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7 KEY FACTS ABOUT PPID

Research advances have expanded understanding of pituitary pars intermedia dysfunction and yielded improved treatments.

If you've been involved with horses for even just a few years, chances are you've encountered at least one with pituitary pars intermedia dysfunction (PPID). Also known as Cushing's disease, this endocrine disorder is common in older horses. In fact, studies estimate that 20 percent of horses over the age of 15 will develop PPID. Add in the fact that horses are living longer than ever before and it's not surprising that most of us have some familiarity with the disorder.

The prevalence of PPID has made it a focus of research efforts. Almost 150 scientific papers on the topic have been published in the past decade alone, a body of work that has yielded significant advances in PPID diagnosis and management. While some equine diseases remain stubborn mysteries, more is understood about PPID with each passing year. Researchers and veterinarians have been eager to disseminate this knowledge through one-on-one conversations, internet groups and publications. All of which makes it easier than ever before to learn the basics of PPID and implement a strategy to keep an affected horse healthy for years.

All this information can feel a bit overwhelming, however. To help summarize the key facts about PPID, we've



turned to Nicholas Frank, DVM, PhD, DACVIM, of Tufts University, one of the world's leading experts on PPID, and Janice E. Kritchevsky, VMD, MS, a professor at Purdue who has been studying PPID in horses for many years. Both veterinarians are members of the Equine Endocrinology Group that reviews all research and collaborates to produce information about PPID for veterinarians.

1. PPID is common but not inevitable

"It is not a given that all old horses get PPID," says Frank. "We do know that the older they get, the more likely it is for PPID to develop, but there are some old horses that never go on to develop PPID."

Why it develops in certain horses and not others is a difficult question to answer, Frank continues. "The way it develops is through oxidative damage to neurons in the brain that go down to the pituitary gland. This seems to happen at a faster rate in some horses and is similar to Parkinson's disease in people. There may be some genetic factors."

Kritchevsky agrees there is a possibility of a genetic component, but the association between breed and PPID may be complex. "Some horses and breeds seem a little more prone to PPID," she says. "Some family lines seem to get PPID at a young age, so there is no doubt there is a genetic component—which is true for most problems," she says.

"It's also more common in Morgans and ponies, but this may be partly

because they tend to be the breeds that live the longest," says Kritchevsky. "I don't think I've ever seen a 30-year-old Belgian [with PPID], for instance. But this makes PPID more challenging to sort out."

2. Management may play a role in PPID incidence

How a horse is kept may influence his PPID risk, says Kritchevsky. "What starts it all is oxidative injury to the brain. Nerve cells from the hypothalamus send signals to the pars intermedia. Oxidative injury kills those nerve cells off, and when that happens the cells in the pars intermedia are no longer inhibited and they begin secreting too much

RESEARCH UPDATE

Keys to successful PPID management

A retrospective study from Australia confirms that horses with pituitary pars intermedia dysfunction (PPID, Cushings) are likely to live longer if treated with the drug pergolide and managed to maintain good body condition.

For the study—a joint project conducted by eight institutions including the universities of Queensland, Adelaide and Melbourne and Murdoch University—researchers analyzed the medical records of 274 horses and ponies from across the island nation. The goal of the research was to determine how clinical features of the PPID differed by geographic locations and to identify factors associated with survival.

Where the information was available, researchers examined radiographs to determine if the horses had laminitis and reviewed laboratory reports from tests for insulin resistance. Nearly 90 percent of the horses tested, across all locations, had some degree of laminitis and 76.5 percent had evidence of insulin dysregulation. In addition, the researchers found that, not surprisingly, horses with PPID in lower latitudes with a hotter climates were more likely to have anhidrosis and polydipsia (increased thirst).

In reviewing the case histories of animals that survived for multiple years, the researchers identified certain common traits. Ponies were more likely to survive, as were animals with a healthy body condition and those who were maintained on the drug pergolide. The researchers conclude that "adequate body condition and administration of pergolide are fundamental in PPID management." The researchers also conclude that in horses with PPID, insulin dysregulation needs to be investigated. — *François-René Bertin, DVM, MS, PhD,*

Reference: "Factors associated with survival, laminitis and insulin dysregulation in horses diagnosed with equine pituitary pars intermedia dysfunction," *Equine Veterinary Journal*, 2018





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hormone. If we can minimize oxidative injury, this would help.”

