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

EQUINE ENDOCRINOLOGY GROUP

2022

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

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Introduction

Equine metabolic syndrome (**EMS**) is a collection of risk factors highly associated with an increased risk of hyperinsulinemia-associated laminitis (**HAL**) and potentially other morbidities. Insulin dysregulation (**ID**) is a consistent feature of EMS and increased generalized or regional adiposity is typical. Additional factors present in some animals include altered adipokine and postprandial incretin concentrations, hypertriglyceridemia, and hypertension. The syndrome may coexist with pituitary pars intermedia dysfunction (**PPID**) in older horses. EMS results from an interaction between genetic and environmental factors, and the risk of laminitis in the individual animal therefore depends on the cumulative effects of these influences. There are high-genetic risk animals that develop EMS with only mild environmental influences and other horses with lower genetic risk that develop EMS through exposure to improper environments (particularly diets that are high in non-structural carbohydrates [**NSC**]). It might therefore be assumed that any horse can develop EMS if exposed to sufficient inciting factors: improper management, exposure to environmental factors, or epigenetic influences on gene expression.

Insulin dysregulation is defined as any combination of basal (resting) hyperinsulinemia, postprandial hyperinsulinemia (response to oral sugar test [**OST**] or consumed feeds), or tissue insulin resistance (**IR**; hepatic and/or peripheral). Insulin dysregulation is the central endocrine disorder of EMS and is typically associated with increased generalized or regional adiposity (obese EMS) but can be detected in lean horses (non-obese EMS). It can exist in the absence of EMS in association with conditions such as PPID and also transiently with systemic illness, stress, pregnancy, and starvation. The severity of ID varies among affected animals, and there exists a subset of markedly hyperinsulinemic horses and ponies that are more challenging to manage and often require medical treatment.

The Equine Endocrinology Group (EEG) is composed of experts in the field of equine endocrinology who provide advice in the form of written guidelines to help veterinary practitioners diagnose and manage equine endocrine disorders. Guidelines are updated every two years or when new information becomes available and can be found on the EEG web site: http://sites.tufts.edu/equineendogroup.

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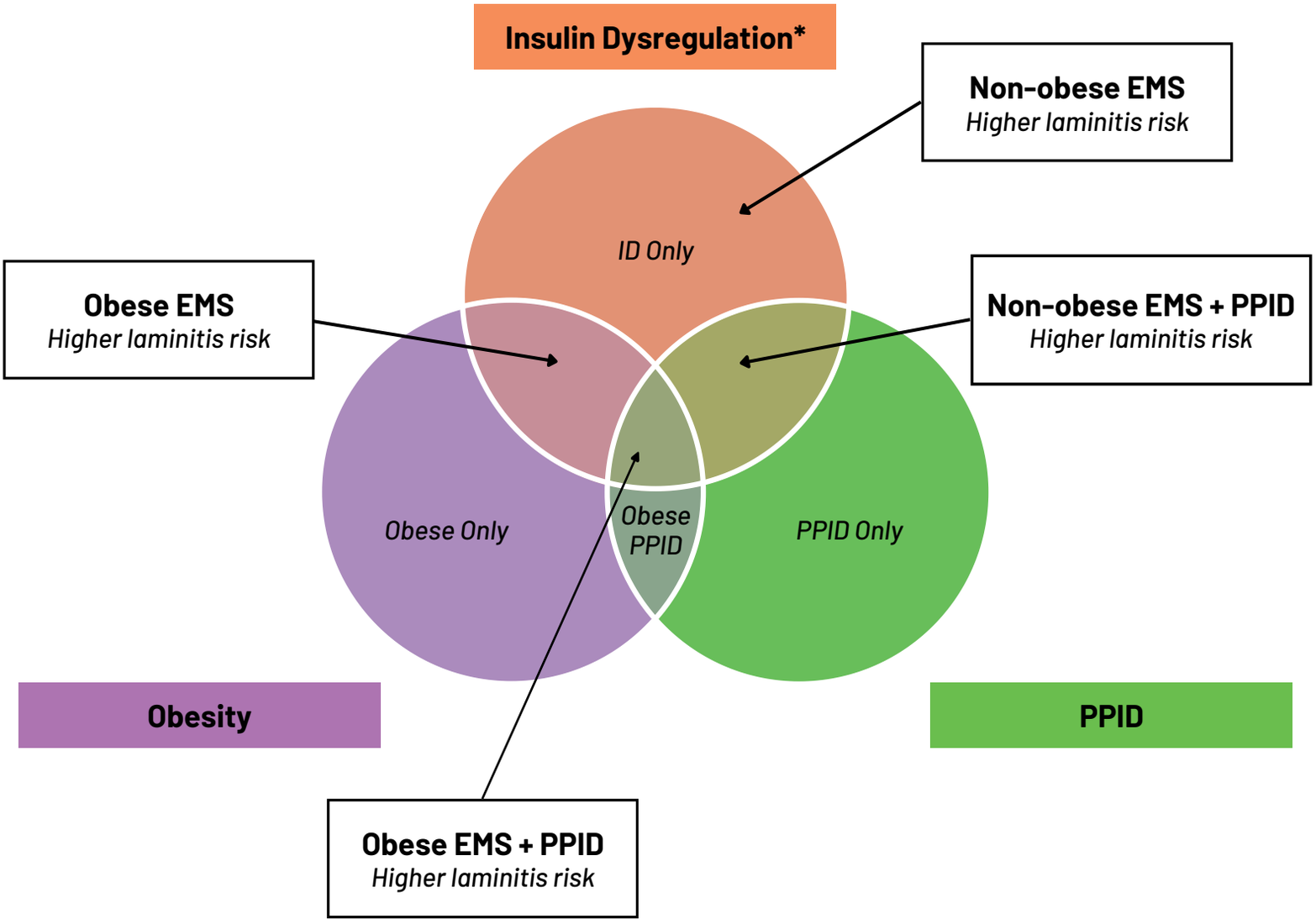
Table 1 – Questions and answers about hyperinsulinemia-associated laminitis

Laminitis is the outcome that poses the greatest health concern with EMS and the following questions and answers are provided for guidance:

How is HAL defined?	Laminitis associated with hyperinsulinemia that may appear to develop insidiously but becomes a chronic condition characterized by episodes of mild to moderate lameness. This form of laminitis begins as stretching and damage to the digital lamellae induced by sustained 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 and supporting-limb laminitis.
How does HAL differ from other forms of laminitis?	HAL is the most common form of laminitis seen in the general horse and pony population and is more likely to manifest as chronic recurrent laminitis. Other forms of laminitis include sepsis-associated laminitis and supporting limb laminitis. All these forms of laminitis have readily identifiable predisposing events and in the case of sepsis-associated laminitis, the primary histopathological change is destruction of the digital lamellar basement membrane. In contrast, HAL episodes usually occur insidiously in association with factors that cause blood insulin concentrations to increase, including increased NSC intake in a predisposed horse. The characteristic histopathological changes of HAL are stretching and elongation of the lamellae without disruption of the basement membrane.
How high do insulin concentrations have to get and for how long do they have to stay increased to induce laminitis?	The exact duration and magnitude of hyperinsulinemia that is needed to precipitate clinical laminitis is unclear and likely depends on the susceptibility of the individual horse and whether or not there is pre-existing lamellar damage. There may also be a distinction between the onset of lamellar damage and the point at which lameness is manifest or noticed by the horse owner. The exact threshold for HAL to develop likely differs among individual animals, but studies of ponies placed on a high-NSC diet suggests that blood insulin concentrations >200 µU/mL sustained for 5 days[1] or experimental infusion of insulin so that blood insulin concentrations are >500 µU/mL for 48-72h[2, 3] can induce HAL. However, it should not be assumed that HAL only develops when insulin concentrations reach these levels, because laminitis might occur when insulin concentrations are increased for an extended period of time but remain below the values above.
How does hyperinsulinemia cause laminitis in equids?	We do not have a definitive answer to this question at present. The most popular theory is that hyperinsulinemia induces inappropriate stimulation of insulin-like growth factor-1 receptors on lamellar epidermal cells.
Can horses with pituitary pars intermedia dysfunction (PPID) have HAL?	Yes, HAL is detected in approximately 30% of horses with PPID[4] and horses greater than 10 years of age should be tested for PPID as well as ID. Refer to the Equine Endocrinology Group Recommendations on PPID for more information.
Is pasture-associated laminitis the same as HAL?	Yes. Sugars and fructans 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?	The association between glucocorticoid administration and the subsequent development of laminitis is incompletely understood but is most likely to result from glucocorticoids exacerbating ID. 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 the degree of lameness observed in an individual animal predict the amount of damage to the digital lamellae?	In general, the answer is yes, because horses with severe pain typically have the most lamellar damage. However, HAL can develop insidiously, and the digital lamellae may undergo structural changes without lameness being readily apparent ('subclinical laminitis'). Divergent growth rings ('founder lines') observed on the outside of the hooves provide evidence of structural changes, and radiographs might reveal rotation or osteitis of the third phalanx.
When is it safe to put a horse with HAL back on pasture?	This depends upon the severity of ID in the individual animal, the quantity and quality (NSC content) of the pasture, and whether the risk of a subsequent laminitis episode occurring has been successfully mitigated. The amount of pasture access must also be defined before this question is answered because limited grazing may be permitted; however, full access to a large pasture is never recommended. One or both of the following approaches can be used to assess the horse before it is reintroduced to pasture grazing. The first approach is to perform an oral sugar test (OST) and if normal results are obtained then reintroduce pasture grazing in a controlled fashion using strategies to limit grass intake such as application of a grazing muzzle. A second approach is to allow the horse to graze on the pasture for 1-2 hours, and then measure the insulin concentration 1-2 hours after it is brought back in to assess the insulinemic effect of the grass in the individual animal. Note that interpretation of insulin values in response to grazing is not a precise science and requires consideration of peak insulin concentrations, the duration of hyperinsulinemia and the inherent laminitis-susceptibility of the individual.

Insulin dysregulation is detected in all equids with EMS and in some with PPID, and this is illustrated in the Venn diagram shown in Figure 1. The following algorithms (Figures 2-4) outline the recommended diagnostic and management pathways for ID and PPID.

Figure 1 – Venn diagram showing the proposed overlaps among endocrine disorders discussed in these recommendations. 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.



*Note that ID can also occur with pregnancy, starvation, and systemic illness

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Table 2 – Clinical presentation of Equine Metabolic Syndrome

Equine Metabolic Syndrome (EMS)

Signalment	*Clinical Features*	
OBESE (TYPICAL) MANIFESTATION OF EMS		
Genetic risk is implied by certain breeds having higher EMS prevalence Examples of higher genetic risk[a] breeds: Pony breeds Spanish Breeds (e.g., Andalusians) Gaited breeds (e.g., Saddlebreds, Paso Finos) Morgans Miniature horses Warmbloods Uncertain genetic risk: Donkeys[b]	*Some or all of the following may be present* Weight loss resistance ('Easy keeper'/'Good Doer') Clinical laminitis Divergent hoof rings (subclinical laminitis) Cresty neck Subcutaneous adipose tissue deposits Preputial or mammary gland enlargement (adipose tissue +/- edema) Clinical problems may be historical or current	
NON-OBESE MANIFESTATION OF EMS		
Genetically at-risk horse kept in controlled environment Obese EMS may be historical	Clinical laminitis Divergent hoof rings (subclinical laminitis)	
EMS with PITUITARY PARS INTERMEDIA DYSFUNCTION (PPID)		
EMS may be historical Genetically at-risk horse that develops PPID (might exacerbate ID)	**Clinical signs of EMS** *(current problem)* Regional adiposity and/or obesity Laminitis	**No clinical signs of EMS currently** *(historical problem)* Lean/thin at present
OTHER CONDITIONS THAT SHOULD PROMPT TESTING FOR ID		
Diabetes mellitus, metabolic derangements detected during critical care, equine hyperlipemia, infertility, colic caused by a pedunculated lipoma (associated with obesity), preputial/mammary gland edema, or detection of divergent hoof rings. Testing should also be considered as part of wellness or pre-purchase examinations in at-risk populations.		

[a] These breeds are overrepresented, and there is evidence of a genetic predisposition in Arabian horses.[7]

[b] An asinine metabolic syndrome has recently been described, and reference intervals for insulin tests are being determined for donkeys.[8]

