Review Article
Management of cases suffering from atypical myopathy: Interpretations of descriptive, epidemiological and pathophysiological findings. Part 1: First aid, cardiovascular, nutritional and digestive care

G. van Galen*†‡ and D.-M. Votion‡

Department of Infectious and Parasitic Diseases (Research Unit of Epidemiology and Risk Analysis – UREAR), FVM, University of Liege, Liege, Belgium; and Department of Infectious and Parasitic Diseases, Infectious and Parasitic Diseases Research Unit, FVM, University of Liege, Liege, Belgium.

*Corresponding author email: gaby@equinespecialists.eu

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Summary
Atypical myopathy is highly fatal, but about a quarter of affected horses survive. This highlights the need for provision of supportive treatment for these cases. This review is a practical guideline for equine practitioners and includes suggestions for close monitoring of involved organ systems and discusses options of supportive treatment based on current knowledge of the condition.

Introduction
Atypical myopathy (AM) is a severe and often fatal condition that can occur in grazing horses. The development of a multiple acyl-CoA dehydrogenase deficiency (MADD) blocks several steps in mitochondrial lipid metabolism and causes an accumulation of specific acylcarnitines in plasma and urinary excretion of organic acids, glycine conjugates and metabolites derived from the accumulated acyl-CoA ester intermediates (Westermann et al. 2008). Moreover, the respiratory capacity of mitochondrial complexes of the electron transport system is significantly decreased (Westermann et al. 2011). These dysfunctions lead to the exhaustion of energy sources in muscle, which is reflected by the increase of uric acid excretion by purine catabolism and by sarcoplasmatic glycogen depletion (Westermann et al. 2011). Rhabdomyolysis is principally seen in muscles that contain a high proportion of oxidative type I fibres (Cassart et al. 2007). In addition, in several studies, cardiac troponin I activity, when measured, has been shown to be consistently elevated (Votion et al. 2007; Verheyen et al. 2012). Cases therefore show clinical signs consistent with affected postural, respiratory and cardiac muscles (Votion et al. 2007; van Galen et al. 2012a). The cause of the development of AM is yet unknown, but an association with Clostridium sordellii’s lethal toxin has been hypothesised (Unger-Torroledo et al. 2010).

Although the condition is highly fatal, the survival rate during recent European outbreaks was reported to be 26% (van Galen et al. 2012a). The possibility for survival indicates the importance of a rapid and correct diagnosis and good case management in order to increase chance of survival. The diagnosis is usually established based on the combination of history, clinical signs, blood analysis (severely increased serum creatine kinase activity), urine analysis (presence of myoglobinuria), and on histological analysis of ante or post mortem samples indicating a multifocal process compatible with Zenker degeneration (swollen and hyerereosinophilic fibres, devoid of cross-striations and myofibrils, and displaying a homogenous hyaline glassy appearance; Cassart et al. 2007) and necrosis in the targeted muscles (Hosie et al. 1986; Whitwell et al. 1988; Votion et al. 2007). However, these histological findings are not pathognomic for AM and a more definitive diagnosis can be made with measuring the concentration of acylcarnitines and organic acids in urine and/or blood (Westermann et al. 2008) and/or with immunohistochemistry to demonstrate excessive intramuscular lipid storage mainly in type I myofibres (Cassart et al. 2007; Palencia and Rivero 2007). Blood and urine acylcarnitines and organic acids can be measured in most human laboratories, since these tests are routinely run for testing human genetic disorders. (Example of a laboratory with established horse reference ranges: Service de Génétique Humaine, CHU de Liège, University of Liege, Belgium; contact via Dr D.-M. Votion.) Although these 2 latter diagnostic tools are promising for diagnosing AM, they should be interpreted carefully with consideration of the entire clinical picture. Some acylcarnitines can be abnormal in other myopathies (Westermann et al. 2007, 2008) and immunohistochemistry of affected muscle samples only demonstrate a problem in lipid metabolism. Future studies are therefore necessary to validate these diagnostic tools.

Recent studies identified clinical signs and blood parameters that were useful to predict survival in AM cases: remaining standing most of the time, normothermia, normal mucous membranes and defaecation. Prognosis is considered to be poor when horses are recumbent, or show sweating, anorexia, dyspnoea, tachypnoea, tachycardia, high packed cell volume (PCV), low chloride concentration, low arterial partial pressure of oxygen (PaO2<60 mmHg) and/or respiratory acidosis (Votion et al. 2007; van Galen et al. 2011, 2012b). It is probably justified to continue treatment in those cases that have none or only a few of these parameters or if these abnormalities are corrected with treatment. Non-survivors usually die or are subjected to euthanasia within 72 h of onset of clinical signs, but can remain alive for up to 10 days (van Galen et al. 2012a).

