Recommendations for the Diagnosis and Management of Equine Metabolic Syndrome (EMS) and Insulin Dysregulation

EQUINE ENDOCRINOLOGY GROUP

2024

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Recommendations for the Diagnosis and Management of Equine Metabolic Syndrome (EMS) and Insulin Dysregulation

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Prepared by the 2024 EMS/ID Working Group

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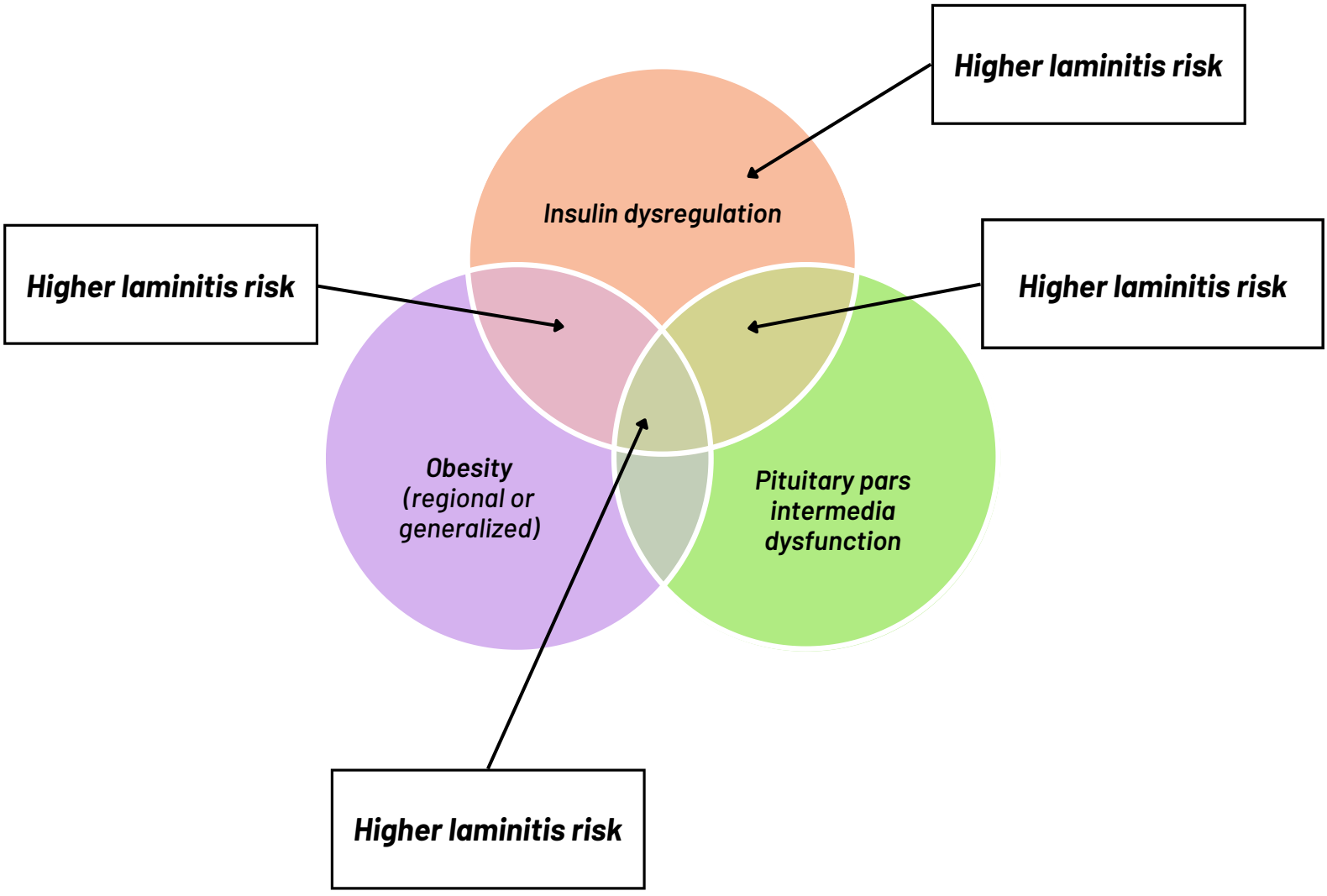
The Equine Endocrinology Group (EEG) is composed of experts in the field of equine endocrinology who provide informed opinion-based advice in the form of written guidelines solely designed to help equine practitioners diagnose and manage equine endocrine disorders. Guidelines are updated every two years and can be found on the EEG web site: https://equineendocrinologygroup.org/

Table 1 – Definitions

EMS	**Equine Metabolic Syndrome** is a collection of metabolic and clinical features that include insulin dysregulation (ID) as a consistent component resulting in an increased risk of laminitis in horses and ponies. Additional factors are inconsistent and include regional or generalized obesity, altered adipokine and postprandial incretin concentrations, hypertriglyceridemia, and hypertension. *An asinine metabolic syndrome has been described, and reference intervals for insulin concentrations are reported for donkeys.*
ID	**Insulin dysregulation** is a disturbance of the relationship between plasma or serum insulin and glucose. It is defined as any combination of resting hyperinsulinemia, post-prandial or post challenge hyperinsulinemia, and peripheral or hepatic insulin resistance. Hyperinsulinemia results from excessive insulin secretion from pancreatic β cells and possibly decreased hepatic clearance of circulating insulin. Pancreatic β cell stimulators mainly include diets high in non-structural carbohydrates (NSC) and incretins such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Decreased insulin clearance might also contribute to hyperinsulinemia. Insulin resistance is the inadequate response of insulin-sensitive tissues to insulin.
HAL	**Hyperinsulinemia-associated laminitis** ("HAL") is the most common form of laminitis in the general horse and pony population (>90% of cases) and it replaces the terms "pasture-associated laminitis" and "endocrinopathic laminitis." It might develop insidiously but frequently becomes a chronic condition characterized by repeated episodes of mild to severe lameness. This form of laminitis begins as stretching and damage to the digital lamellae induced by episodes of hyperinsulinemia that can go undetected at first, but then usually progresses to lameness and more classical signs of laminitis. The pathophysiology and histologic changes associated with HAL are different from those of sepsis-associated laminitis and supporting-limb laminitis. The specific mechanism of HAL is unclear; however, it appears to involve the inappropriate stimulation of insulin-like growth factor-1 receptors (IGF-1R) on lamellar epidermal cells.
NSC	**Non-structural carbohydrates** are a component of the diet and the main drivers of insulin secretion. The NSC content of the diet is calculated by adding water-soluble carbohydrates and starch. Older equations by subtraction are no longer recommended and represent non-fiber carbohydrates that include gums, mucilages, galactans, β-glucans, and neutral detergent soluble cell wall components that do not influence insulin responses.