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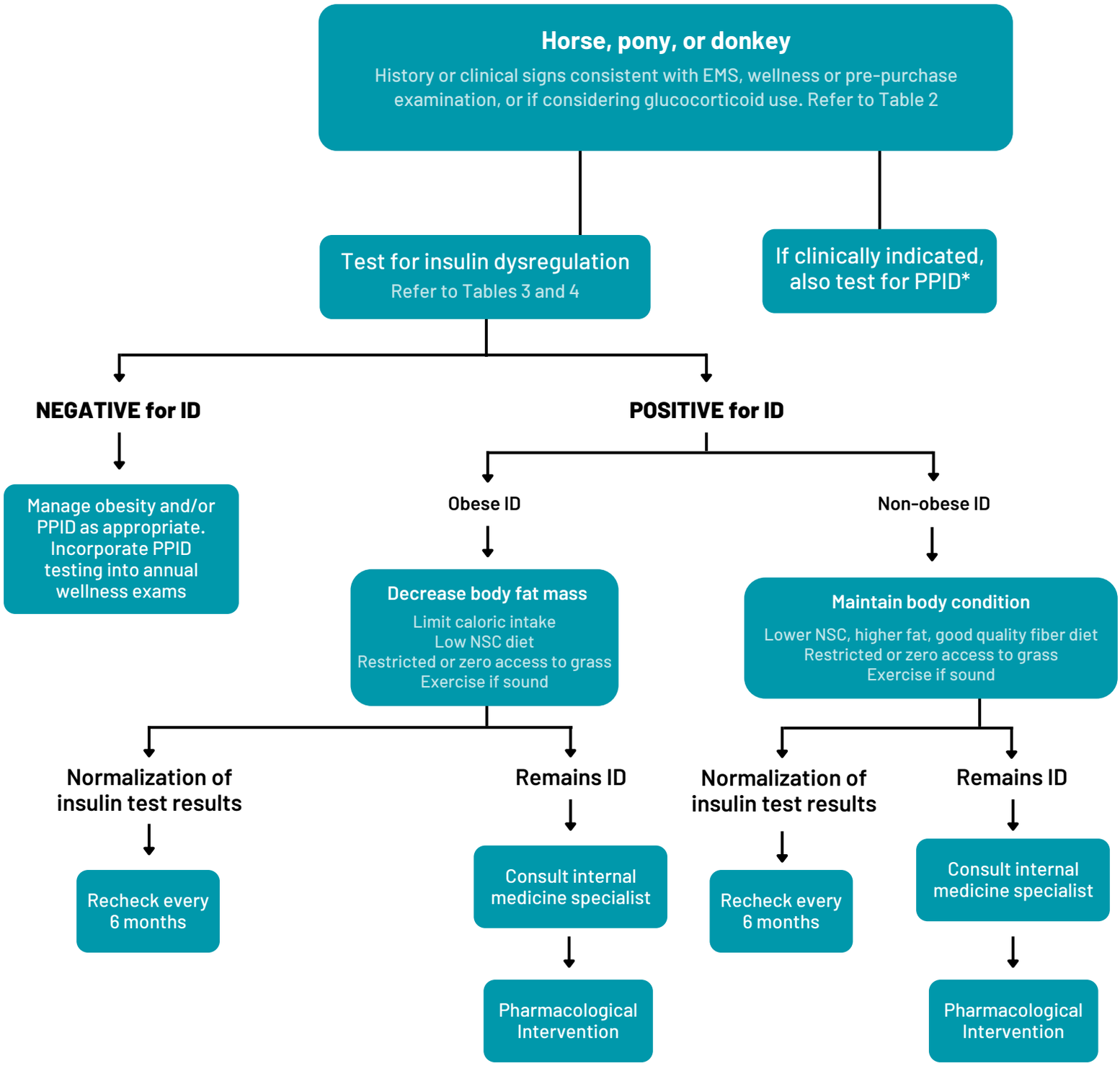
Figure 2 – Algorithm for the diagnosis and management of EMS (June 2022)



*Refer to EEG Recommendations on PPID

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Recommended approach for diagnostic testing

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 if samples cannot be mailed within this time period. Note that samples may be frozen and thawed once, but multiple freeze-thaw cycles will alter insulin concentrations.

• 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/point-of-care insulin analyzers have been recently developed and are now commercially available but have not been critically evaluated at this time. The EEG recommends that referral laboratories be used until further independent research is performed.

Selection of diagnostic tests

• ***Two dynamic tests are recommended:*** the OST and the insulin tolerance test (ITT). The OST is preferred because insulin concentrations measured reflect a more complete sequence of events including digestion and absorption of sugars, incretin hormone responses, secretion of insulin from the pancreas and risk of HAL, whereas the ITT focuses solely upon hepatic and/or peripheral tissue insulin sensitivity. Convenience is a factor in determining use of the ITT because horses do not require fasting prior to testing, and the test can therefore be performed at any time of day.

• ***Oral sugar test (OST):*** Advantages of this test include the ready availability of corn syrup, ease of administering corn syrup, 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 within-horse repeatability of test results. Fasting conditions are often achieved by the owner leaving a small amount of hay (one flake/slice for a 500-kg horse) with the horse before midnight, and then 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. When monitoring horses over time with this test, binary changes in the positive or negative result and major shifts in insulin concentrations (> 30 µU/mL) are considered clinically significant. Test performance is improved by administering 0.45 mL corn syrup/kg body weight instead of 0.15 mL corn syrup/kg,[4,5] and this dose is routinely used in the United Kingdom without apparent safety concerns. In situations where horses are resistant to oral administration, corn syrup may be mixed with a small amount of low-glycemic feed (e.g., chaff). Oral dextrose powder can be used when corn syrup is not available, but the test procedure and cut-off values for interpretation differ. A commercial product is being developed so that owners can feed a measured quantity of glycemic pellets to their horse to stimulate insulin secretion. This product standardizes the amount of sugar provided to the horse, and it is expected to be available for purchase soon.

• ***Insulin tolerance test (ITT):*** Advantages of the ITT are that this test does not require pre-test fasting and blood glucose concentrations can be measured with a glucometer so results are available on the farm.[6] Disadvantages include the cost of purchasing 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 lean insulin-sensitive 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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Recommended approach for diagnostic testing (cont.)

Selection of diagnostic tests (cont.)

• ***Resting (basal) insulin concentrations:*** A single blood sample is collected with the horse in the fed state (hay or pasture, but not grain), and plasma/serum insulin concentrations are measured to detect resting hyperinsulinemia. This approach may be used to assess the insulinemic effect and therefore the laminitis risk of the forage and/or pasture components of the current diet.

• ***Two-step approach to diagnosing ID:*** Testing can be performed in two steps if the owner raises concerns about dynamic tests inducing laminitis. The first step is to measure the resting (basal) insulin concentration to screen the horse for hyperinsulinemia and assess laminitis risk. If the resting insulin concentration is normal, a dynamic test must still be performed as a second step because resting measures have low diagnostic sensitivity - markedly abnormal OST results may be seen in horses with normal resting insulin concentrations. An OST is also recommended when only mild hyperinsulinemia is detected to estimate insulin responses to grazing on pasture or feeds. *Note: It has been the collective experience of the EEG that dynamic tests cause only transient alterations in glucose and insulin concentrations and do not induce laminitis.*

• ***Blood glucose concentrations:*** Diabetes mellitus occurs occasionally in horses and is likely to be detected with higher frequency in equids affected by EMS or PPID. Resting blood glucose concentrations should be measured to detect diabetes mellitus when any of the above tests for ID are performed.

• ***Tests in development:*** A glycemic pellet challenge is being developed using a commercial product that will be 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.

• ***Tests that are no longer recommended*:** The glucose:insulin ratio and proxy measures of insulin sensitivity are not recommended as diagnostic tests for use in clinical practice and are not appropriate substitutes for the OST or ITT. The combined glucose-insulin test, frequently-sampled intravenous glucose tolerance test, and euglycemic-hyperinsulinemic clamp procedure are considered too complex and expensive for routine clinical use but can provide relevant information in a research setting.

