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Practical Surgical Advances in the Performance Horse: Part I
Diagnosis

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Take Home Message: Advanced diagnostic imaging modalities used alone or in combination allow for more precise diagnoses for common causes of lameness or poor performance in equine athletes. Corresponding and presenting author: Ocala Equine Hospital, Ocala, Florida. Email: travistull@gmail.com

1. Introduction

In the author's practice, some specific causes of lameness or poor performance in the sport horse have proven challenging to diagnose early in the disease process. Identifying specific structures involved and managing client expectations has also proven difficult. Early referral for advanced imaging has allowed accurate and early identification of pathology, providing detailed information on the specific structures involved to aid the surgeon in their approach and provide informed prognoses for the client to aid decision-making for pursued treatments. The following are several pathologies commonly seen by the author that impact sport horse performance.

2. Keratomas

Keratomas are well-recognized causes of abnormal hoof growth, chronic abscessation, and infrequent causes of lameness.[1-4] History and clinical signs consistent with diagnosis have been well described as well as findings of magnetic resonance (MRI) and computed tomography (CT) imaging.[1, 3–5] High-field MRI in the author's practice frequently identifies keratomas before significant third phalanx resorption, often without obvious hoof capsule deformity or chronic abscessation. Lameness is typically ameliorated by palmar digital or abaxial sesamoid peripheral analgesia with little to no radiographic findings.

If standard imaging methods, including radiography and ultrasound, are equivocal or the patient is treated for abscessation or lameness isolated to the foot but fails to respond, referral for advanced imaging is recommended. Often, the keratoma is discovered after routine referral for advanced imaging for lameness isolated to the foot. MR findings include irregularities at the junction of the sensitive and non-sensitive laminae causing a laminar defect with corresponding resorption or concavity of the adjacent third phalanx bordered by fluid signal and vascular pattern. Keratomas can be found within any part of the hoof capsule.

Although not diagnostic in isolation, positron emission tomography (PET) may also help with diagnosis due to increased radiopharmaceutical uptake of 18F-sodium fluoride (NaF) in the third phalanx adjacent to the lesion and decreased uptake of 18F-fludeoxyglucose (FDG) in the region of the laminar defect. Computed tomography (CT) also provides cross-sectional imaging for keratomas with moderate to marked radiographic changes of the third phalanx, and coupled with venography or arteriography, can provide beneficial information on space-occupying lesions that are smaller or have produced less structural changes to the third phalanx. (personal communication N. Werpy).

Identifying keratomas before significant enlargement causing derangement of the hoof capsule, or chronic abscessa-

tion may improve outcomes and result in fewer complications.[1, 3, 4] In the author's caseload, early identification has eral advantages. Smaller surgical approaches through the hoof wall, decreased disruption of the laminar junction, and less exposure of the third phalanx have allowed most horses to have minimal post-operative lameness or destabilization of the hoof capsule. Although the size of the surgical approach does not influence the hoof growth rate, it does appear to influence the amount of time off, as a return to exercise is dictated by how quickly the tissue within the surgery site keratinizes. This allows a more precise prediction of when the horse can return to work.

Furthermore, cross-sectional imaging in the author's practices has prevented reoccurrence, which can occur with inadequate resection.

3. Tenosynovitis

In performance horses, lameness-inducing tenosynovitis of the digital flexor tendon sheath (DFTS) is common.[6–9] The author usually addresses acute tenosynovitis with accompanying lameness with bandaging, poulticing/icing, and stall rest with hand walking only for seven to ten days. Ultrasound is recommended initially and repeated after seven to ten days as acute lesions often will not be apparent initially. Intrathecal diagnostic analgesia confirms the source of pain.

Recommendation for advanced imaging and surgery depends on owner preferences, financial constraints, and if medical management is unsuccessful. In general, horses with abnormalities identified on ultrasound are ideally suited for high-field MRI and subsequent surgery as ultrasound tends to underestimate the degree of injury and all the structures involved.

Tenosynovitis can be caused by injury to the deep digital flexor tendon (DDFT), superficial digital flexor tendon (SDFT), manica flexoria (MF), or proximal palmar annular ligament (PAL).[6, 8–11] Determining which structures are involved is complicated, and contrast tenography with and without CT has been described to characterize lesions further.[12–14]

In the author's practice, a high field MRI is performed with surgery immediately following the same general anesthetic period. Most cases tend to be lateral DDFT and/or SDFT lesions, with MF injury or complete tears being second and primary PAL lesions least common. With multiple structures involved or signs of chronicity, such as severe synovitis and adhesion formation, the prognosis is reduced.

There have also been several instances where lesions were inaccessible via tenoscopy or too severe to warrant surgical revision. Before access to high field MRI, tenoscopy was often exploratory; sometimes, all lesions were not identified. With MRI preceding surgery, the correct recumbency and a plan for evaluating and treating injury in specific locations within the DFTS can be decided upon.

4. Subchondral Lucencies

Subchondral lucencies (SL) have been described in nearly every bone in the distal and proximal limb of multiple breeds, and subchondral bone injuries (SBI) have been associated with the development of osteoarthritis and lameness.[15–17] PET is utilized to aid the identification and characterization of both SL and SBI.