Frank agrees that oxidative injury may be a key consideration in prevention. “Regarding why it develops in some animals—in addition to the genetics—since it is oxidative damage, we sometimes wonder if these animals have not received as many antioxidants through their life,” says Frank.

“Providing adequate vitamin E in the diet is a recommendation for all horses and may be particularly important if we want to try to decrease risk of PPID,” he says. “We recommend that all horses receive this vitamin in a multi-vitamin supplement, and in older horses we recommend providing additional vitamin E as a specific supplement. We always suggest vitamin E if we are trying to lower the risk of PPID. There are no studies saying it prevents PPID from occurring, but it may help, and certainly does no harm,” he says.

Horses naturally get vitamin E from grass and green forage. If they are on pasture for much of the year, this would supply all they need. “If they can’t be

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AT A GLANCE: PITUITARY PARS INTERMEDIA DYSFUNCTION (PPID)

WHAT IT IS: Also known as Cushing’s disease, PPID is caused by an enlarged and overactive pituitary gland producing excess levels of adrenocorticotrophic hormone (ACTH). These elevated ACTH levels, in turn, lead to overproduction of the steroid hormone cortisol. What causes PPID to occur is still unclear, but it’s common in older horses: One study found that 85 percent of veterinarians are caring for at least one horse with PPID.

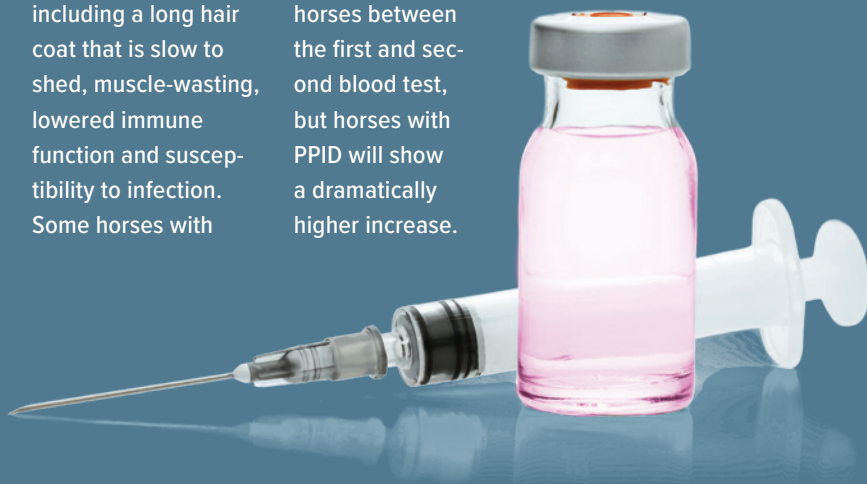
SIGNS: Excess hormones cause a slew of systemic signs, including a long hair coat that is slow to shed, muscle-wasting, lowered immune function and susceptibility to infection. Some horses with

PPID are also prone to slow-onset chronic laminitis that can go undetected until hoof structures have been irreversibly damaged.

DIAGNOSIS: In addition to clinical signs, veterinarians utilize two laboratory tests to diagnose PPID. The first is a blood test to measure resting levels of ACTH. The second is the thyrotropin-releasing hormone stimulation test (TRH stimulation test), which involves taking a blood sample, giving an injection of TRH, and then collecting a blood sample again 10 minutes later. ACTH will increase in all horses between the first and second blood test, but horses with PPID will show a dramatically higher increase.

Because of natural seasonal and geographic fluctuations in ACTH, veterinarians will use published reference ranges to interpret laboratory results.

TREATMENT: PPID can be controlled with the medication pergolide, sold under the brand name Prascend. Pergolide works by binding with receptors in the brain that normally respond to dopamine, decreasing the blood levels of ACTH. The medication is given daily and is considered very effective in reducing the signs of PPID.



