Exertional Rhabdomyolysis: Diagnosis and Treatment

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Exertional rhabdomyolysis (ER), literally the dissolution of striated muscle with exercise, is an age old problem in horses. Over the past century a number of terms have been used to describe this syndrome including tying-up, set fast, Monday morning disease, azoturia, chronic intermittent rhabdomyolysis and equine rhabdomyolysis syndrome. The prevalence of ER is higher among racehorses at about 6%, and in polo horses it is as high as 13%. The development of rhabdomyolysis is influenced by factors such as exercise routines, sex, age, and temperament of the horse, as well as diet and presence of lameness.

Clinical signs: Horses with ER usually show signs of muscle stiffness, shifting hindlimb lameness, elevated respiratory rate, sweating, firm painful hindquarter muscles, and reluctance to move that lasts for several hours. There may be a decrease in the severity of clinical signs as horses get older horses. Subclinical episodes occur in some horses causing decreased performance, painful muscles, and reluctance to maintain collection without other overt signs.

Diagnosis: A diagnosis of ER is based on clinical signs of muscle stiffness and pain following exercise in conjunction with elevations in serum creatine kinase (CK) and aspartate transaminase (AST) activities. The degree of elevation of these enzymes in serum is dependant upon the severity of muscle damage as well as the length of time that has elapsed between sample collection and the occurrence of muscle damage. Peak serum values occur approximately four to six hours, 12 and 24 hours following myonecrosis for CK, lactate dehydrogenase (LDH) and AST, respectively. Clearance of these enzymes from the bloodstream following rhabdomyolysis occurs rapidly for CK, more slowly for LDH, and is most prolonged for AST. Moderate to severe rhabdomyolysis may also produce myoglobinuria detected by urine stick tests as Hb-positive in the absence of hemolysis or RBC in the urine.

With severe rhabdomyolysis, electrolyte abnormalities such as hyponatremia, hypochloremia, hypocalcemia, hyperkalemia and hyperphosphatemia may occur. These derangements result from losses in sweat as well as shifting of fluid and electrolytes (sodium, chloride, calcium) down a concentration gradient into damaged muscle. Release of electrolytes such as potassium and phosphorus from damaged muscle cells can result in increased serum concentrations. A metabolic alkalosis is the most common acid base abnormality with ER, as a compensation for hypochloremia. Lactic academia is rarely, if ever, observed. Azotemia may occur in dehydrated horses from myoglobinuric nephrotoxicity.
Establishing that ER is a primary cause of poor performance is challenging when episodes
of ER are intermittent. Persistent elevation in AST may indicate previous ER. However, if
serum muscle enzymes are normal, an exercise challenge can be of value to detect
underlying subclinical ER. Blood samples are obtained before exercise and about four to
six hours after exercise to evaluate peak changes in CK activity. Fifteen minutes of easy
uncollected trotting will detect significant, yet subclinical muscle damage in horses prone
to ER. This test is selected rather than a maximal exercise tests because it provides more
consistent evidence of subclinical rhabdomyolysis with less risk of over-exertion. If signs
of stiffness develop during the test, exercise should be concluded. A three- to four-fold
increase from basal CK activity is indicative of subclinical ER. Small fluctuations in
serum CK activity may occur with exercise due to enhanced muscle membrane
permeability, particularly if exercise is prolonged or strenuous, and the horse is untrained.

Classification of ER

A great deal of controversy has arisen regarding the cause of this syndrome; however, it
has become clear that these terms really incorporate a number of different disease
processes that share a common manifestation of muscle pain. As mentioned previously ER
represents a syndrome of muscle pain and necrosis that likely has numerous underlying
causes. In practice, it may be useful to initially determine if a horse with ER falls into one
of two main categories: 1) horses in which an intrinsic muscle defect does not appear to be
present, but a temporary imbalance within the muscle cells cause sporadic episodes of ER,
and; 2) Those in which the primary underlying susceptibility appears to be the result of an
intrinsic defect in the muscle, sometimes referred to as chronic ER.

Sporadic cases of ER are usually characterized by a history of adequate performance prior
to onset of episodes and a successful return to performance following a reasonable period
of rest, provision of a balanced diet, and a gradual training program. Horses with these
sporadic occurrences of ER may be of any age, breed, or sex, and involved in a wide
variety of athletic disciplines. A familial history of ER is absent. Episodes of ER may
recur over a period of time prior to resolving. Episodes of sporadic ER appear to be
triggered by external perturbations which affect muscle function, and once corrected
complete resolution is possible. In many cases, horses are initially presumed to have
sporadic ER; however, if over time episodes of ER recur despite the best management, a
diagnosis of chronic ER would be more likely.

