ACUTE RHABDOMYOLYSIS - INVESTIGATION AND MANAGEMENT

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Rhabdomyolysis can be due to a number of genetic and non-genetic causes, and may be associated with an acute life-threatening risk of electrolyte imbalance and/or acute renal failure. Early recognition, investigation and emergency management is vital.
- This document provides a protocol for the evaluation and management of patients suspected of or at risk of having rhabdomyolysis, and should be used in consultation with the Genetic Metabolic Disorders Service, the Nephrology Department and ICU. It covers the following areas:
  - Patient history
  - Tests to confirm rhabdomyolysis
  - Investigations to monitor treatment
  - First line diagnostic investigations
  - Complex diagnostic investigations
  - Acute and long term management

CHANGE SUMMARY

- Mandatory review – No major changes
- Updated references.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st March 2020	**Review Period**: 3 years
Team Leader:	Deputy Head	**Area/Dept**: Genetic Metabolic Disorders Service

Date of Publishing: 3 February 2021 10:34 AM Date of Printing: 3 February 2021

READ ACKNOWLEDGEMENT

This document should be read by medical staff who are likely to be involved in the diagnosis and management of children presenting with clinical or biochemical features suggestive of acute rhabdomyolysis.

Medical staff who are likely to encounter children in an acute medical or surgical setting should be aware of this document.

TABLE OF CONTENTS

1 Introduction

Rhabdomyolysis can be defined as a clinical syndrome of acute muscle weakness, myalgia and muscle swelling, occurring due to the breakdown of skeletal muscle cells and release of their contents into the circulation[1]. It is characterised by a rise of plasma creatine kinase (CK) by fivefold or more[2]. Some of the major consequences of clinical significance include[3]:

- the leakage of myoglobin into the systemic circulation, with a risk of renal impairment and acute renal failure in 13-50% of cases[4]
- the leakage of potassium into the systemic circulation, with potentially life-threatening acute hyperkalaemia
- hyperuricaemia due to release of purines from disintegrating cell nuclei
- hyperphosphataemia may be due to efflux from damaged muscle cells with potential metastatic calcification and hypocalcaemia
- metabolic acidosis and aciduria

Whilst the risk of acute renal failure is associated with higher CK levels, the absolute level is not an accurate predictor of the risk. However, an acutely elevated CK level of 10,000 Units/L or more should be regarded as a potentially dangerous level.

2 Clinical Features and Causes

Clinically, patients may complain of myalgia, muscle stiffness, dark urine and / or weakness with or without fever[3]. In addition, there may be other disease-specific symptoms and signs related to the underlying condition. Some of the more important causes of acute rhabdomyolysis include:

Medications and Toxins

- Neuroleptic malignant syndrome – idiosyncratic reaction associated with the use of neuroleptic medications acting on the central dopaminergic system e.g. phenothiazines.
- Other medications/illicit substances (including statins, fusidic acid, daptomycin, colchicine, lithium, extremely high dose pyridoxine (one report)[5], amphetamines, including MDMA (ecstasy)[6], ethanol, toluene, naltrexone).
- Carbon monoxide poisoning.
- Multiple wasp or hornet stings[7].
- Snake envenomation.

Traumatic

- Crush syndrome, trauma to multiple areas of the body, or
- Coma with immobility for prolonged periods with resultant muscle compression.

Vascular Compromise

- Ischaemia.
- Heat stroke.

Severe Infections

- Bacterial or viral.

Excessive Muscle Activity

- Seizures.
- Strenuous exercise.

Autoimmune Inflammation

- Polymyositis/dermatomyositis.
- Systemic Lupus Erythematosus.
- Polyarteritis nodosum.