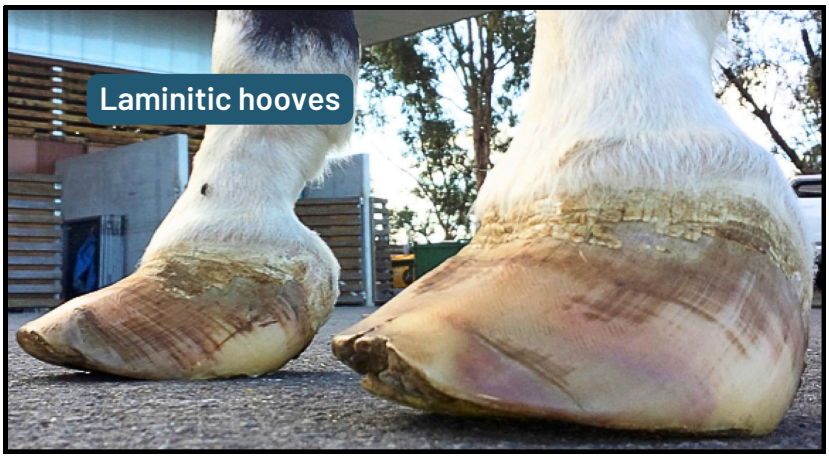
Figure 1 – Intersections among equine endocrine disorders discussed in these recommendations.

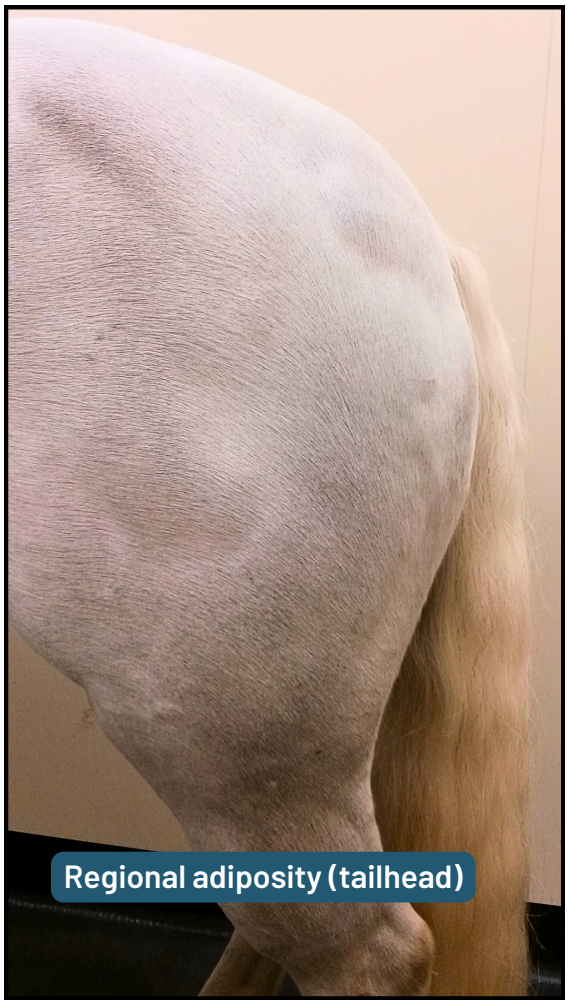


Note that insulin dysregulation can also occur with pregnancy, starvation, systemic illness and administration of glucocorticoids.
Note that the area of each category within the diagram is purely illustrative and is not intended to be proportionate to the size of the population.

Figure 2 – Signalment and clinical features commonly associated with insulin dysregulation

Note that although common, obesity is not a consistent feature.