Horses often develop signs of chronic ER shortly after entering an initial training regime
and with very little prior conditioning. Certain breeds of horses appear to have a higher
prevalence of chronic ER, and within these breeds specific family lines appear
particularly predisposed. This has led to the suggestion that there are intrinsic inherited
defects in muscle function which may predispose horses to chronic forms of ER.
Documented forms of chronic ER include polysaccharide storage myopathy and recurrent
exertional rhabdomyolysis. There are, however, most likely other forms of chronic ER.
which are at present unrecognized.

**Causes of Sporadic ER**

*Over-exertion:* A history of an increase in work intensity without a foundation of consistent training for this level of intensity is usually the basis for suspecting a training imbalance as a cause of ER. Signs of muscle stiffness and gait changes may be mild and are accompanied by modest elevations of serum CK activity.¹⁹

*Heat exhaustion:* Heat exhaustion occurs most commonly in horses exercising in hot, humid weather. Signs of heat exhaustion include weakness, ataxia, rapid breathing, muscle fasciculations sweating and collapse. The body temperature may be elevated to 105 - 108 F. Muscles are frequently not firm on palpation, serum CK activity can be markedly elevated and myoglobinuria may be noted.²²

*Dietary imbalances:* Episodes of ER may be triggered by diets with a high nonstructural carbohydrate (NSC) content, inadequate selenium and vitamin E²³, or electrolyte imbalances.²⁴ Serum vitamin E and either whole blood selenium concentrations, or glutathione peroxidase activity can be helpful in assessing potential deficiencies. Horses with ER are infrequently deficient in selenium; however, anecdotal reports suggest that in some cases supplementation may prevent further episodes of ER.²⁵

*Electrolyte imbalances:* Electrolyte balance within the body is difficult to determine accurately.²⁶ One suggested means to practically assess electrolyte balance in horses is to measure urinary fractional excretion (FE) of electrolytes.²⁴ Measurement of urinary electrolyte excretion as an indicator of electrolyte balance is complicated because marked variation can occur from diet, exercise, and sampling technique between individuals as well as within individuals from day to day.²⁶,²⁷ Furthermore, the high calcium crystal concentration of alkaline equine urine requires acidification to accurately assess calcium and magnesium content.²⁷

**Treatment of Acute ER**

Treatment of ER is directed at relieving anxiety and muscle pain and replacing fluid and electrolyte losses. Tranquilizers such as acepromazine (0.04 – 0.07 mg/kg), xylazine (0.2- 0.5 mg/kg) or detomidine (0.02 - .04 mcg/kg) combined with butorphanol (0.01 – 0.04 mg/kg) provide excellent sedation and analgesia. For horses with extreme pain and distress a constant rate infusion of detomidine, lidocaine or butorphanol may provide additional pain relief. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ketoprofen (2.2 mg/kg), phenylbutazone (2.2 – 4.4. mg/kg) or flunixin meglumine (1.1.mg/kg) are frequently used to relieve pain but should be used with caution on dehydrated animals. Intravenous or intragastric dimethyl sulfoxide (as a < 20% solution) is used as an antioxidant, anti-inflammatory and osmotic diuretic for severely affected horses. Methyl prednisolone succinate (2 –4 mg/kg IV) has been advocated by some veterinarians in the
acute stage if horses are recumbent. Muscle relaxants such as methocarbamol (5–22 mg/kg, IV slowly) seem to produce variable results possibly depending on the dosage used. The administration of dantrium sodium (2-4 mg/kg orally) in severely affected horses may decrease muscle contractures and possibly prevent further muscle necrosis. The dose can be repeated every 4-6 h if necessary and best absorption occurs when given proceeded by at least 3 h fasting. Overdosing produces muscle weakness.

Severe rhabdomyolysis can lead to renal compromise due to the ischemic and the combined nephrotoxic effects of myoglobinuria, dehydration and NSAIDs. In mildly dehydrated horses, provision of free choice electrolytes and water or administration of fluids via a nasogastric tube may be adequate. Horses with moderate to severe dehydration require IV administration of balanced polyionic electrolyte solutions. Hyperkalemia can occur with severe rhabdomyolysis, necessitating the use of isotonic sodium chloride. If hypocalcaemia is present then supplementing intravenous fluids 100 – 200 ml of 24% calcium borogluconate is recommended, but serum calcium should not exceed a low normal range. Affected animals are usually alkalotic, making bicarbonate therapy inappropriate. In severely affected animals, regular monitoring of serum creatinine is advised to assess the extent of renal damage.

Horses should be stall rested on a hay diet for a few days. Small paddock turn-out in a quiet area for a few hours twice a day is then helpful. Horses may be hand walked at this time, but not for more than 5-10 minutes at a time. For horses with sporadic forms of tying-up, rest with regular access to a paddock should continue until serum muscle enzyme concentrations are normal. For chronic cases of tying-up this much rest may not be appropriate. Training should be resumed gradually, and a regular exercise schedule that matches the degree of exertion to the horses underlying state of training, should be established.