Inborn Errors of Metabolism

- Fatty acid oxidation defects[8, 9] (precipitated by prolonged exercise, fasting or infection; no "second wind" phenomenon):
    - Carnitine palmitoyltransferase II deficiency.
    - Very long chain acyl-CoA dehydrogenase deficiency.
    - Others less common (eg long chain fatty acid oxidation disorders, carnitine – acylcarnitine translocase deficiency, medium chain ketoacyl-CoA thiolase deficiency, multiple acyl CoA dehydrogenase deficiency).
- Mitochondrial respiratory chain defects[10, 11].
- Glycogen storage diseases[12]:
    - Myophosphorylase deficiency (type V; McArdle disease):
        - Painful muscle contractures with exercise.
        - Unusual to have symptomatic presentation before puberty.
        - If pain stops with brief cessation of activity and rest, can then resume activity again ("second wind" phenomenon).
    - Muscle phosphofructokinase deficiency (type VII; Tarui disease) – similar to type V, but:
        - Exercise intolerance is more obvious in childhood.
        - Also have compensated haemolytic anaemia.
        - Exercise intolerance worse after high carbohydrate meals.
    - Debrancher deficiency (type III; Cori disease) – seen in some adults.

  - Phosphorylase b kinase deficiency (type IX) – some patients have a muscle-specific form.
  - Pompe disease (GSD II)

- Glycolytic defects[12]:
  - Phosphoglycerate kinase deficiency (seizures, intellectual disability, haemolytic anaemia; X-linked).
  - Phosphoglycerate mutase deficiency (clinically like GSD VII).
  - Fructose-1, 6-bisphosphate aldolase deficiency (also with haemolytic anaemia).
  - Lactate dehydrogenase deficiency.
  - Pyruvate kinase deficiency.
- Myoadenylate deaminase deficiency.
- X-linked adrenoleukodystrophy (a consequence of an Addisonian crisis)[13] .

Muscular Dystrophies

- Nemaline myopathy[14].
- Duchenne andBecker muscular dystrophy, as well as other dystrophinopathies [15].
- Other congenital muscular dystrophies[16].

Other Genetic Disorders

- *LPIN1* deficiency[17]:
  - Encodes Lipin-1, a phosphatidic acid phosphatase, which plays a prominent role in triglyceride metabolism.
  - Usually precipitated by intercurrent febrile illnesses.
  - During acute episodes CPK is often in excess of 100,000U/L.
  - Second most common cause, after fatty acid oxidation disorders, of severe early-onset rhabdomyolysis[18].
  - Up to a third of individuals may die during an acute episode, usually due a cardiac arrhythmia[18].
- MECRCN ('Metabolic encephalomyopathic crises, with rhabdomyolysis, cardiac arrhythmias and neurodegeneration') [19, 20]
  - *TANGO* family proteins load synthesized secretory proteins into the endoplasmic reticulum
  - Deletions, point mutations or alterations in splicing of the *TANGO2* gene are thought to cause a defect in mitochondrial fatty acid oxidation
  - Inherited in an autosomal recessive fashion and causes recurrent episodes of severe rhabdomyolysis

- Malignant hyperthermia: an autosomal dominant pharmacogenetic disorder due to abnormal skeletal muscle calcium regulation, due to variants in the skeletal muscle ryanodine receptor gene (*RYR1*) [21].
    - Provoked classically by volatile anaesthetics (e.g. halothane, isoflourane) and depolarising muscle relaxants (e.g. suxamethonium), but more commonly by exercise and heat
    - Clinical features include muscle contractions, tachycardia, metabolic acidosis, hyperthermia.
    - Central core myopathy – a congenital myopathy that is allelic with malignant hyperthermia[22].

3 Investigation

3.1 History

Questions to ask:

- Medication/illicit substance ingestion.
- Nature and severity of recent trauma, including risk of snake bite.
- History of recent excessive exertion.
- Provoking/relieving factors e.g. infection, fasting, emotional stress, cold, anaesthetics.
- History of recurrences.
- Careful family history.
- "Second wind" phenomenon (GSD V, GSD IX) [The patient rests when myalgia and stiffness first become evident. On resumption of activity, symptoms do not recur. This is thought to be the result of increased delivery of glucose and free fatty acids to muscle because of a hyperdynamic circulation.]
- "Out of wind" phenomenon (GSD VII) [Extra ingested glucose leads to a reduction in work ability. This is because there is a reduced delivery of free fatty acids and ketone bodies to muscle, which are the preferred substrates in this disorder.]
- Associated haemolytic anaemia (GSD VII, phosphoglycerate kinase deficiency, fructose-1, 6-bisphosphate aldolase deficiency).

