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Revision

Acute Kidney Injury Due to Rhabdomyolysis: A Review of Pathophysiology, Causes, and Cases Reported in the Literature, 2011-2021

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Abstract

Introduction: Rhabdomyolysis (RML) is characterized by the destruction of muscle fibers and the release of intracellular constituents, with the potential to cause local and systemic complications, such as acute kidney injury (AKI).

Methodology: Literature review in which articles were analyzed between 2011 and 2021, from the PubMed database.

Results: RML can occur directly, indirectly, or secondary to trauma, metabolic disorders, medications and exogenous intoxication. Clinically, it may present asymptomatically, but a classic triad consisting of myalgia, generalized weakness and dark urine is common. AKI, despite being

Keywords: rhabdomyolysis, acute kidney injury, pathophysiology, creatine kinase, review.

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a late complication, is common. Laboratory markers used to diagnose RML are serum Creatine Kinase (CK) and serum and urinary Myoglobin, with CK being more sensitive. The approach can occur through classic strategies, such as hydration, diuretics, alkalinization and renal replacement therapy (RRT), but also through new strategies, such as iron chelators and antioxidants; anti-inflammatories and new extracorporeal blood filter.
Discussion: Trauma was the most common etiology of AKI due to RML, with a minority of patients requiring RRT. Furthermore, it was found that COVID-19 infection did not result in major kidney complications. Strenuous exercise has been shown to be a rare etiology of AKI due to RML. Other less common causes were drug use/intoxication and metabolic diseases, the majority of which patients did not require RRT or had a favorable outcome.
Conclusion: RML is a potentially serious condition, making it important to know its causes and management in order to reduce the chances of serious complications and to avoid patient death.

Lesión renal aguda por rabdomiólisis: revisión de la fisiopatología, las causas y los casos informados en la literatura, 2011-2021

Resumen
Introducción: la rabdomiólisis (RML) se caracteriza por la destrucción de las fibras musculares y la liberación de constituyentes intracelulares, con el potencial de causar complicaciones locales y sistémicas, como la lesión renal aguda (LRA).
Métodología: revisión bibliográfica en la que se analizaron artículos entre 2011 y 2021, de la base de datos PubMed.
Resultados: la RML puede ocurrir de forma directa, indirecta o secundaria a traumatismos, trastornos metabólicos, medicamentos e intoxicaciones exógenas. Clínicamente, puede presentarse de forma asintomática, pero es frecuente una tríada clásica consistente en mialgia, debilidad generalizada y orina oscura. La LRA, a pesar de ser una complicación tardía, es frecuente. Los marcadores de laboratorio utilizados para diagnosticar la RML son la creatina quinasa (CK) sérica y la mioglobina sérica y urinaria, siendo la CK más sensible. El abordaje puede realizarse mediante estrategias clásicas, como la hidratación, los diuréticos, la alcalinización y la terapia renal sustitutiva (TRS), pero también mediante nuevas estrategias, como los quelantes del hierro y los antioxidantes; los antiinflamatorios y el nuevo filtro sanguíneo extracorpóreo.
Discusión: el traumatismo fue la etiología más frecuente de LRA debida a RML, con una minoría de pacientes que requirieron TRS. Además, se observó que la infección por COVID-19 no provocó complicaciones renales importantes. Se ha demostrado que el ejercicio extenuante es una etiología poco frecuente de IRA debida a RML. Otras causas menos frecuentes fueron el consumo de fármacos/intoxicación y las enfermedades metabólicas, la mayoría de cuyos pacientes no requirieron TRS o tuvieron un resultado favorable.
Conclusiones: la RML es una patología potencialmente grave, por lo que es importante conocer sus causas y manejo para reducir las posibilidades de complicaciones graves y evitar la muerte del paciente.

Palabras clave: rabdomiólisis, lesión renal aguda, fisiopatología, creatina quinasa, revisión.

Introduction

Rhabdomyolysis (RML) is a clinical syndrome resulting from the destruction of muscle fibers and the consequent release of intracellular constituents, such as myoglobin, creatine kinase (CK), and lactate dehydrogenase (LDH) into the bloodstream, which have the potential to cause local and systemic complications [1, 2]. The oldest recorded description of RML is possibly found in the Bible, comprising cases of poisoning due to the consumption of birds of the *Coturnix coturnix* species (common quail) [3].

Among the systemic complications, the most common and the most severe is acute kidney injury (AKI). Its incidence, associated with RML, has been reported in 17 to 35 % of cases. In some studies, this percentage can reach 50 % in adults. In patients who develop a severe form of RML, AKI can be found in up to 81 % of cases, with 26 % requiring kidney transplantation [4,5].

However, although most patients recover and kidney function is normalized, they suffer structural kidney changes that promote the evolution to chronic disease. Finally, it is also worth mentioning that this association can have a mortality of up to 59 % in critically ill patients [4].

The causes of RML may vary according to the age group and location. Traumatic causes are more common in high-income countries, while substance abuse is more prevalent in low- and middle-income countries. Infections and congenital diseases are more common in children, whereas trauma and illicit drug use account for more than 80 % of adult cases. The list of causes is extensive, and men, African descendants, extreme ages, and psychiatric patients are additional risk factors for disease development [4–6].

Additionally, as reported in the previous paragraph, viral infections constitute one of the causes of RML, especially those caused by the influenza virus. However, a relevant and recent fact is that, given the scenario of coping with the disease caused by the new coronavirus (COVID-19), RML has been described, in some cases, as an atypical complication resulting from such disease [1, 7, 8].

The patient with RML may present with the oligo or asymptomatic form of the disease. When symptomatic, it shows symptoms such as myalgia, weakness, significant electrolyte disturbances, and increased muscle enzymes [4,9]. An elevation of at least five times the upper normal limit of CK levels is usually accepted for confirming the diagnosis of RML [10].

Pathophysiology

Although the initial cause of muscle damage from RML can vary, its pathophysiology is well established, regardless of the etiology. Thus, muscle injury can occur directly or indirectly or secondary to other causes, such as trauma, metabolic disorders, adverse drug effects, and exogenous poisoning [6].

The initial event in the pathogenesis of RML is the sarcolemmal membrane destruction, which allows intracellular components to be released into the circulation [10]. Moreover, the massive release of intracellular electrolytes and enzymes into the bloodstream perpetuates the cycle of cell damage and death, leading to local and systemic complications such as compartment syndrome, as injured muscles sequester up to 10–12 liters of fluid in a few days [5, 6, 11].