**Causes of Chronic ER**

Known causes of chronic ER include recurrent exertional rhabdomyolysis (RER) and two forms of polysaccharide storage myopathy (PSSM). There may well be yet other unrecognized causes.
Recurrent Exertional Rhabdomyolysis (RER)

The term RER is used to describe a subset of ER that is believed to be due to an abnormality in intracellular calcium regulation.\(^{13, 28, 29}\) Research into RER has primarily been performed in Thoroughbreds, and to a lesser extent Standardbred horses.\(^{28-31}\) There are undocumented reports of some Arabian horses with ER that may also suffer from this specific form of myopathy.

The prevalence of RER in Thoroughbred racehorses is remarkably similar around the world with estimates ranging from 4.9% in the US\(^2\), 5.4% in Australia\(^1\), and 6.7% in the UK.\(^3\) Exercise obviously increases the prevalence of RER in horses and episodes are observed more frequently once horses achieve a level of fitness.\(^2, 3\) The type of exercise seems to be of importance with episodes of rhabdomyolysis occurring most often when horses are restrained to a slower pace during exercise and occurring infrequently after racing.\(^2\) Thoroughbred horses often show evidence of rhabdomyolysis after the steeplechase or at the beginning of the cross-country phase of a three-day event.

Mares are more commonly show signs of RER than males, however, no general correlation has been observed between episodes of rhabdomyolysis and stages of the estrus cycle. There appears to be an interaction between age and gender in RER horses such that the proportion of affected females to males is much higher in young horses compared to older age groups. Temperament exhibits a strong effect on the expression of RER, with nervous horses having a significantly higher incidence of rhabdomyolysis than calm horses. Young fillies are more likely to have a nervous temperament than mares or male horses. Horses on a high grain diet are more likely to show signs of RER, and one study found a higher prevalence of rhabdomyolysis among horses with various lameness.

**Genetics:** A genetic susceptibility to RER appears to exist in Thoroughbred horses. Studies of RER-afflicted horses have shown that affected horses may pass the trait along to 50% or more of their offspring.\(^{16, 17}\) A breeding trial conducted at the University of Minnesota, as well as pedigree studies from a variety of farms, suggest that susceptibility to RER is inherited as an autosomal dominant trait.\(^{16, 17}\) Studies of Standardbred horses with RER suggest that there is potentially a heritable basis for this condition in this breed as well.\(^{32}\) There are anecdotal reports of higher prevalence of RER in certain Arabian horse families.

**Diagnosis:** In practice, many trainers evaluated serum CK or AST activities to identify horses with reduced performance due to subclinical episodes of RER. A number of factors may affect muscle enzyme elevations in serum, and reliability can be improved if blood samples are obtained at a standardized time, preferably four to six hour after exercise (when CK peaks), and consistently with regard to exercise on the preceding day, since serum CK activity is higher on exercise days that are preceded by a day or more of rest.\(^6, 33, 34\) In addition, normal values need to be adjusted for the age and sex of horses. Two year old fillies generally appear to show greater fluctuations in serum CK activity during race training than three year old fillies or geldings.\(^6, 34\)
A presumptive diagnosis of RER is based on clinical signs of muscle pain and the presence of risk factors commonly associated with RER. Skeletal muscle biopsies from Thoroughbred and Standardbred horses with active signs of RER often show an increased number of mature muscle fibers with centrally displaced nuclei, increased subsarcolemmal staining for glycogen, and a variable amount of muscle necrosis and regeneration.\textsuperscript{8,13} There is a notable absence of abnormal amylase-resistant polysaccharide in muscle biopsies from RER horses.\textsuperscript{13} Research is currently underway to identify a genetic marker that would help to identify horses susceptible to this genetic disease.\textsuperscript{16}

\textit{Cause of RER}: Several studies have clearly demonstrated the rhabdomyolysis is not due to a lactic acidosis.\textsuperscript{12,33,35} More recent research suggests that horses with RER may inherit an abnormality in intramuscular calcium regulation that is intermittently manifested during exercise.\textsuperscript{28,29} Studies of intact intercostal muscles from Thoroughbred horses with RER found an abnormal sensitivity to the development of muscle contracture upon exposure to potassium, caffeine, and halothane in RER compared to normal horses.\textsuperscript{29} Calcium imaging of myotubes derived from RER horses also showed enhanced calcium release in response to caffeine.\textsuperscript{28} The characteristics of RER muscle are very similar but not identical to those of humans and swine with malignant hyperthermia. At present the exact defect in intracellular calcium regulation with RER is not known.