3.2 Confirm the Rhabdomyolysis

- Plasma CK.
- Urine analysis – dipstick and microscopy

3.3 Baseline Investigations to Monitor Treatment

- CK, electrolytes (especially potassium, calcium and phosphate), acid-base status, uric acid, liver function tests, urea and creatinine measurements. If snake envenomation is possible also arrange full coagulation studies including PT/INR, aPTT, D-Dimer and fibrinogen.

- Cardiac monitoring to be considered
- Monitor patient clinically for respiratory signs of fluid overload / pulmonary oedema
- Monitor peripheral pulses and perfusion for signs of compartment tightness

3.4 Baseline Diagnostic Investigations

- Urine amino and organic acid analyses.
- Plasma carnitine and acylcarnitines.
- Blood lactate and pyruvate.
- ESR, serology for investigation of autoimmune causes.
- DNA (5 – 10 ml EDTA blood) in anticipation of possible genetic testing.

3.5 Specialised diagnostic investigations

(depending on clinical indications, should only be performed in consultation with the Neurology and/or Metabolic teams)

- Forearm ischaemic exercise test (see[23]).
- Non-ischaemic forearm test may be considered as an alternative to the forearm ischaemic test[24].
- White blood cell (CPT II deficiency) or fibroblast fatty acid oxidation studies.
- Muscle biopsy for histopathology, histochemistry, electron microscopy.
- Other specific enzyme studies as advised by metabolic team. *In vitro* contracture test for malignant hyperthermia after recovery
- Genetic testing as appropriate.

3.6 Specific Muscle Histopathological Features

- GSD III, V, IX – mild-moderate accumulation of glycogen.
- GSD VII – amylopectin-like polysaccharide accumulation (PAS positive, diastase resistant).
- Fatty acid oxidation defects – micro- or macrovesicular lipid accumulation.
- Autoimmune disorders – inflammatory changes.

4 Management

4.1 Acute Management

It is important to note that early consultation with the Renal Team is vital so that management can be planned appropriately. Much of the experience with regards to acute management is based on experience with crush syndrome victims [25, 26].

- Stabilise patient, in particular monitor cardiac rhythm, blood pressure, urinalysis and record a strict fluid balance.
- Baseline and regular CK, electrolytes (especially potassium, calcium and phosphate), acid-base, urea, creatinine and uric acid measurements. CK may not peak until 12 hours post-admission with acute causes. Kidney function and electrolytes will also change progressively.
- Consult the Genetic Metabolic Disorders and Nephrology teams as soon as diagnosis is suspected. If poisoning is suspected (eg snake bite) contact the NSW Poisons Information Centre on 131126 as soon as possible.
- Consult ICU if there are severe electrolyte disturbances, trauma, renal impairment, coagulopathy or any concerns about patient stability.
- "Compartment syndrome" represents a surgical emergency, and urgent involvement of surgical teams to measure limb compartment pressures with possible subsequent fasciotomies, is essential and can be limb-saving.
- Maintenance of adequate preload and urine outputare important management principles and may require consideration of various strategies being mindful of renal function. [26]
- Maintenance fluid at 2 – 3 x normal requirements with strict fluid balance.
- Alkalinisation of urine, (sodium bicarbonate 1 – 3 mmol/kg/day IV or orally depending on the clinical status of the patient), administered in divided doses every 4 to 8 hours) has been historically recommended to protect against myoglobin-induced renal failure; more recent publications suggest the benefit of bicarbonate is less clear, and can paradoxically worsen intracellular acidosis [27]. One should consider bicarbonate therefore only if there is significant systemic acidosis. If administering via the intravenous route, use local intravenous administration guidelines for information about compatibility and dilution, asextravasation can cause severe tissue damage. Discuss with Nephrology team.

