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

2020

EQUINE ENDOCRINOLOGY GROUP

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

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Prepared by the EMS Working Group
Nicholas Frank (Group Coordinator; Tufts University)
Simon Bailey (University of Melbourne)
François-René Bertin (The University of Queensland)
Melody de Laat (Queensland University of Technology)
Andy Durham (Liphook Equine Hospital)
Janice Kritchevsky (Purdue University)
Nicola Menzies-Gow (Royal Veterinary College)

Introduction

Equine metabolic syndrome (**EMS**) is a collection of risk factors highly associated with an increased risk of hyperinsulinemia-associated laminitis (**HAL**) and other morbidities. Insulin dysregulation (**ID**) is a consistent feature of EMS and increased adiposity is typical. Additional factors present in some animals include increased generalized or regional adiposity, 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 relative weighting 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 or consumed feeds), or tissue insulin resistance (**IR**; hepatic and/or peripheral). Insulin dysregulation is the central endocrine disorder of EMS. ID is typically associated with increased adiposity (obese EMS) but can be detected in lean horses (non-obese EMS). It can also exist in the absence of EMS in association with conditions such as PPID, systemic illness, stress, pregnancy and starvation.

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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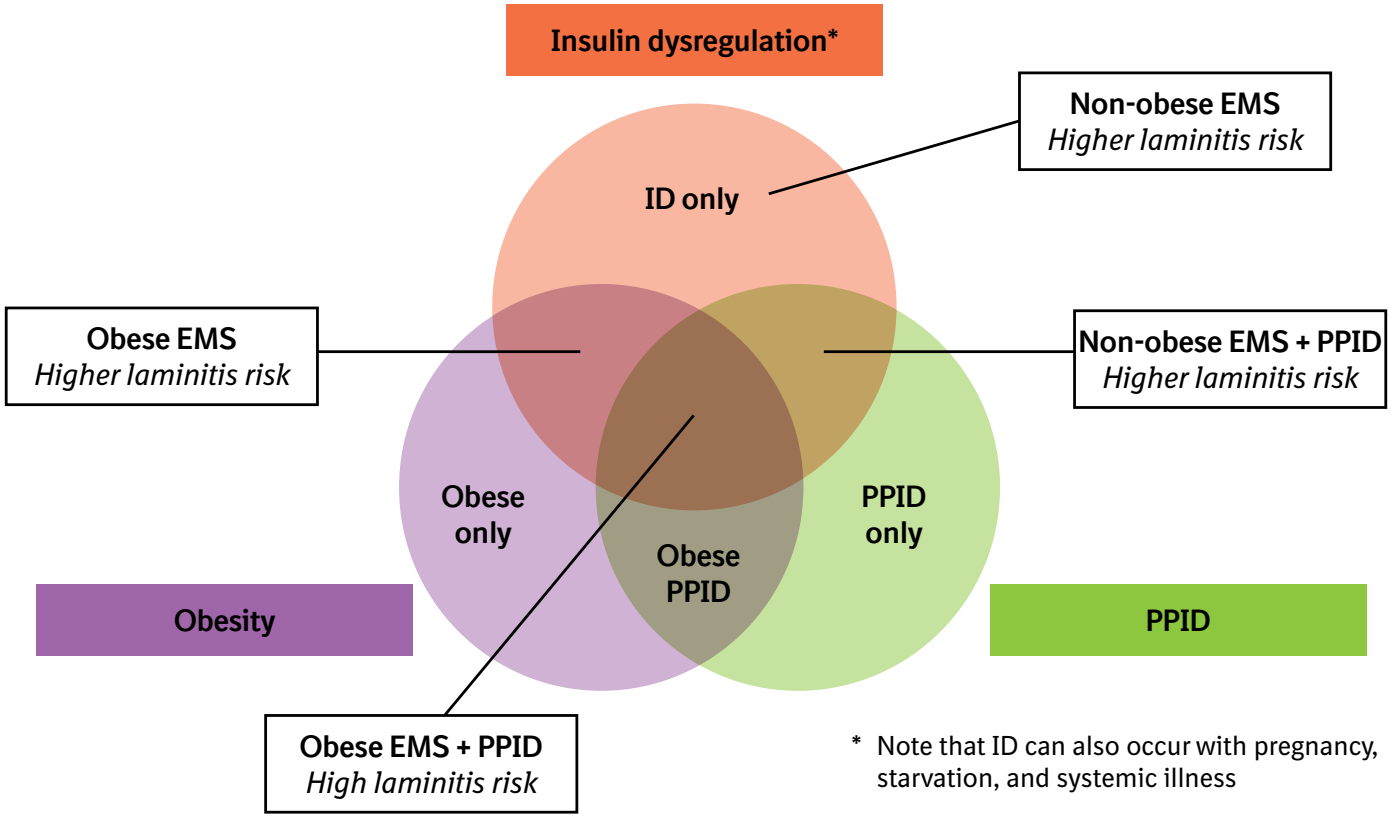
Table 1 - Questions and answers about hyperinsulinemia-associated laminitis