\textbf{Management of ER}

\textit{Environment}: If one of the main triggering factors for ER appears to be excitement, finding ways to reduce stress is recommended to help decrease episodes of rhabdomyolysis in susceptible horses. Many horses respond to a regular routine including feeding first prior to other horses and training first before other horses, especially if the horse becomes impatient while waiting. Other ways to decrease excitement include housing in an area of the barn where horses are not always walking past and next to calm companionable horses. The use of hot walkers, exercise machines, and swimming pools should be evaluated on an individual basis, as some horses develop rhabdomyolysis when using this type of equipment. Horses which develop rhabdomyolysis at specific events, such as horse shows, may need to be reconditioned to decrease the stress level associated with such events. Providing daily turn out with compatible companions can be very beneficial for RER horses, and may decrease anxiety and thereby the likelihood of rhabdomyolysis.

\textit{Exercise}: Many horses with mild episodes of tying-up are best turned out for a few days and then returned gradually to regular daily exercise. Horse with more severe damage may require additional time off before gradually resuming exercise. Once back in training, it is recommended to avoid days off exercise, because serum CK activity is higher when horses are exercised after a day of rest. A prolonged warm-up with adequate stretching is believed to decrease episodes of rhabdomyolysis. Rest periods that allow horses to relax and stretch their muscles between periods of collection under saddle may be of benefit.
Event horses may require training that incorporates calm exposure to steeplechase, as well as interval training at the speeds achieved during the steeplechase, to prevent rhabdomyolysis during competitions. Thoroughbred racehorses often develop rhabdomyolysis when riders fight to keep horses at a slower speed and therefore this should be avoided. Standardbred horses often develop rhabdomyolysis after 15-30 minutes of submaximal trotting and therefore interval training and reduction of jog miles to no more than 15 minutes per session is recommended.

Medications: Low doses of tranquillizers, such as acepromazine, prior to exercise have been used in RER horses prone to excitement. A dose of 7 mg IV 20 minutes before exercise is reported to make horses more relaxed and manageable. Reserpine and fluphenazine, which have a longer duration of effect, have also been used for this purpose. Horses given fluphenazine may occasionally exhibit bizarre behavior. Use of tranquillizers may only be necessary when horses are in their initial phase of training and accommodation to a new environment. Horses obviously cannot compete on these medications.

Dantrolene sodium acts to decrease release of calcium from the calcium release channel in skeletal muscle and is used to treat malignant hyperthermia. Recent experimental and field studies have shown that when given appropriately it can significantly decrease signs of rhabdomyolysis in RER horses. Dantrium does not achieve any measurable blood levels when given to horses on full feed; however, when 4 mg/kg PO was given to horses fasted for 12 hours, dantrium was detected in plasma one hour before exercise and abnormal elevations in CK did not occur following exercise. A dose of 800 mg of dantrium was given to Thoroughbred horses in the UK one hour prior to exercise and resulted in significantly lower post exercise CK activity than a placebo.

Phenytoin (1.4-2.7 mg/kg PO BID) is an alternative medication that has been reported to be effective in preventing rhabdomyolysis in horses with RER. Phenytoin acts on a number of ion channels within muscle and nerves including sodium and calcium channels. Phenytoin also affects triglyceride metabolism (Beech 1994). Therapeutic levels vary, so oral doses are adjusted by monitoring serum levels to achieve 8 ug/ml and not to exceed 12 ug/ml. Drowsiness and ataxia are evidence that the dose of phenytoin is too high and the dose should be decreased by half. Initial dosages start at 6 to 8 mg/kg orally twice a day for three to five days. If the horse is still experiencing rhabdomyolysis but is not drowsy, the dose can be increased by 1 mg/kg increments every three to four days. Phenytoin is a monoaminoxidase activator and can affect dosages of other medications. Unfortunately long-term treatment with dantrolene or phenytoin is expensive and these drugs must be withdrawn prior to competition.

Intramuscular injections of vitamin E and selenium are commonly used by veterinarians in an attempt to prevent RER. Horses usually do not have a demonstrated deficiency however, these supplements are given in an attempt to counteract oxidant injury. Ensuring adequate oral intake may prevent the muscle soreness associated with IM injections. Daily dietary recommendations for vitamin E and selenium are provided in...
Table 1.

Some mares appear to exhibit signs of rhabdomyolysis during estrus and it may well be of benefit in these horses to suppress estrus behavior using progesterone injections. Testosterone and anabolic steroids are used at racetracks to prevent signs of RER, but the efficacy has not been evaluated.

*Adjunct therapies:* Massage, myofascial release, mesotherapy, stretching, and hot/cold therapy performed by experienced therapists may be of benefit in individual cases of ER.