  Aim to keep urinary pH above 6.5. If metabolic alkalosis develops (pH > 7.45) there is a theoretical risk of enhancing metastatic calcification[26]. It has been suggested that acetazolamide could be given as this can improve metabolic alkalosis by increasing renal clearance of bicarbonate[3]. This is best discussed with the Nephrology Team if the above measurements do not preserve renal function.
- Calcium supplementation for hypocalcaemia is usually only required if is symptomatic, eg. perioral tingling,or positive clinical signs
- Haemodialysis or CVVH may be necessary for acute renal failure. CVVH is very effective in clearing myoglobin[28]. However, whether it has any impact on established acute kidney injury, or reduces risk of progression to chronic kidney injury, are yet to be determined[29].
- Acute disease-specific caloric support (e.g. MCT oil for long-chain fatty acid oxidation defects).
- Dantrolene or bromocriptine using established protocols (malignant hyperthermia and neuroleptic malignant syndrome)[1]. Discuss with Neurology team.

4.2 Long-term Management

- Avoidance of triggering agents.
- Prevention of catabolic episodes.
- Provision of preferred energy substrates.
    - Low fat-high carbohydrate diet: - long chain fatty acid oxidation defects.
    - Medium chain triglyceride (MCT) oil- CPT II, long chain fatty acid oxidation defects trifunctional protein defect, translocase.
    - Carbohydrate supplementation – Fatty acid oxidation and Glycogen storage disorders
    - Triheptanoin is a potential therapy for some long chain fatty acid oxidation disorders and CPT II deficiency[30-33].

5 References

1. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. J Neurol. 2020; 267(4):877-82.
2. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis.
3. Better OS, Stein JH. Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. N Engl J Med. 1990;322:825-9.
4. Cervellin G, Comelli I, Benatti M, Sanchis-Gomar F, Bassi A, Lippi G. Non-traumatic rhabdomyolysis: background, laboratory features, and acute clinical management. Clin Biochem. 2017;50(12):656-62.
5. Ames EG, Scott AJ, Pappas KB, Moloney SM, Conway RL, Ahmad A. A cautionary tale of pyridoxine toxicity in cystathionine beta-synthase deficiency detected by two-tier newborn screening highlights the need for clear pyridoxine dosing guidelines. Am J Med Genet A. 2020;182(11):2704-8.
6. Ghaffari-Rafi A, Eum KS, Villanueva J, Jahanmir J. Protracted hyperthermia and delayed rhabdomyolysis in ectasy toxicity. Med. 2020;99(41):e21842.
7. Ambasari CG, Sindih RM, Saraswati M, Trihono PP. Delayed admission and management of pediatric acute kidney injury and multiple organ dysfunction syndrome in children with multiple wasp stings: a case series. Case Rep Nephrol Dial. 2019;9:137-48.
8. Terrone G, Ruoppolo M, Brunetti-Perri N, Cozzolino C, Scolamiero E, Parenti G, et al. Child neurology: recurrent rhabdomyolysis due to a fatty acid oxidation disorder. Neurology. 2014;82(1):e.1-4.
9. Roe CR, Ding J. Mitochondrial fatty acid oxidation defects. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, et al., editors. The Metabolic and Molecular Bases of Inherited Disease. 2. New York: McGraw-Hill; 2001. p. 2297-326.
10. Kollberg G, Moslemi A-R, Lindberg C, Holme E, Olfors A. Mitochondrial myopathy and rhabdomyolysis associated with a novel nonsense mutation in the gene encoding cytochrome c oxidase subunit 1. J Neuropathol Exp Neurol. 2005; 64(2):123-8.
11. Shoffner JM. Oxidative phosphorylation diseases. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, et al., editors. The Metabolic and Molecular Bases of Inherited Disease. 2. New York: McGraw-Hill; 2001. p. 2367-423.
12. Chen Y-T. Glycogen storage diseases. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, et al., editors. The Metabolic and Molecular Bases of Inherited Disease. 1. New York: McGraw-Hill; 2001. p. 1521-51.
13. Ng Y-T, Johnsyon HM. Clinical rhabdomyolysis. J Paediatr Child Health. 2000;36:397-400.
14. Ishikawa A, Tanaka S, Ogawa Y, Fukushima N, Takase A, Wagatsuma Y, et al. A case of nemaline myopathy combined with recurrent rhabdomyolysis. Brain Dev. 1994;26:340-4.
15. Allen NM, Ewer A, Nakou V, Konstantoulaki E, Wraige E, Gowda V et al. Unusual presentations of dystrophinopathies in childhood. Pediatrics. 141(Suppl. 5):S510-4.
16. Dick M, Bertorini TE, Igarashi M. Congenital muscular dystrophy presenting with respiratory failure. Dev Med Child Neurol. 1992;34:262-5.