The AKI process associated with RML involves understanding concepts such as myoglobin release and circulating volume depletion [6]. Myoglobin release will act in the kidney injury process in two ways: through a direct lesion. When the kidney filters the blood, the myoglobin goes along, and iron radicals are released from its catabolism. This iron can undergo the Fenton reaction in the kidney and produce reactive oxygen species, which are nephrotoxic, thus resulting in a direct tubular injury [9, 12, 13].

Furthermore, this same myoglobin joins with the Tamm-Horsfall protein, forming precipitates that lead to intratubular obstruction and oxidative damage. What occurs is that under physiological conditions, myoglobin is reabsorbed by the renal tubular cells; however, when it is present in amounts that exceed the body's reabsorptive capacity, it precipitates, creating hyaline casts and generating endothelial dysfunction and tissue damage through the release of cytokines such as TNF-alpha, thromboxane A2, and endothelin [14].

This tissue damage can cause inflammation and subsequent intravascular fluid leakage, resulting in circulating volume depletion and decreased kidney blood flow. All this activates the sympathetic nervous system, the Renin-Angiotensin- Aldosterone System (RAAS), and the release of vasopressin to compensate for this functional hypovolemia. These mechanisms, in turn, can lead to renal vasoconstriction and, consequently, renal ischemia [4, 12, 13, 15].

Ultimately, the skeletal muscle tissue damage leads to the release of uric acid, which contributes to metabolic acidosis and the deposition of urate crystals in the kidney, thus constituting another cause of renal tubular obstruction and metabolic disarray [14].

An illustration of RML pathophysiology can be seen in Figure 1.

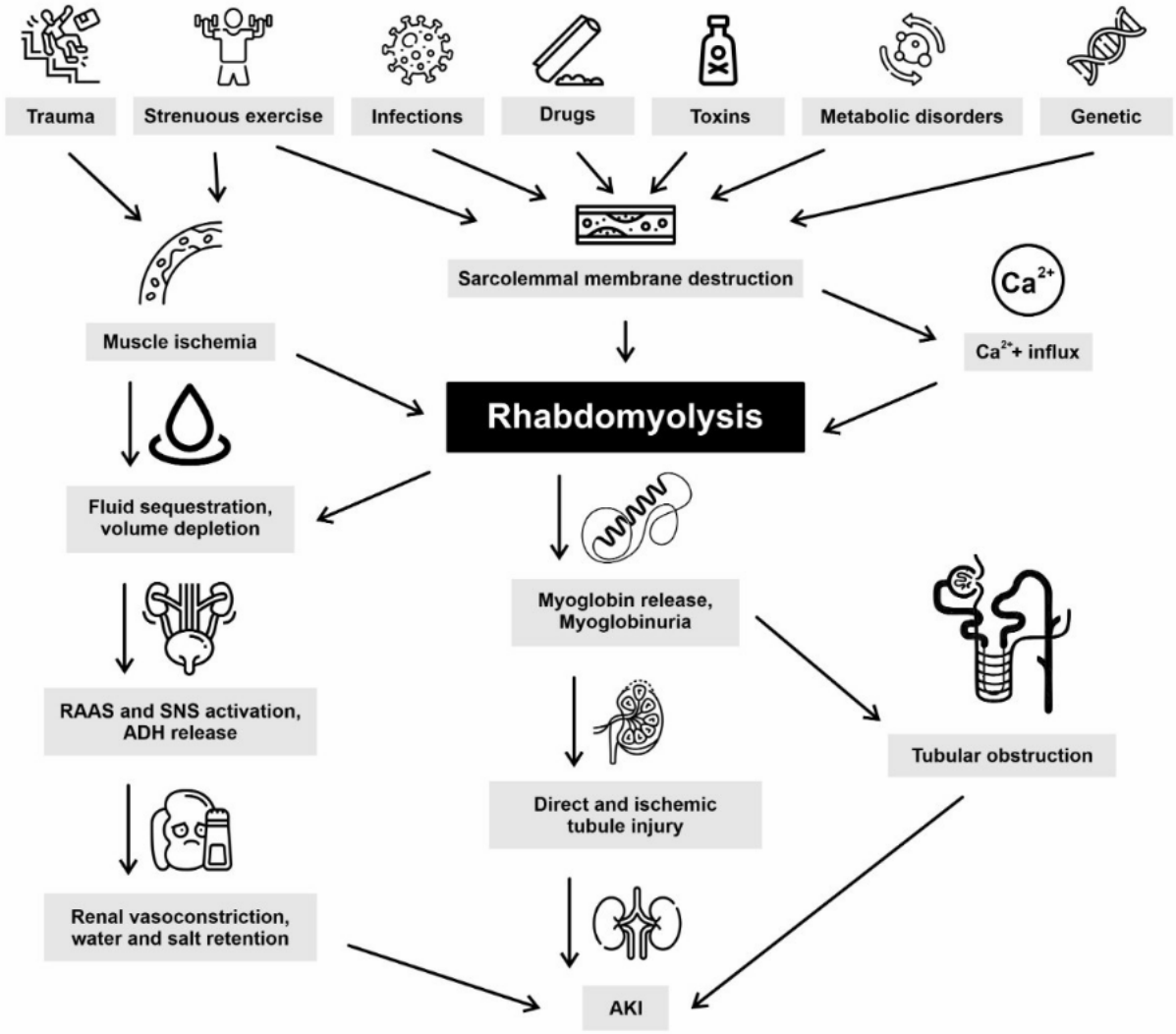

Figura 1. Pathophysiology of rhabdomyolysis

Note. *Ca2+: calcium; RAAS: renin-angiotensin-aldosterone system; ADH: anti-diuretic hormone; SNS: sympathetic nervous system; AKI: acute kidney injury.
Source: The Authors.

Etiology

RML is a multifactorial condition; however, Egoryan *et al.* [1] reported that the main etiologies related to the disease were trauma, infections, medications, illicit drugs, alcohol intake, and autoimmune diseases. Regarding the following topics, a search was performed on PubMed using the descriptors ("Rhabdomyolysis"[Mesh]) AND "Acute Kidney Injury"[Mesh], resulting in 504 articles published in the past ten years. The main findings of each are shown in the following tables.

Trauma

Several studies show trauma as the most frequent etiology of AKI caused by RML in adults [12, 15, 16]. Traumatic injury can result in compartment syndrome, which leads to massive muscle destruction, CK elevation, and AKI [17]. A history of trauma and edema in the limbs should increase suspicion of compartment syndrome. However, there are risk factors for compartment syndrome of non-traumatic etiology, such as vascular abnormalities, blood dyscrasias, anticoagulant use, infection, illicit drug use, and metabolic diseases [17].