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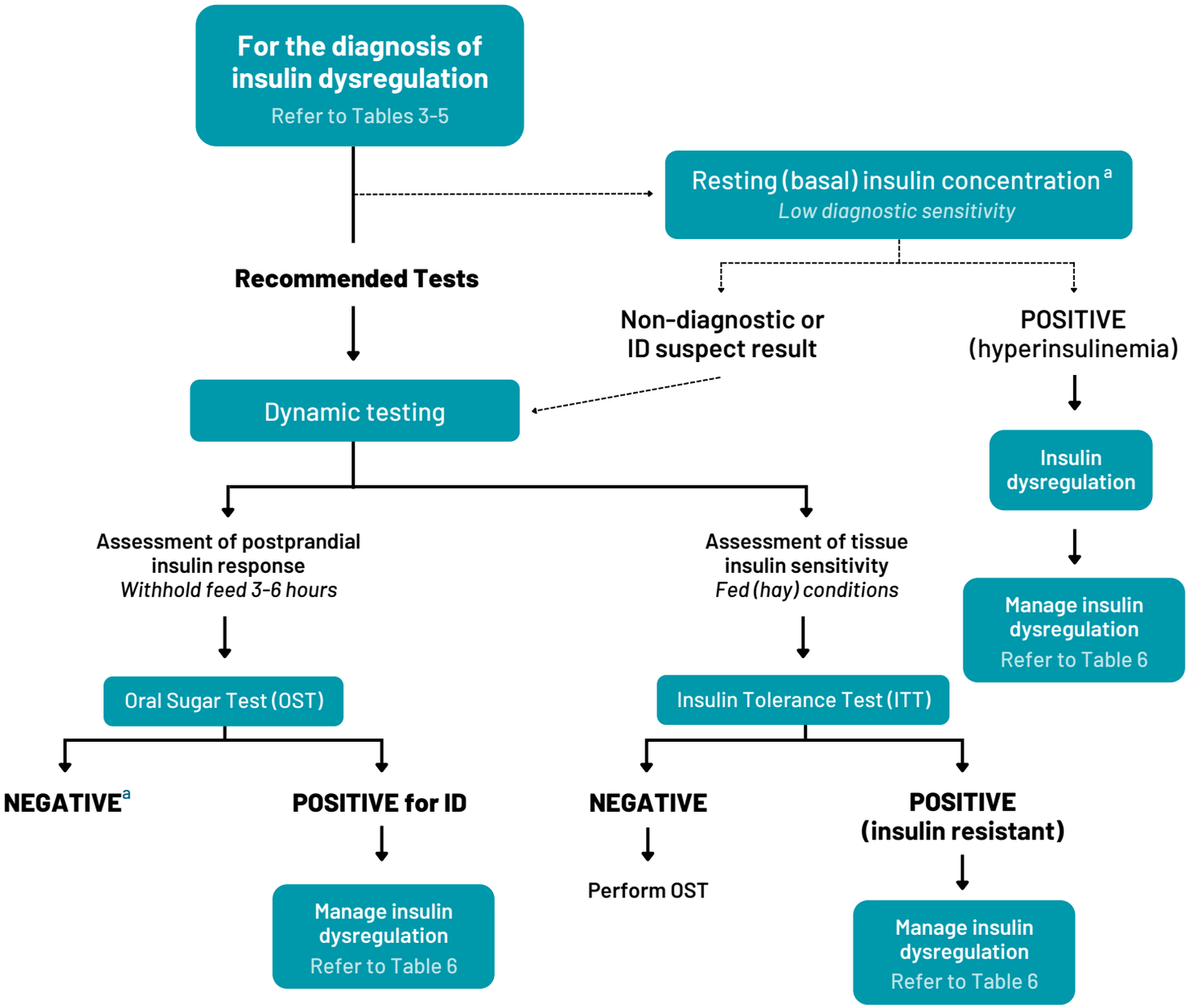
Figure 3 – Algorithm for detection of insulin dysregulation (June 2022)



[a] Ideally a dynamic test should also be performed but basal insulin concentrations can be used as an alternative if there are financial or other practical considerations.

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Table 3 – Recommended diagnostic testing: Dynamic insulin testing

	Postprandial insulin response	*Insulin sensitivity*
	Oral Sugar Test [a]	**Insulin Tolerance Test** [b]
Procedure	Fast 3 - 6 hours Administer 0.15 or 0.45 mL/kg corn syrup orally via dose syringe Collect blood at 60 and/or 90 minutes Measure insulin and glucose	Fed (pasture or hay) state; do not fast Collect blood at time 0 and administer 0.10 IU/kg regular (soluble) insulin Collect blood at 30 minutes Measure glucose Feed hay and small amount of grain immediately after last sample It is not recommended to perform the OST and ITT on the same day
Interpretation[c]	>45 µU/mL positive for 0.15 mL/kg test and RIA >65 µU/mL for 0.45 mL/kg test and RIA[d] >63 µU/mL positive for 0.45 mL/kg test and Immulite 2000 xpi Assess baseline (fasting) glucose concentration to detect diabetes mellitus (rare)	< 50% decrease in blood glucose concentrations from baseline is consistent with insulin resistance
Alternative Tests	In-feed oral glucose tolerance test (OGTT)	Combined glucose-insulin test (CGIT)

[a] Use of a higher dose of corn syrup (0.45 mL/kg) improves test performance.[5]
[b] Note that hypoglycemia is a risk associated with this test.
[c] Try to minimize stress prior to testing.
[d] Based upon RIA used by the Cornell University laboratory and an initial study with 14 ponies (Menzies-Gow, unpublished data).

Practice Tip: When reassessing horses after management or treatment, a normal OST result is a positive outcome, but owners must be advised that hyperinsulinemia can return in the at-risk horse if conditions that exacerbate ID are encountered.

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Table 4 – Resting insulin concentrations for convenience testing and monitoring

Resting (basal) insulin concentration*

Uses: Only used for convenience sampling or monitoring. Will only identify more severely affected animals (test has low sensitivity/high specificity).		
Update: Evidence is mounting that insulin concentrations are affected by season, with higher concentrations detected in December, January, and February in the Northern hemisphere, suggesting a winter-associated exacerbation of ID.		
Procedure	<u>After hay (no grain)</u> Do not feed grain within 4 hours Collect into serum or EDTA tube (check with laboratory) (assessment of the horse)	<u>While on pasture</u> Used to assess insulin concentrations during grazing[a] (assessment of current management)
Assays Used	***Results must be interpreted in the context of the insulin assay used (chemiluminescent assay, radioimmunoassay, or ELISA)***	
Results	**Interpretation [b]**	**Recommendation**
RIA & Immulite 1000: **<20 µU/mL** Immulite 2000 xpi: **<31 µU/mL**	Non-diagnostic	Dynamic test recommended to better assess
RIA & Immulite 1000: **20-50[c] µU/mL** Immulite 2000 xpi: **30-75 µU/mL**	ID suspect if consistent clinical signs	Dynamic test recommended to better assess
RIA & Immulite 1000: **>50[c] µU/mL** Immulite 2000 xpi: **>75 µU/mL**	**ID**	**Proceed with ID management**

*Resting insulin concentrations are not ideal for diagnosis of ID because they are significantly dependent on diet and should be interpreted accordingly.

a Values reflect the NSC content of the grass consumed at the time of testing.

b Quality and NSC content of forages can vary and affect results; cut-off values for horses on low-NSC hay

c Note that an insulin concentration of 47 µU/mL is used to define a positive response for the OST, compared to 50 µU/mL for resting insulin concentrations. This discrepancy exists because the OST is performed after fasting, whereas resting insulin concentrations are measured in the fed state.