17. Zeharia A, Shaag A, Houtkooper RH, Hindi T, de Lonlay P, Erez G, et al. Mutations in LPIN1 cause recurrent acute myoglobinuria in childhood. Am J Hum Genet. 2008;83(4):489-94.
18. Michot C, Hubert L, Brivet M, De Meirleir L, Valayannopoulos V, Muller-Felber W, et al. LPIN1 gene mutations: a major cause of severe rhabdomyolysis in early childhood. Human Mutation. 2010;31(7):E1564-73.
19. Kremer L, Distelmaier F, Alhaddad B, Hempel M, Iuso A, Kupper C et al. Bi-allelic truncating mutations in TANGO2 cause infancy-onset recurrent metabolic crises with encephalocardiomyopathy. Am J Hum Genet. 2016;98(2):358-62.
20. Lalani S, Liu P, Rosenfeld J, Watkin L, Chiang T, Leduc M, et al. Recurrent muscle weakness with rhabdomyolysis, metabolic crises, and cardiac arrythmia due to bi-allelic TANGO2 mutations. Am J Hum Genet. 2016;98(2): 347-57.
21. Voermans NC, Snoeck M, Jungbluth H. RYR1-related rhabdomyolysis: a common but probably underdiagnosed manifetation of skeletal muscle ryanodine receptor dysfunction. Rev Neurol (Paris). 2016;172(10):546-58.
22. McCarthy TV, Quane KA, Lynch PJ. Ryanodine receptor mutations in malignant hyperthermia and central core disease. Hum Mut. 2000;10:410-7.
23. Tarnopolsky M, Stevens L, MacDonald JR, Rodriguez C, Mahoney D, Rush J, et al. Diagnostic utility of a modified forearm ischemic exercise test and technical issues relevant to exercise testing. Muscle Nerve. 2003;27(3):359-66.
24. Kazemi-Esfarjani P, Skomorowska E, Jensen TDH, R.G. , Vissing J. A nonischemic forearm exercise test for McArdle disease. Annals Neurol. 2002;52(2):153-9.
25. Peiris D. A historical perspective on crush syndrome: the clinical application of its pathogenesis, established by the study of wartime crush injuries. J Clin Pathol. 2017;70(4):277-81.
26. Esposito P, Estienne L, Serpieri N, Ronchi D, Comi GP, Moggio M, et al. Rhabdomyolysis-associated acute kidney injury. Am J Kidney Dis. 2018;71(6):A12-4.
27. Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit Care. 2016;20(1):135.
28. Zhang L, Kang Y, Fu P, Cao Y, Shi Y, Liu F. Myoglobin clearance by continuous venous-venous haemofiltration in rhabdomyolysis with acute kidney injury: a case series. Injury. 2012; 43(5):619-23.
29. Zeng X, Zhang L, Wu T, Fu P. Continuous renal replacement therapy (CRRT) for rhabdomyolysis. Cochrane Database Syst Rev. 2014;6:CD008566.
30. Roe CR, Sweetman L, Roe DS, David F, Brunengraber H. Treatment of cardiomyopathy and rhabdomyolysis in long-chain fat oxidation disorders using an anaplerotic odd-chain triglyceride. Journal of Clinical Investigation. 2002;110(2):259-69.
31. Roe CR, Yang BZ, Brunengraber H, Roe DS, Wallace M, Garritson BK. Carnitine palmitoyltransferase II deficiency: successful anaplerotic diet therapy. Neurology. 2008;71(4):260-4.
32. Spiekerkoetter U, Bastin J, Gillingham M, Morris A, Wijburg F, Wilcken B. Current issues regarding treatment of mitochondrial fatty acid oxidation disorders. J Inherit Metab Dis. 2010;33(5):555-61
33. Vockley J, Burton B, Berry G, Longo N, Phillips J, Sanchez-Valle A, et al. Effects of triheptanoin (UX007) in patients with long-chain fatty acid oxidation disorders: results from an open-label, long-term extension study. J Inherit Metab Dis. 2020; DOI:10.1002/jimd.12313.