Daily management plays a key role in supporting soundness when horses are challenged by equine metabolic syndrome (EMS) or Cushing's disease (PPID). A combination of proper nutrition, adequate exercise and safe turnout, along with the right combination of medications, works together to reduce the risk of laminitis.

DIETARY ADJUSTMENTS

- Pasture should be eliminated or severely restricted by using a grazing muzzle. Pasture is particularly dangerous in the spring and the fall in areas where cool-season grasses flourish.
- Avoid high-starch and high-sugar feeds and treats. Choose feeds with a nonstructural carbohydrate (NSC) level of 10% or less.
- Limit dietary NSC in forage to 12% or less. 10% is optimal, particularly in horses with a history of laminitis. There are several specialized hay chaff and hay cube products on the market that meet this criterion. Long hay should be tested before feeding to determine NSC levels.
- Soak hay that is above 10% NSC to reduce sugar content. Completely submerge hay for 60 minutes in cold water or 30 minutes in hot water. Drain well before feeding.
- In overweight horses, to encourage weight loss, slowly reduce forage intake from 1.5% to 1.25% of ideal body weight over 30 days. Do not feed less than 1% of ideal body weight. Once ideal weight is attained, increase level fed to 1.5% to 2% of ideal body weight. Sudden feed restrictions should be avoided.

MANAGEMENT TIPS FOR HORSES WITH EMS AND PPID



- If additional calories are needed once optimal forage intake is achieved, supply fortified concentrates that are 10% or less NSC.

EXERCISE

Adequate exercise is important. Physical exercise has been shown to reduce insulin resistance by assisting in weight management. Horses that are sound should be exercised on a routine basis. Caution must be used with laminitic horses; exercise should be restricted until the horse is sound and then be introduced slowly to protect damaged laminae.

SUPPLEMENTS

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GETTY IMAGES

on pasture for various reasons, such as equine metabolic syndrome and an associated predisposition to grass founder, a vitamin E supplementation is definitely recommended. Those are factors we can do something about, but even keeping a horse on a vitamin E supplement his whole life does not stop PPID from happening. There are still the genetic influences that lead to some horses developing it,” he explains.

Good care, good feed and preventive care are best management practices, agrees Kritchevsky, but even with those in place a horse who lives long enough may still develop PPID. “In a way, PPID is a good problem to have because it means that your horse has lived to an old age,” she says.

3. PPID signs can vary among different horses

“One of the reasons we see different signs with PPID is that when there is

One of the reasons we see different signs with PPID is that when small pituitary gland tumors develop, multiple hormones are released.

development of small pituitary tumors, they are sending out multiple hormones,” says Frank.

One of these hormones is adrenocorticotrophic hormone (ACTH), which plays an important role by stimulating the production of cortisol in the adrenal glands. Cortisol is a hormone that is important for regulating glucose, protein and lipid metabolism. It also suppresses immune system responses and helps maintain blood pressure. “When you consider cortisol and its effects throughout the body,

this provides some of the explanation as to why we see so many different systems affected in PPID,” says Frank.

It’s not just ACTH and cortisol at work, however. “We can measure the ACTH, but there are other hormones being secreted from these tumors as well,” Frank continues. “Multiple hormones can lead to different body systems being affected.”

For instance, the heavy hair coat seen in PPID horses may be due to an increase in alpha-MSH (alpha-melanocyte-stimulating hormone) in addition to the increased ACTH. “This [increase in alpha-MSH] is part of what goes on in the fall when horses start growing their winter hair coat. This is also linked to the long hair coat not shedding. The hair is not just long, but is often curly and matted. It may also be a bit greasy; the hair is abnormal,” says Kritchevsky.

This classic PPID sign is seasonal and develops gradually, which means it can go unnoticed and delay diagnosis. “The average age of diagnosis with PPID based on a long hair coat is 25, but when you look for changes in the horse’s hormones,

the average age is 15. This is one of the frustrating things about this syndrome—the insidious onset.”