Lameness localized to the distal limb with minimal or equivocal findings on standard radiography and ultrasound undergo PET to rule in or out SBI or aid in determining if a visible SL has metabolic activity. Any horse with an SL identified radiographically that has had the lameness isolated to the region is a good candidate for advanced imaging to determine how active the lesion is, its size, and its relationship to other anatomical structures.

If there is positive uptake on PET, CT is utilized to evaluate the degree of structural injury. Performance horses frequently have SL/SBI identified on the proximal first phalanx (P1) sagittal groove, or condyles, and the distal dorsal third metacarpal/tarsal (MC/T3) condyles. The degree of standardized uptake, lesion appearance on CT, and previous response to treatment guide recommendations on surgical intervention or conservative therapy.

The information can also help determine prognosis and rehabilitation and guide a return to work via recheck PET.

5. Exostoses

Exostoses of the second (MC/MT2) and fourth metacarpal/tarsal (MC/MT4) bones are common occurrences secondary to trauma or training. They are typically treated conservatively and will often become quiescent. Occasionally, they will enlarge significantly axially, impinge on the suspensory ligament and the horse will have lameness that fails to respond to conservative therapy.[18]

For horses that fail to respond to conservative therapy, the exostosis continues to enlarge, and continued lameness all warrant referral for advanced imaging/evaluation. Ultrasound of the region in both weight-bearing and non- weight

bearing can help determine if there is involvement of the proximal suspensory. Diagnostic analgesia of the proximal third metacarpus/metatarsus generally ameliorates the lameness. However, it is non-specific as it will not differentiate the exostosis from the proximal aspect of the suspensory ligament. Local blocking at the site of the exostosis can also lead to confusing or equivocal results.

Combining CT with MRI provides three-dimensional imaging of the exostosis and information about the pathology of the suspensory ligament. The CT evaluates the exostosis, and the MT/MC 3, while MRI evaluates the suspensory ligament, soft tissues, and gives information on bone edema. This allows prognostication, as several patients have been diagnosed with proximal suspensory ligament pathology in conjunction with exostosis impingement and adhesions to the suspensory. This information is vital to management, post-operative rehabilitation, and client expectations.

6. Tarsal Region

Performance horses with lameness isolated to the proximal suspensory/subtarsal region are common in practice. The complexity of the anatomy of the proximal suspensory ligament, distal tarsal, and proximal third metatarsal region makes precise diagnosis of pain isolated to this region difficult.

When there is an apparent ultrasonographic lesion of the proximal suspensory ligament, diagnosis is straightforward and can focus on treating proximal suspensory desmitis. When the lameness is ameliorated with diagnostic analgesia in the subtarsal region with minimal changes to the proximal suspensory on ultrasound, a precise diagnosis becomes more difficult, and these horses are good candidates for referral and advanced imaging.

Diffusion of local anesthetic proximally and distally to the tarsal sheath, lower hock joints, and other structures has been well documented.[19–21] Additionally, involvement of the proximal plantar MT3, tarsal bones, and adjacent structures in conjunction with the suspensory ligament can result in treatment failure or misdiagnosis. In one study, 53% of limbs blocked to the proximal suspensory ligament that underwent high field MRI were found to have desmopathy.[22]

In horses with monetary restrictions or owners adverse to further imaging, the author will often treat either the proximal suspensory ligament conservatively or the distal intertarsal/tarsometatarsal joints and gauge the clinical response. Horses that block to the proximal MT3, with minimal or equivocal ultrasound findings, and no monetary restrictions, currently undergo CT followed by MRI in the same anesthetic period.

Based on the findings, PET can be performed a day later. The CT allows structural evaluation of the proximal metacarpal bones, the tarsal bones, and distal tarsal joints. The high field MRI evaluates the proximal suspensory ligament, metatarsal and tarsal ligaments, proximal metacarpal bones, and the tarsal bones. The PET will then further indicate the severity of subchondral bone injury to the proximal metacarpal region, tarsal bones, and distal tarsal joints. Utilizing these modalities together allows a specific diagnosis in a complex region to guide recommendations.

7. The Neck

Cervical pain and dysfunction have increasingly been recognized as a significant source of lameness and poor performance.[23,24] Any horse with neurologic deficits, pain isolated to the cervical spine, significant radiographic abnormalities of the cervical spine, behavior changes, or forelimb lameness that cannot be isolated with diagnostic analgesia are candidates for referral and three-dimensional imaging.

The author's practice has recently developed a method of dynamic CT myelogram allowing three-dimensional imaging of the cervical spine in neutral, flexion, and extension. Results of dynamic CT myelograms can be grouped into spinal cord compression/impingement, abnormalities of the articular process joints (APJ)/intervertebral foramen (IVF), pathology of the intervertebral disc (IVD), and anomalous findings.