*Diet:* A nutritionally balanced diet with appropriate caloric intake and adequate vitamins and minerals are the core elements of treating RER. As with any horse, forage is recommended at a rate of 1.5-2% of body weight as good quality grass hay. Out of the total daily calories required, it is recommended that less than 20% digestible energy (DE) be supplied by starch and at least 15% be supplied by fat. Controlled experimental studies using Thoroughbreds with RER show that serum CK activity is significantly lower when if horses are fed a specially formulated high fat, low starch feed\(^1\) rather than an isocaloric amount of high starch grain.\(^{33, 35, 44}\) Serum CK activity declined within one week of making the recommended diet change in the five Thoroughbred horses studied by McKenzie. The beneficial effects of this type of diet may be due to the exclusion of dietary starch rather than specific protective effects of high dietary fat. Given the close relationship between nervousness and RER, assuaging anxiety and excitability by reducing dietary starch and increasing dietary fat may decrease susceptibility by making these horses calmer prior to exercise.\(^2, 3\)

The challenge in altering the diet of Thoroughbred horses with RER is in supplying an adequate number of calories in a highly palatable feed to meet their daily energy demands. This can be very difficult to achieve by blending individual components, but may be achieved by feeding pelleted specialized commercial diets. These feeds typically should contain less than 20% starch or nonstructural carbohydrate (NSC) by weight and more than 10% fat by weight with a high fiber component. Other feed companies offer similar nutritional content by blending two or more of their manufactured feeds or by supplementing with additional oils or rice bran. At present, the NSC content of equine feed products is not listed on the feed tag, and consultation with the feed manufacturer is necessary to obtain this information. Nutritional support is available through most feed manufacturers to design an appropriate diet using recommendation provided in Table 1. The Neuromuscular Diagnostic Laboratory at the University of Minnesota also provides a list of suggested diets together with the results of muscle biopsy evaluation.

*Electrolyte supplementation:* Horses require daily dietary supplementation with sodium and chloride either in the form of loose salt (30-50 g/day) or a salt block. Additional electrolyte supplementation is indicated in hot humid conditions. Some studies suggest that electrolyte imbalances, as reflected by low urinary fraction excretion of sodium or high dietary excretion of phosphorus, may contribute to rhabdomyolysis\(^24\), although others

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\(^1\) Re-Leve Hallway Feeds 251 W Loudon Ave, Lexington KY 40508
have not found a consistent abnormality.\textsuperscript{13, 26, 27} Dietary supplementation with sodium or calcium may be of benefit in cases with inadequate sodium or excessive phosphorus excretion.

Other dietary supplements: A number of supplements are sold which are purported to decrease lactic acid build up in skeletal muscle of RER horses. These include sodium bicarbonate, B vitamins, branched chain amino acids, and dimethylglycine. Since lactic acidosis is no longer implicated as a cause for rhabdomyolysis it is difficult to find a rationale for their use.

Table 1. Nutritional requirements for an average sized horse (500 kg /1100 lbs) for RER at varying levels of exertion*. Note NSC refers to the soluble sugar + starch. Fructans in forage are not considered in this calculation as they are not considered likely to impact the glycemic index.

<table>
<thead>
<tr>
<th></th>
<th>Maintenance</th>
<th>Light Exercise</th>
<th>Moderate Exercise</th>
<th>Intense Exercise</th>
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</thead>
<tbody>
<tr>
<td>DE (MCal/day)</td>
<td>16.4</td>
<td>20.5</td>
<td>24.6</td>
<td>32.8</td>
</tr>
<tr>
<td>% DE as NSC</td>
<td>&lt;20%</td>
<td>&lt;20%</td>
<td>&lt;20%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>% DE as fat</td>
<td>15%</td>
<td>15%</td>
<td>15%-20%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Forage % bodyweight</td>
<td>1.5- 2 %</td>
<td>1.5- 2 %</td>
<td>1.5- 2 %</td>
<td>1.5- 2 %</td>
</tr>
<tr>
<td>Protein (g/day)</td>
<td>697</td>
<td>767</td>
<td>836</td>
<td>906</td>
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<td>Calcium (g/day)</td>
<td>30</td>
<td>33</td>
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</tr>
<tr>
<td>Phosphorus (g/day)</td>
<td>20</td>
<td>22</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Sodium (g/day)</td>
<td>22.5</td>
<td>33.5</td>
<td>33.8</td>
<td>41.3</td>
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<tr>
<td>Chloride (g/day)</td>
<td>33.8</td>
<td>50.3</td>
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<tr>
<td>Potassium (g/day)</td>
<td>52.5</td>
<td>78.3</td>
<td>78.8</td>
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<tr>
<td>Selenium (mg/day)</td>
<td>1.88</td>
<td>2.2</td>
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<tr>
<td>Vitamin E (IU/day)</td>
<td>375</td>
<td>700</td>
<td>900</td>
<td>1000</td>
</tr>
</tbody>
</table>

DE = Digestible Energy  
MCal = Megacalories  
NSC = nonstructural carbohydrate  
*Daily requirements derived from multiple research studies (%NSC and %fat) and Kentucky Equine Research recommendations.

