

2021 EQUINE ENDOCRINOLOGY GROUP

PITUITARY PARS INTERMEDIA DYSFUNCTION (PPID)

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 North American veterinary practitioners diagnose and manage equine endocrine disorders. Guidelines are updated every two years and can be found on the EEG website: <http://sites.tufts.edu/equineendogroup>.

Recommendations for the Diagnosis and Treatment of Pituitary Pars Intermedia Dysfunction (PPID)

Revised October 2021 by the PPID Working Group

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INTRODUCTION

Pituitary pars intermedia dysfunction (PPID) is a slowly progressive degenerative disease of hypothalamic dopaminergic neurons. Loss of dopaminergic inhibitory control of pars intermedia (PI) melanotropes leads to hyperplasia and adenoma formation in the PI. Melanotropes in the enlarged PI produce increased amounts of pro-opiomelanocortin, a large prohormone that is subsequently cleaved into smaller peptides, including adrenocorticotrophic hormone (ACTH). PPID is more common in older equids, with a documented prevalence of approximately 20% in equids 15 years and older. Disease prevalence increases to 30% in equids over 30 years of age. There is no apparent breed or sex predilection and the only documented risk factor for development of PPID is advancing age. Hypertrichosis, a long hair coat that often fails to shed, is essentially a pathognomonic clinical sign for PPID. However, PPID can be manifested by a constellation of other clinical signs/syndromes (Figures 1 and 2, Table 1); consequently, PPID should be considered as a potential contributing factor for many disorders in horses 15 years age or older.

Measurement of baseline ACTH concentration is a practical test for diagnosis of PPID, though variation in ACTH concentrations in individuals and over time results in some overlap in ACTH concentrations between normal and PPID populations. As ACTH concentrations increase in the autumn in healthy and PPID animals, interpretation of ACTH testing for PPID diagnosis requires seasonally adjusted values. We have revised our 2019 recommendations to refine this seasonal interpretation and expanded the equivocal zone (Table 2 and Figure 5) to maximize this test's ability to rule in or out PPID for animals with ACTH concentrations outside the equivocal zone. When baseline ACTH concentrations fall in this equivocal zone, veterinarians should use clinical information such as age and severity of signs to decide whether to monitor and re-test, follow-up with dynamic TRH stimulation testing, or in some cases, to treat (Figure 4). Because baseline ACTH is more likely to fall in the equivocal zone in early-stage disease, the TRH stimulation test may also be an appropriate first line test in many cases. PPID can also be accompanied by insulin dysregulation, increasing the risk of hyperinsulinemia-associated laminitis, so assessing insulin dynamics is recommended in concert with PPID testing (see Equine Endocrinology Group's Recommendations for Diagnosis and Treatment of Equine Metabolic Syndrome).