In a study by Omrani *et al.* [18], 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 [19]. Table 1 summarizes the cases reported in literature associating AKI with RML caused by trauma.

Strenuous exercise

Although rare, it is considered a triggering factor for RML. It is commonly associated with high-intensity physical activities, especially in patients not used to practicing them. However, there have been reports that moderate-intensity physical activities can also trigger RML, mainly if associated with other aggravating factors, such as drug administration, alcohol intake, high or low temperatures, and inadequate hydration [33]. A study published by Valverde *et al.*, whose objective was to expand the findings on exertional RML and AKI in endurance sports, found that in a sample of 813 people, 345 had RML-and 130 of them had RML associated with AKI [34]. Table 2 summarizes the cases of RML caused by exertional exercise complicating with AKI.

Infections

As previously reported, among the viral causes of RML, approximately 44 % are caused by the influenza virus, and the latter is the most likely to show complications with AKI [40]. Among the bacterial causes that can lead to RML is *Legionella*, a rare infection but one that can still happen [41]. In the past two years, due to the COVID-19 pandemic, reports of several complications have emerged, including RML. Perez *et al.* [42] reported the case of a 35-year-old woman with a history of SARS-CoV-2 infection who was hospitalized for respiratory failure and developed AKI. The etiological study showed elevated levels of total CK, and magnetic resonance imaging (MRI) confirmed the presence of RML [42].

Table 1. Acute kidney injury associated with rhabdomyolysis and trauma. Cases reported in the literature, 2011–2021

Trauma						
Reference	**Age (years)**	**N. of cases**	**Agent**	**Manifestations**	**Laboratory tests**	**Outcome**
Chen *et al.* [20]	33 (mean age)	202 cases	Not reported	Dark urine, metabolic acidosis, and change in temperature	Initial CK: 15,575 U/L; Peak CK: 19,698 U/L; Initial Mb: 2236 Peak Mb: 2551; AST: 471.4 U/L; ALT: 204.3 U/L; Cr: 4.0 mg/dL; Ur-n: 50.1	A total of 202 patients had RML; 29 progressed to AKI, of which 4 were due to unspecified traumatic causes. RRT was indicated for 5 of these 29 patients.
Chen *et al.* [21]	Mean of 10	37 cases	Heatstroke	Fever, weakness and seizures	Initial CK: 1192 U/L; CK (peak): 6810 U/L Cr: 2.2 mg/dL	Of 37 patients with RML, 3 developed AKI. Of these 3, one case was due to heatstroke, who is alive and does not require dialysis.
Chakravartty *et al.* [22]	39 (mean)	145 cases	Bariatric surgery	Myalgia	CK = 20,066 U/L	A total of 145 patients developed post-bariatric RML. Of these, 20 developed AKI and 5 died.
Bridi *et al.* [23]	56	1 case	Bee attack	Unconscious, hypotension, tachycardia	Cr: 6.5mg/dL CK: 14,000U/L	Death
Papasotiriou *et al.* [24]	64	1 case	Acupuncture	Lower-limb pain and weakness, disequilibrium	Cr: 2.6 mg/dL	Discharged

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					CK: 81400 U/L	
Lazarus *et al.* [25]	5	1 case	Physical assault	Dehydration, vomiting, diarrhea	Cr: 9.06 mg/dL; CK: 15378 U/L	Discharged
Tsai *et al.* [26]	40.9 (mean)	23 cases	Compartment syndrome	Pain, paresthesia, paralysis, absence of pulse, pallor	Not reported	52 patients had compartment syndrome, of which 23 developed RML and 9 developed AKI. Of these 9, four patients required RRT.
Pollanen [27]	Middle age	1 case	Dizziness	Multiple abrasions	Necropsy: kidney with Mb deposition	Death
Krieger *et al.* [28]	37	1 case	Physical assault + sickle cell anemia	Tachycardia and diffuse abdominal stiffness	Cr: 5.8 mg/dL CK: 338350 U/L	Discharged
Omar *et al.* [29]	47 (Mean)	17 cases	Cardiac surgery	Not reported	CK: 83.4 U/L Mb: 1120	201 patients were included in the study. 17 developed RML, of which 7 evolved with AKI. 2 patients required RRT.
Poloni and Perazella [30]	34	1 case	Fasciotomy	Not reported	Cr: 5.09 mg/dL CK: 49.155U/L	Death
DeWolf *et al.* [17]	31	1 case	Fall from one's own height	Lower limb pain and edema	Cr: 2.83 mg/dL; CK: 24,000 U/L 	Discharge, with 5-week follow-up with ankle dorsiflexion weakness and sensory improvement
Das *et al.* [31]	21	1 case	Multiple contusions	Dyspnea and myalgia	Hyponatremia (Na 127 mEq/L); Hyperkalemia (K: 7.4 mEq/L); Hypophosphatemia; Cr:12.3 mg/dL; Ur:185 mg/dL; AST: 189 UI/L;	Death

					ALT: 153 UI/L; Total CK: 4257 U/L	
Khu *et al.* [15]	32 - 58	793 cases	Not reported	Not reported	CK:3873 – 10, 478 U/L	Patients with AKI (213); Patients undergoing dialysis (91); Deaths (53)
Di Wang *et al.* [34]	38 - 71	15 cases	Trauma; muscle hypoxia	Not reported	CK: 1779.50–10,105.75 U/L; Mb: 82.45 – 7834.00; ALT: 38.35 - 344.25; AST: 84.38 - 567.28; Cr: 153 - 356.50 mg/dL; Ur-n: 12.38 - 27.42;	Not reported
Omrani *et al.* [18]	17,5-65,7	10 cases	Earthquake	Fracture (6), soft tissue injury (9), unconscious (2)	Cr:1.25-2.55 mg/dL CK: 1,072,2 - 5,908.8 U/L	Not reported

Note. CK: Creatine Kinase; Mb: Myoglobin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; Cr: Creatinine; Ur: Urea; Ur-n: Urea nitrogen; AKI: Acute Kidney Injury; Na: Sodium; K: Potassium; RML: Rhabdomyolysis; RRT: Renal Replacement Therapy.

Source: The Authors.

