

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
- SCHN policy

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

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Page 1 of 10

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This Guideline may be varied, withdrawn or replaced at any time.

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	3
2	Clinical Features and Causes	3
	<i>Drugs and Toxins</i>	3
	<i>Traumatic</i>	3
	<i>Vascular Compromise</i>	3
	<i>Severe Infections</i>	4
	<i>Excessive Muscle Activity</i>	4
	<i>Autoimmune Inflammation</i>	4
	<i>Inborn Errors of Metabolism</i>	4
	<i>Muscular Dystrophies</i>	5
	<i>Other Genetic Disorders</i>	5
3	Investigation	6
3.1	History	6
3.2	Confirm the Rhabdomyolysis.....	6
3.3	Baseline Investigations to Monitor Treatment	6
3.4	Baseline Diagnostic Investigations	6
3.5	Special Tests	7
3.6	Specific Muscle Histopathological Features	7
4	Management	7
4.1	Acute Management	7
4.2	Long-term Management	8
5	References	9

1 Introduction

Rhabdomyolysis can be defined as the breakdown of skeletal muscle cells, with the subsequent release of their contents into the circulation⁽¹⁾. It is characterised by a rise of plasma creatine phosphokinase (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 vasoconstriction and acute renal failure⁽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 acute CK level of 10,000Units/L or more should be regarded as a potentially dangerous level.

2 Clinical Features and Causes

Clinically, patients may complain of muscle stiffness, weakness and myalgia, 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 drugs, e.g. phenothiazines.
- Other drugs (including statins, fusidic acid, colchicine, lithium, extremely high dose pyridoxine (one report)⁽⁵⁾, MDMA (ecstasy)⁽⁶⁾, ethanol, toluene, naltrexone).
- Carbon monoxide poisoning.
- Multiple wasp or hornet stings⁽⁷⁾.
- Snake venom.

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 stop activity as soon as pain starts and rest briefly, can then resume activities 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 or Becker muscular dystrophy⁽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 – autosomal dominant pharmacogenetic disorder due to abnormal skeletal muscle calcium regulation, with mutations in the skeletal muscle ryanodine receptor (*RYR1*) in over 50%⁽²¹⁾.
 - Provoked by volatile anaesthetics (e.g. halothane, isoflourane) and depolarising muscle relaxants (e.g. suxamethonium).
 - Muscle contractions, tachycardia, metabolic acidosis, hyperthermia.

Central core myopathy – is allelic with malignant hyperthermia⁽²²⁾.

3 Investigation

3.1 History

Questions to ask:

- Drug 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.
- Urinalysis

3.3 Baseline Investigations to Monitor Treatment

- CK, electrolytes (especially potassium, calcium and phosphate), acid-base status, uric acid, urea and creatinine measurements.
- Cardiac monitor
- 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 Special Tests

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

- Forearm ischaemic exercise test (see^(1,.)).
- 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 (tissues to be tested may include liver, muscle, cultured skin fibroblasts, or red blood cells). *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^(4, 25, 26).

- Attend to and stabilise the ABCs. 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.
- Consult the Genetic Metabolic Diseases and Nephrology teams as soon as diagnosis is suspected.
- 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 output are important management principles and may require consideration of various strategies being mindful of renal function. ⁽²⁶⁾
- Maintenance fluid at 2 – 3 x normal requirements.
- Alkalinisation of urine, (sodium bicarbonate 1 – 3mmol/kg/day IV or orally depending on the clinical status of the patient), administered in divided doses every 4 to 8 hours) to protect against myoglobin-induced renal failure⁽²⁷⁾. If administering via the intravenous route, use local intravenous administration guidelines for information about compatibility and dilution. Extravasation can cause severe tissue damage.

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, 25, 26). This is best discussed with the Nephrology Team if the above measurements do not preserve renal function.

- Haemodialysis or CVVH may be necessary for acute renal failure. CVVH is very effective in clearing myoglobin⁽²⁸⁾, however it remains unknown whether it would alter or shorten the course of acute renal failure once it has developed⁽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⁾.

4.2 Long-term Management

- Avoidance of triggering agents.
- Prevention of catabolic episodes.
- Provision of preferred energy substrates.
 - Low fat-high carbohydrate diet: - fatty acid oxidation defects.
 - MCT oil - CPT II, VLCAD, trifunctional protein defect, translocase.
 - Carbohydrate supplementation - GSD V, IX ***but not*** VII).
 - Triheptanoin is an emerging potential therapy for long chain fatty acid oxidation disorders and CPT II deficiency⁽³⁰⁻³²⁾.

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