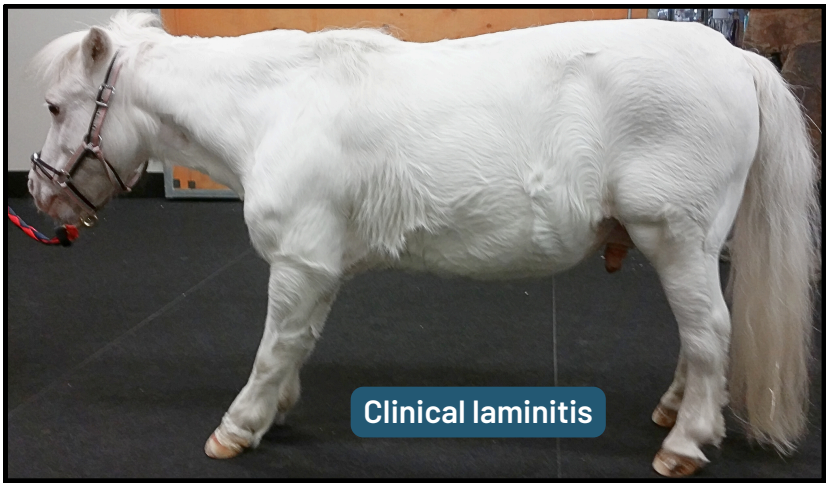
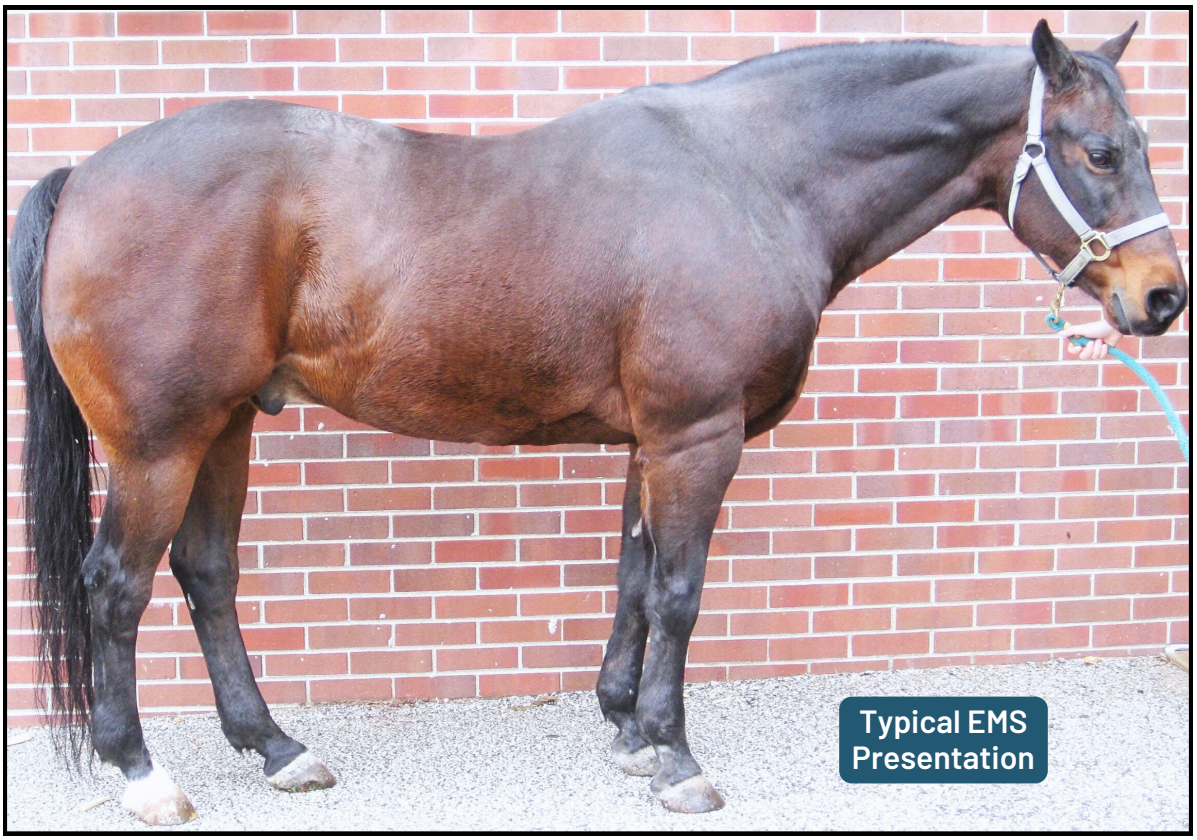
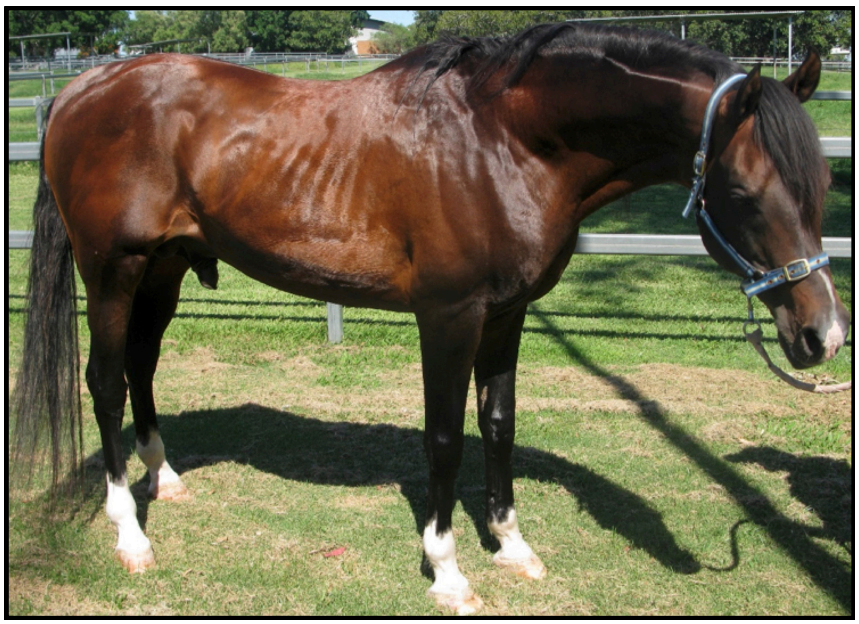


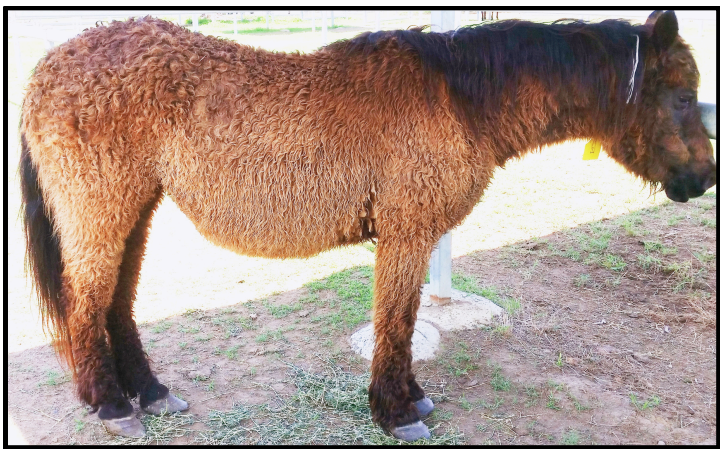
Figure 2 (cont.) – Signalment and clinical features commonly associated with insulin dysregulation

Note that although common, obesity is not a consistent feature.