Spinal cord compression/impingement is categorized as circumferential or focal with notation of cervical position and if there is attenuation of the contrast column and/or shape change of the spinal cord. Dural diameter and dorsal contrast column measurements are also made. Findings unique to dynamic CT myelogram include focal dorsolateral or lateral spinal cord compression and discrepancies with published dural diameter changes related to specific sites.

Standing CT myelogram also does not evaluate flexion and extension. Few CTs can image the caudal cervical spine standing as well. A radiographic myelogram only demonstrates changes to the subarachnoid contrast and dural diameter dorsal to ventral. Also, particularly at C3-4 and C4-5, published sagittal dural diameter measurements tend to overestimate compression compared to transverse images on CT both in neutral and flexion.[25, 26]

The APJs have an array of abnormalities ranging from osteoarthritic changes to osteochondritis dissecans (OCD) and size/shape changes. Enlargement of the APJ has been observed in our population to either occur in a dorsal abaxial direction, axially, ventroaxially, or a combination. If the enlargement occurs dorsal abaxially, the subarachnoid contrast column is unaffected, as is the IVF. Axial enlargement can cause spinal cord impingement or compression, while ventral enlargement can reduce the cross-sectional area of the IVF.

The cervical spinal nerve exits the IVF mid to cau dally.[27–29] These findings become increasingly important dynamically as, typically, neck extension narrows the IVF, and flexion increases the IVF size.[27] Contrast arthrogram has also allowed investigation into the APJ capsule in abnormal joints. Previous reports have been modeled on normal horses.[30]

In the author's experience, the joint capsule in an abnormal APJ can push axially toward the spinal cord with the cervical spine in extension. In flexion, it tends to push caudally out the IVF. In several cases, a soft tissue extradural mass effect in neutral, extended, and flexion has been confirmed to be the joint capsule through arthrogra-phy. In some cases, the joint capsule, not bone proliferation, of an abnormal APJ is causing spinal cord compression. This also has implications for soft tissue impingement on the cervical spinal nerve, playing a role in the pathogenesis of cervical radiculopathy.

Pathology of the IVD has been increasingly recognized as a cause of cervical pain/dysfunction or ataxia in horses.[31–34] In our population, some dorsal protrusion of the IVD at C3-4 and C4-5 is extremely common in flexion and rarely accompanied by other abnormalities. However, C5-6, C6-7, and C7-T1 should have minimal dorsal disc protrusion, no mineralization, or endplate remodeling. These findings are indicative of a pathologic process.

CT also underestimates the degree of change in the IVD, as demonstrated by comparing post-mortem MRI, gross pathology, and histopathology. Identifying the specific pathology of the cervical spine and correlating the clinical findings allows targeted treatment recommendations, which include pharmacologic treatments both locally and systemic, non-pharmacological and nonsurgical treatments like acupuncture, chiropractic, rehabilitation, massage, and surgical therapies, namely cervical spinal fusion or endoscopic foraminotomy.

8. Upper Airway

Upper airway disorders occur in any athletic horse. The author's practice sees many English and Western performance horses with a history of upper airway noise and poor performance. Overground endoscopy is essential to diagnose and manage upper airway disorders. It closely mimics working conditions and allows evaluation at maximal speeds required by the athlete to perform.

Candidates for overground endoscopy are horses that make noise with normal or equivocal resting endoscopy, poor performance with normal endoscopy, screening for purchase examinations or after surgery, or Havemeyer grade 3 laryngeal function.[35, 36] It is important to ensure that the horse is fit enough for the examination, has no lameness/concurrent problems elsewhere, and closely mimics its vocation in speed and head carriage.

Pharyngeal collapse can manifest as the dynamic collapse of the dorsal pharynx, the lateral walls, or circumferentially. It is more common in sport horses and has been associated with head carriage.[36, 37] The etiology is unknown, although there has been some good research demonstrating dysfunction of the stylopharyngeus muscles.[38] It also can be associated with inflammatory airway disease, higher grades of pharyngeal lymphoid hyperplasia, and concurrent upper airway abnormalities like recurrent laryngeal neuropathy (RLN) or axial deviation of aryepiglottic folds.

Palatal instability and intermittent dorsal displacement of the soft palate (DDSP) are only confirmed on overground endoscopy. The etiology has yet to be identified although the pathogenesis appears to be dysfunction of the thyrohyoid muscles, resulting in an inability to hold the larynx in a more rostral position at high-speed work.[39] Many horses will displace the soft palate briefly at the beginning of exercise which is a normal finding. It is abnormal for DDSP that occurs for several strides during high-speed work resulting in poor or altered performance.

Laryngeal dysfunction that is observed during overground endoscopy typically involves the arytenoid cartilages, aryepiglottic folds, or epiglottis.[36, 40] Arytenoid collapse is a manifestation of early onset RLN.[35, 36] Ventroaxial luxation of the apex of the arytenoid has also been observed and is thought to be related to dysfunction of the transverse ligament between the arytenoid cartilages.[40] Rostral displacement of the aryepiglottic fold has been observed and can be related to laryngeal dysplasia, while axial displacement of the aryepiglottic folds also occurs and can create airway noise and poor performance.[41]

Epiglottic retroversion is rare, only observed on overground endoscopy and occurs secondary to dysfunction of the hyoepiglotticus muscle.[42-44] Combinations of dynamic abnormalities are prevalent and noted to effect up to 27% of sport horses with poor performance and/or noise in one study.[36] Often when multiple abnormalities appear on overground endoscopy, it is important to note which occurs first as turbulent airflow or altered airway pressures could result in a second abnormality. In some cases, treating the primary problem may lead to the resolution of other dynamic abnormalities.