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

Questions	Answers
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 laminae induced by sustained hyperinsulinemia that can go undetected at first, but then progresses to lameness and more classical signs of laminitis. This form of laminitis differs from the sepsis-associated and supporting-limb laminitis in terms of the pathophysiology and histologic changes.
How does HAL differ from other forms of laminitis?	Other forms of laminitis include sepsis-associated laminitis, supporting limb laminitis, and mechanical/traumatic laminitis ('road founder'). All of 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 basement membrane of the epidermal laminae. In contrast, HAL episodes usually occur insidiously in association with factors that cause blood insulin concentrations to increase including increased NSC intake. The characteristic histopathological changes of HAL are stretching and elongation of the laminae without destruction or lysis of the basement membrane.
How much do insulin concentrations have to increase and for how long do they have to stay elevated 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 laminar damage. There may also be a distinction between the onset of laminar 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 >1,000 µU/mL for 48-72h[2] can induce HAL.
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 laminar epidermal cells. Decreased lamellar perfusion and altered energy regulation have also been considered.[3]
Do horses with pituitary pars intermedia dysfunction (PPID) develop HAL?	Yes, HAL is detected in approximately 30% of horses with PPID[4] and it is recommended that 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. The carbohydrate content in pasture can cause abnormally increased blood insulin concentrations in susceptible horses.
Is corticosteroid-associated laminitis the same as HAL?	The association between glucocorticoid administration and the subsequent development of laminitis is poorly defined. Corticosteroids should be used with caution in horses with endocrine diseases. If a horse develops laminitis after corticosteroid administration, the presence of an underlying endocrine disorder should be investigated.
Does the degree of lameness observed in an individual animal predict the amount of damage to the laminae of the feet?	In general, the answer is yes because horses with severe pain typically have the most łaminar damage. However, HAL can develop insidiously, and laminae 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 may 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 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 but full access to a large pasture is never recommended. The general recommendation is to reassess the horse by performing an oral sugar test (OST) and if negative results are obtained then reintroduce pasture access in a controlled fashion using strategies to limit grass intake including strip grazing or application of a grazing muzzle. Further measurements of insulin concentrations should then be taken following grazing to assess the insulinemic effect of the grass in the individual horse.

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.