Some PPID horses don’t have a long hair coat. “Any horse older than 10 that has any of these other signs—like laminitis and you can’t figure out why, or has hoof abscesses that won’t resolve, or seems to have various unexplained issues, should be tested for PPID—even if they don’t have the long hair coat,” says

Kritchevsky. “Often that situation comes fairly late in the game.”

Beyond hormone fluctuations, physical changes in the horse can also account for some of the signs of PPID, such as the horse drinking more. “One of the reasons for excess drinking may be the fact that as the tumor in the pituitary gets bigger, other parts of the pituitary are compressed, and one of them is the part that regulates thirst,” Kritchevsky explains.

4. Different tests can diagnose PPID, depending on the circumstances

“We use two tests to identify PPID in a horse,” says Frank. “One is a measure of the resting or ‘basal’ ACTH concentration. This is very straightforward and involves taking a blood sample and measuring the ACTH concentration. The second test is the thyrotropin-releasing hormone stimulation test (TRH stimulation test),” says Frank. “This involves injection of TRH and collection of a blood sample 10 minutes later. Because we are stimulating the endocrine system, we see the ACTH go up in all horses, but in a horse that’s developing PPID we see a higher increase in the ACTH.”

Which test a veterinarian chooses will depend on severity of clinical signs. “If we see obvious clinical signs that suggest the horse has moderate or advanced PPID, we take blood and check the resting ACTH,” says Frank. “It will be increased, confirming the diagnosis. The challenge arises when we are dealing with a horse that has early clinical signs—which are very subtle—the resting ACTH test is not sensitive enough to pick up on this disease in the early stages,” he says. “In these cases we need a test that will stimulate the system, so that we can then see when a horse is developing PPID even in the earliest stages. That’s when we use the TRH stimulation test.”

Diagnosis, then, requires a consideration of clinical signs as well as laboratory reports. “The first determination a veterinarian makes is what stage of the disease they think they are looking at,” explains Frank. “If it’s early, they have to consider using the TRH stimulation test, whereas if it’s more advanced the veterinarian



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PPID DIAGNOSTIC TECHNIQUE ADVANCES

Year-round diagnosis of pituitary pars intermedia dysfunction (PPID, also known as Cushing's) just got easier, thanks to the joint efforts of equine researchers in England and mathematicians in Australia.

Caused by an enlarged and overactive pituitary gland, PPID is characterized by overproduction of adrenocorticotrophic hormone (ACTH). This hormonal imbalance can lead to a slew of complications, including a long-haired, slow-to-shed coat, muscle weakness and compromised immunity. PPID also increases susceptibility to laminitis. Although typically found in horses 15 years old or older, PPID can also occur earlier in life.

PPID diagnosis usually requires tests that measure the ACTH levels in a horse's blood. These levels naturally fluctuate by season, however, which can make interpreting results difficult. "The pituitary gland controls several processes that are seasonally variable—such as reproductive hormones," explains Andy

E. Durham BVSc,

MRCVS, of the Liphook Equine Hospital in England. "Exactly why the pars intermedia (a specific areas of the pituitary gland) changes activity through the year is not understood. It might be that this is a process that has simply remained during evolution and is of no value or benefit to the horse."

Because ACTH levels are naturally elevated in the autumn, veterinarians used to avoid testing horses for PPID at that time of year. Eventually, more research led to a better understanding of seasonal changes and testing year-round became feasible, though week-to-week fluctuations in hormone levels still complicate the process. Clinicians must weigh the horse's clinical signs and the test results in making a diagnosis.

To provide clinicians with more accurate baselines, Durham and his team gathered information on ACTH testing in 75,892 horses from across the United Kingdom over a four-year period. In addition to the test results and the exact date the blood was drawn, information from each case included whether the horse had high or low probability of PPID based on clinical signs. An older, laminitic horse with a non-shedding coat, for instance, would fall into "high suspicion" of having PPID group.