Practice Tip: Although insulin ranges are provided, the upper limits of ranges are not absolute values and results just above or below these values must be interpreted accordingly. Also note that inter-day variability in insulin concentrations is observed in some horses, and results of dynamic tests such as the OST 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.

Table 5 – Additional tests for assessment of horses with EMS (not meant to replace the diagnostic testing described above)

Test	Procedure	Interpretation
Leptin Available in USA[a]	Collect blood in serum or EDTA tube; keep refrigerated	Consult reference interval provided by laboratory. Higher leptin concentrations are associated with increased adiposity and metabolic derangement. Useful for providing evidence of increased internal adiposity. This hormone is more directly associated with obesity than ID.
Triglyceride concentrations Available from most clinical pathology laboratories	Collect blood in serum tube	Consult reference interval for laboratory. Hypertriglyceridemia associated with ID and obesity, exacerbated by negative energy balance. Hypertriglyceridemia is a predictor of laminitis risk in ponies, with cut-off values of 57 and 94 mg/dL previously reported.[9]
Adiponectin concentrations Available in UK[b]	Depends upon assay used. At the time of writing, only total adiponectin is available.	Total adiponectin concentrations <7.9 ug/mL are consistent with EMS and an increased risk of laminitis.
Potential Future Tests		
Glucagon-like peptide-1 and -2 concentrations, C-peptide concentrations, fecal microbiome analysis, and genetic and metabolomic testing		

[a] Animal Health Diagnostic Center at Cornell University (https://ahdc.vet.cornell.edu/)

[b] https://axiomfarm.com/ and Liphook Equine Hospital Laboratory offer a total adiponectin assay at the time of writing. Cut off values derived using samples from Menzies-Gow et al 2017.[10]

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Table 6 – Management recommendations for equine metabolic syndrome

Management Recommendations: Obese (typical) EMS BCS 6-9/9

Initial Diet	Restrict grazing by placing horse in a small paddock that has little or no grass growing on it, along with a companion, or eliminate grazing altogether if ID is severe. Do not feed grain or treats. For weight loss, feed grass hay with low NSC content in amounts equivalent to 1.5% (in dry matter) of current body weight on an as-fed basis daily. Hay should be selected because it has low NSC content and/or because it induces a low peak insulin concentration after feeding. Reassess body weight every 30 days using a weight scale or weight tape and gradually lower to a minimum of 1.2% (in dry matter) of body weight as-fed if weight loss resistant. Avoid stress as much as possible. NSC analysis of hay recommended, particularly if severe ID is detected. Select hay with NSC content < 10% as-fed if available. Good quality straw can be fed as a low-NSC forage for up to approximately 50% of the daily feed provided (75% or more for donkeys).[11] Introduce straw to the diet gradually and monitor for signs of colic. Soak hay in cold water for at least 60 minutes before feeding to lower the water-soluble carbohydrate content.[a] Incorporate slow feeder 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	Continue to restrict grazing as described above, and do not feed grain or treats. Maintain on initial hay amount until body condition 5/9 is achieved. Improvement in the values obtained from the same test(s) used to diagnose EMS is desirable when re-tested under similar conditions. However, it may take several months to reach a BCS of 5/9, and severely affected animals can remain obese in the face of appropriate management. When a negative dynamic test result cannot be attained, focus should be placed on selecting feeds that elicit the lowest insulin responses and postprandial insulin concentrations should be monitored. Blood is collected one hour after the horse has fed for at least one hour. 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 1-2 hours of pasture grazing (see below). 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 through the use of mazes and other activity systems. If chronic laminitis becomes more painful, grazing should be stopped until horse has stabilized.
Exercise	Exercise is recommended unless laminitis is present. *All levels of exercise are likely to be 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 (fast trot to canter unridden; or heart rates 130-150 bpm) for >30 minutes, >3 times per week, whilst carefully monitoring for signs of lameness. Heart rate monitors can be used to help with implementation of appropriate exercise regimens. In horses with ID and no signs of lameness, minimum recommendations are low to moderate intensity exercise > 5 times per week such as canter to fast canter (ridden or unridden) achieving heart rates of 150-170 bpm for >30 minutes.[12] However, it has also been shown that 15 minutes of moderate trotting (with 5 min walking to warm up and warm down) 5 times per week has a significant beneficial effect on insulin sensitivity in obese equids,[13] and these recommendations may be easier for owners of ponies and horses to achieve.

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Management Recommendations (continued): Obese (typical) EMS BCS 6-9/9

Housing	Stress should be avoided, and the affected horse should ideally be housed in a small bare paddock with a companion, instead of being confined to a stall (once laminitis has been addressed). Stereotypic behavior can be limited through the use of slow feeders. Turnout on pasture is strongly discouraged until the problems of obesity and ID are successfully addressed.
Monitoring	Regular monitoring of ID is recommended in EMS horses, and methods include measuring insulin concentrations while the horse is on its current diet (e.g., hay or hay plus limited 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. If horses are not on pasture, collect blood after a minimum of 2 hours of hay feeding. For horses on pasture, allow 1-2 hours of grazing, remove the horse from the pasture, and collect blood 1-2 hours later. 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 December, January, and February in the Northern hemisphere, suggesting a winter-associated exacerbation of ID. Accordingly, care should be taken to avoid overfeeding or adding high-NSC feeds in the winter months. Close monitoring for early signs of laminitis is recommended, and a new scoring system has been developed to better assess horses with HAL.[14]
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.
Medical Therapy	**Note: Drugs described below are currently being used off-label** ***High-dose levothyroxine*** Indications: 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 in acute laminitis cases. Administer levothyroxine at a high dose of 0.1 mg/kg (48 mg or 4 teaspoons of the powdered product for a 500-kg horse) daily in the feed or by mouth while also controlling caloric intake. Gradually reduce the dose and discontinue treatment after weight loss achieved or after 3-6 months of therapy. ***Sodium-glucose co-transporter 2 (SGLT2) inhibitors*** Indications: Used when horses are affected by laminitis and severe ID are not responding to other measures, and the owner has sufficient resources to pay for an expensive medical treatment. Drugs in this group act by inhibiting the reuptake of glucose from the glomerular filtrate, with more glucose lost in the urine as a result. Blood glucose concentrations decrease in response to treatment, and the amount of insulin needed to maintain euglycemia decreases proportionally. In initial studies in ponies, blood insulin concentrations significantly decreased over time when the SGLT2 inhibitor velagliflozin was administered orally at a dose of 0.3 mg/kg every 24 hours.[15, 16] Velagliflozin is not available for purchase at present, but two drugs in the same group, canagliflozin (0.5 mg/kg, PO, q24h) and ertugliflozin (0.05 mg/kg POq24h), are available. They are labeled for the treatment of diabetes mellitus in humans. Both drugs have been used with some success in a small number of horses with severe ID, but they are expensive in some countries and are reserved for horses with laminitis and severe ID that do not respond to recommended management changes. Smaller equids may be treated at a more reasonable cost. Lipid mobilization is stimulated in many horses treated with SGLT2 inhibitors, and hypertriglyceridemia might develop as a consequence. Thus, horses with marked hypertriglyceridemia should not be treated with these drugs.