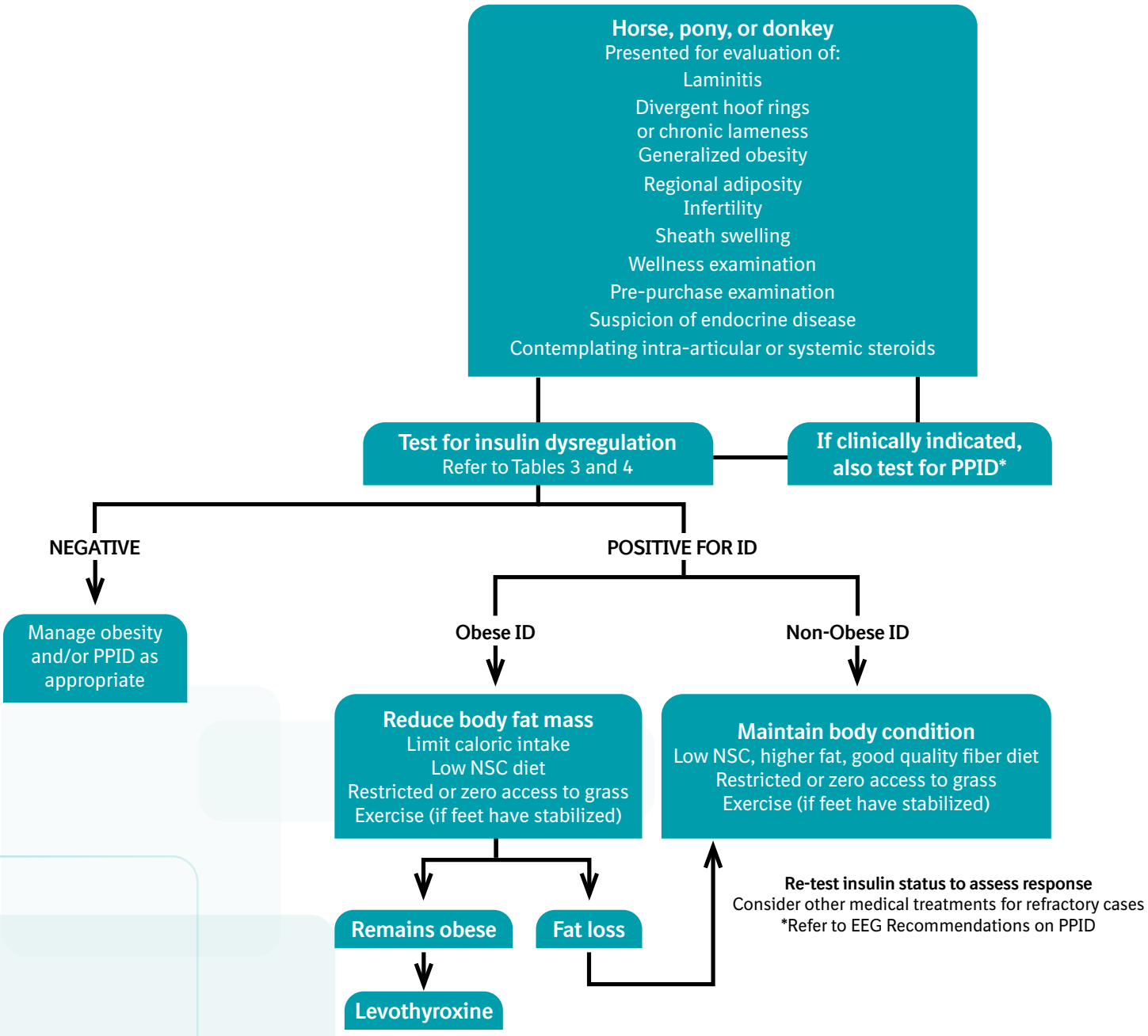
Figure 1 - Venn diagram showing the proposed overlaps among endocrine disorders discussed in these recommendations. Note that the area of each category within the diagram is purely illustrative and is not intended to be proportionate to the size of the population.



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

Figure 2 - Algorithm for the diagnosis and management of EMS

The following algorithm (Figure 2) outlines the recommended diagnostic and management pathways once ID is diagnosed in both groups of animals.



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Recommended approach for diagnostic testing