Lean EMS



Pituitary Pars Intermedia Dysfunction

Table 2 – Risk factors for insulin dysregulation

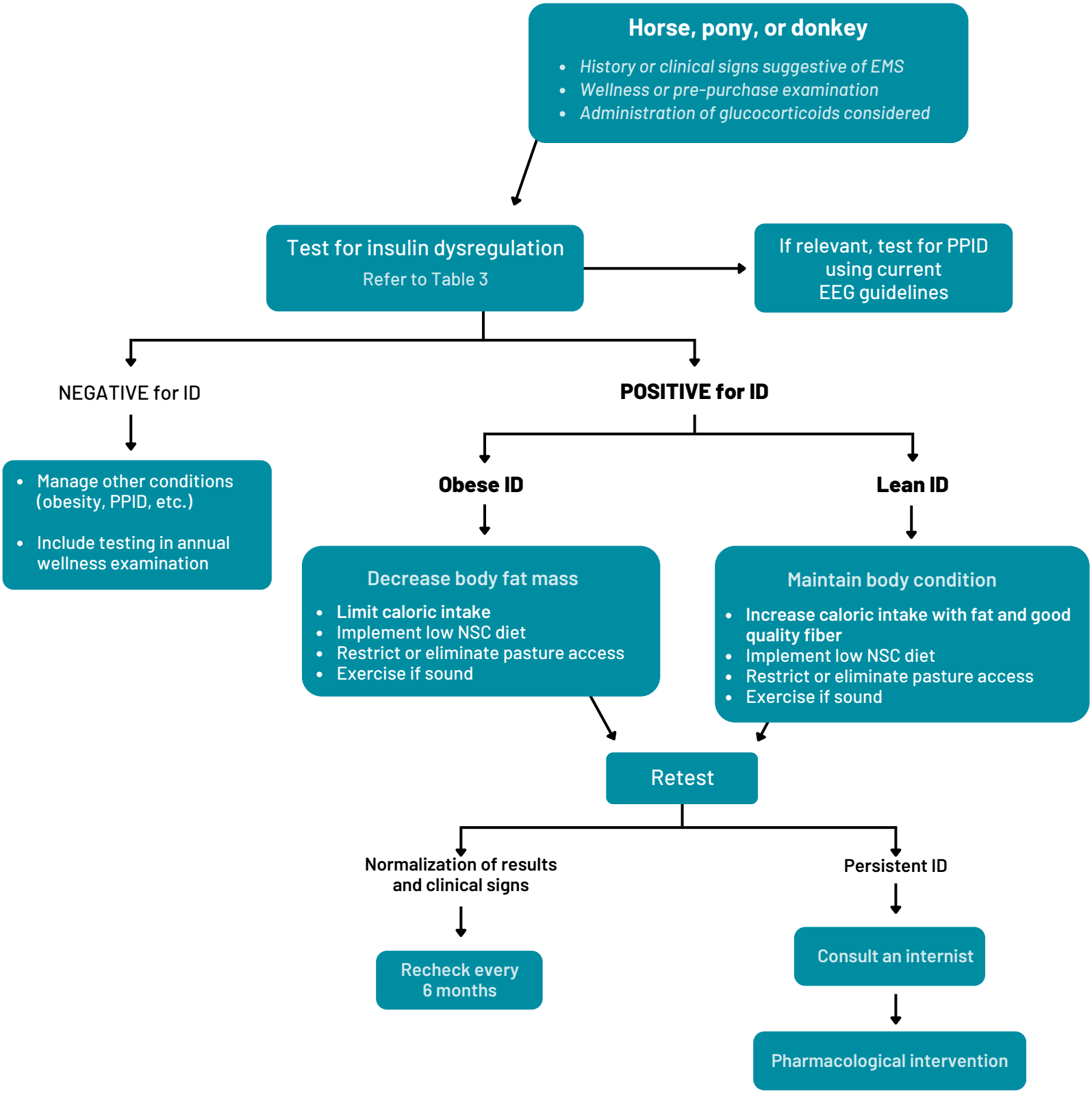
Breed	Some breeds have an increased risk of developing ID. At-risk breeds include pony breeds, Iberic breeds (Andalusians), gaited breeds (Saddlebreds, Paso Finos), Morgans, Miniature horses, Arabian horses, and Warmbloods.
Genetics	Some genes have been associated with the development of ID; however, the condition is a complex genetic disease (involving multiple genes) and the contribution of currently identified genes seems limited compared to environmental factors. This means that ID is therefore a manageable disease in most affected cases.
Age	Age has been identified as a risk factor for ID; therefore, it is recommended to include yearly testing of at-risk horses as they get older than 5 years of age.
Obesity	Obesity is considered an exacerbating factor of ID and associations between obesity (regional and general) and ID have been inconsistent; therefore, testing should not be limited to obese horses.
Diet	A diet high in NSC is a risk factor for the development of ID regardless of genetic predispositions; any horse on an NSC-rich diet is at risk of developing ID and HAL.
PPID	PPID is a risk factor for the development of ID; however, the specific link between the two conditions is unclear. Investigation of ID in horses diagnosed with PPID is strongly recommended.

PRACTITIONER'S TIP

Diabetes mellitus, metabolic derangements detected during critical care, equine hyperlipemia, infertility, colic caused by a pedunculated lipoma (associated with obesity), or preputial/mammary gland edema are other conditions that should prompt testing for ID.

Testing should also be considered as part of wellness or pre-purchase examinations or when considering corticosteroids administration in at-risk populations.

Figure 3 – Algorithm for the diagnosis and management of ID



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Selection of diagnostic tests

Two dynamic tests are recommended: the **oral sugar test (OST)** and the **insulin tolerance test (ITT).** The tests do not evaluate the same arm of ID: while the ITT assesses tissue insulin resistance, the OST tests hyperinsulinemia and performs better at predicting the risk of laminitis. In addition, the OST reflects a more complete sequence of events, including digestion and absorption of sugars, incretin responses, and secretion of insulin from the pancreas. Ideally, both tests would be performed, but there are obvious logistical issues with this approach.