This article will discuss in depth the management of AM cases based on descriptive data available in the literature, prognostic factors and the recent advances in
understanding the aetiopathogenesis of the condition. These treatments are based on current knowledge and future research should demonstrate their true clinical impact. This article is a practical guideline and includes suggestions for close monitoring of involved organ systems and discusses options of supportive treatment.

**First aid**

Horses affected by AM are often found recumbent but in the early stages are often still able to get up (Votion et al. 2004, 2007). Whilst still capable of walking, the horse should be placed in a well-bedded stable as soon as possible. In addition, some horses that are recumbent in a cold environment may become severely hypothermic (Brandt et al. 1997; Delguste et al. 2002; Votion et al. 2007; van Galen et al. 2012a). Increasing the body temperature can be accomplished by placing the horse in a warmer environment (stable instead of pasture), administering intravenous or oral fluids at body temperature and using blankets (normal or electric) and heat lamps. If the horse has circulatory compromise one should be prudent with active external heating since this can cause peripheral vasodilatation followed by aggravation of inadequate perfusion. In this case, it is probably best to focus on passive heating by avoiding loss of heat.

Further contact with the pasture and thus the suspected causative agent should be avoided. Recumbent horses should be regularly turned in order to limit ischaemic muscle damage and cardiovascular and/or respiratory problems (Nout and Reed 2005). However, with the current knowledge, the authors believe that attempting to get the horse up or to place it in a sling is not good practice.

Physical effort, stress and transport should probably be avoided as much as possible. These might aggravate the myopathy and the energetic imbalance (Westermann et al. 2008) and may, through the induction of hyperventilation, induce or aggravate a respiratory alkalosis as is commonly seen in AM (van Galen et al. 2011). In the authors’ opinion, treatment should be attempted at home and the affected horse should only be referred and transported to a clinic if treatment at home is impossible.

**Cardiovascular monitoring and treatment**

**Hydration, acid-base and electrolyte status**

Correction of hydration, acid-base and electrolyte disturbances of horses that are affected by AM is of major importance to optimise cardiovascular, respiratory, muscular, renal and digestive function, and is therefore the first treatment to install.

**Monitoring hydration, acid-base and electrolyte status**

Clinical examination

Heart rate and the colour and capillary refill time of the mucous membranes are valuable clinical parameters to evaluate hydration status in a sick horse. Normal mucous membranes have been associated with survival and tachycardia with mortality (mean heart rate of survivors: 53 ± 13 beats/min (54 cases); mean heart rate of nonsurvivors: 62 ± 18 beats/min (155 cases; van Galen et al. 2012b)).

**Blood analysis**

- Packed cell volume: PCV is often increased (Votion et al. 2007) and nonsurvivors have a significantly higher PCV than survivors of AM (van Galen et al. 2011).
- Lactate: most affected horses have increased lactate levels (up to 19 mmol/l), but this was not associated with survival (van Galen et al. 2011).
- Venous blood gases: the majority of affected horses suffer from metabolic acidosis on admission with or without respiratory alkalosis (van Galen et al. 2011). Respiratory alkalosis is regularly encountered on admission (van Galen et al. 2011), possibly caused by pain, stress, or compensation for the metabolic acidosis or anaerobic muscle metabolism due to hyperventilation. The presence of respiratory acidosis, related to hypoventilation due to severely affected respiratory musculature, seems to be associated with mortality (van Galen et al. 2011).
- Electrolytes (Na⁺, Cl⁻, K⁺, Ca²⁺, Mg²⁺): hypocalcaemia, mild hypernatraemia and hypochloroaemia are common in AM cases, but mild hypernatraemia and mild hyperkalaemia also can occur (Delguste et al. 2002; Puyalto-Moussu et al. 2004; Finno et al. 2006; Votion et al. 2007; van Galen et al. 2011). Chloride concentrations are often low in nonsurvivors (van Galen et al. 2011).

