances, myoglobinuria also results in reddish-brown urine. Basic labs such as a complete blood count, basic metabolic panel, liver function test, CRP, ESR, and CPK levels, urine, EKG, and a chest X-ray should be acquired after triaging and taking vital signs.[25] Myoglobin that contains heme is excreted in urine. The outcome of an excess quantity of myoglobin being released gives urine a tea-colored appearance. It is converted into bilirubin, whose half-life is between two and four hours. Reddish-brown urine is only seen in 50% of rhabdomyolysis patients; myoglobinemia can be detected prior to an increase in CPK. Myoglobinuria may not always be recognized due to its rapid metabolism and shorter half-life. In order to rule out hemoglobinuria, A subsequent microscopic examination for RBC needs to be done. Urine dipsticks can identify hemoglobin and myoglobin as blood. Less than 25% of people have myoglobinuria sensitivity to rhabdomyolysis.[26] In some cases, Additionally, proteinuria can be seen as the outcome of proteins released by harmed myocytes and glomerulus changes. Several indicators are being researched for preventing AKI by early identification caused by heme-containing pigments.[27] Simple radiographs have the ability to diagnose underlying bone fractures, joint dislocations, and, in rare cases, soft tissue edema. The affected muscle group can be scanned using a CT scan to identify compartment syndrome.[28]

DIAGNOSIS

It is imperative that rhabdomyolysis be recognized immediately in order to prevent its possibly fatal sequelae.[29] The identification of rhabdomyolysis is made by comparing the history of current and previous events with physical examinations, blood tests, and urine analysis. A comprehensive history and physical examination are required by the doctor for an accurate diagnosis of rhabdomyolysis. [14] Despite the multifactorial etiology, all possible causes share a common pathophysiological pathway that involves an increase in intracellular calcium. [29] Doctors should be aware of all of the aforementioned pathogenetic pathways because they are connected to the clinical symptoms and lab findings of the disease. Since only around 10% of people have the classic triad, rhabdomyolysis should be considered in any patient who has a history of trauma, infection, disease of the muscles, or immobilization. [14] Two more indirect markers are the existence of muscle injury and an unanticipated rise in serum phosphate or aspartate transaminase.[14] carrying out a neuromuscular assessment Furthermore, by concentrating on the extremities, important bodily cues are provided. Even in nonverbal patients, color, pulse, sensation, muscle strength, and all sizes are instructive. Plasma CK measurement is the benchmark for laboratory testing and diagnosis. [14] It is standard practice to use a concentration of 1,000 IU/L, which is five times the upper limit of the typical reference range, even though a cutoff point hasn't been chosen yet. [14] The

development of kidney injury is closely related to concentrations >5,000 IU/L, and CK levels are widely considered to be predictive of the chance of developing ARF.[14] The half-life of CK is 1.5 days. So, compared to myoglobin concentration, whose half-life is 2-4 hours, CK blood levels last longer.[14] Myoglobinuria (myoglobin present in the urine) or a significant increase in serum CK levels are the two main criteria used to diagnose rhabdomyolysis. [14] Plasma myoglobin increases sharply after muscle damage, is quickly excreted by the kidneys, and returns to normal within 24 hours.[14] Myoglobin levels typically return to normal within 6–8 hours after a muscle injury. [14] Plasma myoglobin's short half-life makes it less sensitive than CK for diagnosis, which can result in false-negative testing. [14] The presence of erythrocytes is shown by the blue coloration of the Ortho toluidine section of the urine dipstick caused by urine myoglobin.[14] It should be emphasized that in patients with chronic muscle illnesses such as inflammatory myopathies and muscular dystrophies, CK levels can be markedly higher than the usual upper limit. When acute symptoms such as muscle soreness, weakness, and swelling are present, rhabdomyolysis can be separated from these illnesses. [14]