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References


28. Lentz LR, Valberg SJ, Herold LV, Onan GW, Mickelson JR, Gallant EM.


POLYSACCHARIDE STORAGE MYOPATHY
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Polysaccharide storage myopathy (PSSM) was first identified in Quarter Horse-related breeds in 1992 and is characterized by two-fold higher glycogen concentrations and abnormal granular amylase-resistant inclusions in skeletal muscle. Several different acronyms have been used to describe PSSM, including EPSM and EPSSM. The variety of acronyms used are in part related to preferences of different laboratories, as well as to differences in the criteria used to diagnose polysaccharide storage myopathy. The prevalence of abnormal polysaccharide in muscle biopsies of Quarter Horses is approximately 12% and is approximately 35% in Belgians and Percherons. Recently, an autosomal dominant point mutation in the glycogen synthase 1 gene (GYS1) has been identified which appears to cause unregulated synthesis of glycogen. This GYS1 mutation, present in horses for over a 1000 years, is the same disorder described as “Monday Morning Disease or Azoturia” in draft horses in the early 20th century.

The GYS1 mutation is found in Quarter Horses and 5 Draft horse breeds, Paint horses, Appaloosa horses, 3 Warmblood breeds, Haflinger, Morgan, Mustang, Rocky Mountain Horse and Tennessee Walking Horse breeds, as well as mixed breed horses. When all horses diagnosed with PSSM at the University of Minnesota Neuromuscular Diagnostic Laboratory by muscle biopsy were screened for the genetic mutation it was clear that there was a subset of horses with PSSM that did not have the GYS1 mutation. Nomenclature for PSSM therefore has changed such that type 1 PSSM refers to horses with the GYS1 mutation and type 2 PSSM refers to horses diagnosed with abnormal glycogen storage in muscle biopsy that lack the GYS1 mutation. Type 2 PSSM occurs in Warmblood breeds such as Dutch Warmbloods, Hannoverian, Westfalian, Canadian Warmblood, Irish Sport Horse, Gerdlander, Hussien, and Rheinlander, about 28% of Quarter Horses with PSSM as well as other light breeds of horses.

Clinical Signs

Quarter Horses: The most common signs of both forms of PSSM in Quarter Horses are firm painful muscles, stiffness, fasciculations, sweating, weakness and reluctance to move. The hindquarters are frequently most affected, but back muscles, abdomen, and forelimb muscles may also be involved. During exercise, horses may stop and posture as if to urinate perhaps as a means to alleviate muscle cramping. Signs of pain can be particularly severe with 30% of horses exhibiting muscle pain for more than 2 hours and about 10% of cases becoming recumbent. Less common signs of PSSM in Quarter Horses include gait abnormalities, mild colic, and muscle wasting. There is no significant temperament, body type, or gender predilection for PSSM. Muscle pain often occurs with less than 20 minutes of exercise at a walk and trot, particularly if the horse has been rested for several days.
prior to exercise on a high grain diet. The average age of onset of clinical signs is 5 years and ranges from 1 to 14 years of age. Serum CK and possibly AST activity are often persistently elevated in Quarter Horses with PSSM. The median CK and AST activity for all PSSM Quarter Horses with muscle biopsies submitted to the University of Minnesota was 2,809 and 1,792 U/L, respectively.

**Draft Horses:** Belgian and Percheron horses appear to have a high prevalence of type 1 PSSM but other draft breeds are also afflicted. Many draft horses with PSSM are asymptomatic. Signs of severe rhabdomyolysis and myoglobinuria may occur in horses fed high grain diets, exercised irregularly with little turn out or horses that undergo general anesthesia. Other signs include progressive weakness and muscle loss resulting in difficulty rising in horses with normal serum CK activity. Gait abnormalities, such as excessive limb flexion, fasciculations, and trembling are also reported in draft horses. Although the condition Shivers was previously attributed to PSSM, a recent study found no causal association between these two conditions. The very high prevalence of PSSM in draft horses in essence means that there is a 36% chance that any clinical sign could be falsely associated with PSSM, this clinical judgment needs to be exercised in interpreting test results. The average age of draft horses diagnosed with PSSM is about eight years of age. No particular gender predilection has been identified. The median serum CK and AST activity in draft horses from which biopsies were sent to the University of Minnesota was 459 and 537 U/L.