FIGURE 1 - Clinical signs and syndromes with PPID vary in affected equids



Pathognomonic Hypertrichosis



Loss of Topline Musculature



Hair Color Changes & Patchy Shedding



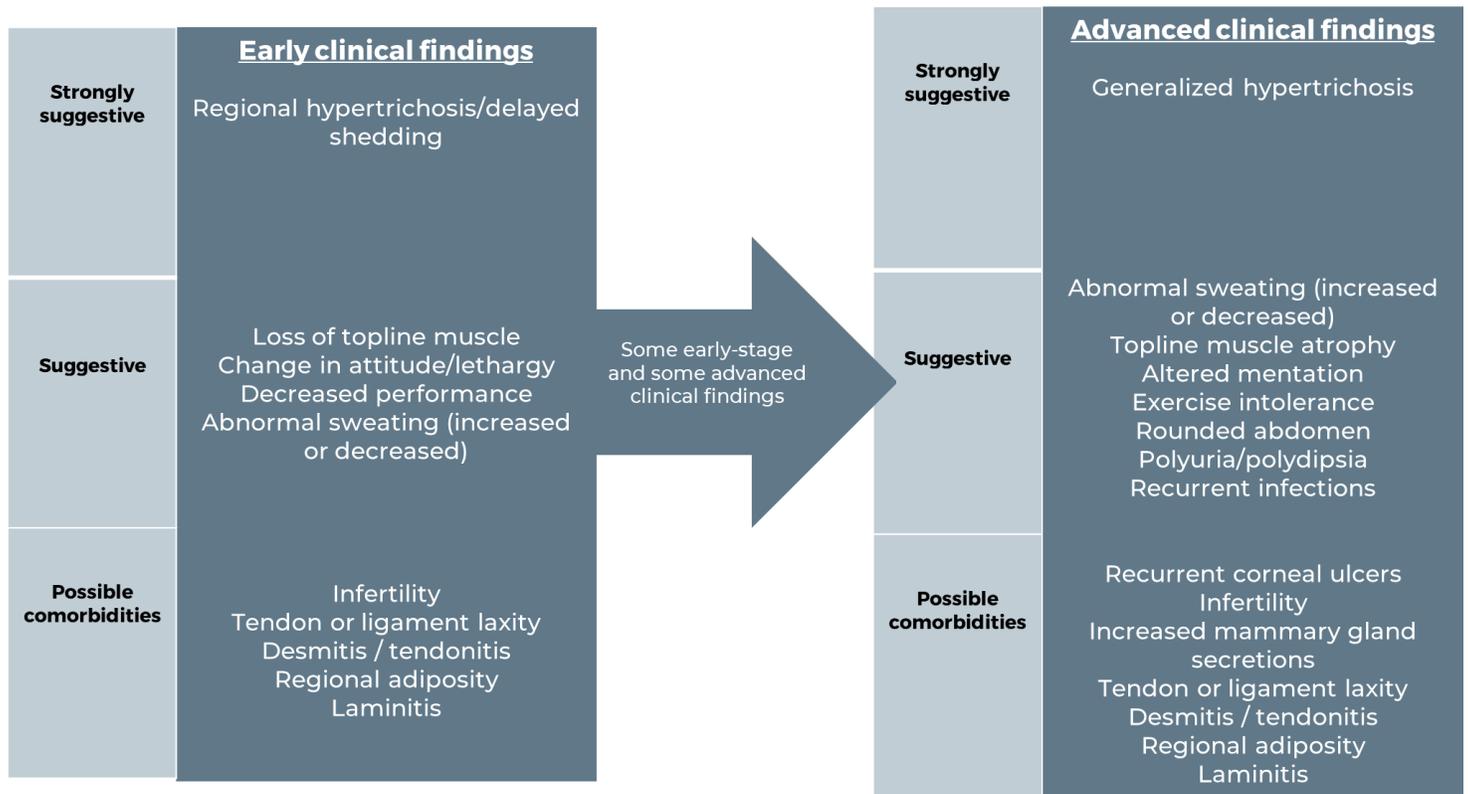
Suspensory Ligament Breakdown



Chronic Laminitis

Figure 2 – Clinical progression of PPID

**Note: affected animals may have only one, several or many of the listed signs*

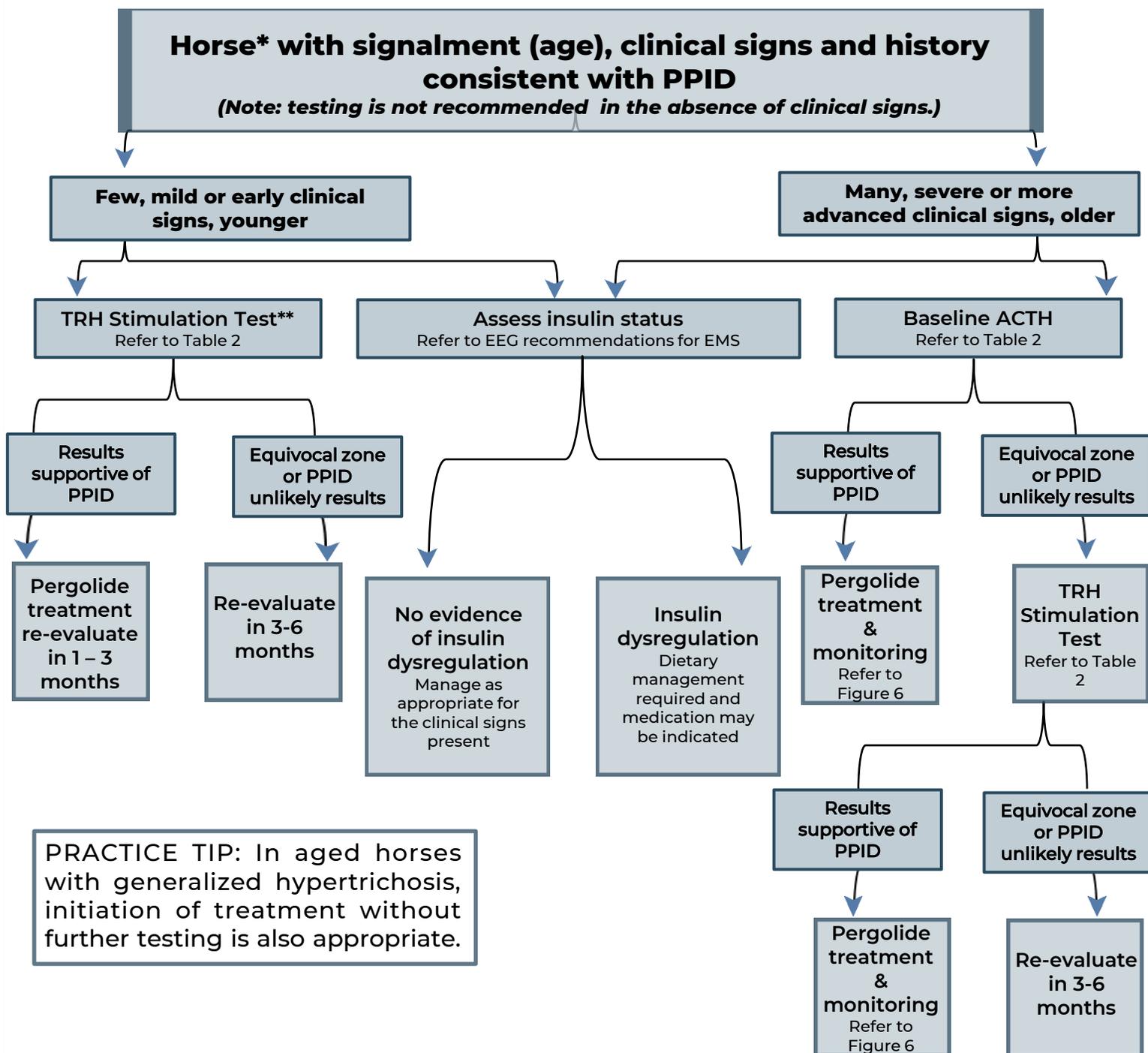


PRACTICE TIP: Increasing animal age and number of concurrent clinical signs increases the likelihood that these clinical signs are truly associated with PPID.

TABLE 1 - Laboratory findings that may accompany PPID

- Hyperglycemia
- Hyperinsulinemia
- Hypertriglyceridemia
- High fecal egg count

FIGURE 3 - Algorithm for the diagnosis and management of PPID



* At present this algorithm is largely based on data collected in horses but it can be applied to other equids (ponies, donkeys, and mules) until further data becomes available.

** The TRH stimulation test is recommended as a first line test for suspected early-stage PPID in North America. In locations where TRH is not readily available, or use is restricted, initial testing may begin with measurement of baseline ACTH concentration regardless of suspected disease stage. However, baseline ACTH is more likely to be non-supportive of PPID diagnosis in early-stage disease than TRH stimulation testing.

TABLE 2 - Baseline ACTH concentration and TRH stimulation test

Procedure for Baseline ACTH

- Collect into EDTA containing tube (purple top) at any time of the day
- Keep samples cool (ice packs or refrigerator) at all times
- Centrifuge and separate plasma prior to shipping
- Ship via overnight mail with ice packs
- Plasma can be frozen (centrifuged samples only) but avoid freeze-thaw cycles

Procedure for TRH stimulation test

- Horses can be tested after hay is fed, but not within 12 hours after a grain meal. Testing can be performed immediately before an oral sugar test (OST) but do not perform within 12 hours after an OST.
- Administer 0.5 mg (equids <250 kg) or 1.0 mg (equids >250 kg) of TRH intravenously. Side effects after administration are transient and include coughing, flehmen response, and yawning.
- Collect blood into EDTA containing tubes (purple top) at 0 and **exactly** 10 minutes after TRH administration.
- Submit plasma for measurement of ACTH as described above.