SYMPTOMS

The present symptoms typically reflect the underlying illness process as well as any superimposed signs of muscle injury or renal failure. The classic trifecta of rhabdomyolysis symptoms includes myalgia, weakness, and tea-colored urine. Urine color may change based on the patient's glomerular activity, urine concentration, and muscle mass. In a review of 87 cases (CK > 500 IU/L), Gabow et al. showed that 26% of patients failed to test positive for myoglobin using the dipstick test for urine Ortho tolidine-toluidine. [30] There could be alterations in the patient's mental state and low blood pressure, which can cause lightheadedness, dizziness, decreased urine production, and other symptoms of dehydration. There may also be a fever. [31] Urine that appears discolored may be the first clinical symptom of rhabdomyolysis. Urine can have a pink tint, a Coca-Cola color, or a deep black color. [32]

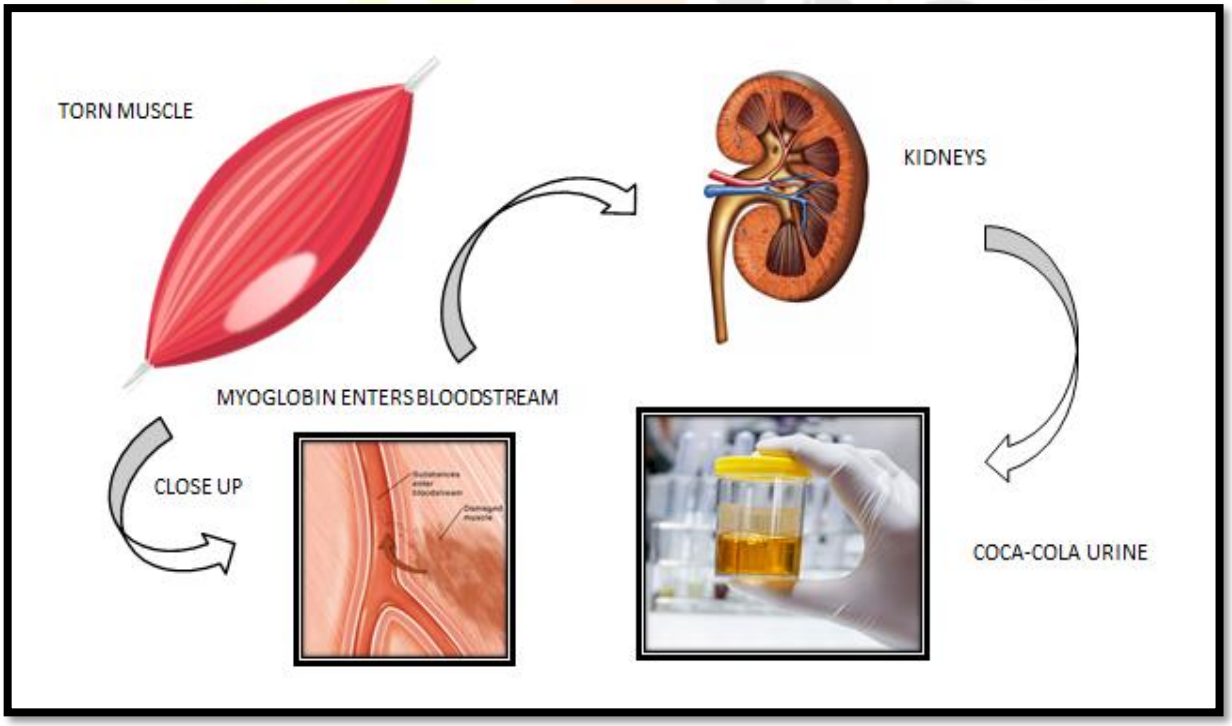

Fig. 1.2 Symptoms of Rhabdomyolysis

Massive muscle breakdown results in severe hyperkalemia, which might result in cardiac arrhythmias and even cardiac arrest. 25% of rhabdomyolysis patients had hepatic impairment. Hepatic damage is brought on by proteases secreted by injured muscles. [33] On inspection, patients may also have stiff and inflamed muscles. The traditional trio is present. Only 10% of patients have complaints of muscle soreness or weakness, whereas >50% of patients do not. Non-specific systemic symptoms can include fever, nausea,

vomiting, tachycardia, and general malaise. ARF, diffuse intravascular coagulation, and multiorgan failure may then develop as clinical symptoms.[34]