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Table 2. Acute kidney injury associated with exertional rhabdomyolysis. Cases reported in the literature, 2011–2021

Exertional rhabdomyolysis						
Reference	**Age (years)**	**N. of cases**	**Event**	**Manifestations**	**Laboratory tests**	**Outcome**
Shelmadine *et al.* [35]	19	1 case	Physical exertion + sickle cell anemia	Sudoresis, myalgia, tachycardia	Cr: 4.8 mg/dL CK: 408.545UI/L	Discharged
Chen *et al.* [20]	33 (Mean age)	202 cases	Not reported	Dark urine, metabolic acidosis, and change in temperature	Initial CK: 15,575 U/L; Peak CK: 19,698 U/L; Initial Mb: 2236 Peak Mb: 2551; AST: 471.4 U/L; ALT: 204.3 U/L; Cr: 4.0 mg/dL; Ur-n: 50.1	A total of 202 patients had RML. Of these, 29 developed AKI, 5 of which were due to unspecified physical exercise practice. RRT was indicated for 5 of these 29 patients.
Oh *et al.* [36]	25.7 (mean)	30 cases	Military training (12); Weight lifting, increasing intensity exercise and martial arts (13); CrossFit (4) and P90X (1)	Not reported	Initial CK: 61,391 U/L Peak CK: 84,725 U/L; Ur-n: 15.8 Cr: 1.18 mg/dL; ALT: 406.8 U/L; AST 932.3	In this study, 30 patients developed RML as a result of physical exercise, of which 6 progressed to AKI. An appropriate CK level for discharge was not identified, and there seems to be no significant relationship between peak CK and worsening renal function.

Esposito *et al.* [37]	66	1 case	Strenuous physical activity	Dyspnea, nausea, polyarthralgia, dysuria	Cr: 201.5μmol/L CK: 167,000U/L	Discharged
Abbas *et al.* [38]	31	1 case	Marathon	Severe myalgia, oliguria, vomiting	Cr: 705 μmol/ ; CK: 131.900 U/L	Discharged
Das *et al.* [31], 2020	27	1 case	Dance festival + inadequate hydration	Sensory alteration and vomiting	AST: 11.375 U/L; ALT: 1771 U/L; TB: 5.18; CK: 35.652; Extensive tubular necrosis	Death
Khu *et al.* [15]	32 - 58	499 cases	Not reported	Not reported	CK: 3694 - 8540 U/L	Classified as non-traumatic causes, whose total number of cases resulting in RML was 499. Of this total number: 104 patients with AKI; 60 undergoing dialysis; 40 deaths
Di Wang *et al.* [32], 2021	38 - 71	2 cases	Not reported	Not reported	CK: 1779.50 – 10,105.75 U/L; Mb: 982.45 – 7834.00; ALT: 38.35 - 344.25 U/L; AST: 84.38 - 567.28 U/L; Cr: 153 - 356.50; 	Not reported

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					Ur-n: 12.38 - 27.42;	
Wang *et al.* [39]	20 - 28	41 cases	Exercise + heatstroke	Not reported	CK:1614 - 7894 U/L; ALT: 57 - 177 U/L; AST: 115 - 158 U/L; Ur-n: 6.4 - 10.3; Mb: 979.8 - 1000	Not reported

Note. CK: Creatine Kinase; Mb: Myoglobin; RML: Rhabdomyolysis; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; Cr: Creatinine; Ur-n: Urea nitrogen; AKI: Acute Kidney Injury; TB: Total Bilirubin.

Source: The Authors.

Table 3. Acute kidney injury associated with rhabdomyolysis and infections. Cases reported in the literature, 2011–2021

Infection						
Reference	**Age (years)**	**N. of cases**	**Agent**	**Manifestations**	**Laboratory tests**	**Outcome**
Hung *et al.* [43], 2013	15 years	1 case	Influenza B infection	Fever, adynamia, cough with yellowish secretion, dyspnea,	Cr: 407,421 IU/L CK: 1.47 mg/dL	Discharged
Rodriguez *et al.* [44], 2013	54 (mean)	126 cases	Hepatitis C	choluria, oliguria Not reported	CK: 12,750 U/L; Cr: 2.5 mg/dL ALT $\geq$ 259 U/L; AST $\geq$ 95 U/L; Metabolic acidosis;	In this study, 126 patients had RML. 73 developed AKI, of which 26 were due to infection by the Hepatitis C virus. Of these 73 patients, 59 were discharged, 14 died, and 12 required RRT.
Chen *et al.* [21], 2013	33 (mean age)	202 cases	Not reported	Dark urine, metabolic acidosis, change in temperature	Initial CK: 15,575 U/L; Peak CK: 19,698 U/L; Initial Mb: 2236 Peak Mb: 2551; AST: 471.4 U/L; ALT: 204.3 U/L; Cr: 4.0 mg/dL; Ur-n: 50.1	A total of 202 patients had RML. 29 progressed to AKI, of which six were due to unspecified infectious causes. RRT was indicated for 5 of these 29 patients.

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Chen *et al.* [22], 2013	Mean of 10	37 cases	Septic shock	Fever, watery diarrhea, lower limb muscle pain, weakness	CK: 1224 U/L; Cr: 3.4 mg/dL	Of a total of 37 patients who developed RML, 3 developed AKI. Of these 3, one was due to septic shock, who is
Siriyakorn and Insiripong [45]	17	1 case	Dengue fever	Not reported	Not reported	alive and not requiring dialysis. Death
Mishra *et al.* [46]	21	1 case	Dengue fever	Fever, oliguria, choluria, myalgia	Cr: 2.7 mg/dL CK: 7800U/L	Discharged
Nelson *et al.* [47], 2016	23	1 case	Syphilis	Muscle spasm, fatigue, anuria, maculopapular lesions	Cr: 7.37 mg/dl CK: 1,029.475 U/l	Discharged
Meng *et al.* [48], 2017	1 month - 15	18 cases	RTI (8); CNSI (5); GITI (2); Sepsis (2); PI (1)	in hands and feet Fever, MOD, seizure, oliguria or anuria, choluria	CK >1000 UI/L Elevation in AST, ALT, LDH and Mb levels	7 had the treatment discontinued and 19 regained kidney function
Padiyar, *et al.* [49]	6	1 case	Influenza B and Enterovirus	Fever and lower-limb myalgia	Not reported	Discharged, with good evolution
Navarro-Blackaller *et al.* [14]	60	1 case	Clostridium difficile	Diarrhea	Cr: 1 mg/dL CK: 32.437 U/L	Discharged without symptoms
Tram *et al.* [50]	15	1 case	COVID-19	Intense myalgia, abdominal pain, vomiting, diarrhea, choluria, polydipsia, polyuria, fatigue	Cr: 8.91mg/dL CK: 21,876 U/L	Discharged