Oral sugar test (OST):

- Advantages of this test include the availability of light corn syrup, ease of administering corn syrup (by the veterinarian or the owner), and the test's assessment of insulin responses to ingested sugars.
- Disadvantages include the recommendation for horses to be fasted for 3-6 hours prior to testing and relatively low repeatability of test results. Fasting conditions are often achieved by the owner leaving a small amount of hay with the horse before midnight, and the test is performed the following morning. Variability in results is attributed to multi-factorial influences such as the NSC content of the current diet, differences in gastric and intestinal transit times, digestion of NSC, absorption of sugars, incretin responses, and insulin secretion.
- An alternative test is the oral glucose test (OGT) that uses dextrose powder mixed with a small amount of chaff or administered with a nasogastric tube, but the test procedure and cut-off values for interpretation differ.

Insulin tolerance test (ITT):

- Advantages of the ITT include that it does not require fasting and blood glucose concentrations can be measured with a glucometer, so results are available on the farm.
- Disadvantages include the cost of insulin and the risk of clinical hypoglycemia. The risk of hypoglycemia is low in horses selected for testing on suspicion of ID, but there is higher risk of this complication occurring in non-ID animals. An additional blood glucose measurement at 15 minutes is recommended for these animals as an added precaution. Horses should be monitored for the duration of the test, and hay and a small amount of grain should be fed immediately after the 30-minute sample is collected to further mitigate hypoglycemia risk.

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Selection of diagnostic tests (cont.)

Resting (basal) insulin concentrations: Advantages include that a single blood sample is collected with the horse in the fed state (hay or pasture, but not grain), and insulin concentrations are measured to detect resting hyperinsulinemia. This approach might be used as a first step. Higher resting insulin concentration indicates higher laminitis risk, although if the resting insulin concentration is normal, a dynamic test must be performed.

Post-grazing insulin concentrations: The postprandial insulin concentration assesses the insulinemic effects of what the horse is currently eating and therefore the laminitis risk of the individual components of the current diet. A blood sample is collected around two hours after the horse has finished its meal (grass or hay). The advantage of the test is that it reflects the actual risk of laminitis of the horse under the current management. The main disadvantage of the test is the absence of specific cut-offs for sampling times and insulin concentrations. Therefore, this test is primarily recommended for monitoring purposes, rather than for diagnosis, when a horse with a history of ID is allowed to graze on grass. Current results can be compared with previous results in the same horse to monitor its laminitis risk and assess insulinemic response to preserved forage.

Resting blood glucose concentrations: Diabetes mellitus occurs occasionally in horses and is likely to be detected with higher frequency in equids affected by EMS, or more commonly PPID. Resting blood glucose concentrations should be measured to detect diabetes mellitus when any of the above tests are performed; however, it has no diagnostic value for ID.

Other tests:

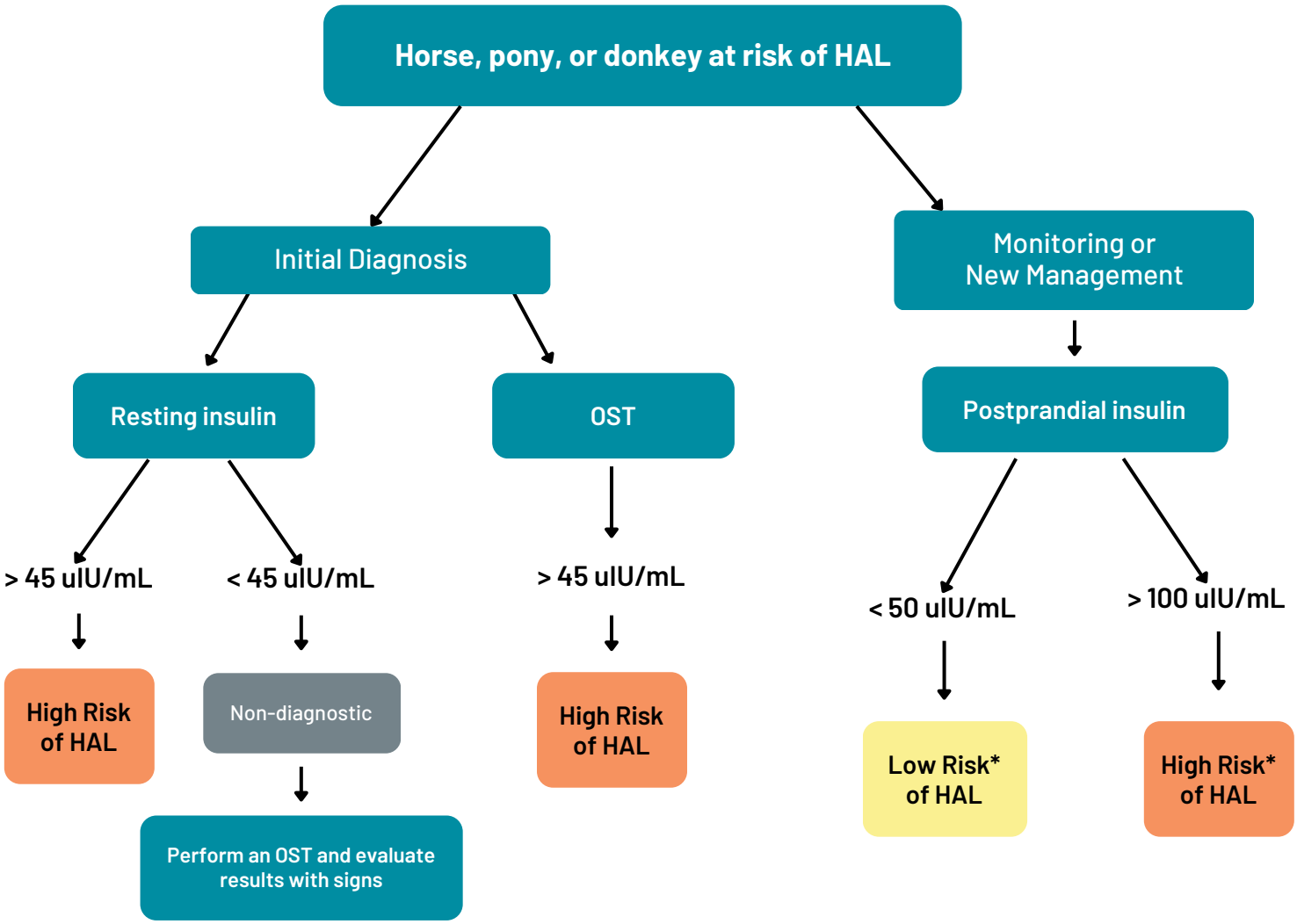
- A glycemic pellet challenge is being developed using a commercial product that will be made available for purchase soon. The horse is fasted overnight, and glycemic pellets are fed in an amount calculated according to body weight, with the horse having up to 10 minutes to consume the meal. A blood sample is collected at 120 min, and glucose and insulin concentrations are measured.