Seasonal interpretation of results * (Also refer to Figures 4 and 5)		PPID unlikely	Equivocal* <i>Requires strong clinical signs, re-testing, or TRH stim to confirm diagnosis</i>	PPID likely
Baseline ACTH or TRH time 0 (pg/ml) *see important note below	Dec - Jun	< 15 *	15 – 40*	> 40
	Jul & Nov	< 15 *	15 – 50*	> 50
	Aug	< 20 *	20 – 75*	> 75
	Sept-Oct	<30 *	30-90*	>90
10 min after TRH (pg/ml)	Jan – Jun	< 100	100 – 200	> 200
	Jul – Dec	< 100	TRH stimulation testing can only be used to identify negative cases in these months due to many false positives	

IMPORTANT NOTES:

- The analyzer used to measure ACTH has changed since the 2019 EEG recommendations were released, with the Immulite 2000XPI chemiluminescent immunoassay now used in many laboratories. ACTH values are lower with this method, so ACTH concentrations provided here have been adjusted accordingly.
- In addition, the equivocal zone for baseline ACTH has been expanded to maximize diagnostic accuracy outside of this zone, and to **emphasize the importance of assessing results in the context of the horse's clinical signs.**
 - Current data in a large group of animals with suspected PPID suggests that **approximately 25% of horses and ponies with PPID, particularly those of certain breeds, may have results that are in this equivocal zone;** a diagnosis of PPID is still appropriate in an aged animal when strong clinical signs are present. **Up to 30% of horses may have results that fall within the equivocal zone because of stress, breed, and other factors,** and are unlikely to have PPID if strong clinical signs are not present. Further study to refine these criteria in animals with and without confirmed PPID is needed.
 - Re-evaluation of baseline ACTH concentration in 3-6 months or follow-up TRH stimulation testing is recommended for most animals with results in the equivocal zone (see figure 4).
 - A board-certified internal medicine specialist should be consulted for complicated cases.