Taxbro *et al.* [8]	38	1 case	COVID-19	Fever, myalgia, nausea, vomiting, dry cough, dyspnea, abdominal pain	GFR: 18mL/min/1.73m^2	Discharged
Samies *et al.* [51]	16	1 case	COVID-19	Fever, sore throat, dry cough, myalgia, choluria	Cr: 2.08 mg/dL; CK: >426,700 U/L	Discharged
Chedid *et al.* [52]	51	1 case	COVID-19	Myalgia, dry cough, fever	Cr: 2.48 mg/dL CK: 339,500 U/L	Discharged requiring dialysis
Chong and Saha [53]	37	1 case	COVID-19	Dyspnea, asthenia, edema in extremities	Cr: 5 mg/dL CK: 35,000 U/L	Death
Khu *et al.* [15]	32 - 58	499 cases	Sepsis	Not reported	CK: 3694 - 8540 U/L	Classified as non-traumatic causes, whose total number of cases resulting in RML was 499. Of this: 104 patients with AKI; 60 on dialysis; 40 deaths
Di Wang *et al.* [32]	38 - 71	34 cases	Not reported	Not reported	CK: 1779.50 – 10,105.75 U/L; Mb: 982.45 – 7834.00; ALT: 38.35 - 344.25 U/L; AST: 84.38 - 567.28 U/L; Cr: 153 - 356.50 mg/dL; Ur-n: 12.38 - 27.42;	Not reported
Lamzouri *et al.* [7]	63	1 case	COVID-19	Myalgia, fever, hypoxia	Cr: 229.89μmol/L 	Discharged, with good evolution

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					CK: 7.098U/L	
Egoryan *et al.* [1]	50	1 case	COVID-19	Oliguria, dark urine, constipation,	Cr: 2.29 mg/dL	Discharged
					CK: 359,910 U/L	
Pérez *et al.* [42]	35	1 case	COVID-19	Fever, diffuse polymyalgia, asthenia, dyspnea	Cr: 2.26 mg/dL	Discharged, with good evolution
					CK: 269.328 U/L	
Li and Liu [54]	37	1 case	Tetanus	Trismus, painful calf spasms, fever, tachycardia	Cr: 327.1 μmol/L	Discharged
					CK: 20,105 U/L	

Note. CK: Creatine Kinase; Mb: Myoglobin; RML: Rhabdomyolysis; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; Cr: Creatinine; Ur-n: Urea nitrogen; AKI: Acute Kidney Injury; RTI: Respiratory Tract Infection; CNSI: Central Nervous System Infection; GITI: Gastrointestinal Tract Infection; PI: Parasitic Infection; MOD: Multiple Organ Dysfunction; GFR: Glomerular Filtration Rate; LL: Lower Limbs; RRT: Renal Replacement Therapy.

Source: The Authors.

Table 4. Acute kidney injury associated with rhabdomyolysis and drugs/toxins/illicit drugs. Cases reported in the literature, 2011–2021

Drugs/Toxins						
Reference	**Age**	**N. of cases**	**Agent**	**Manifestations**	**Laboratory tests**	**Outcome**
Scarfia *et al.* [61]	81	1 case	Simvastatin + Cyclosporine	Weakness and loss of function of lower limb muscles	Cr: 3mg/dL CK: 25,834IU/L	Discharged
Chen *et al.* [20]	33 (mean age)	202 cases	Not reported	Dark urine, metabolic acidosis, change in temperature	Initial CK: 15,575 U/L; Peak CK: 19,698 U/L; Initial Mb: 2236 Peak Mb: 2551; AST: 471.4 U/L; ALT: 204.3 U/L; Cr: 4,0 mg/dL; Ur-n: 50.1	A total of 202 patients had RML. 29 progressed to AKI, of which three were due to unspecified illicit drugs. RRT was indicated for 5 of these 29 patients.
Rodriguez *et al.* [44]	54 (mean)	126 cases	Heroin, cocaine, narcotics, alcohol	Not reported	CK: 12,750 U/L; Cr: 2.5 mg/dL ALT $\geq$ 259 U/L; AST $\geq$ 95 U/L; Metabolic acidosis;	In this study, 126 patients had RML. 73 developed AKI, of which 32 were caused by substance abuse. Of these 73 patients, 59 were discharged, 14 died, and 12 required RRT.
Campana *et al.* [62]	42	1 case	Caffeine	Sudoresis, vomiting, diarrhea, anxiety, auditory hallucinations	Cr: 10.2 mg/mL	Discharged

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					CK: 59,360 U/L	
Bachoumas *et al.* [63]	67	1 case	Fusidic acid + Pravastatin	Fatigue, nausea, vomiting, jaundice	Cr: 400 mmol/L CK: 160,800 U/L	Death
Jullian-Desayes *et al.* [64]	25	1 case	Antipsychotic drugs (risperidone + loxapine + levomepromazine	Orbital edema, calf contracture	Cr: 392 μmol/L CK: 43,650 U/L	Discharged
Gangahar [65]	21	1 case	Opioid abstinence	Vomiting, cramps, disorientation	Cr: 5.05 mg/dL CK: 29,661 U/L	Discharged
Wu *et al.* [66]	34	1 case	Olanzapine + Mirtazapine	Altered consciousness, sweating, stiffness of all limbs, lower-limb clonus	Cr: 1.9 mg/dL CK: 46,814 U/L	Discharged
Dogan *et al.* [67]	50 and 71	2 cases	Poisoning caused by the ingestion of quail meat	Lower-limb weakness	Cr: 6 and 1.2 mg/dL CK: 1597 and 1310 U/L	Discharged
Peña-Porta *et al.* [68]	91	1 case	Rosuvastatina	Sudden-onset right flank pain, oliguria, lower limb weakness	Cr: 4.47 mg/dL CK: 9.612 U/L	Discharged
Argamany *et al.* [69]	27	1 case	Synthetic marijuana	Myalgia, muscle weakness, vomiting, paresthesia, sudoresis, jaw spasms	Cr: 13.88 mg/dL CK: 40,000 U/L	Discharged
Lam *et al.* [70]	35	1 case	Methoxphenidine	Hypertension, incomprehensible speech	Cr: 512 umol/L CK:200,660 U/L	Discharged
Pourmand *et al.* [71]	40	1 case	Dietary supplement + exercise	Altered consciousness, syncope	Cr: 2.1mg/dL CK: 158,894U/L	Discharged