Table 3 – Recommended dynamic testing for a diagnosis of ID

	Hyperinsulinemia	*Tissue insulin resistance*
	Oral Sugar Test (OST)	**Insulin Tolerance Test (ITT)**
Procedure	**Fast 3 - 6 hours** Administer 0.15 mL/kg corn syrup orally via dose syringe Collect blood at 60 and/or 90 minutes Measure insulin and glucose	**Do not fast** Collect blood at time 0 minutes Administer 0.10 IU/kg regular (soluble) insulin Collect blood at 30 minutes Measure glucose Feed hay and small amount of grain after last sample
Interpretation	>45 µIU/mL are consistent with post-prandial hyperinsulinemia	< 50% decrease in blood glucose concentrations from baseline is consistent with insulin resistance

Note that hypoglycemia is a risk associated with the ITT and try to minimize stress prior to testing. A higher dose of 0.45 mL/kg corn syrup can also be used for the OST, and insulin concentrations >65 µIU/mL (RIA) or >63 µIU/mL (Immulite 2000 xpi) are consistent with post-prandial hyperinsulinemia.

Figure 4 – Algorithm for detecting the risk of HAL



PRACTITIONER'S TIP

Although insulin ranges are provided, the upper limits of ranges are not absolute thresholds and results just above or below these values must be interpreted accordingly. Also note that inter- and intra-day variability in insulin concentrations is observed in some horses, and results of dynamic tests can show up to approximately 30% variability when repeated. **The guiding principle for interpretation of insulin results is that the risk of HAL increases as insulin concentrations increase.**

*Between 50 and 100 µIU/mL, the risk of laminitis cannot be estimated.

The ITT is a recommended test to diagnose ID; however, the OST is better at assessing the risk of laminitis. Note that 45 µIU/mL is the same insulin concentration selected for diagnosing ID using resting (fed) insulin concentrations and the OST. The OST is performed under fasting conditions when insulin concentrations are normally low, so insulin concentrations increasing above 45 µIU/mL is considered of greater significance.

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Sample handling & analysis

Insulin is stable in plasma or serum for at least three days when separated from red blood cells and refrigerated (4°C). The decision to submit plasma or serum depends on the assay used by the laboratory, and specific recommendations should be reviewed before samples are collected. Freeze serum or plasma samples immediately if samples cannot be mailed within this period. Note that samples may be frozen and thawed once, but multiple freeze-thaw cycles will alter insulin concentrations and should be avoided.

Insulin results vary according to the assay (radioimmunoassay, chemiluminescent assay, or enzyme-linked immunosorbent assay) and analyzer (e.g., Immulite 1000®, Immulite 2000xpi®) used to measure the hormone, and cut-off values must be considered accordingly. Contact the diagnostic laboratory to confirm that the insulin assay in use has been validated for use with equine serum/plasma and that reference intervals are specific to the assay and analyzer that are being used. The cut-off values used in this document were obtained with the RIA, Immulite 1000® and Immulite 2000xpi® and might not apply to the assay used in another diagnostic laboratory.

PRACTICE TIP
Stall-side insulin analysers have been recently developed and are now commercially available and have been shown to correlate well with concentrations obtained in referral laboratories.

Table 4 – Additional tests for the assessment of horses with EMS
(not meant to replace diagnostic testing for ID)

Test	Interpretation
Adiponectin	Total adiponectin concentrations <7.9 ug/mL are supportive of EMS and an increased risk of HAL.
Leptin	Higher leptin concentrations are associated with increased adiposity and metabolic derangement. Useful for providing evidence of increased internal adiposity; however, this hormone is more directly associated with obesity than ID.
Triglycerides	Hypertriglyceridemia is associated with ID and obesity, exacerbated by negative energy balance. Hypertriglyceridemia is a predictor of HAL risk in ponies, with cut-off values 57 mg/dL (0.64 mmol/L) in the presence of tissue insulin resistance, hyperinsulinemia, or obesity, and 94 mg/dL (1.1 mmol/L) as an independent marker.

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Table 5 – Management recommendations for EMS