For instance, it is common for arytenoid collapse to occur and soon after axial deviation of the contralateral aryepiglottic fold, or DDSP, or sometimes pharyngeal collapse. Often, treating the primary airflow disturbance in these scenarios will eliminate secondary abnormalities.

Overground endoscopy, has allowed a dynamic examination of the upper airway during work. This has significantly improved the ability to diagnose upper airway obstruction, and pursue treatment based on visual confirmation of the problem. It also allows re-evaluation after treatment if noise or poor performance is not resolved after treatment.

9. Conclusion

Advanced imaging including CT, PET, high field, MRI, and overground endoscopy has significantly affected the author's approach to diagnosing and prognosticating performance-limiting problems in sport horses. The next discussion will focus on utilizing advanced imaging for surgical treatment and monitoring progression.

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Declaration of Ethics

The author adhered to the AVMA Principles of Veterinary Medical Ethics.

Disclosure of Financial Interests

The author has no financial interests (including ownership, employment, consultancy arrangements, and/or service as an officer or board member).

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Practical Surgical Advances in the Performance Horse: Part II

Utilizing Advanced Imaging in Surgical Planning, Intra-Operative Guidance and Injury Resolution

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Take Home Message: The utilization of advanced imaging modalities for pre-operative planning and intra-operative guidance have allowed more precise treatment and prognostication in common causes of decreased performance in sport horses. Corresponding and presenting author: Ocala Equine Hospital, Ocala, Florida. Email: travistull@gmail.com

1. Introduction

Advanced imaging assists with diagnosis and is integral in presurgical planning, intra-operative guidance, and determining prognosis for return to work.

2. Surgical Approach to Keratoma Removal

Once a keratoma is diagnosed, the horse is placed under general anesthesia in lateral recumbency and the hoof wall prepared for aseptic surgery. Computed tomography (CT) is performed and the keratoma margins are determined and marked on the hoof. A Dremel drill is then utilized to score the hoof outlining the site of the partial hoof wall resection. A second surgical preparation is performed; analgesia is provided by local abaxial nerve block with 5% bupivacaine HCL, and hemostasis is supplied with a combination of Esmarch and vet wrap tourniquet over the distal third metacarpus/metatarsus (MC/T3). This is combined with intravenous regional limb perfusion (RLP) if there is an active infection at the time of surgery.

A partial hoof wall resection is performed and preferred due to decreased complication rate.[1–3] The author scores the stratum externum or periople with a cordless rotary tool utilizing a round metal cutting wheel. Monopolar cautery is then used to cut through the stratum externum, medium and internum. An osteotome then removes the section of hoof wall and the keratoma. The area is lavaged thoroughly and curettage peformed on the third phalanx as deemed necessary on a case-by-case basis. Using a ball nose rotary carving bit a hole is made in the sole preserving the hoof bridge to allow ventral drainage. The surgery site is copiously lavaged, and dilute 2% chlorhexidine soaked sponges are placed within the cavity. A foot bandage is then placed.

The keratoma is sent off for histopathology at the owner's request and is not performed in every case. Aftercare includes stall rest with hand walking and bandage changes every other day, cleaning the defect carefully, and packing it with dilute 2% chlorhexidine-soaked sponges. Specialized shoeing or a treatment plate is not used initially, although owners may elect to have one placed five to seven days post-operatively. A treatment plate shoe consists of a glue-on or nailed-on wide web shoe or bar shoe with toe clips to stabilize the hoof capsule and sole support. The bottom of the shoe is altered to allow access to the solar defect. Sterile gauze soaked with 2% chlorhexidine is placed within the solar defect, more sterile gauze placed over the bottom of the solar defect and the plate is re-attached to the shoe with bolts or screws. Duct tape is placed around the perimeter of the shoe/plate interface to prevent moisture or sand from entering the treatment shoe.

Stall confinement with hand walking is continued until the granulation tissue within the hoof wall defect begins to cornify and toughen. At that time a shoe may be placed.

Recommendations for shoeing include a wide web shoe or bar shoe with decreased break-over (rockered, squared etc), toe clips to limit hoof capsule expansion, and sole support to dampen impact. As the defect grows out with hoof growth, the distal bridge of the hoof left intra-operatively is removed. Depending on the size of the defect, the horse may need additional support in the form of equilox, bars, or screws and wires to stabilize the defect in the hoof wall. Once shoes are applied, a gradual return to turnout and exercise is allowed, provided the defect is covered and kept clean and dry.