Meng *et al.* [48]	1 month - 15 years	1 case	Carbon monoxide poisoning	Fever, MOD, seizure, oliguria or anuria, choluria	CK >1,000 UI/L	This article assessed a total of 26 cases of RML with different etiologies, which progressed to AKI. Of these:
						7 had the treatment discontinued and 19 regained kidney function
					Elevation in AST, ALT, LDH, and Mb levels	
Dalugama *et al.* [72]	62	1 case	Atorvastatin + Gemfibrozil	Muscle symptoms	Not reported	Not reported
Kamal *et al.* [73]	32	1 case	Opioid + cocaine + marijuana	Coma	Cr: 2.7 mg/dL CK: 156 U/L	Discharged
Watanabe *et al.* [74]	70	1 case	Warfarin + trauma	Dysstasia, pain in lower limbs.	Cr: 1.71 mg/dL; CK: 17,504 IU/L;	Discharged, with good and slow evolution
Gnanapandithan *et al.* [75]	33	1 case	Trenbolone (anabolic steroid)	Generalized weakness, myalgia, oliguria, choluria	Cr: 4.7 mg/dL; CK: >100,000 U/L	Discharged, requiring dialysis for some time
Godinho *et al.* [76]	54	1 case	Antiretroviral + Simvastatin	Asthenia, myalgia, jaundice, oliguria, hepatomegaly	Cr: 553μmol/L CK: 185,190U/I	Discharged, without long-term complications
Lima Filho *et al.* [77]	25-34	3 cases	Cocaine	Oliguria, edema, myalgia, fever	CK: 1,731 U/L	Renal function recovery

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Khu *et al.* [15]	32 - 58	499 cases	Alcohol, statins and stimulants/psychotropics	Not reported	CK: 3,694 – 8,540 U/L	Classified as related to non-traumatic causes, whose total number of cases resulting in RML was 499. Of this total:
						104 patients with AKI;
						60 on dialysis;
						40 deaths
Wang *et al.* [32]	38 - 71	6 cases	Not reported	Not reported	CK: 1,779.50 – 10,105.75 U/L;	Not reported
					Mb: 982.45 – 7834.00;	
					ALT: 38.35 - 344.25 U/L;	
					AST: 84.38 - 567.28 U/L;	
					Cr: 153 - 356.50 mg/dL;	
					Ur-n: 12.38 - 27.42;	
Samuel *et al.* [78]	21 - 34	4 cases	Snakebite; Haloperidol/Benzodiazepines; high doses of rosuvastatin and substance abuse (marijuana and methamphetamine)	Oliguria (4), ptosis (1), proximal myopathy (1)	Ur: 65 - 225	Total renal recovery: 3
					Cr: 4 - 17.8	Partial renal recovery: 1
					CK:5.162 - 26.600 U/L	
					LDH: 961 – 3,100	
Mitaritonno *et al.* [59]	45	1 case	Rosuvastatin + cocaine/heroine	Asthenia, diffuse myalgia, mental confusion, nausea, restlessness, hypotension	Cr: 10.75 mg/dL	Submitted to hemodialysis and slow improvement of renal function
					CK: 551,820 U/L	
Ould-Nana *et al.* [79]	74	1 case	Rosuvastatin + abiraterone acetate	Diffuse myalgia, hyporexia, asthenia	Cr: 9.12 mg/dL	Discharged, with good evolution
					CK: 5,763 U/L	

Note. CK: Creatine Kinase; Mb: Myoglobin; RML: Rhabdomyolysis; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; Cr: Creatinine; Ur: Urea; Ur-n: Urea nitrogen; AKI: Acute Kidney Injury; MOD: Multiple Organ Dysfunction; RRT: Renal Replacement Therapy.
Source: The Authors.

Table 5. Acute kidney injury associated with rhabdomyolysis and metabolic diseases. Cases reported in the literature, 2011–2021

Metabolic diseases						
Reference	**Age (years)**	**N. of cases**	**Disease**	**Manifestations**	**Laboratory tests**	
Chen *et al.* [21], 2013	33 (mean age)	202 cases	Not reported	Dark urine, metabolic acidosis, change in temperature	Initial CK: 15,575 U/L; Peak CK: 19,698 U/L; Initial Mb: 2,236 Peak Mb: 2,551; AST: 471.4 U/L; ALT: 204.3 U/L; Cr: 4.0 mg/dL; Ur-n: 50.1	A total of 202 patients had RML. 29 progressed to AKI, of which two were due to unspecified metabolic diseases. RRT was indicated for 5 of these 29 patients.

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Chen *et al.* [22]	Mean of 10	37 cases	CAH	Abdominal pain, vomiting, and lower-limb weakness with spasms	CK: 1,429 U/L; Cr: 3.8 mg/dL	Of a total of 37 patients who developed RML, 3 developed AKI. Of these 3, one was due to CAH,
Rodriguez *et al.* [44]	54 (mean)	126 cases	DIC	Not reported	CK: 12,750 U/L; Cr: 2.5 mg/dL ALT $\geq$ 259 U/L; AST $\geq$ 95 U/L; Metabolic acidosis;	who is alive and does not require dialysis. In this study, 126 patients had RML. 73 developed AKI, of which 17 were due to DIC. Of these 73 patients, 59 were discharged, 14 died, and 12 required RRT.
Ditch and Tosh [81]	21	1 case	Bulimia nervosa	Cramps, nausea, vomiting, muscle weakness, tremor in lower limbs	Cr: 11.42 mg/dL CK: 16,796 U/L	Discharged
Celik *et al.* [82]	41	1 case	Pheochromocytoma	Severe myalgia, nausea, vomiting, dizziness, mental confusion, fever	Cr: 4.9 mg/dL CK: 5,055U/L	Discharged
Meng *et al.* [48]	1 month – 15 years	6 cases	Diabetes (3) Glutaric acidemia (1); Mitochondrial disease (1); 	Fever, MOD, seizure, oliguria or anuria, choluria	CK >1,000 UI/L Elevation in AST, ALT, LDH and Mb levels	This article evaluated a total of 26 cases of RML, with different etiologies, that progressed to AKI. Of these: 7 had the treatment discontinued and 19 regained kidney function