Diet	**Initial diet (obese patients)** • Restrict grazing by placing horse in a small paddock that has little or no grass, along with a companion, or eliminate grazing altogether if ID is severe. Do not feed any grain or treats. • For weight loss, feed grass hay with low NSC content (<10%) in amounts equivalent to 1.5% in dry matter of current body weight (or 1.7% of current body weight on an as-fed basis) daily. Hay should be selected because it has low NSC content and because it induces a low peak insulin concentration after feeding. • Reassess body weight every 30 days using a weigh scale or weigh tape and gradually lower intake to a minimum of 1.2% of body weight as-fed if weight loss resistant. Avoid stress as much as possible to limit the risks of hyperlipemia. • Good quality straw can be fed mixed with the current forage as a low-NSC forage for up to approximately 50% of the daily feed provided (75% or more for donkeys). Introduce straw to the diet gradually over at least 2 weeks and monitor fecal output and for signs of colic. • Soak hay in cold water for at least 60 minutes before feeding to lower the water-soluble carbohydrate content. This should be if hay has NSC >10% on analysis or for all hays if the hay is not analyzed. • Incorporate slow feeder methods or divide forage into frequent, small meals so that prolonged fasting is avoided. • Provide a mineral/vitamin/protein ration balancer. Care should be taken to select a ration balancer with low sugar content. **Maintenance diet (or non-obese patients)** • Restrict grazing as described above, and do not feed grain or treats. • Feed hay that has low NSC content (<10%) and that induces a low peak insulin concentration 2 hours after feeding **(Figure 4)**. • Maintain on initial hay amount until body condition 5/9 is achieved; however, it can take several months to reach a BCS of 5/9, and severely affected animals can remain obese in the face of appropriate management. • Soak hay (see above) • Substitute good quality straw as described above • Provide low sugar mineral/vitamin/protein ration balancer • The decision to allow or increase the amount of grazing should be made after clinical signs of laminitis have resolved and be based upon follow-up testing with collection of blood after 2 hours of pasture grazing (post-prandial insulin). Pasture access should be reintroduced gradually with regular insulin measurements while the horse is fed on pasture. Strategies to restrict grass intake include use of a grazing muzzle. Rate of grass intake can also be decreased by track systems and other activity systems. If laminitis recurs, grazing should be stopped until horse has stabilized.
Foot Care	Hoof care is essential in all cases. Laminitis can occur without inducing easily detectable lameness, and radiographs are recommended to identify structural changes, even if the horse is not lame. In at-risk cases, regular care based on repeated radiographs, every 4 weeks by an experienced farrier is highly recommended.
Exercise	Any exercise is good unless laminitis is present. All levels of exercise are beneficial for accelerating weight loss in obese animals and improving insulin sensitivity. • In previously laminitic horses with recovered and stable hoof lamellae, minimum exercise recommendations are low intensity exercise on a soft surface: 5 minutes walking, 15 minutes brisk trotting, and 5 minutes walking 5 days per week whilst carefully monitoring for signs of lameness. • In horses with ID and no signs of lameness, low to moderate intensity exercise >5 days per week is recommended, such as canter to fast canter (ridden or unridden) for >30 minutes.

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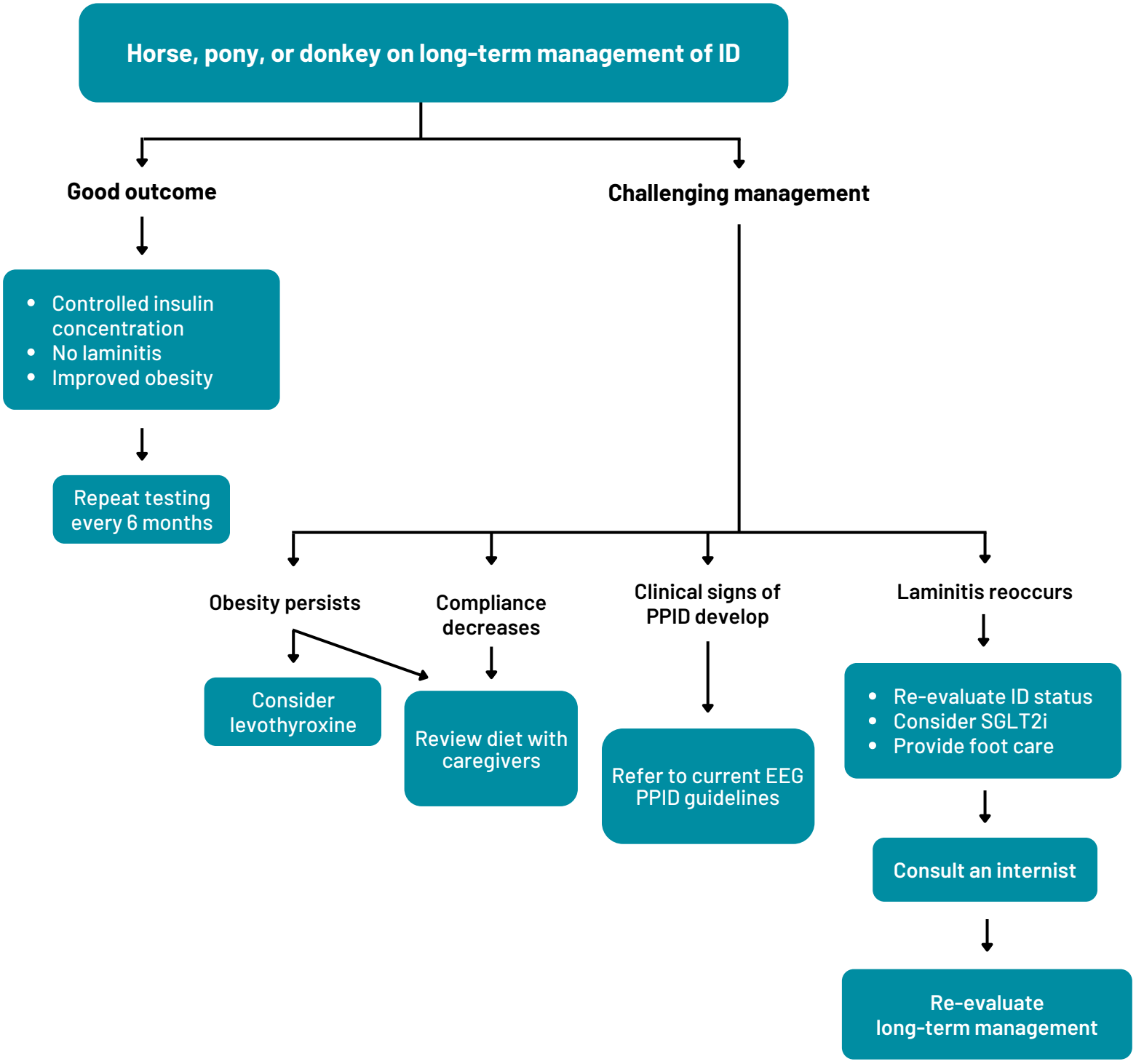
Table 5 – Management recommendations for EMS (cont.)