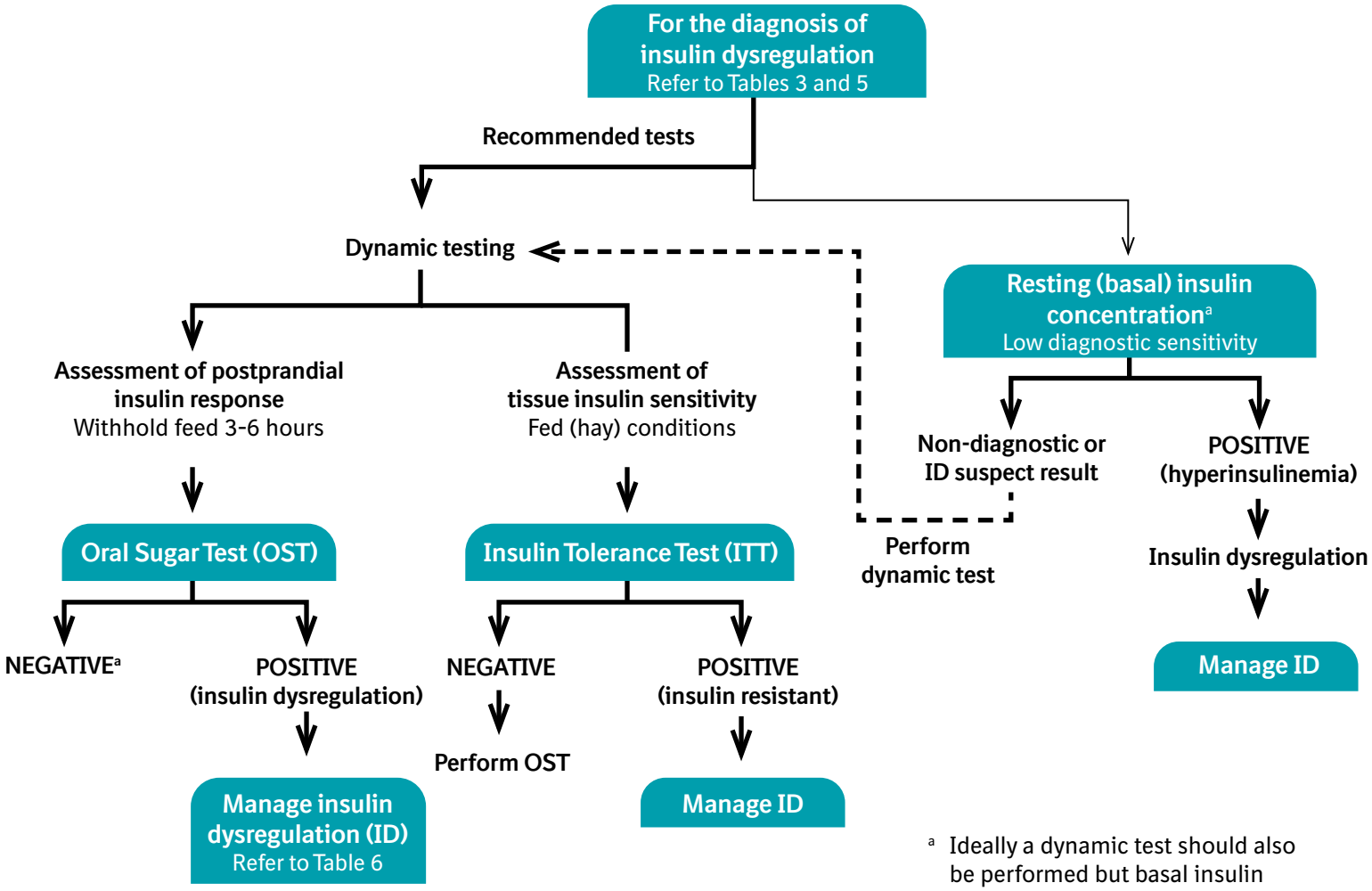
Sample handling & analysis

- 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 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 your 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.

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.
- *Oral sugar test*: 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 in test results. Fasting conditions are often achieved by the owner leaving one flake/slice of hay 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 clinically significant. Test performance is improved by administering 0.45 mL corn syrup/kg body weight instead of 0.15 mL corn syrup/kg,[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.
- *Insulin tolerance test*: 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 preliminary results are available on the farm.[6] Disadvantages include the cost of purchasing insulin and the risk of clinical hypoglycemia developing (although this is unlikely to occur in horses selected for testing on suspicion of ID). A small amount of grain may be fed to the horse or IV dextrose administered immediately after the 30-minute sample is collected to further mitigate hypoglycemia risk.
- *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 current diet (forage or pasture).
- *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 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.

Figure 3 - Algorithm for detection of insulin dysregulation



[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 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') Laminitis (subclinical or clinical) Cresty neck Subcutaneous adipose deposits Clinical problems may be historical or current	
LEAN MANIFESTATION OF EMS		
Genetically at-risk horse kept in controlled environment	Laminitis (subclinical or clinical) only	
EMS with PITUITARY PARS INTERMEDIA DYSFUNCTION (PPID)		
EMS may be historical Genetically at-risk horse that develops PPID (exacerbates insulin dysregulation)	**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] EMS is poorly characterized in donkeys because reference intervals for insulin tests are still being determined.