			Renal tubular acidosis (1)			
Mai *et al.* [11]	50	1 case	Undifferentiated connective tissue disease	Choluria, oliguria, upper limb edema	Cr: 182.0umol/L; CK: 962 U/L; Mb: 1,599 ng/mL	Discharged, with good evolution
Giri *et al.* [83]	abr-14	8 cases	DKA	Hypotension, oliguria, lowered level of consciousness	Cr: 1.4 (0.83 - 4.11) CK: 10.368 U/L (1,295 – 14,580 U/L)	RRT (5) Death (2)
Chiniwalar *et al.* [84]	24	1 case	Acute myeloid leukemia	Fever, altered consciousness epistaxis, oliguria, hematuria, pallor, hepatosplenomegaly	Cr: 4 mg/dL CK: 3485 U/L	Death
Wang *et al.* [32]	38 - 71	4 cases	Not reported	Not reported	CK: 1,779.50 – 10,105.75 U/L; Mb: 982.45 – 7,834.00; ALT: 38.35 - 344.25; AST: 84.38 - 567.28; Cr: 153 - 356.50 mg/dL; Ur-n: 12.38 - 27.42;	Not reported
Hamadeh *et al.* [80]	26	1 case	McArdle disease	Myalgia, vomiting, choluria, dry cough, deltoid muscle weakness	Cr: 7.71 mg/dL CK: 89,243 U/L	Discharged

Note. CK: Creatine Kinase; Mb: Myoglobin; RML: Rhabdomyolysis; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; Cr: Creatinine; Ur- n: Urea nitrogen; AKI: Acute Kidney Injury; MOD: Multiple Organ Dysfunction; DKA: Diabetic Ketoacidosis; RRT: Renal Replacement Therapy; LL: Lower Limbs; CAH: Congenital Adrenal Hyperplasia; DIC: Disseminated Intravascular Coagulation.

Source: The Authors.

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The pathophysiological mechanism of the virus that leads to muscle destruction remains unclear. However, two hypotheses have been proposed: muscle necrosis related to direct viral invasion of myocytes and the toxic effect on myocytes caused by the exacerbated host response. Once again, it is worth mentioning that its pathogenesis remains uncertain, and further studies are required for a better understanding [7]. Recent studies suggest that in COVID-19, RML would be an initial manifestation, not a late complication of the infection [1]. Table 3 summarizes the cases reported of infections causing RML and AKI.

Medications, toxins, and illicit drugs

Exposure to toxic agents, including alcohol, medications, and illicit drugs, can be the reason for RML. These substances can exert both a direct toxic effect on muscle and indirectly predispose to RML.

Regarding alcohol consumption, its pathophysiology in the disease can be explained by the fact that ethanol inhibits calcium accumulation in the sarcoplasmic reticulum of muscles, affects the cell membranes of the muscles, and inhibits the sodium-potassium pump that maintains cell integrity [55].

Among the medications, statins (simvastatin, atorvastatin, and pravastatin) in treating dyslipidemia are an essential cause of RML. The mechanism by which it occurs is yet to be clarified, probably being multifactorial; however, there is a consistent understanding that their use in association with other medications, especially fibrates and ciclosporins, in elderly patients and patients with renal and hepatic impairment seems to increase the risk of developing RML [56, 57].

Hence, in a report published by Hafouda *et al.* [58], the history of a 73-year-old female patient who attended the dermatology service for exacerbation of psoriasis was collected. She used multiple medications, such as gabapentin, omeprazole, simvastatin, zopiclone, and amiloride-furosemide. A cyclosporine treatment regimen was proposed for her lesions. Three weeks later, she was admitted to the emergency department with RML symptoms.

Therefore, combining statins, especially simvastatin or lovastatin, with cyclosporine is associated with an increased risk of RML. On the other hand, fluvastatin and pravastatin are less susceptible to this interaction and should, therefore, be the statins of choice for patients already being treated with cyclosporine [58].

Several cases of cocaine-induced RML have been described in recent decades, and the severity of muscle damage seems to align with the severity of cocaine intoxication. Studies of cocaine-intoxicated patients in the emergency department disclosed a 5–24 % incidence of increased CK activity [59]. The drugs have a direct toxic effect on the muscle and indirectly impact by leading to prolonged immobilization. Additionally, cocaine increases sympathetic-mimetic activity, causing arterial vasoconstriction, infarctions, and muscle ischemia [60].

Bee stings have also caused reports of RML. Bridi *et al.* [23] report the case of a 53-year-old man who suffered a bee attack in which he received more than 1,000 bee stings. He was admitted to the emergency room unconscious, with hypoxia, hypotensive, tachycardic, and with CK levels at 790 U/L, requiring hemodialysis. The pathophysiology of AKI secondary to Africanized bee stings is a complex process. There may be a combination of direct nephrotoxicity, RML with myoglobinuria, and hypovolemia after anaphylaxis or low cardiac output. Bee venom contains peptides such as melittin and phospholipase A, which can cause RML and hemolysis. They have cytolytic effects on the phospholipids of blood cell membranes, muscles, and vascular endothelium, producing pro-inflammatory and hepatocellular substances [23]. Table 4 summarizes the cases of RML caused by drugs, toxins, and illicit drugs complicating with AKI.

Metabolic disorders

McArdle disease is a rare genetic disorder, more common in children, with an autosomal recessive inheritance pattern resulting from a mutation in two alleles that encode the myophosphorylase enzyme in skeletal muscle. Its absence results in the impairment of glycogen degradation and ATP formation, which causes a decrease in exercise tolerance. Thus, RML results from the combination of glycogen accumulation, which leads to cellular stress; counter-regulation of the sodium- potassium pump; increased sarcoplasmic calcium; oxidative stress; and purine nucleotide metabolism, which compromises cell integrity. Some factors predispose to AKI in McArdle disease, such as RML severity, delay in therapeutic support, and substance abuse [81]. Table 5 summarizes the cases of RML associated with metabolic diseases complicating with AKI.

Clinical and laboratory evaluation

Clinical evaluation

Muscle injury may even be asymptomatic, although it is common for patients to show the classic triad, consisting of myalgia, generalized weakness, and dark urine [1]. However, its

symptomatic presentation can vary greatly. It is worth mentioning, however, that less than 10 % of patients have these classic characteristics [5].

Muscle involvement may occur in specific or generalized muscles. The muscle groups most often involved are the calves and lower back. Muscles may become tender and swollen, and there may be changes in the skin, indicating pressure necrosis. Dark urine occurs due to myoglobinuria and myoglobin's relatively rapid renal clearance; this symptom usually lasts a short period and may go unnoticed by doctors and patients [5].

Other non-specific clinical findings that may be verified are malaise, fever, nausea, or vomiting. Cardiovascular symptoms resulting from electrolyte disturbances (calcium, potassium, and phosphate) may range from arrhythmia to cardiac arrest [6].