**Fluid therapy**

Fluid therapy in AM affected horses should be provided in order to restore circulating volume, promote myoglobin excretion and correct acid-base and electrolytic imbalances. Table 1 describes the fluid choices for specific metabolic disturbances. Sodium bicarbonate is not indicated to treat lactic acidosis, especially if the horse demonstrates respiratory difficulties, hypocalcaemia and/or heart failure (Corley and Marr 1998), all of which may occur in AM. Calcium supplementation is debatable, since it has been shown to exacerbate endotoxaemia and increase mortality in rodents (Malcolm et al. 1989; Zaloga et al. 1992). However, hypocalcaemia can lead to clinical signs such as diaphragmatic flutter, tetany, seizures, cardiac problems (Glazier et al. 1979) and may be associated with ileus (Delesalle et al. 2005). Although it seems obvious that the development of these clinical signs of hypocalcaemia needs to be avoided, the level of intervention in the horse is currently unknown. Also, intrasacroplasmatic accumulations of calcium have been suggested to be an important part of the common final pathway to muscle fibre degeneration and necrosis (Wrognemann and Pena 1976; MacLeay 2004). Even though calcium accumulations have not been demonstrated on histology in AM affected muscles (Cassart et al. 2007), calcium should be used prudently since the effects of calcium supplementation in AM are yet unknown.

**Cardiac function**

Horses affected with AM frequently demonstrate significant myocardial damage on post mortem examination (Cassart et al. 2007). In addition, they may have reduced myocardial function, pericardial effusion, increased troponin I levels and arrhythmias (Votion et al. 2007; Verheyen et al. 2012; van Galen et al. 2012a). Although arrhythmias are often not severe, and are mostly ventricular premature contractions (Verheyen et al. 2012), some horses develop life-threatening arrhythmias such as ventricular tachycardia (personal observation).
**Monitoring cardiac function**
Cardiac function can be monitored by regular cardiac auscultation, measuring serum troponin I concentrations, and by performing an ECG and echocardiography. Complementary monitoring of hydration status and cardiac function might be useful with, for example, pulse oximetry, blood pressure measurements, cardiac output monitoring, and central venous pressure measurements.

**Cardiac treatment**
If the horse demonstrates tachycardia, circulating volume and cardiac function should be checked and/or more intensive pain management (see below) considered. Administration of digoxin (2.2 μg/kg bwt i.v. or 11 μg/kg bwt per os) might be considered in cases that demonstrate reduced myocardial function. Digoxin has a positive inotropic action and improves renal blood flow. If the horse develops arrhythmias, electrolytes should be checked and disturbances corrected if present. If the arrhythmias are severe, administration of anti-arrhythmic drugs should be considered (Muir and McGuirk 1985; Baggot 1995; Durando 2008).

**Nutritional support**
Nutritional support is important in all severely ill cases, but has an even larger impact in AM cases because affected fibres have derangements of lipid metabolism and must rely on less efficient carbohydrate metabolism (Westermann et al. 2008). Additionally anorexia was shown to be related to poor prognosis (van Galen et al. 2012b).


<table>
<thead>
<tr>
<th>Disturbance</th>
<th>Ideal fluid</th>
<th>Dosage/rate</th>
<th>Suggestions on when to initiate treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of disturbance</td>
<td>Polyionic crystalloids</td>
<td>Rate depends on requirements</td>
<td>Blood lactate &gt;3.0 mmol/l</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>Polyionic crystalloids</td>
<td>Up to 60–80 ml/kg bwt as bolus, maintenance rate depends on requirements</td>
<td></td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>Colloids</td>
<td>Up to 10 ml/kg bwt as bolus Sodium should not be corrected faster than 1 mmol/l/h</td>
<td>Plasma sodium &lt;122 mmol/l</td>
</tr>
<tr>
<td>- With hypochloraemia</td>
<td>Sodium chloride (0.9–1.8%)</td>
<td>Sodium should not be decreased faster than 0.5 mmol/l/h</td>
<td>Mild: plasma sodium 144–150 mmol/l Moderate to severe: plasma sodium &gt;150 mmol/l</td>
</tr>
<tr>
<td>- Without hypochloraemia</td>
<td>Sodium bicarbonate (1.3–5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypernatraemia</td>
<td>Polyionic crystalloids</td>
<td>2.5% dextrose / 0.45% sodium chloride</td>
<td></td>
</tr>
<tr>
<td>- Mild</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Moderate to severe</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypokalaemia</td>
<td>Potassium chloride i.v.</td>
<td>0.2–0.5 mmol/kg bwt/h, not to exceed 0.5 mmol/kg bwt/h</td>
<td>Plasma potassium &lt;3.5 mmol/l</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Potassium chloride per os</td>
<td>0.1–0.2 g/kg bwt per os</td>
<td></td>
</tr>
<tr>
<td>- No clinical signs</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- With clinical signs or &gt;7 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperchloreaemia</td>
<td>Sodium chloride (0.9–1.8%)</td>
<td>To effect</td>
<td>Blood potassium &lt;5–7 mmol/l</td>
</tr>
<tr>
<td>- Mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Moderate to severe with hypertension</td>
<td>Sodium bicarbonate (1.3–5%)</td>
<td>To effect</td>
<td>Plasma chloride &gt;95 mmol/l</td>
</tr>
<tr>
<td>- Moderate to severe without hypenatraemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>Calcium gluconate 23%</td>
<td>0.2–1.0 ml/kg bwt in 2–3 h</td>
<td>Plasma ionised calcium &lt;1 mmol/l</td>
</tr>
<tr>
<td>- Calcium borogluconate 40%</td>
<td></td>
<td>0.1–0.5 ml/kg bwt in 2–3 h</td>
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be useful (Westermann et al. 2003, 2004). From AM might exceed those for healthy horses (12 mg for a blockage, supplementation with riboflavin (vitamin B2) might be encouraged to eat. It is probably best to support the energetic metabolism with a diet poor in lipids and rich in carbohydrates. This is contradictory to nutritional advice for other equine myopathies such as polysaccharide storage myopathy or recurrent exertional rhabdomyolysis, where a reduction of carbohydrates and an increase of lipid content is suggested (MacLeah et al. 1999; McKenzie and Fishman 2009). Although nutritional studies are needed in the future to determine the optimal diet composition for these cases, some suggestions can be made. Some examples of carbohydrate rich food are grass, good quality hay, alfalfa, grains, molasses, sugar water, carrots and apples. To avoid important peaks and drops in glycaemia it is advised to offer the horse small quantities of feed multiple times per day instead of one or 2 large meals and to allow free access to structural fibres such as grass, hay or alfalfa. It is recommended for structural fibres to make up the majority of the diet without a large amount of soluble carbohydrates (grains or concentrates).