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Table 3 - Diagnostic testing: resting insulin concentrations

Resting (basal) insulin concentration		
Uses: Only use for identifying more severely affected animals (test has low sensitivity/high specificity) Convenience sampling		
Fasting samples are no longer recommended for the initial diagnosis but may provide additional information for horses with marked basal (fed) hyperinsulinemia. *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</u> (no grain) Do not feed grain within 4 hours Collect into serum or EDTA tube (check with laboratory)	<u>While on pasture</u> Used to assess insulin concentrations during grazing[b] (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[a]	Recommendation
< 20 µU/mL (RIA and Immulite 1000) < 31 µU/mL (Immulite 2000 xpi)	Non-diagnostic	Dynamic test recommended to better assess
20-50 µU/mL (RIA and Immulite 1000) 30-75 µU/mL (Immulite 2000 xpi)	ID suspect if consistent clinical signs	
> 50 µU/mL (RIA and Immulite 1000) > 75 µU/mL (Immulite 2000 xpi)	Insulin dysregulation	Proceed with ID management

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

[b] Values reflect the NSC content of the grass consumed at the time of testing.

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Table 4 - Dynamic insulin tests

	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 meal immediately after last sample
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. Provide feed after collecting the second blood sample. In rare cases, dextrose solution has been administered intravenously to address hypoglycemia.

[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).

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Table 5 - Additional tests for assessment of horses with equine metabolic syndrome

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.[8]
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
Glucose-dependent insulinotropic (poly)peptide (GIP) concentrations, 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.[9]

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Table 6 - Management recommendations for equine metabolic syndrome

Management and monitoring of EMS	
Obese (typical) EMS BCS 6-9/9	**Initial diet** Restrict or eliminate grazing and do not feed grain. For weight loss, feed grass hay with low NSC content in amounts equivalent to 1.5% of current body weight on an as-fed basis daily. Reassess body weight every 30 days using a weight scale or weight tape and gradually lower to a minimum of 1.2% of body weight as-fed if weight loss resistant. House in a dry-lot or small paddock with a companion. 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. 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** Restrict grazing and do not feed grain 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 expected when re-tested under similar conditions. An additional monitoring approach is to measure insulin concentrations on the current feed, with blood collected two hours after feeding. Soak hay (see 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 one hour of pasture grazing (see below). Pasture access should be reintroduced gradually and strategies to restrict grass intake include use of a grazing muzzle or strip grazing. 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 laminae, 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.[10] 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,[11] and these recommendations may be easier for owners of ponies and horses to achieve.

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Management and monitoring of EMS (continued)

Obese (typical) EMS
BCS 6-9/9
(continued)

Housing

Stress should be avoided, and the affected horse should ideally be housed in a small paddock with a companion, instead of being confined to a stall (once laminitis has been addressed). Take precautions to limit stereotypic behavior by using 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 repeating the OST or measuring fed 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 developing. If horses are not on pasture, collect blood 2 hours after hay feeding. For horses on pasture, allow one hour of grazing, remove the horse from the pasture and collect blood one hour 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.

Medical therapy

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

Available in the USA, but high cost restricts use in the UK or Europe. 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 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 and more glucose is 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 conducted in Australia with 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.[12,13] Velagliflozin is not available for purchase at present but two drugs in the same group, canagliflozin and ertugliflozin, are available. They are labeled for the treatment of diabetes mellitus in humans. Both of these drugs have been used with some success in a small number of horses with severe ID, but they are very expensive and should be 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 because of their size. Lipid mobilization is stimulated in many horses treated with SGLT2 inhibitors and hypertriglyceridemia may develop as a consequence. Thus, horses with marked hypertriglyceridemia should not be treated with these drugs.