All of the data was then sent to a team of mathematicians at Murdoch University in Australia for a series of statistical calculations. "The mathematics part is essentially a rather clever method of examining a lot of ACTH data, some from normal horses and some from horses with PPID, and then working out the numerical characteristics--means and

standard deviations---of the two different populations, allowing them to be separated out," says Durham. "The big advantage of this method is that you don't have to rely on clinical examination to decide whether they have PPID—the math can do this."

The statistical model ultimately yielded weekly thresholds---ranges of normal ACTH readings---for each week of the year. With this information, available online through the published paper, veterinarians can make more accurate PPID diagnoses generally, and especially during times of the year when ACTH levels naturally rise. A comparison of the thresholds generated by the calculations to clinical descriptions of the study horses confirmed that the mathematical method was accurate, says Durham.

"Apart from a different way of determining thresholds for diagnosis, the other novel thing that we did was present different thresholds for different scenarios," says Durham. "Where there is a very strong clinical suspicion of PPID (for instance, an elderly, hairy, laminitic horse) then it is valid to use the lower threshold, and where it is a highly speculative test it is best to use the higher threshold. For most scenarios somewhere between the two the balanced threshold can be applied."

Although the study was based on ACTH levels among horses in England, Durham says the findings should be applicable to those in the United States as well. "There is some debate about a possible small effect of higher or lower latitudes on ACTH values, although the timing would not differ. I seriously doubt that would have much, if any, effect."

Reference: "Clinically and temporally specific diagnostic thresholds for plasma ACTH in the horse," Equine Veterinary Journal, May 2020



would just check the resting ACTH, which is the easier test.”

An important consideration with both tests is the time of year at which they were performed. Horses have natural fluctuations in their ACTH levels, depending on the season and geographic location. These fluctuations can lead to false negative and false positive results. There was a time when veterinarians did not recommend testing horses during the fall months because of difficulty interpreting the results, but research has led to the development of “reference ranges” for different times of the year and locations. This data can be used to determine if a horse’s ACTH levels are within normal ranges for that particular time and place.

5. Pergolide is the primary PPID medication but supplemental measures may help

Pergolide, sold under the name Prascend, is the only drug approved by the FDA to treat PPID in horses. It has been scientifically proven safe and effective and is the first line of treatment in nearly all cases. “How well pergolide controls PPID depends upon the stage of the disease,” says Frank. “If we are diagnosing it early—and the signs are mild—we expect a very good response to pergolide. The horse may even return to a normal appearance, and the clinical signs go away.”

Sometimes, however, a second medication is called for. “The experience we’ve had in treating PPID has shown that pergolide is the most effective—so it is the drug that is recommended,” says Frank. “There are times, however, with the more severely affected horses, that we will have



Pergolide is the most effective treatment for PPID, but managing affected horses requires looking beyond the medicine chest.

increased the dosage of pergolide, and have come to a point where we will add cyproheptadine (a serotonin receptor antagonist) as a second, additional treatment. We give both drugs at the same time. In these situations we are generally giving the horse 3 milligrams (3 tablets) of pergolide daily and add the cyproheptadine to try to get additional improvement.”

Even while using both drugs, the improvement in the horse may be limited. “If the horse has moderate or advanced disease we are usually looking at simply being able to reduce the severity of the clinical signs, since we may not be able

to resolve them,” says Frank. “The horse probably can’t return back to normal but will be improved.”

He adds that there are some supplements that sometimes help horses with PPID but should not be used in place of pergolide. “The most common supplement used in PPID horses is chasteberry, which is a natural supplement that’s been shown to help improve some of the clinical signs of PPID. It is not recommended to replace pergolide but can be given in addition. The supplement I recommend for all horses with PPID is vitamin E.”

Kritchevsky says that its possible improvements seen in PPID horses given supplements are a result of care by an attentive owner, not the supplement itself. “There are other treatments/supplements that some people use and talk about, but none have been shown in research studies to actually help,” she says. “I have seen some of these PPID horses that simply received good care after their diagnosis, and they got much better. Sometimes other treatments/supplements get the credit for the improvement, when in fact it was simply due to good management.”