FIGURE 4 - Algorithm for interpretation of baseline ACTH concentrations

Baseline ACTH concentration

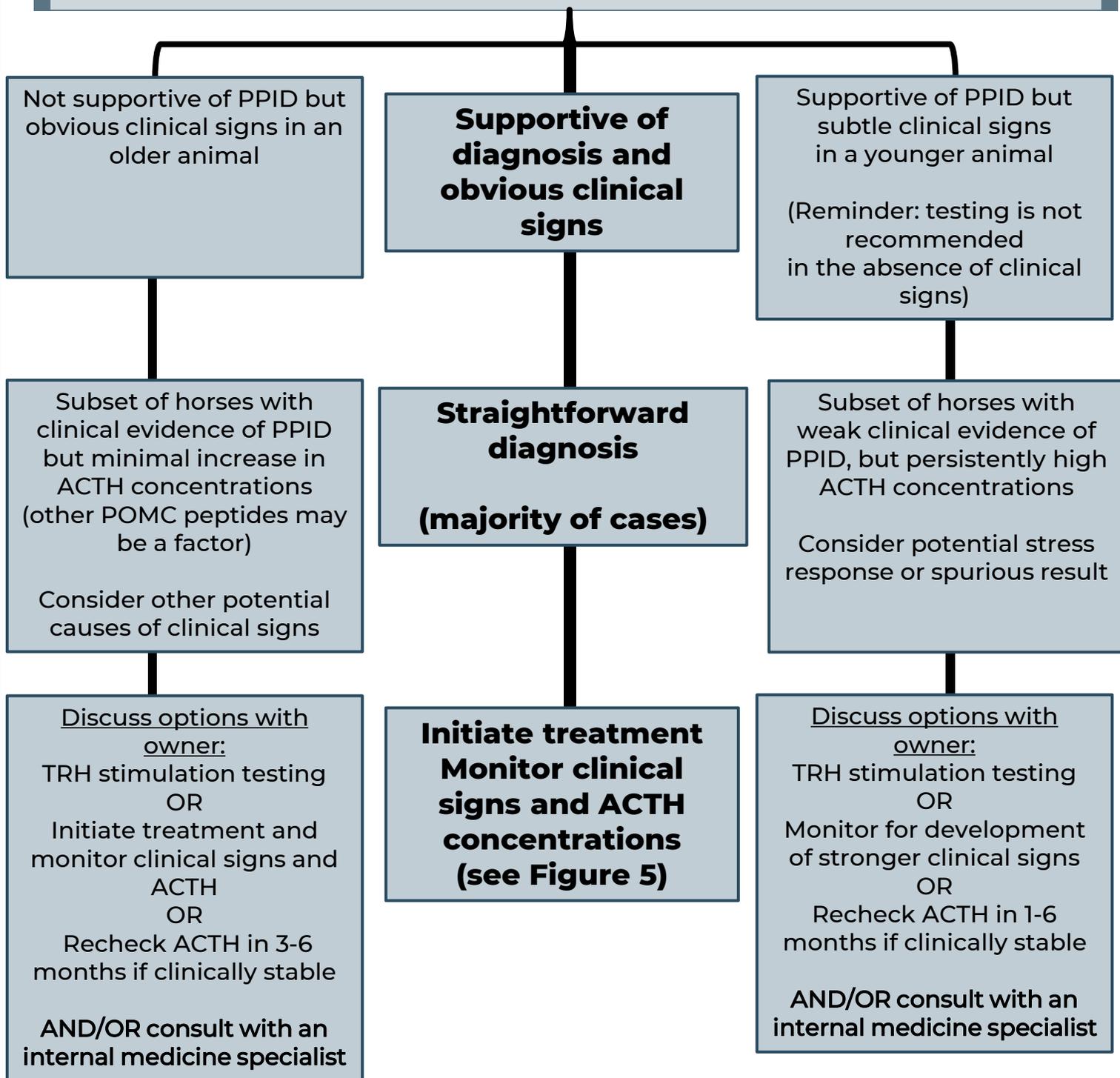
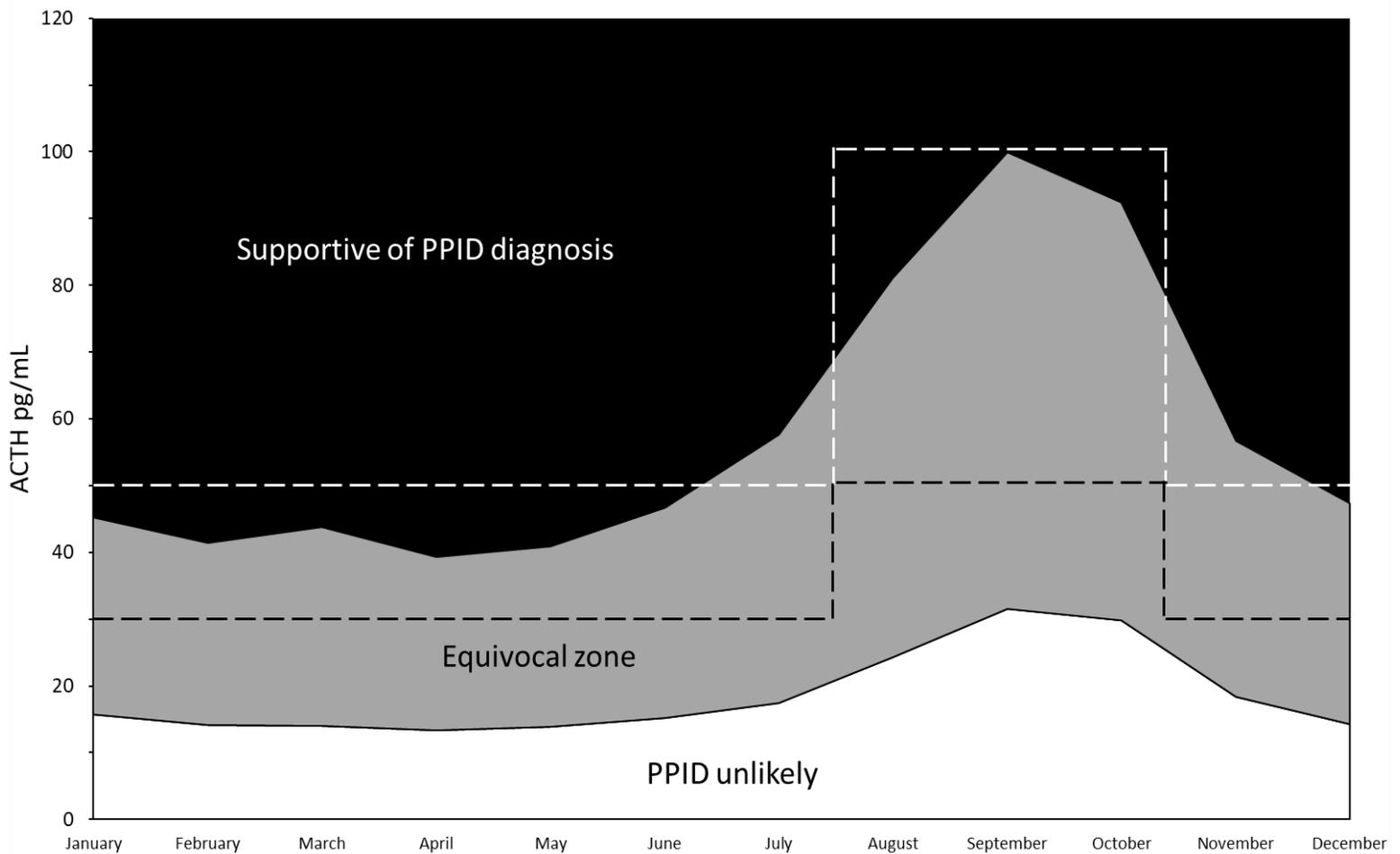