On average, horses return to work at 6-8 weeks postoperatively, and the defect is grown out in 9-12 months, depending on location. The use of CT to delineate surgical margins in the hoof has led to smaller surgical windows, good margins, and to date, the author has had no known instances of keratoma regrowth. Although the time for the defect to grow out is not affected by width, the smaller the window, the more comfortable horses seem to be post-operatively. Smaller surgical windows also lead to decreased disruption of dorsal lamina thus reducing the chances of destabilization of the third phalanx. Horses also tend to have less granulation tissue with decreased surgical window size, allowing for faster cornification and return to work.

3. Surgical Approach to the Digital Flexor Tendon Sheath

Horses with lameness isolated to the digital flexor tendon sheath (DFTS) are placed under general anesthesia in right lateral recumbency. High field magnetic resonance imaging (MRI) is performed and read during the procedure by the radiologist. Abnormalities amenable to tenoscopic surgery include lesions accessible tenoscopically such as marginal tears of the deep digital flexor tendon (DDFT) and superficial digital flexor tendon (SDFT), mild to moderate amount of adhesions between the DDFT or SDFT and tendon sheath, manica flexora (MF) tears, and palmar annular ligament desmitis. Findings not amenable to tenoscopic surgery but can be associated with flexor tendon sheath synovitis include distal sesamoidian ligament desmitis (straight or either oblique) and very distal or dorsal DDFT or SDFT lesions that would not be accessible through the flexor tendon sheath. Prognosis often depends on the size of tendon lesions, the number of damaged structures, chronicity, and the amount of adhesion formation.

If the horse is deemed an acceptable candidate for tenoscopy, they are placed on a surgical table in the most appropriate recumbency for the lesions. The surgical site is aseptically prepared and draped and a 2.7 mm 30 degree forward facing arthroscope inserted at the base of the proximal sesamoid bones as previously described.[4] A smaller scope is utilized initially to avoid iatrogenic damage to the flexor tendons and to allow easier exploration due to its small size. A stan-dard 4 mm 30 degree forward facing arthroscope is then placed through the same portal. Instrument portals area placed as necessary based on lesion location. Lesions are debrided with a combination of synovial resector and radiofrequency ablation. The palmar annular ligament (PAL) is usually transected freehand under arthroscopic visualization. The DFTS is lavaged copiously and the portals closed routinely.

Aftercare consists of stall rest with hand walking two to three times daily, beginning with 5 minutes, gradually increasing the amount of time not exceeding thirty minutes total for thirty days. Intrathecal administration of corticosteroids with hyaluronic acid or an orthobiologic autologous protein solution, (autologous conditioned serum, platelet-rich plasma, amnion, mesenchymal stem cells) is recommended ten to twelve days post-operatively. Horses are rechecked at thirty days, and if doing well, rehabilitation is performed based on each patient and the availability of rehabilitation modalities. High field MRI immediately pre-operatively has resulted in subjectively improved outcomes as owner expectations and patient rehabilitation are better managed.

A horse with multiple lesions that are chronic and extensive would have a reduced prognosis and longer rehabilitation period versus a horse with one structure minimally affected. This approach has also eliminated unnecessary tenoscopy in horses where the lesions were inaccessible.

4. Management of Subchondral Bone Lesions

Subchondral bone lucencies (SL) and subchondral bone injury (SBI) once diagnosed via positron emission tomography (PET) and CT are often treated conservatively if not previously treated. For SL, the affected joint is treated intraarticularly with an orthobiologic or corticosteroid with hyaluronic acid. A percentage of SL will either resolve radiographically in young horses or not appear to cause a clinical problem after initial treatment of the joint.

Horses with SBI are generally treated with rest in the form of small paddock turnout for ninety days and rechecked with PET to determine bone metabolic activity. Horses with SBI that has resolved will have no significant radiopharmaceutical or significantly improved uptake. Horses with SL or SBI that have been previously treated conservatively and did not resolve are usually treated with lag screw fixation. Surgery is CT-guided, given the proximity of SL and SBI to the joint, and to improve the accuracy of the screw placement.

The horse is placed under general anesthesia in the appropriate recumbency for the lesion, and the surgery site is aseptically prepared and draped. A marker is placed at the lesion sight, or an aiming device is utilized, and adjustments are made based on intra-operative CT to guarantee appropriate placement and length of the screw without perturbation of adjacent structures. Aftercare includes stall rest and hand walking for 30 days with recheck radiographs to guide further rehabilitation. Utilizing CT has allowed precise placement of implants through the lesion without adjacent damage to articular surfaces or soft tissues.

5. Surgical Management of Splint Exostoses

Second or fourth metacarpal (MC2/MC4) or metatarsal (MT2/MT4) exostosis with impingement or adhesions to the proximal suspensory ligament can be frustrating to document with standard imaging techniques. Horses are placed under general anesthesia, and a CT is performed prior to a high field MRI. The CT evaluates the three-dimensional structure of the affected splint bone and readily identifies axial exostoses and if they encroach upon the suspensory ligament. High field MRI can then assess the soft tissues in the region including the suspensory ligament origin, body and branches.