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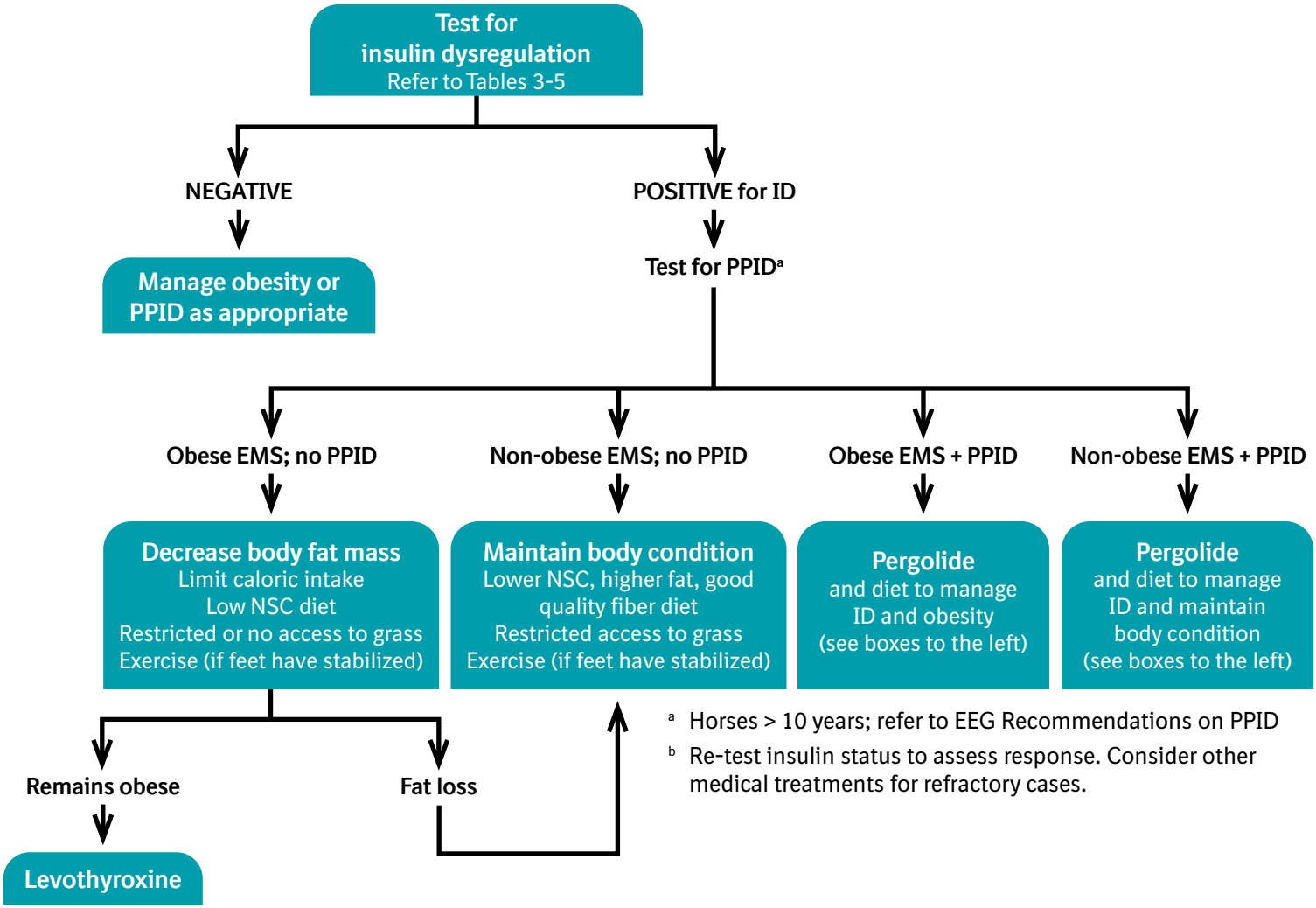
Management and monitoring of EMS (continued)	
Obese (typical) EMS BCS 6-9/9 (continued)	*Metformin hydrochloride* Indications: For animals with persistent hyperinsulinemia, even after management changes have been followed. Metformin is sometimes prescribed for the first two weeks when a horse is transitioned back to pasture to reduce the insulinemic response, but additional research is required to assess this approach. 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 because metformin does not improve insulin status in all cases. *Medical treatments in development* Thiazolidinediones (e.g. pioglitazone) have been evaluated as drugs for medically managing ID in horses. 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. **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.
Lean EMS BCS 4-5/9	Diet: Maintain on low-glycemic diet, with severity of restriction dependent on postprandial insulin response. Analyze NSC content of hay if severely affected. Provide 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: Levothyroxine not recommended, as weight loss is not required.
EMS with diagnosed PPID	Follow appropriate recommendations from above, depending upon body condition. Medical: Administer pergolide [Prascend® (pergolide tablets); Boehringer Ingelheim Animal Health USA Inc.); refer to EEG Recommendations on PPID.