**Warmbloods:** The most common clinical signs reported in warmbloods with PSSM are painful firm back and hindquarter muscles, reluctance to collect and engage the hindquarters, poor rounding over fences, gait abnormalities, and atrophy. Overt signs of exertional rhabdomyolysis were reported in less than 15% of warmbloods with PSSM. Warmbloods derived from crosses with draft horses often have type 1 PSSM, whereas other specific Warmblood breeds may have a higher prevalence of type 2 PSSM. The mean age of onset of clinical signs in warmbloods is between 8 and 11 years of age with the median CK and AST activity being 323 and 331U/L, respectively.

**Other breeds:** A small number of horses of other breeds have been reported to have PSSM. The prevalence of PSSM within these breeds appears to be quite low. For example, although more than 50% of biopsies of Quarter Horses, Draft horses and Warmbloods were diagnosed with PSSM, fewer than 10% of muscle biopsies from 178 Thoroughbreds, 40 Arabians and 32 Standardbreds with neuromuscular disease were diagnosed with PSSM. A slightly higher prevalence was found for Morgan and Tennessee Walking horses. Previous published reports of PSSM based on amylase-resistant polysaccharide include small numbers of horses of warmblood cross, Anglo-Arabs, Andalusions, Morgan, Arabian, Welsh cross, and Standardbred breeds. Some of the controversy regarding the number of breeds affected with PSSM may be a result of inclusion of cases with sarcoplasmic masses and increased PAS staining for glycogen as horses positive for PSSM.

**Diagnosis**
Genetic testing for type 1 PSSM is now available at the University of Minnesota Veterinary Diagnostic Laboratory (http://www.vdl.umn.edu/vdl/ourservices/neuromuscular.html). It is performed on whole blood samples or hairs roots. If a definitive diagnosis of a muscle disorder is required all at one time, submission of the genetic test and muscle biopsy may be most expedient. Muscle biopsies from adult horses with type 1 PSSM are characterized by amylase-resistant granular polysaccharide in amylase-Periodic acid Schiff’s (PAS) stains. Since a genetic test for type 2 PSSM is not available this disorder must be diagnosed by muscle biopsy where increased or abnormal PAS positive material that is usually amylase-sensitive is apparent. Due to the subjective nature of a diagnosis of PSSM based solely on increased staining for amylase sensitive glycogen, (often termed mild PSSM) there is a high chance for a false positive diagnosis and the horse should also receive a full evaluation to ensure that there are not other underlying causes for performance problems.

Supportive evidence of PSSM in Quarter Horses includes clinical signs of exertional rhabdomyolysis, persistent elevations in serum CK and AST activities, and a minimum of a three-fold elevation in CK activity four hours after an exercise test consisting of a maximum of 15 minutes lunging at a walk and trot. Supportive evidence in Draft and Warmblood breeds include exercise intolerance, muscle atrophy, weakness, and some gait abnormalities without necessarily finding elevations in muscle enzymes.

A muscle biopsy of any locomotor muscle that provides a 2 cm by 1 cm block of tissue for evaluation is often sufficient for analysis. The site most easily sampled in the field using an open surgical approach is the semimembranosus or semitendinosus muscle. Clinics that can rapidly process muscle for frozen sections often use a modified Bergstrom biopsy instrument inserted into the gluteal muscle through a 1 cm incision. A diagnosis can be made irrespective of diet and proximity of sampling to recent episodes of rhabdomyolysis.

Management of PSSM

A horse diagnosed with PSSM will always have an underlying predilection for muscle soreness. The best that can be done is to manage horses in the most appropriate fashion to minimize clinical signs. With adherence to both the diet and exercise recommendations provided below, at least 80% of horses show notable improvement in clinical signs and many return to acceptable levels of performance. There is, however, a wide range in the severity of clinical signs shown by horses with PSSM; those horses with severe or recurrent clinical signs will require more stringent adherence to diet and exercise recommendations in order to regain muscle function.