If the horse is anorexic or dysphagic, but its intestinal tract is capable of handling food, the horse can be fed through a stomach tube (assisted enteral feeding). Soaked alfalfa pellets are easy to use for this method of feeding but commercial liquid diets are also available (Sweeney and Hansen 1990; Durham et al. 2008). Good quality hay, alfalfa or grass usually contain enough to fulfil normal daily requirements (Rooney 2004). However, the requirements in horses suffering from AM might exceed those for healthy horses (12 mg for a mature horse with stall rest) and therefore it is advised to supplement riboflavin in the form of a vitamin B complex.

The most important part of the treatment of hyperlipaemia consists of providing good nutritional support to the horse in order to reverse the negative energy balance. In addition, intravenous administration of glucose/dextrose solutions can be administered to provide the horse with some additional energy (Dunkel 2003). However, glucose/dextrose solutions (5 or 10%) need to be administered in large amounts in order to meet the energy requirements of the horse, which might lead to overhydration or electrolyte imbalances. Therefore 50% glucose/dextrose solutions might be a better option (0.15–0.25 ml/kg bwt/h i.v.; Dunkel 2008). Glucose solutions should not be used as the sole energy provider (Corley 2008; Stratton-Pelps 2008); it is thus important to provide other nutritional support in addition. Moreover, glucose should only be administered while blood glucose levels are closely monitored, especially since hyperglycaemia is frequently encountered in AM cases even before glucose supplementation (Votion et al. 2007). Hyperglycaemia should be avoided and treated since it induces osmotic diuresis and has been demonstrated in other species to be detrimental in acute renal failure (Moursi et al. 1987). As in human medicine, preventing hyperglycaemia in sick horses might have a positive effect on outcome (Krisley et al. 2012; van Herpe et al. 2012). The authors believe that even if cases have mild to moderate hyperglycaemia (still under the renal threshold of <1.80 g/l or 10 mmol/l; Stratton-Pelps 2008), they still might benefit from glucose solutions. Because of the disturbances in energy metabolism in AM cases, one of the hypotheses regarding the origin of hyperglycaemia is gluconeogenesis. This indicates that glucose levels will normalise by giving glucose, because providing an external energy source will decrease the hepatic production of glucose from internal energy sources. However, if hyperglycaemia continues or develops while supplementing, insulin should be administered (cf. Table 2).

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Action</th>
<th>Dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular insulin (used by preference)</td>
<td>Fast acting</td>
<td>CRI titrated to effect from a starting rate of 0.01 iu/kg bwt/h Not to change by more than 0.02 iu/kg bwt/h CRI 0.07 iu/kg bwt/h 0.1–0.5 iu/kg bwt subcut. q. 12 h 50–100 iu/horse i.v. up to q. 2 h 0.1–0.3 iu/kg bwt subcut. every 12 h</td>
<td>Corley and Stephen 2008; Stratton-Pelps 2008 Han, McKenzie et al. 2011 Corley and Stephen 2008 Barker, Roberts et al. 2008 Stratton-Pelps 2008</td>
</tr>
<tr>
<td>Protamine zinc insulin</td>
<td>Slow acting</td>
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</table>

CRI = continuous rate infusion.