Combining the modalities under a single anesthesia allows the complementary data to identify bone and soft tissue pathology so these injuries can be correctly diagnosed, treated simultaneously, and owner expectations managed. When a splint exostosis is verified to be impinging on the suspensory body surgical resection is performed either via segmental ostectomy or amputation proximal to the exostosis and including the distal splint bone.[5,6] If the exostosis is quite proximal on the splint bone the exostosis is surgically approached and axial portion removed with osteotome and smoothed with a bone rasp. The incision is lavaged copiously, and closed in two to three layers.

Aftercare includes stall rest with hand walking for 30 days with laser therapy or shockwave beginning after suture removal. At 30 days the horse is re-evaluated to guide further care. If there appears to be exostosis formation at the amputation site local administration of corticosteroids is recommended with continued shockwave therapy once weekly for three to four treatments.

6. Management of Subtarsal Lameness

Lameness localized to the subtarsal region in performance horses can be confusing, principally when there are minimal ultrasound changes to the proximal suspensory ligament with equivocal changes to the distal intertarsal and tarsometatarsal joints radiographically. By combining CT, MRI, and PET, the author can provide a definitive diagnosis that will lead to targeted treatments.

Computed tomography provides cross-sectional imaging of the proximal MT3, tarsal bones, tarsometatarsal, distal intertarsal, proximal intertarsal, tarsocrural, and talocalcaneal joints. The high field MRI then provides crucial information about the proximal suspensory ligament, other soft tissue struc tures, and bone edema.

If the primary issue is the proximal suspensory ligament, conservative therapy, including local injection with biologics, shockwave, and rest, is instituted. If conservative treatment is ineffective or previously implemented, plantar fasciotomy and neurectomy of the deep branch of the lateral plantar nerve is performed as previously described. [7]

If the distal intertarsal and tarsometatarsal joints have significant signs of osteoarthritis (OA) or the tarsal bones have significant bone edema on MRI or radiopharmaceutical uptake on PET, horses are treated like other SBI, with varying amounts of small paddock turnout. If there are severe osteoarthritic changes, surgical options include facilitated ankylosis via drilling the distal intertarsal or tarsometatarsal joints with or without internal fixation.

In lame horses that block to the tarsometatarsal joints or subtarsal region the combination of CT and MRI and/or PET has allowed a specific diagnosis, resulting in tailored treatments to the primary problem.

7. Medical and Surgical Approaches to Cervical Pathology

Dynamic computed tomographic myelogram or CT of the cervical spine has allowed elucidation of the pathology of the cervical spine. In the author's practice, horses with pain localized to the cervical spine are candidates for CT of the cervical spine or dynamic CT myelogram. A thorough clinical examination is performed, and horses are evaluated for lameness and neurologic status.

Horses are placed under general anesthesia and CT or dynamic CT myelogram is performed. In the instance of neurologic signs and spinal cord compression, cervical fusion remains the treatment of choice, with the number of sites affected and concurrent pathology driving prognosis.

Articular process joint enlargement with no intervertebral foraminal stenosis (IVFS) is treated with ultrasound guided

intra-articular corticosteroid administration and adjunctive therapy (rehabilitation, acupuncture, chiropractic, physiotherapy). Mild to moderate IVFS is treated with ultrasound-guided cervical spinal nerve injection with corticosteroids and adjunctive treatment.

More severe IVFS or instances where cervical spinal nerve injection fails or lasts an inadequate amount of time are treated with percutaneous endoscopic foraminotomy, which will be discussed at length in other proceedings.[8]

8. Medical and Surgical Approaches to Upper Airway Dysfunction

Dynamic upper airway abnormalities diagnosed in sport horses with overground endoscopy include pharyngeal collapse (PC), palatal instability (PI) and/or dorsal displacement of the soft palate (DDSP), arytenoid collapse (AC) and rarely epiglottic retroversion (ER). Pharyngeal collapse, PI, and DDSP have been associated with lower airway inflammation.

If excessive mucus is seen on overground endoscopy bronchoalveolar lavage is recommended followed by conservative treatment with nebulization and corticosteroids. If conservative therapy fails or there is no associated lower airway inflammation dorsal PC is treated with laser salpingopharyngeal fistula via the nasopharyngeal dorsal recess to normalize airway pressures between the pharynx and guttural pouches.[9]

For lateral and circumferential pharyngeal collapse, standing transendoscopic laser energy is applied in multiple sites on the pharyngeal mucosal walls to induce fibrosis and decrease the pliability of the tissues. Palatal instability and DDSP are treated at the author's practice with sternothyroideus tenectomy and staphylectomy or laryngeal advancement (tie-forward), depending on the client's wishes. Arytenoid collapse is treated with laryngoplasty and ipsilateral laser ventriculocordectomy or standing transendoscopic laser ventriculocordectomy alone.

Epiglottic retroversion occurs secondary to dysfunction of the hyoepiglotticus muscle and is only observed during work. It is the rarest abnormality seen in the author's practice, and there is no definitive surgery to correct the problem, although a recent publication has detailed a promising technique.[10] Overground endoscopy is also helpful to determine response to treatment.