Practice Tip: Although the SGLT2 inhibitors are promising drugs, it is essential that TG concentrations be monitored when treatment is initiated because individual horses might develop severe hypertriglyceridemia (>1,000 mg/dL; 26 mmol/L). Collect blood at 7 and 14 days, and then every 1-3 months thereafter. A risk/benefit assessment is needed if hypertriglyceridemia develops, and treatment decisions should be based on the severity of laminitis. Moderate hypertriglyceridemia (>100 mg/dL; 2.6 mmol/L) may affect the liver and other organs, and gamma glutamyl transferase (GGT) concentrations should be monitored if this problem develops. Management practices to address hyperinsulinemia must also be instituted at the same time, with the goal of discontinuing SGLT2 inhibitor treatment once the horse's condition stabilizes. The EEG does not condone prescribing drugs for the treatment of ID without making appropriate management changes. The outcomes and health consequences of long-term treatment with SGLT2 inhibitors have not yet been evaluated in horses so these drugs should only be used in the short term (three months) until more research has been performed.

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Management Recommendations (continued): Obese (typical) EMS BCS 6-9/9

Medical Therapy (cont.)	***Metformin hydrochloride*** Indications: For animals with persistent hyperinsulinemia, even after management changes have been followed. The drug is only effective in a small percentage of horses and may lose efficacy over time. Administer 30 mg/kg metformin hydrochloride in the feed or by mouth, ideally 30 minutes prior to feeding or turnout, up to 3 times daily. Metformin can also be administered at a higher dose of 50 mg/kg, but oral irritation may occur at this dose. Check insulin concentrations 2 hours post-feeding before and 7 days after initiating metformin treatment, as metformin does not improve insulin status in all cases. ***Nutraceuticals*** Nutritional supplements including chromium, resveratrol and magnesium are commonly recommended for the management of ID. While it is important that horses receive the recommended daily amounts of magnesium and chromium, the effect of larger amounts of these minerals on insulin sensitivity is not well understood.

Management Recommendations (cont.): Non-obese EMS BCS 4-5/9 EMS with Diagnosed PPID

Non-obese EMS BCS 4-5/9	***Diet:*** Maintain on a low-glycemic diet, with the severity of restriction dependent on the postprandial insulin response. Analyze the NSC content of hay if severely affected. Provide a diet with low-NSC, high-fat, and high-quality fiber content such as beet pulp or soy hulls. Provide a low-sugar mineral/vitamin/protein ration balancer. ***Exercise:*** As above. ***Medical Therapy:*** Levothyroxine is not recommended as weight loss is not required. The other drugs described above may be administered if management changes are not sufficient to improve insulin sensitivity.
EMS with Diagnosed PPID	Follow appropriate recommendations from above, depending upon body condition. ***Medical Therapy:*** Administer Prascend® (pergolide tablets); Boehringer Ingelheim Animal Health, Duluth, GA. Refer to EEG Recommendations on PPID.

[a] Acknowledging that this will not reliably lower the NSC content to <10% in all hays.

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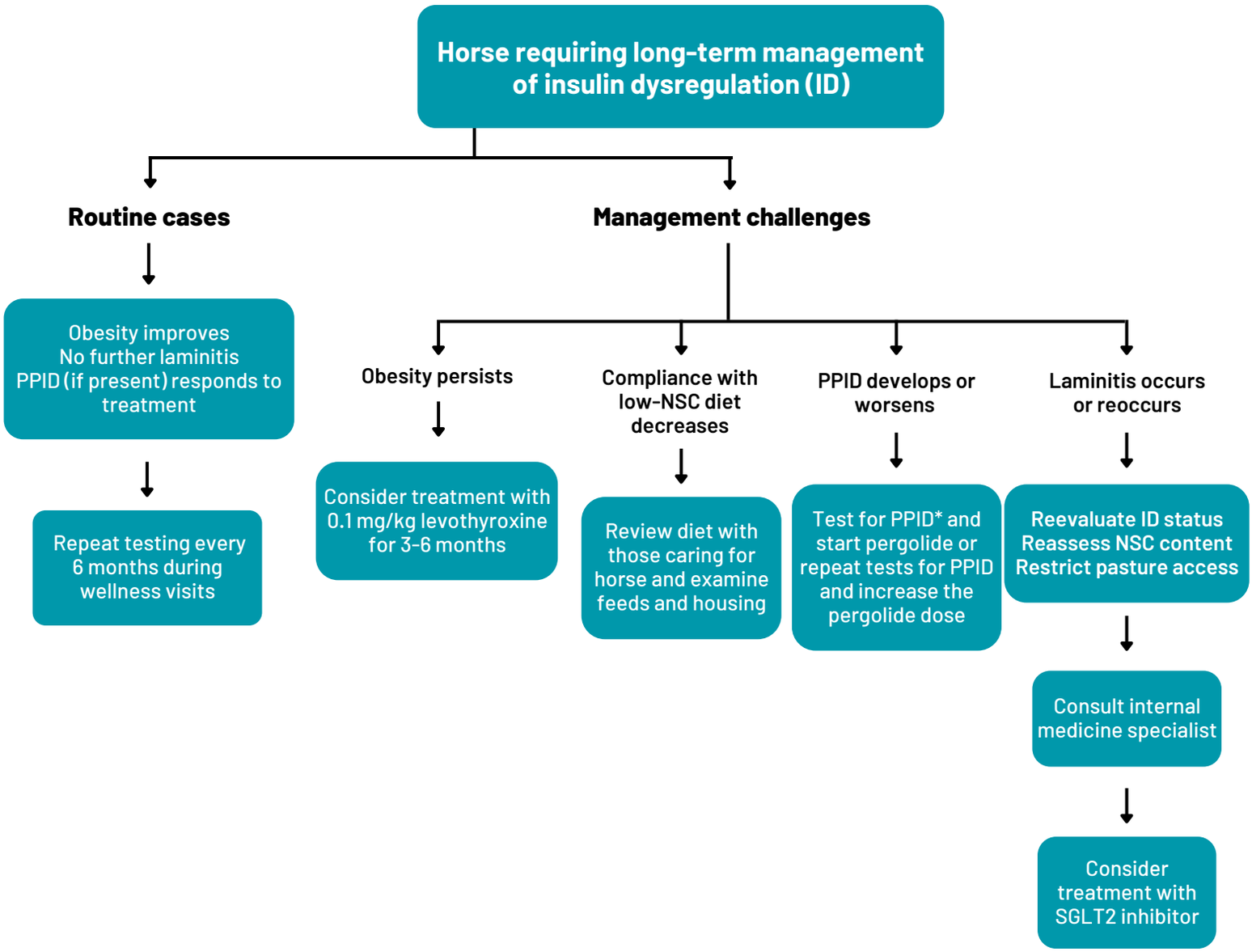
Figure 4 – Algorithm for management of challenging cases (June 2022)