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

Figure 4 - Algorithm for management of insulin dysregulation and pituitary pars intermedia dysfunction



[a] Horses > 10 years; refer to EEG Recommendations on PPID

[b] Re-test insulin status to assess response. Consider other medical treatments for refractory cases.

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Table 7 - Consideration of pituitary pars intermedia dysfunction (Cushing's Disease) 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.[14] The TRH stimulation test can also be performed just before the OST to combine these tests for PPID and ID, respectively.[15] 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 pergolide [Prascend® (pergolide tablets); Boehringer Ingelheim Animal Health USA Inc.] **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 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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References

Only key articles and publications released since the last set of recommendations are included:

1. Meier AD, de Laat MA, Reiche DB, et al. The oral glucose test predicts laminitis risk in ponies fed a diet high in nonstructural carbohydrates. *Domest Anim Endocrinol* 2018;63:1-9.
2. Asplin KE, Sillence MN, Pollitt CC, et al. Induction of laminitis by prolonged hyperinsulinaemia in clinically normal ponies. *Vet J* 2007;174:530-535.
3. Stokes SM, Bertin FR, Stefanovski D, et al. Lamellar energy metabolism and perfusion in the euglycaemic hyperinsulinaemic clamp model of equine laminitis. *Equine Vet J* 2020;52:577-584.
4. McGowan TW, Pinchbeck GP, McGowan CM. Prevalence, risk factors and clinical signs predictive for equine pituitary pars intermedia dysfunction in aged horses. *Equine Vet J* 2013;45:74-79.
5. Jocelyn NA, Harris PA, Menzies-Gow NJ. Effect of varying the dose of corn syrup on the insulin and glucose response to the oral sugar test. *Equine Vet J* 2018;50:836-841.
6. Bertin FR, Sojka-Kritchevsky JE. Comparison of a 2-step insulin-response test to conventional insulin-sensitivity testing in horses. *Domest Anim Endocrinol* 2013;44:19-25.
7. Lewis SL, Holl HM, Streeter C, et al. Genomewide association study reveals a risk locus for equine metabolic syndrome in the Arabian horse. *J Anim Sci* 2017;95:1071-1079.
8. Carter RA, Treiber KH, Geor RJ, et al. Prediction of incipient pasture-associated laminitis from hyperinsulinaemia, hyperleptinaemia and generalised and localised obesity in a cohort of ponies. *Equine Vet J* 2009;41:171-178.
9. Menzies-Gow NJ, Harris PA, Elliott J. Prospective cohort study evaluating risk factors for the development of pasture-associated laminitis in the United Kingdom. *Equine Vet J* 2017;49:300-306.
10. Durham AE, Frank N, McGowan CM, et al. ECEIM consensus statement on equine metabolic syndrome. *J Vet Intern Med* 2019;33:335-349.
11. Bamford NJ, Potter SJ, Baskerville CL, et al. Influence of dietary restriction and low-intensity exercise on weight loss and insulin sensitivity in obese equids. *J Vet Intern Med* 2019;33:280-286.
12. Meier A, Reiche D, de Laat M, et al. The sodium-glucose co-transporter 2 inhibitor velagliflozin reduces hyperinsulinemia and prevents laminitis in insulin-dysregulated ponies. *PLoS One* 2018;13:e0203655.
13. Meier A, de Laat M, Reiche D, et al. The efficacy and safety of velagliflozin over 16 weeks as a treatment for insulin dysregulation in ponies. *BMC Vet Res* 2019;15:65.
14. Horn R, Bertin FR. Evaluation of combined testing to simultaneously diagnose pituitary pars intermedia dysfunction and insulin dysregulation in horses. *J Vet Intern Med* 2019;33:2249-2256.
15. Hodge E, Kowalski A, Torcivia C, et al. Effect of thyrotropin-releasing hormone stimulation testing on the oral sugar test in horses when performed as a combined protocol. *J Vet Intern Med* 2019;33:2272-2279.

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