6. Management is important to keeping PPID horses healthy and happy

Pergolide is the most effective treatment for PPID, but managing affected horses requires looking beyond the medicine chest. “You can’t just put them on a pill and forget about them,” says Kritchevsky. “The drug does prevent some of the effects but it doesn’t change the underlying immune problems. The horse will still be vulnerable to infections, for instance, compared to a normal horse.

You definitely want to keep up nutrition, parasite control, vaccinations and special hoof care.”

Diet can be the most complex management challenge in PPID horses because of the condition’s association with insulin dysregulation and related laminitis risk.

“In terms of management changes, the big one is diet,” says Frank. “We know that some horses with PPID already have insulin dysregulation and the PPID can make it worse. We must work out whether the horse has insulin dysregulation or not, though, before we make any recommendation in terms of diet. We encourage all veterinarians who are managing horses with PPID to check their insulin status. This is particularly important in old horses.”

Senior feeds can be an excellent source of additional calories PPID horses may need, but increasing feed in a horse with insulin dysregulation can be risky. “If [the horse] has problems with insulin dysregulation, we need to provide the calories, but be cautious with the amount of sugars in the diet,” says Frank. “We can’t determine the best recommendation until we know the insulin status. Information about the insulin status will also determine whether the horse can go out on pasture and how much grass it has access to.”

Parasite control is also important in PPID horses. “We know that horses with untreated PPID or advanced PPID—those are cases that are only responding partially to treatment—may have higher numbers of parasites,” says Frank. “Their immune system is impaired. We sometimes see roundworms in older horses with PPID, and we normally don’t see

round-worms except in foals and yearlings. So it is important in managing horses with PPID to have regular fecal egg counts done to see what the parasite burden is, and address that as needed.” Lowered immune function also means horses with PPID will need to stay current on their vaccinations.

7. PPID horses require regular monitoring

“Once a horse is on pergolide, your veterinarian should check hormone levels every six months or so, just to make sure everything is ok,” says Kritchevsky. “If a horse has chronic laminitis, this is what people tend to use as a guide: If the laminitis is under control and the horse is comfortable, we figure the horse is doing ok. If the laminitis flares up again, then it’s time to re-evaluate and look at what is going on.”

There are other, less dramatic, signs a PPID horse may need his medication

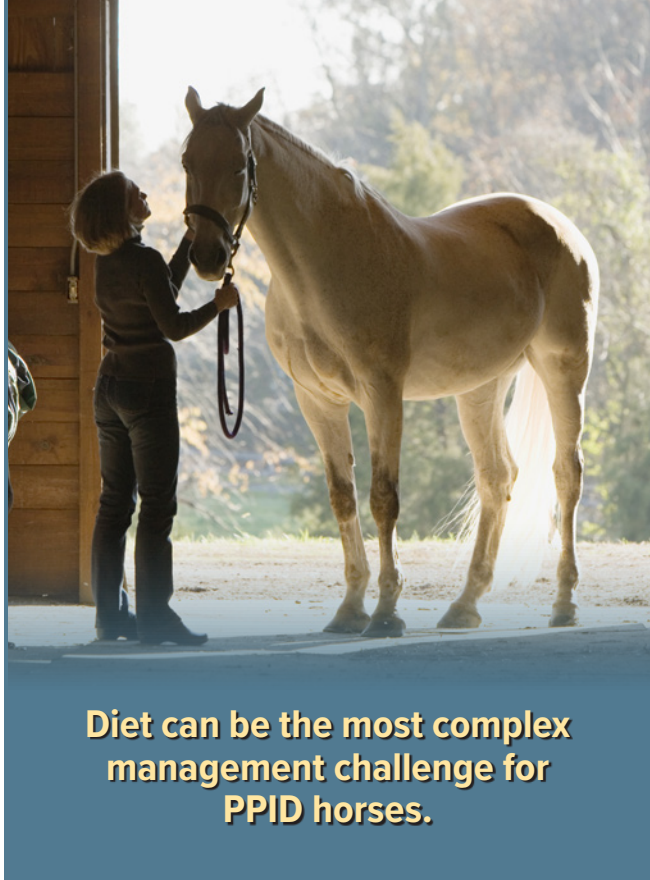
adjusted. “Horse owners who are very attuned to their horses might notice that the horse is beginning to look duller again, and more lethargic—spending more time sleeping,” says Frank. “We sometimes see the horse beginning to lose muscle mass again, and the hair coat will grow longer again. If the horse is urinating more frequently, and drinking more, this is also a sign that the treatment dose is not high enough.”