*Refer to EEG Recommendations on PPID

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Table 7 – Consideration of pituitary pars intermedia dysfunction status

Refer to the most recent Equine Endocrinology Group recommendations on diagnosing and managing PPID in horses: https://sites.tufts.edu/equineendogroup/

	Consideration
Age	EMS affects horses across a wide range of ages. PPID is a common comorbidity in horses above 10 years, and the likelihood of PPID increases as the age of the horse increases.
Impact on ID	PPID is an exacerbating factor for ID speculated to be a consequence of hormone products such as corticotropin-like intermediate peptide secreted from the pars intermedia. Age alone alters insulin dynamics and responses to different diets, with higher insulin secretion and lower insulin sensitivity detected in aged horses.
Diagnostic Testing	Early affected horses should undergo thyrotropin-releasing hormone (**TRH**) stimulation testing (test results are difficult to interpret in late summer-fall). A combined ITT/TRH stimulation test has been developed and for this test, insulin and TRH are administered together as a single IV injection.[17] The TRH stimulation test can also be performed just before, but not just after the OST to combine these tests for PPID and ID, respectively.[18] Basal plasma ACTH concentrations are measured for more advanced cases. Detection of a high ACTH concentration confirms the diagnosis of PPID, but horses with suggestive clinical signs and negative results should undergo TRH stimulation testing.
Management	**Diet:** Based upon the postprandial insulin response. An OST or oral glucose test is recommended for all horses diagnosed with PPID. **Exercise:** Refer to Table 6. **Medical:** Administer Prascend® (pergolide tablets); Boehringer Ingelheim Animal Health, Duluth, GA. **Comorbidities:** May require management of other medical problems related to PPID and age, including bacterial infections, dental disease, organ dysfunction, and parasitism. **Critical illness:** Insulin dysregulation and PPID are complicating factors in patients with critical illness and may predispose affected patients to hyperglycemia and hypertriglyceridemia. Endocrine system decompensation may adversely affect treatment outcomes.

Disclosures

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

Boehringer-Ingelheim 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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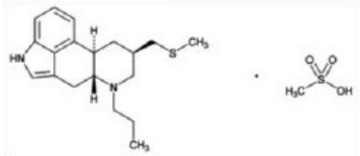
Notes

Dopamine receptor agonist for oral use in horses only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: PRASCEND Tablets are rectangular light red colored, half-scored tablets containing 1 mg pergolide, as pergolide mesylate. Pergolide mesylate is a synthetic ergot derivative and is a potent dopamine receptor agonist. The chemical name of pergolide mesylate is 8β-[(Methylthio) methyl]-6-propylergoline monomethanesulfonate. The chemical structure is:



Indication: For the control of clinical signs associated with Pituitary Pars Intermedia Dysfunction (Equine Cushing's Disease) in horses.

Dosage and Administration: Administer orally at a starting dose of 2 mcg/kg once daily. Dosage may be adjusted to effect, not to exceed 4 mcg/kg daily.

It has been reported that pergolide tablets may cause eye irritation, an irritating smell, or headache when PRASCEND Tablets are split or crushed. PRASCEND Tablets should not be crushed due to the potential for increased human exposure and care should be taken to minimize exposure when splitting tablets.

The tablets are scored and the calculated dosage should be provided to the nearest one-half tablet increment (see Table 1).

Table 1 Dosing Table

Body weight	Dosage 2 mcg/kg	Dosage 4 mcg/kg
136 - 340 kg (300 - 749 lb)	0.5 tablet	1 tablet
341 - 567 kg (750 - 1,249 lb)	1 tablet	2 tablets
568 - 795 kg (1,250 - 1,749 lb)	1.5 tablets	3 tablets
796 - 1,022 kg (1,750 - 2,249 lb)	2 tablets	4 tablets

Dosing should be titrated according to individual response to therapy to achieve the lowest effective dose. Dose titration is based on improvement in clinical signs associated with Pituitary Pars Intermedia Dysfunction (PPID) and/or improvement or normalization of endocrine tests (for example, dexamethasone suppression test or endogenous ACTH test).

In some cases, adverse events were reported after a dose increase (see **Post-Approval Experience**).

If signs of dose intolerance develop, the dose should be decreased by half for 3 to 5 days and then titrated back up in 2 mcg/kg increments every 2 weeks until the desired effect is achieved.

Contraindications: PRASCEND is contraindicated in horses with hypersensitivity to pergolide mesylate or other ergot derivatives.

Warnings: Do not use in horses intended for human consumption.

Keep PRASCEND in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Dogs have eaten PRASCEND tablets that were placed in food intended for horses or dropped during administration of the tablets to the horses. Adverse reactions may occur if animals other than horses ingest PRASCEND tablets (see **Post-Approval Experience**).

Human Warnings: Not for use in humans. Do not ingest the product. Keep this and all medications out of the reach of children. PRASCEND should not be administered by persons who have had adverse reactions to ergotamine or other ergot derivatives.

Pergolide, like other ergot derivatives, may cause emesis, dizziness, lethargy or low blood pressure.

Pregnant or lactating women should wear gloves when administering this product. It has been reported that pergolide tablets may cause eye irritation, an irritating smell, or headache when PRASCEND Tablets are split or crushed. PRASCEND Tablets should not be crushed due to the potential for increased human exposure and care should be taken to minimize exposure when splitting tablets. Store this product separately away from human medicinal products and handle this product with care to avoid accidental ingestion.

In case of accidental ingestion seek medical advice immediately and show the package leaflet or the label to the physician.

Precautions: Treatment with PRASCEND may cause inappetence.

The use of PRASCEND in breeding, pregnant, or lactating horses has not been evaluated. The effects of pergolide mesylate on breeding, pregnant, or lactating horses are not known; however, the pharmacologic action of pergolide mesylate suggests that it may interfere with reproductive functions such as lactation.

PRASCEND is approximately 90% associated with plasma proteins. Use caution if administering PRASCEND with other drugs that affect protein binding. Dopamine antagonists, such as neuroleptics (phenothiazines, domperidone) or metoclopramide, ordinarily should not be administered concurrently with PRASCEND (a dopamine agonist) since these agents may diminish the effectiveness of Prascend.

Adverse Reactions:
Pre-Approval Experience: A total of 122 horses treated with PRASCEND Tablets for six months were included in a field study safety analysis.

Table 2 Summary of the most common adverse reactions (N=122)

Clinical sign	# Cases	Cases (%)
Decreased appetite	40	32.8
Lameness	22	18.0
Diarrhea/Loose stool	12	9.8
Colic	12	9.8
Lethargy	12	9.8
Abnormal Weight Loss	11	9.0
Laminitis*	10	8.2
Heart murmur	10	8.2
Death	8	6.6
Tooth disorder	8	6.6
Skin abscess	7	5.7
Musculoskeletal pain	6	4.9
Behavior change	6	4.9

*Three new cases and 7 pre-existing, recurring cases

Inappetence or decreased appetite occurred at one or more meals in 40 of 122 horses treated with Prascend. At the baseline evaluation 1.6% of owners reported a history of inappetence or decreased appetite as compared to the 32.8% of horses that experienced inappetence or decreased appetite during the study. Most cases of inappetence were transient and occurred during the first month of treatment; however, some horses experienced sporadic inappetence throughout the study. Two horses required a temporary reduction in dose due to inappetence during the first month of the study. Both horses returned to their original dose within 30 days.