Other possible complications include respiratory failure or discomfort; hepatic dysfunction due to released proteases caused by muscle damage, which may occur in up to 25 % of patients with RML; AKI, which, despite being a late complication, is quite common, initially presenting with oliguria that may progress to polyuria and may also present with metabolic acidosis due to uremia and lactic acid resulting from ischemia [5, 6].

Laboratory evaluation

Serum Creatine Kinase (CK)

It is the most sensitive muscle damage marker; its normal levels range from 45 to 260 U/L. In RML, its levels increase in the first 12 hours after the lesion, reaching a peak after 3 to 5 days [6]. When the levels exceed the upper limit of normality by 5-fold, and in a favorable clinical context, a diagnosis of RML can be attained. In the case of RML associated with statins, the diagnosis can be made when the levels exceed the upper limit of normality by 50-fold. The association between high levels of CK and AKI is still unclear, as CK is just a marker of myoglobin nephrotoxicity [5].

In COVID-19 cases, Egoryan *et al.* [1] reported that there had been several case reports associating RML and COVID-19, and in none of these reports the CK level exceeds 30,000 U/L. In one, including a study with ten patients in the age group of 55 years who were not using statins or other medications considered risk factors for RML, the mean CK level obtained was 4,460 U/L.

Serum and urinary myoglobin

Serum and urinary myoglobin tests are not considered sensitive diagnostic procedures. Myoglobinuria does not occur without the presence of RML; when RML does occur, it will not necessarily result in visible myoglobinuria. This is due to myoglobin's relatively rapid renal clearance [2].

In any case, the normal concentration of myoglobin in plasma is <5.7 nmol/L (100 μg/L) and in urine, <0.57 nmol/L (10 μg/L). In RML, the serum myoglobin level increases within 1 to 3 hours, peaks at 8 to 12 hours, and returns to normal levels within 24 hours after the lesion onset. Thus, myoglobin detection in blood or urine is pathognomonic for diagnosing RML, provided it is performed in the early stages of the syndrome. A systematic review showed that myoglobinuria is detected in 17 % of patients with RML [5].

It is worth mentioning, however, that in a study by Vangstad, Bjornaas, and Jacobsen [20], it was concluded that the serum concentration of myoglobin was a better predictor of AKI than the CK serum activity. The myoglobin/CK ratio may be helpful to assess the likelihood of developing AKI [19].

Other exams

Muscle and kidney biopsies are not usually required to diagnose RML, just as imaging tests are not. The latter can be considered in cases of persistent diagnostic doubt and when fasciotomy is considered in compartment syndrome [5].

In a study by Wang *et al.* [39], high D-Dimer values were an independent risk factor and probably associated with AKI, especially in patients with RML induced by exertional hyperthermia.

The renal function test must also be performed, and it may be altered; however, in a study carried out by Butkus *et al.* [6], a 21-year-old patient showed preserved renal function, even in the presence of high levels of CK, showing that in patients with protective factors, such as age and adequate oral hydration, this parameter can remain preserved.

Electrolytes should be evaluated, especially potassium, as it is the main intracellular ion and tends to increase both due to kidney damage and muscle rupture, resulting in greater release. Moreover, there is a trend towards hyperphosphatemia and hypocalcemia [6].

These electrolyte disturbances may also mainly be associated with cardiac alterations, such as arrhythmia and cardiac arrest. Therefore, performing an electrocardiogram is also important [6].

As previously mentioned, infections are significant causes of RML, so a blood count can help to determine the specific etiology associated with infectious processes.

Treatment

Kwiatkowska *et al.* [4], in their study, mention two ways of managing RML: classic strategies (hydration, diuretics, alkalinization, and renal replacement therapy) and new strategies (iron chelators and antioxidants, anti-inflammatory drugs, and a new extracorporeal blood filter). The most critical objective of RML treatment is to prevent AKI or provide early intervention to avoid further damage and progression to severe kidney disease [85].

Classic strategies

The primary therapeutic measure for RML is early hydration, aiming to fight volume depletion and tubular damage caused by myoglobin release. This stimulates diuresis and reduces the risk of intratubular obstruction. Therefore, within the first six hours after the accident or onset of the clinical condition, vigorous hydration of 1 to 2 L/hour is performed until an adequate urinary output of 300 mL/hour is reached [5].

The use of diuretics is still controversial. In the presence of volume overload, the need to use them is obvious. However, there are still very scarce data in other situations. Typically, loop diuretics and mannitol are used. Mannitol increases urine flow and prevents myoglobin precipitation. Some studies show a reduction in oxidative stress [4].

Urine alkalinization with bicarbonate-containing solutions is a traditional therapeutic method, and its goal is to achieve a urinary pH >6.5 to mitigate intratubular myoglobin precipitation, thus reducing the risk of direct tubular injury, as well as the risk of uric acid crystal formation [4, 5, 85].

Renal replacement therapy (RRT) is indicated when the patient has uremic encephalopathy, deterioration of renal function, uncontrolled hyperkalemia, metabolic acidosis, and hypervolemia [5]. However, it is worth noting that dialysis is ineffective in removing myoglobin and uric acid [1]. There is a score that can be used to predict the requirement of RRT in AKI, the McMahon score, which indicates RRT need when higher than six [10].

New strategies

Considering the pathophysiological mechanism, iron chelators and antioxidants such as deferoxamine, vitamins E and C, acetaminophen, N-acetylcysteine, and flavonoids may be part of the treatment, but scientific evidence of their benefit in the treatment of RML is still lacking. Anti-inflammatory measures can be used, such as clodronate, suramin, pentoxifylline, mesenchymal stem cells, and, finally, the use of a new extracorporeal blood purification device, CytoSorb. Because they are new, these therapeutic options still require further studies to prove their effectiveness [4].

Authors' contributions

Gustavo Neves Pinto: data analysis and/or interpretation, data Curation, project management, original draft preparation, review and editing; Yuri Campelo Fraga: data analysis and/or interpretation, data curation, project administration, original draft preparation, review and editing; Elizabeth De Francesco Daher: data analysis and/or interpretation, study conception and design, conceptualization, data curation, final manuscript approval, research, methodology, project management, supervision, validation, original draft preparation, review and editing; Geraldo Bezerra da Silva Junior: data analysis and/or interpretation, study conception and design, conceptualization, data curation, final manuscript approval, research, methodology, project management, supervision, validation, original draft preparation, review and editing.

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Ethical implications

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