Blood tests to check for insulin levels can also indicate the efficacy of ongoing PPID treatment. “If we are dealing with a PPID horse who also has insulin dys-

regulation, and we’ve got that down to a reasonable level by treating the horse’s PPID with pergolide, we can do an insulin check. If it has gone up again, this would suggest that control of this disease is slipping and we need to increase the dose of pergolide.”

Frank says such checks can be done every six to 12 months, with associated recalibrations. “It’s not a simple regular dosing increase; there is no formula,” he says. “We can’t just tell people to increase it by half a tablet every 2 years. It must be case by case, based on the clinical signs and test results.”

PPID is a serious diagnosis but not a devastating one. With proper medication and management, most horses with the condition can live long, comfortable lives. But that doesn’t mean questions won’t arise. When they do, consult with your veterinarian for the latest information—because as research into PPID continues, our collective understanding of the condition is going to advance even further. 🐾



Diet can be the most complex management challenge for PPID horses.

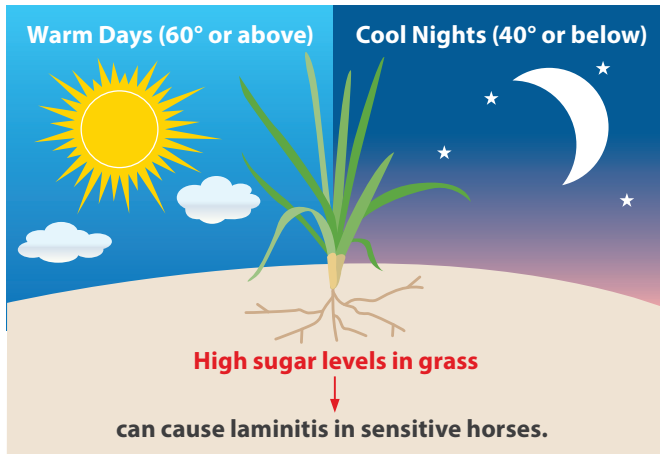
Spring Turnout Tips for Sugar-Sensitive Horses

It is that time of the year—the cold, gray winter is transforming into a warm, sunny spring and the grass is starting to grow! For normal horses, the spring grass is a lovely change from hay, but for sugar-sensitive horses it is a dangerous time of year.

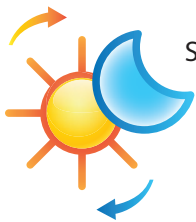
Things to know about spring grass

Sugar levels in the leaves of grasses increase dramatically during the spring growing season when days are sunny and warm, and the nights are cool.

Why? Because grass does not grow on cool nights (40° degrees or below), so high concentrations of sugar remain in the leaves instead of being used to fuel growth of stems and roots.



Grazing Strategies



Stop grazing completely when days are warm and nights are cold (40° F or less).



Limit intake with a muzzle and graze in the early morning when days and nights are warm.

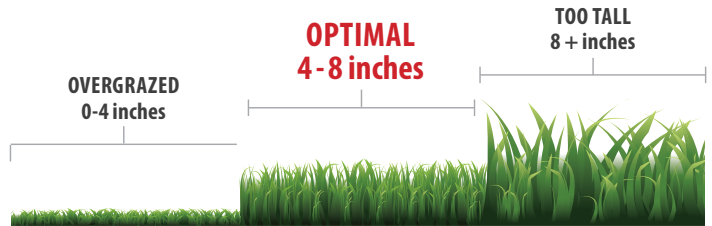
Stop grazing when grasses are under stress. ➡



Utilize a dry lot for horses that can't be turned out at all.



Overgrazing stresses grasses and increases sugar levels. Keep pastures between four to eight inches in height to reduce overgrazing stress.



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