FIGURE 5 - Seasonal interpretation of baseline ACTH concentrations

Notes: ACTH values presented here were determined using the Immulite 2000xpi analyzer. ACTH concentrations falling in the black shaded area are supportive of PPID diagnosis, and those falling in the white shaded area suggest a PPID diagnosis is unlikely at that time. ACTH concentrations falling in the grey shaded area are in the equivocal zone, and require further interpretation based on the clinical picture. The dashed lines denote previous diagnostic cutoff values from the 2019 EEG recommendations (white dashed line = upper values, black dashed line = lower values).



ACTH concentrations throughout the year gradually increase from June to late September / early October, followed by a more rapid fall until December in the Northern hemisphere. ACTH concentrations should only be used to make a diagnosis of PPID in combination with clinical signs, especially when ACTH values fall within the equivocal zone. The equivocal zone is wider and lower than the 2019 recommendations, due to new data and the implementation of the Immulite 2000xpi analyzer in many labs.

TABLE 3 - Diagnostic tests for Pituitary Pars Intermedia Dysfunction (PPID)

RECOMMENDED TESTS

- **Early PPID:** TRH stimulation test with ACTH measured or baseline ACTH if TRH is not readily available
- **Moderate to advanced PPID:** Baseline ACTH concentration or TRH stimulation test with ACTH measured

OTHER POTENTIALLY SUPPORTIVE TESTS

- Overnight dexamethasone suppression test
- Magnetic resonance imaging (MRI) specific for pars intermedia enlargement

NO LONGER RECOMMENDED

- Oral domperidone challenge test
- Combined dexamethasone suppression/TRH stimulation test with cortisol measured