If a horse has had a previous treatment and continues to have poor performance or upper respiratory noise, repeat overground endoscopy can determine if there was a treatment failure or an additional or new problem. Overground endoscopy has facilitated the diagnosis of specific problems only observed during work, allowing treatments that are not based solely on clinical signs or presumed diagnoses. It is also essential in monitoring response to treatment.

9. Conclusion

Combining advanced imaging modalities has significantly affected the author's practice by providing more specific diagnoses, guiding surgical planning, evaluating responses to treatment, and prognostication.

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Declaration of Ethics

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Update on Joint Therapies

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Take Home Message: There are a plethora of intra-articular medications available to treat equine joint disease. Understanding the mechanisms of action and pros and cons of each can help practitioners select the best option for each individual case. Corresponding and presenting author: Colorado State University College of Veterinary Medicine, Fort Collins, Colorado. Email: erin.contino@colostate.edu

1. Introduction

Treating equine joint disease is a multipronged approach that often than entail some form of intra-articular therapy. The number of intra-articular (IA) medications available to the practitioner are seemingly endless and range from corticosteroids, to orthobiologics and numerous other synthetic products. Unfortunately, the use of many of these products in a clinical setting far outpace the research to support such use. We will explore updates on more traditional medications such as corticosteroids, discuss various orthobiologics and examine newer synthetic products that are available.

2. Corticosteroids

Corticosteroids have long been a mainstay of intra-articular medication in the equine veterinary industry. They remain a cornerstone of intra-articular therapy because they are widely available, inexpensive, and effective in decreasing joint pain and inflammation. Past research investigating the symptom- and disease-modifying effects of various corticosteroids has shown some effects to be drug dependent. Notably, in an in vivo experimental model of osteoarthritis, compared to saline controls, methylprednisolone was shown to be degradative to articular cartilage[1] while triamcinolone was shown to be chondroprotective.[2] Conversely, a recent study concluded that methylprednisolone produced superior results to triamcinolone when injected into the sacroiliac region in horses affected with sacroiliac pain.[3]

Newer research on the systemic effects of intra-articular corticosteroids have demonstrated improved lung function[4] and increased baseline insulin levels[5, 6] following intra-articular triamcinolone administration. Additional studies that have added to the body of literature surrounding use of intra-articular corticosteroids include one study that showed a dose-dependent deleterious effect of amikacin on chondrocytes[7] and another study that demonstrated no clinical benefit to adding hyaluronic acid (HA) to corticosteroid injections in terms of efficacy and longevity of the response to treatment.[8] Clinically, these studies may support the use of intra-articular corticosteroids without the concurrent use of amikacin and/or HA. Additionally, there continue to be investigations into the suspected correlation between corticosteroid administration, particularly triamcinolone, and iatrogenic laminitis though a definitive correlation has yet to be proven.[9]

3. Orthobiologics

Orthobiologics (or biologics), defined as products derived from biologic tissue or fluid, are becoming commonplace

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for use among sport horse practitioners. Despite the booming popularity of orthobiologics, there are few scientific studies that compare the efficacy of biologics to one another or to corticosteroids. Interestingly, human trials have demonstrated a larger placebo effect with biologic therapies because the patients perceive that they are being treated with a regenerative product.[10]

Orthobiologics are often used when corticosteroids are contra-indicated such as in horses with endocrine disorders or soft tissue injury. From a management perspective, due to the long detection times, increasing withdrawal times, and/or the low level of detection of some corticosteroids, orthobiologics are being used with increasing frequency in sports with stricter drug regulations such as the FEI and Thoroughbred racing. While neither corticosteroids or orthobiologics should be injected into an injured joint in order to get an otherwise unfit horse to competition, orthobiologics do offer more flexibility in terms of timing of treatment around competition and racing schedules.

Autologous Conditioned Serum

Autologous conditioned serum (ACS) is commonly known as IRAP (IL-1 receptor antagonist protein/ IL-1ra). IL-1 is well established as playing a major role in the pathogenesis of osteoarthritis (OA) so it is not surprising that research widely demonstrates that antagonizing IL-1 is effective in the treatment of OA.[11-14] ACS is produced by incubating the horse's own blood over coated glass beads (e.g. chromium sulfate coated beads) for 20 to 24 hours, which yields a serum with an increased IL-1Ra concentration and a higher ratio of IL-1Ra to IL-1 than circulating serum. Like other orthobiologic products, it also contains a variety of other cytokines and growth factors.[15]

Research in humans with osteoarthritis supports the use ACS with results demonstrating decreased pain and increased quality of life in multiple studies.[15-18] In horses, in a well-established OA model, horses treated with ACS (6 mL, IA, q 7d for 4 treatments) had significantly less lameness compared to saline controls at day 70.[19] The ACS treatment group also showed significantly less synovial membrane hyperplasia indicating that ACS has both disease- and symptom-modifying effects in horses.