Rest: PSSM horses that are confined for days to weeks following an episode of rhabdomyolysis often have persistently elevated serum CK activity. In contrast, PSSM horses kept on pasture with little grain supplementation often show few clinical signs of rhabdomyolysis and have normal serum CK activity. As a result, stall confinement of PSSM horses should be limited to less than 48 hours after an episode of rhabdomyolysis, and access to turnout should be provided. Hand-walking horses recovering from an episode of PSSM for more than 5-10 minutes at time may trigger another episode of rhabdomyolysis.
**Exercise regimes:** Important principles to follow when starting exercise programs in PSSM horses include 1) providing adequate time for adaptation to a new diet prior to commencing exercise, 2) recognizing that the duration of exercise, not just the intensity of exercise should be restricted 3) ensuring the exercise is gradually introduced and consistently performed and 4) minimizing any days without some form of exercise.\textsuperscript{2,4} If horses have experienced an episode of rhabdomyolysis recently, two weeks of turn-out and diet change are often beneficial prior to recommencing exercise. Exercise should be very relaxed, and the horse should achieve a long, low frame without collection. For many horses this is most readily done in a round pen or on a lunge-line. Successive daily addition of two minute intervals of walk and trot beginning with only four minutes of exercise and working up to 30 minutes after three weeks is often recommended.\textsuperscript{2,4} Advancing the horse too quickly often results in an episode of rhabdomyolysis and repeated frustration for the owner. Work under saddle after 3 weeks of ground work should be a gradually accelerating program that adds two minute intervals of collection or canter to the initial relaxed warm-up period at a walk and trot. Unless a horse shows an episode of overt rhabdomyolysis during the initial first four weeks of exercise, re-evaluating serum CK activity is not usually helpful for the first month. This is because it is very common to have subclinical elevations in CK activity when exercise is re-introduced and a return to normal levels often requires four to six weeks of gradual exercise.\textsuperscript{4,11} Keeping horses with PSSM fit seems the best prevention against further episodes of rhabdomyolysis. This gradual approach to re-introducing exercise aims to enhance the oxidative capacity of skeletal muscle without causing further cellular damage. The oxidative capacity of locomotor muscles in most Quarter Horses is very low but can be increased with daily exercise.\textsuperscript{11,25} The objective of enhancing oxidative metabolism is to facilitate the metabolism of fat and blood born as energy substrates.

**Diet:** It is vital to provide the right caloric balance for PSSM horses. If horses are overweight, reducing caloric intake by using a grazing muzzle, restricting hay to 1.5% of body weight and providing a ration balancer is recommended. Adding excessive calories in the form of fat to an obese horse may produce metabolic syndrome. Caloric restriction elevates plasma free fatty acids equally effectively as feeding dietary fat.

Once a horse has achieved the desired body weight, the dietary modification for PSSM horses combines reducing glucose load and providing fat as an alternate energy source. Anecdotally, owners report that this type of diet improves clinical signs of muscle pain, stiffness and exercise tolerance in draft horses, warmbloods, Quarter Horses and other breeds.\textsuperscript{2,17,26} Dietary change appears to have lesser impact on alleviating gait changes such as Shivers. The effect of low starch high fat diets on exercise-induced muscle damage has only been demonstrated under controlled conditions in Quarter Horses.\textsuperscript{11} In PSSM Quarter Horses providing less than 10% of daily digestible energy as dietary starch and 13% of daily digestible energy as dietary fat resulted in normal serum CK activity four hours post exercise during a six week trial.\textsuperscript{11} Provision of similar fat content and higher starch content resulted in increased serum CK activity in the most severely clinically affected horses. The beneficial effect of the low starch, high fat diet used in this study (Re-Leve®)\textsuperscript{2} was believed to be the result of less glucose uptake into muscle cells and...
provision of more plasma free fatty acids for use in muscle fibers during aerobic exercise.\textsuperscript{11} Quarter Horses naturally have very little lipid stored within muscle fibers and provision of free fatty acids may overcome the disruption in energy metabolism that appears to occur in PSSM Quarter Horses during aerobic exercise.\textsuperscript{25} Studies clearly show, however, that the addition of fat alone is not beneficial and an exercise program must be instituted for PSSM horses to show clinical improvement.\textsuperscript{2}

A wide variety of low starch high fat diets are available for horses. The most important dietary principle appears to be that out of the total daily calories required (Digestible energy: DE) less than 10% should be supplied by starch and at least 13% supplied by fat. Based on anecdotal experience, some authors recommend that >20\% of daily caloric intake be supplied by fat (0.5 kg of fat)\textsuperscript{17} There are no controlled studies that support the need to feed “one pound of fat” (25\% of daily digestible energy or 3 cups or more of oil) a day to PSSM horses whereas controlled trials indicate 13\% of caloric intake in fat reduces CK to normal values after exercise.\textsuperscript{2,11,26} There is a great deal of variation in individual tolerance to dietary starch however; horses with more severe clinical signs of PSSM appear to require the greatest restriction in starch intake.\textsuperscript{11}

A number of well balanced low starch high fat commercial diets are suitable for horses with PSSM. There is at present no research to suggest that one form of fat is more beneficial than another. Some commercial feeds meet the recommended nutritional needs of PSSM horses in one pelleted ration, These feeds typically contain 10-15\% fat by weight and less than 20\% starch or nonstructural carbohydrate (NSC) by weight. Some feed companies offer similar nutritional content by blending two or more manufactured feeds or by supplementing with oils or rice bran. Palatability of pelleted feeds is usually higher than feeds containing pour on oils or loose rice bran. At present, the NSC content of equine feed products is not listed on the feed tag, and consultation with the feed manufacturer is necessary to obtain this information. Nutritional support is available through most feed manufacturers in designing an appropriate diet.

References


\textsuperscript{2} Re-Leve, Hallway Feeds, Lexington KY 40508