NOT APPROPRIATE FOR PPID DIAGNOSIS

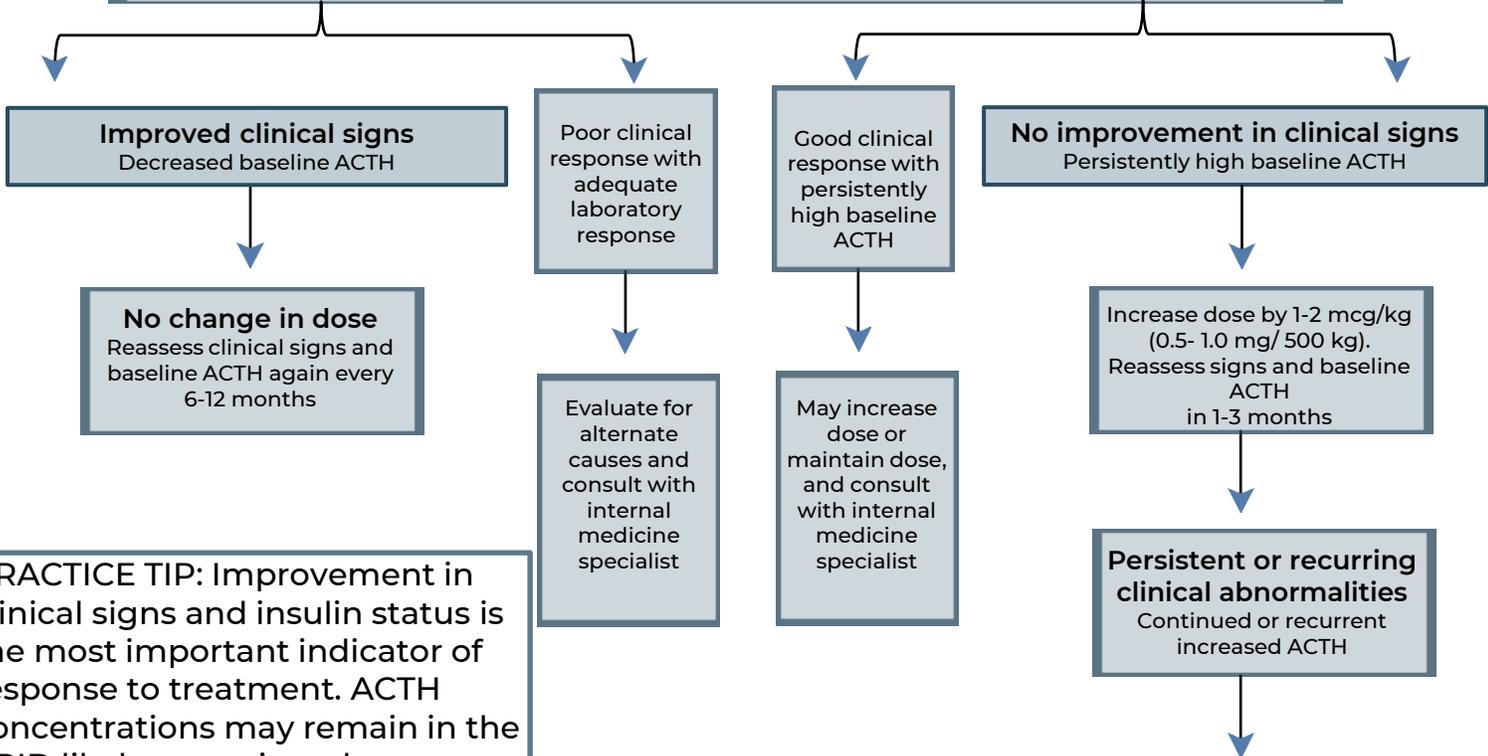
- ACTH stimulation test
- Baseline cortisol concentration
- Diurnal cortisol rhythm

Figure 6 - Treatment and monitoring of PPID

Initial treatment plan

The FDA-approved pergolide Prascend® (pergolide tablets); [Boehringer Ingelheim Animal Health, USA, Inc.] is recommended at an initial dosage of 2 mcg/kg (0.5 mg for a 250-kg pony and 1.0 mg for a 500 kg horse). The dosage is not to exceed 4 mcg/kg bodyweight once daily. Perform baseline diagnostic testing before starting treatment. Some horses show a transient reduction in appetite. To address this problem, stop treatment until appetite returns and or decrease by half for 3 to 5 days and then titrate back up in 0.5 -1mcg/kg increments every 2 weeks until the desired dose is achieved.

**Evaluate clinical signs and baseline ACTH
1-3 months after starting treatment, and then every 6-12 months**



PRACTICE TIP: Improvement in clinical signs and insulin status is the most important indicator of response to treatment. ACTH concentrations may remain in the PPID likely or equivocal zone despite clinical improvement, and do not always warrant a dosage increase.