Medical Therapy	*Drugs described below are currently being used off-label* ***Sodium-glucose co-transporter 2 (SGLT2) inhibitors*** This class of drug is to be used when horses are affected by HAL and severe ID and are not responding to other measures. They can also be used as a first line management strategy for confirmed acute HAL to rapidly decrease insulin concentrations. These drugs should be used for a certain duration (3 months); however, it is the experience of the group that some extreme cases might require longer treatments, even if managed properly with diet and foot care. Pharmacokinetic data are limited for this class of drug, and currently used doses are 0.3 mg/kg, PO, q24h for velagliflozin; 0.2-0.6 mg/kg, PO, q24h for canagliflozin; 0.02-0.06 mg/kg, PO, q24h for ertugliflozin and empagliflozin. In some cases, lower doses seem appropriate. Monitoring of postprandial insulin concentrations, hepatic enzymes, and triglyceride concentrations is strongly recommended. A transient increase in triglyceride concentrations is expected and usually not associated with hyperlipemia. In some cases, however, marked hypertriglyceridemia associated with clinical signs have been reported. *Levothyroxine* This drug is to be used for cases with weight loss resistance (no documented response after a minimum of 30 days on weight loss diet, with or without exercise) or for accelerated management of obesity. Levothyroxine is to be administered at 0.1 mg/kg, PO, q24h (48 mg or 4 teaspoons of the powdered product for a 500-kg horse) while also controlling caloric intake. Weight loss is usually achieved after 3-6 months of therapy. At that time, treatment can be gradually reduced and discontinued.
PPID	Refer to current EEG guidelines. PPID is an exacerbating factor for ID.
Monitoring	Regular monitoring of ID cases is recommended, and methods include measuring insulin concentrations while the horse is on its current diet (hay or hay and controlled pasture access). As feeds are changed, postprandial insulin concentrations provide useful information on the individual horse's response to their new diet and, indirectly, the risk of laminitis. Pasture grass represents a source of sugars and amino acids that varies over time and season, depending on temperature, sunlight, rainfall, and use of fertilizers, and it is useful to assess the individual horse's response to this component of their diet before easing restrictions on grazing. It is noted that insulin concentrations are affected by season, with higher concentrations detected in winter, suggesting a winter-associated exacerbation of ID. Accordingly, care should be taken to avoid overfeeding or adding high-NSC feeds in the winter months. As age and PPID are factors that can exacerbate ID, it is recommended to reassess horses as they grow older using postprandial insulin concentrations and PPID testing (>10 years). Close monitoring for early signs of laminitis is recommended, and the modified-Obel scoring system is recommended to better assess horses with HAL.

PRACTICE TIP

Each horse has an individual response to its diet and even if fed NSC < 10% at 1.5% of body weight, some severely affected horses can have an inappropriate insulin response and be at risk of laminitis. In those cases, the use of SGLT2i is recommended.

Figure 5 – Algorithm for the management of challenging cases



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Frequently Asked Questions

How high do insulin concentrations have to get and for how long do they have to stay increased to induce laminitis?	The specific insulin concentration and duration of hyperinsulinemia needed to cause laminitis are not clearly defined. It varies based on each horse's susceptibility and any existing hoof damage. There is also a distinction between the onset of lamellar damage and the point at which lameness is manifest or noticed. The exact threshold for HAL to develop likely differs among individual animals. Experimental studies in ponies on a high-NSC diet suggest that blood insulin concentrations >200 µIU/mL sustained for 5 days resulted in subclinical laminitis and infusion of insulin in healthy Standardbreds resulting in insulin concentrations are >1,000 µIU/mL for 48h induced clinical and histological laminitis. It should not, however, be assumed that HAL only develops when insulin concentrations reach these levels, because laminitis might occur when insulin concentrations are high for a more extended period but remain below the values above. Therefore, the area under the insulin concentration curve might be more relevant than the peak insulin concentrations.
Can horses with PPID have HAL?	Yes, ID is detected in approximately 30% of horses with PPID and horses greater than 10 years of age should be tested for PPID as well as ID. Refer to EEG Guidelines on PPID for more information.
Is pasture-associated laminitis the same as HAL?	Yes, NSC in pasture grass can increase blood insulin concentrations and susceptible horses have higher than normal insulin concentrations and develop HAL.
Can glucocorticoid use be associated with laminitis?	Yes, there is an association between glucocorticoid use and laminitis in animals with underlying endocrine disorders or severe systemic disease. Horses should be assessed for the risk of ID (breed, age, adiposity), presence of other endocrine diseases, and subclinical laminitis prior to their administration. A risk/benefit assessment must be made prior to administration of glucocorticoids in any form (including intra-articular and aerosol formulations).
Does pergolide help manage ID horses without PPID?	No, multiple studies have demonstrated that administration of pergolide to horses with ID but not PPID does not improve their insulin regulation. There is, however, a positive effect in the management of ID in horses suffering from both ID and PPID. This emphasizes the relevance of testing for both PPID and ID in at-risk populations.
Should I test for ID during an acute laminitis episode?	Yes, in absence of clear indicators of another type of laminitis (e.g., sepsis-associated laminitis in cases of colitis, pneumonia, other infectious diseases, or supporting-limb laminitis in cases of contralateral limb pain), hyperinsulinemia should be considered as the cause of laminitis and resting insulin concentrations measured. One should, however, keep in mind that resting insulin concentrations might be normal if management has changed and dynamic testing might be required once the acute episode has resolved and is recommended before the horse returns to its routine. In addition, re-testing is required after the resolution of the acute laminitis to determine the ID status under the post-laminitis management regime.

Disclosures

Andy Durham is affiliated with the Liphook Equine Hospital and this institution offers endocrine testing.

Boehringer Ingelheim Animal Health USA Inc. facilitates the development of EEG guidelines by supporting travel expenses for participants but does not influence the recommendations made by the group.

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Notes