Weight loss occurred in more than half of the horses in this study; however, weight loss that was considered abnormal was only reported in 11 horses.

Lethargy was reported in 9.8% of horses during the study, and was not reported in any horses at the baseline evaluation.

Behavioral changes were noted in 6 horses including aggression, kicking, agitation, nervous behavior and increased activity. One horse required a temporary reduction in dose due to energetic behavior during the first month of the study.

Eight horses died or were euthanized during the study due to worsening of pre-existing conditions (laminitis, dental disease, septic tenosynovitis) or colic (strangulating lipomas, large colon volvulus).

One mare was inadvertently enrolled in the study while pregnant and experienced dystocia resulting in the death of the foal.

Post-Approval Experience (2019):

The following adverse events are based on post approval adverse drug experience reporting for PRASCEND. Not all adverse events are reported. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.

The following adverse events in horses are categorized in order of decreasing reporting frequency by body system and in decreasing order of reporting frequency within each body system:

General: anorexia, lethargy, weight loss
Gastrointestinal: diarrhea, abdominal pain/colic
Dermatological: alopecia, hyperhidrosis, dermatitis
Musculoskeletal: laminitis, muscle stiffness/soreness
Neurological: ataxia, seizure, muscle tremors
Behavioral: aggression (to other horses and humans), hyperactivity (anxiety, agitation), other behavioral changes (stud-like behavior, spooky, unpredictable, confused)
Clinical pathology: anemia, elevated liver enzymes, thrombocytopenia

The above adverse events were reported in some horses at starting dose levels, while in the others following a dose increase.

Death (including euthanasia) has been reported.

Adverse events have been reported in dogs following ingestion of tablets prepared for administration to horses.

To report suspected adverse reactions, to obtain a Safety Data Sheet (SDS), or for technical assistance, contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

Clinical Pharmacology: Pergolide mesylate is a synthetic ergot derivative and is a potent dopamine receptor agonist. As with other dopamine agonists, pergolide inhibits the release of prolactin which suggests that it may interfere with lactation. In horses with PPID, pergolide is believed to exert its therapeutic effect by stimulating dopamine receptors, and has been shown to decrease the plasma levels of adrenocorticotropic hormone (ACTH), melanocyte stimulating hormone (MSH), and other pro-opiomelanocortin peptides.[1]

Pharmacokinetic information in the horse is based on a study using single oral doses of 10 mcg/kg in six healthy mares between 3 and 17 years of age.[2] Pergolide was rapidly absorbed; the mean maximum concentration (Cmax) was 4.05±2.02 ng/mL with the median time to maximum concentration (Tmax) being 0.415 hours.

The area under the curve (AUC) was 14.08±7.46 hr·ng/mL. The mean half life (T1/2) was 5.86±3.42 hours; the mean apparent oral clearance (CL/F) was 1204 mL/kg/hr; and the mean apparent volume of distribution (V/F) was 3082±1354 mL/kg.

Effectiveness: An open-label, historical control, field study evaluated the effectiveness of PRASCEND for the control of clinical signs of PPID. A total of 122 horses with PPID were enrolled in the study, 113 of which were included in effectiveness evaluations. The success of each horse was based on results of endocrinology testing (dexamethasone suppression test or endogenous ACTH test) and/or improvement in clinical signs related to PPID (hirsutism, hyperhidrosis, polyuria/polydypsia, abnormal fat distribution, and/or muscle-wasting) on the Day 180 evaluation. Based on endocrine testing and investigators' clinical assessment scores, 86 (76.1%) of the 113 evaluable cases were treatment successes.

Table 3 Proportion of Treatment Successes on Day 180

Percent success	Lower bound: one-sided 95% confidence interval
76.1% (86/113)	68.6%

Enrolled horses were diagnosed with PPID based on the presence of hirsutism and an abnormal pre-study endocrine test result. All horses were treated with 2 mcg/kg PRASCEND (to the nearest one-half tablet) orally once daily for the first three months. If the endocrine test result on Day 90 was normal or adequately improved, the horse continued on the same dose through Day 180. If the endocrine test result on Day 90 was abnormal, the dose increased to 4 mcg/kg given once daily through Day 180.
Forty-seven (41.6%) of the 113 horses included in the effectiveness database required a dose increase at Day 90.

Improvement was noted in scores for all clinical sign categories and in mean results for endocrine tests.

Table 4 Percent of Animals with Improvement in Clinical Signs Relative to Baseline Scores

Clinical sign	Day 90±7 (%)	Day 180±7 (%)
Hirsutism	32.7%	89.2%
Hyperhidrosis	27.4%	42.3%
Polyuria / polydypsia	31.0%	34.2%
Abnormal fat distribution	21.2%	33.3%
Muscle wasting	36.3%	46.0%

Table 5 Endocrine test results (mean values)

Test	# Animals	Baseline	Day 90	Day 180
ACTH (pg/mL)	20	73.53	51.12	45.08
DST** (mcg/dL)	93	3.12	1.39	1.47

** Dexamethasone suppression test: Post dexamethasone cortisol concentration

Animal Safety: In a six month target animal safety study healthy adult horses received PRASCEND administered orally, once daily, at doses of either 0 mcg/kg, 4 mcg/kg, 6 mcg/kg, or 8 mcg/kg (0X, 1X, 1.5X, or 2X the maximum recommended dose). There were eight healthy horses (four males and four females) in each treatment group. Doses were prepared by dissolving tablets in approximately 10 mL of a 50% sugar water solution.

PRASCEND treated groups had lower mean heart rates and higher mean temperatures than the control group. Horses in all treatment groups had minimum heart rates within the normal range and maximum temperatures below 101.5°F. One 1.5X horse experienced a mild episode of spasmodic colic on Day 3 that resolved after treatment with flunixin meglumine.

Mean red blood cell counts and hemoglobin values were lower in PRASCEND treated groups as compared to the control group. Other hematology parameters including hematocrit, white blood cells, absolute neutrophils, and absolute lymphocytes exhibited mild, transient decreases as compared to the control group. The hematology parameters generally decreased over the first 30 to 60 days after treatment initiation and then returned to values similar to pre-treatment levels. No treatment related alterations were identified on histopathology evaluation of bone marrow.

Storage: Store at or below 25°C (77°F).

How Supplied: PRASCEND Tablets are available in 1 mg strength – packaged 10 tablets per blister and 60 or 160 tablets per carton.
NDC 0010-4489-01 - 60 tablets
NDC 0010-4489-02 - 160 tablets

Approved by FDA under NADA # 141-331

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