**Treatment**

**Nutrition**

Fasting should be avoided at all times and the horse should be encouraged to eat. It is probably best to support the energetic metabolism with a diet poor in lipids and rich in carbohydrates. This is contradictory to nutritional advice for other equine myopathies such as polysaccharide storage myopathy or recurrent exertional rhabdomyolysis, where a reduction of carbohydrates and an increase of lipid content is suggested (MacLeah et al. 1999; McKenzie and Fishman 2009). Although nutritional studies are needed in the future to determine the optimal diet composition for these cases, some suggestions can be made. Some examples of carbohydrate rich food are grass, good quality hay, alfalfa, grains, molasses, sugar water, carrots and apples. To avoid important peaks and drops in glycaemia it is advised to offer the horse small quantities of feed multiple times per day instead of one or 2 large meals and to allow free access to structural fibres such as grass, hay or alfalfa. It is recommended for structural fibres to make up the majority of the diet without a large amount of soluble carbohydrates (grains or concentrates).

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**Treat hyperlipaemia and hyperglycaemia**

Affected horses often demonstrate hyperlipaemia (Votion et al. 2007), even if they are still eating (personal observation).
mucous covered faecal matter, impactions of the large and/or small colon, colon displacements), and mild diarrhoea (Sherlock and Mair 2008; van Galen et al. 2012a). In addition, some cases display lesions of haemorrhagic gastroenteritis on post mortem examination (Cassart et al. 2007). Since it has been suggested that the as yet undiscovered causative agent is ingested (Votion et al. 2009), the authors hypothesise that some of these digestive problems (buccal ulceration, gastroenteritis, mild diarrhoea) are caused by a local inflammatory reaction. The importance of an adequately functioning digestive system in horses suffering from AM has been demonstrated by the fact that defaecation was related to survival and anorexia to mortality (van Galen et al. 2012b).

Monitoring
The digestive system can be monitored by evaluating appetite, dysphagia, defaecation, amount and consistency of faecal matter, borborygmi, and by rectal examination.

Treatment
Since the causative agent is believed to enter the body through the digestive system, laxative treatment with paraffin and/or electrolytes and intestinal absorbants such as active charcoal (1–3 g/kg bwt diluted in water per os; Corley and Stephen 2008) or di-tri octahedral smectite (Biosponge: 0.5 kg per os q. 24 h; Hasel et al. 2009), can be considered.

Omeprazole (Gastroguard: 1–4 mg/kg bwt per os q. 24 h; Lester et al. 2005; White et al. 2007) and/or sucralfate (22 mg/kg bwt per os q. 8 h; Galvin et al. 2004) may be indicated as pain, anorexia and stress might increase the susceptibility to development of gastric ulcers, and haemorrhagic gastroenteritis can occur in AM (Cassart et al. 2007). Moreover, by avoiding or treating gastric ulcers, omeprazole might help in preserving a good appetite, which is of major importance. However, it should be mentioned that the use of omeprazole in foals and human patients is a risk factor for infectious complications such as diarrhoea (Furr et al. 2012). At the time of writing, negative effects on mature horses and more specifically those suffering from AM have not been reported. Nevertheless, the possibility of complications should be kept in mind as well as the possibility that a decreased gastric acidity enhances the dispersion of the unknown aetiological agent through the body.

An oesophageal obstruction should be treated with the use of sedatives with or without nasogastric intubation. When the horse develops diarrhoea, antimicrobials and nonsteroidal anti-inflammatory drugs have to be used with caution. Medical management of colic signs should be attempted; surgical intervention should be avoided if possible, because anaesthesia can seriously aggravate rhabdomyolysis and therefore limit the chance of survival (Serteyn et al. 1990; Sherlock and Mair 2008). If buccal ulcerations or necrosis are present, the mouth of the horse can be flushed with water or diluted chlorhexidine to encourage healing and limit interference with appetite.

Importantly remark considering drugs
The directions for use of drugs and their dosage in this article have been compiled on the basis of information provided in the scientific literature. As such, some drugs have not been validated according to quality, safety, and effectiveness criteria necessary for drug approval and commercialisation. This list of drugs does not take into account national or community laws, regulations or policies regarding the use and commercialisation of a series of substances and some drugs cited have not received legal approval.

The authors decline all responsibility in the event of an accident. The veterinary practitioner engages his full responsibility.

Authors’ declaration of interests
No conflicts of interest have been declared.

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References

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