PROGNOSIS

Many people with rhabdomyolysis complete their healing after getting treatment. However, the majority of patients continued to feel weak in the muscles for a few weeks after the injury. Up to 50% of those who experience rhabdomyolysis develop acute renal impairment. Some people with failing kidneys need long-term dialysis treatments. [35] The fundamental reason will determine the prognosis and whether complications arise. Rhabdomyolysis aggravated by acute kidney failure may have a mortality rate of 20% in patients with severe damage. When there is no acute renal injury, the mortality rate associated with admission to the critical care unit is 22%; when there is kidney impairment, it is 59%. Most people with renal impairment brought on by rhabdomyolysis recover completely.[36]

COMPLICATIONS

Arrhythmias
Acute kidney injury
Infections brought on by an extended hospital stay
Electrolyte abnormalities
Compartment syndrome
End-stage kidney disease necessitating kidney replacement treatment
Disseminated intravascular coagulation[14]

CAUSES

Trauma, strain, muscular hypoxia, infections, issues with metabolism and electrolytes, medications, toxins, and genetic defects are commonly associated with rhabdomyolysis.[37] There are several potential causes of rhabdomyolysis, both physical and nonphysical. 1) Cocaine, exercise, and immobilization were listed as the three basic causes of rhabdomyolysis in humans. brought to emergency rooms in the USA's urban population. [30] Heat stroke brought on by high temperatures is a risk factor.[38]

TRAUMATIC

- Lightning and voltage electric shock can directly damage the sarcoplasmic membrane, resulting in a huge calcium influx and severe rhabdomyolysis.
- Fire accidents and explosions.[39]
- Extended immobility resulting from a coma, alcohol and drug intoxication, hip fracture, and operations necessitating prolonged positioning.[40]

NON-TRAUMATIC

- Hornet bites, carbon monoxide poisoning, Haff sickness, mushroom poisoning, and snake venom.[41]
- Autoimmune myositis, polymyositis, and dermatomyositis. [42]

MECHANISM

Skeletal muscle harm can come in many different kinds.[43] While non-physical factors obstruct muscle cell metabolism, physical injuries like crushes and other physical harm directly harm muscle cells or obstruct blood flow. [43] Muscle cells could be damaged by the swelling itself, but those that survive are exposed to a variety of disturbances that cause an increase in intracellular calcium ions. ATP depletion and constant muscle contraction are brought on by calcium buildup outside the sarcoplasmic reticulum, which

is the primary energy transporter in a cell. [43] Loss of ATP can cause an unchecked calcium influx on its own. The muscle cell's constant contraction causes intracellular proteins to break down and the cell to disintegrate. [43] The most common type of white blood cell, neutrophil granulocytes, penetrate the muscle tissue, inducing an inflammatory reaction and producing reactive oxygen species, especially after crush damage. [43&44] When a decompressed muscle's blood supply is suddenly restored, the crush syndrome may also result in reperfusion damage.[43] Additionally, the swelling may worsen the region's blood supply. [43] Last but not least, damaged muscle cells discharge into potassium and phosphate ions in the blood, as well as the myoglobin protein that contains heme, the breakdown result of purines from DNA, uric acid, and the enzyme creatine kinase. Disseminated intravascular coagulation may occur as a result of the coagulation system being activated. Heart rhythm disturbances brought on by high potassium levels have the potential to be deadly. Low blood calcium levels are brought on by phosphate's binding to calcium removed from circulation.[43]

SUMMERY & CONCLUSION

A significant clinical problem is still rhabdomyolysis. The diagnosis and management of this ailment are made difficult by the condition's diffuse symptoms, varied etiologies, and systemic consequences. Aggressive fluid therapy is continuing to be the mainstay of care for kidney damage brought on by myoglobin parenchyma, which has been pathophysiology. RCTs, however, are terribly inadequate when it comes to the use of fluids and adjuvant pharmacological therapy (mannitol and bicarbonate) for AKI prophylaxis. However, mortality is unaffected by CRRT, which increases myoglobin clearance. Future research should focus on a number of crucial rhabdomyolysis-related issues, including a homogenous definition for this syndrome, the identification and validation of the most accurate marker for anticipating AKI development, and multidisciplinary randomized controlled trials that contrast fluids with normal intravenous fluid treatment.

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