Refractory case, consult with an internal medicine specialist

Strategies* used by the EEG for such cases include gradually increasing pergolide to 3 mg/500 kg/day (6 mcg/kg) and adding cyproheptadine (0.25 mg/kg PO BID or 0.5 mg/kg PO SID) OR gradually increasing pergolide to 5 mg/500 kg/day (10 mcg/kg).

*These dosages would be considered extra-label. The manufacturers recommendations are to administer orally at a starting dosage 2 mcg/kg once daily not to exceed 4 mcg/kg daily.

TABLE 4 - Other considerations for managing horses with PPID

Switching horses from compounded pergolide

It may be possible to reduce the dosage of pergolide when switching from compounded pergolide to Prascend® (pergolide tablets). First consider the current status of the horse. If PPID is well controlled, consider a lower dosage of PRASCEND (maximum recommended reduction of 50%). Retest the horse after 1 – 2 months (consider history and physical examination findings) to assess response to treatment.

Removing horses from pergolide treatment

In the event that a horse on pergolide treatment misses a dose or is removed from treatment for exhibition/competition, ACTH concentrations may begin to increase within 48 hours, but the risk of clinical signs worsening during this period is low. Drug clearance varies substantially among individual horses and can result in detectable drug levels for much longer than 48 hours in some animals.

Quality of Life

The majority of horses with PPID are aged and therefore susceptible to non-PPID conditions. Therefore, horse owners should be advised that while medical management of PPID improves quality of life, it does not necessarily prolong lifespan.

Wellness care

In addition to medical management, horses with PPID should receive regular wellness care. Special attention should be paid to body condition, hoof care, dentistry, and parasite control. Inadequately controlled PPID horses are also at risk for bacterial infections. Adequate water should be available if polydipsia and polyuria are persistent problems.

Diet and exercise recommendations

Feed selection should be based upon body condition score and evidence for insulin dysregulation. Some PPID horses are lean and have normal insulin status, and senior feeds and pasture grazing are appropriate in these cases. Obese horses should be fed a lower energy diet and be encouraged to follow an exercise program if soundness permits. Those with insulin dysregulation require lower non-structural carbohydrate feeds and limited access to pasture. Feed requirements of aged horses, especially those with PPID, may change over time and monthly monitoring of BCS by owners is recommended. Dietary supplements have also been suggested for the management of PPID, but to date scientific evidence for their efficacy is lacking.

TABLE 4 cont. - Other considerations for managing horses with PPID

Management of glucose, insulin, and lipid disorders

Assessment for insulin dysregulation should also be pursued in all patients with PPID (see Equine Endocrine Group Recommendations for Diagnosis and Management of Equine Metabolic Syndrome). Insulin dysregulation is detected in approximately one-third of cases and is most likely a result of PPID developing in equids genetically predisposed to EMS. Less commonly, diabetes mellitus develops in horses with PPID and is characterized by persistent hyperglycemia and glucosuria. Hypertriglyceridemia is detected in some horses, and blood lipid concentrations markedly increase if the animal enters negative energy balance. Pergolide treatment has been associated with improved glycemic control and normalization of blood triglyceride concentrations in some of these cases with positive effects often seen within 48-72 hours. Attention should also be paid to the horse's diet and access to pasture (see below).

Testing in the face of laminitis pain and other stress

Stress, excitement, and trailering can result in a transient increase in ACTH concentrations. Samples for PPID diagnosis via baseline ACTH should not be collected within 30 minutes of trailering, or in an animal that is visibly excited. Low to moderate pain of at least 24 hours duration does not appear to impact diagnostic testing with baseline ACTH or TRH stimulation testing. Testing may be performed in laminitic horses, but it is ideal to postpone until severe pain is controlled.

Testing after sedation

Sedation may impact endocrine responses. Diagnostic testing with baseline ACTH concentration only can be performed immediately (within 5-10 minutes) after sedation with xylazine or detomidine, with or without butorphanol, without substantial impact on the test interpretation. TRH stimulation testing and assessment of insulin status are impacted by sedation for at least several hours. Thus, it is ideal to avoid diagnostic testing for PPID and insulin status within 24-48 hours of sedation.

TABLE 5. – Suggested further reading

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