In the author's experience, ACS seems to be as effective as IA corticosteroid treatment though no direct comparison studies exist in horses. It is typically administered every 7 to 10 days for 3 treatments, especially when used to manage an acute synovitis or injury. When being used in place of corticosteroids, some practitioners use it is as a single IA treatment. ACS must be incubated for 20-24 hours prior to processing, thus the horse cannot be treated the same day as the blood draw. This is in contrast to some other biologics that can be processed and administered on the same day as the examination. Conversely, the large volume of ACS yielded from a single blood draw, and its ability to be stored frozen for long periods of time (at least 1 year) enables its use for repeated treatments on multiple joints.

Autologous Protein Solution

Autologous protein solution (APS) is a relatively new biologic that is a combination of anti-inflammatory and anabolic products. Due to the increased concentration of white blood cells, APS contains both pro- and anti-inflammatory cytokines, including anti-IL1 and anti-TNF proteins, with the end product containing more anti- than pro-inflammatory mediators.[20-22] The platelet fraction of the APS product provides various growth factors (e.g., EGF, IGF-1, PDGF, VEGF, and TGF-β1) which contribute to its anabolic properties. In vitro, APS can aid in preventing cartilage matrix degradation[23], which supports its use for the treatment of OA.

Scientific investigation of APS is more limited than some other biologic products. A double-blinded placebo-controlled study in humans with knee OA demonstrated minimal differences between APS and saline treatment groups within the first year but significant improvement in pain beyond one year.[24] Additionally, APS treated patients did not have radiographic progression of disease, unlike controls. The landmark study in horses was a prospective, blinded, placebo-controlled study of horses with naturally occurring OA (n=40) that demonstrated a significant decrease in lameness and pain to passive range of joint motion in treated horses.[25]

It appears that the use of IA APS is gaining traction in the industry faster than any other therapy. Unlike ACS, it can be processed stall side and reinjected into the patient the same day which may be a factor in its growing popularity. It is most frequently administered as a single injection, unlike ACS which typically requires a series of injections. The volume yielded is typically 3 to 4 mL which is usually sufficient to treat a single joint. When more than one joint is being medicated, some practitioners elect to dilute the concentrated fraction with platelet poor plasma (an intermediary product in the processing) to increase the volume of injectate.

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is concentrated fraction of platelets produced from the patient's peripheral blood. Platelets, via their alpha granules, provide a rich source of

growth factors including PDGF, TGFβ, VEGF and IGF-1.[26, 27] It is difficult to classify PRP products due to differences in platelet concentration, white blood cell content, presence of red blood cells, number of centrifugations, and activation method, if any.[28] The wide variability of PRP products makes meaningful comparison between studies nearly impossible.

The largest body of literature on the therapeutic benefits of PRP is in the treatment of humans with knee OA. Multiple recent meta-analyses have generally concluded that PRP is effective in treating knee OA, particularly in the longer term (6 to 12 months), and is usually superior to serial injections of HA.[29-33] Importantly, one meta-analysis concluded that leukocyte-poor PRP may be superior to leukocyte-rich PRP in the treatment of knee OA.[33] Despite the large body of research on the use of PRP in humans, it is far more limited in animals. A small, blinded study in dogs (n=10) with elbow OA showed improvement, but no difference between treatment groups, following treatment with either PRP or corticosteroids and HA.[34] At present, there is limited support for the use of IA PRP in horses and more research is needed to determine its role in the treatment of joint disease.

In clinical use, PRP is widely available, relatively inexpensive and can often be processed in the field, all of which contribute to its fairly widespread use in equine veterinary medicine. In the authors practice, PRP is used primarily to treat soft tissues and rarely as an IA therapy. There is some evidence in the literature that excessively concentrated PRP may be inferior to less concentrated formulations and therefore, target platelet concentration is generally 2 to 6x that of peripheral blood.[35]

Alpha2 Macroglobulin

Alpha 2 macroglobulins (A2M) are large plasma proteins produced primarily by the liver that serve as serum protease inhibitors. To a lesser extent, A2M can also be synthesized by chondrocytes and the synovial membrane, though levels are decreased in OA joints.[36] In humans, exogenous A2M inhibits IL-1 driven MMP-13 activity in a dose-dependent fashion and decreases catabolic cytokines and enzymes.[36] For these reasons, A2M has recently been explored for the treatment of OA. Preliminary experimental studies of traumatic OA in rats have shown that IA A2M is chondroprotective[37], more so than HA. A clinical study in humans with knee OA (n=75) found a single IA injection of A2M to have similar efficacy to corticosteroids and for most outcome criteria, both treatments were marginally, but not significantly, better than PRP.[38]

Overall, while the preliminary research on A2M appears promising, much more research is needed to support its use clinically. A commercially available equine product has undergone a basic clinical safety study in which no adverse injection reactions were reported in 50 horses.[39] At present, there are no scientific studies on its efficacy in horses.

Mesenchymal Stem Cells

MSCs describe cells that are pluripotent and can differentiate into a variety of other cell types. There are a wide variety of tissues from which MSCs can be harvested including fat, bone marrow, amniotic fluid, umbilical cord tissue, umbilical cord blood, dental pulp, and peripheral blood, to name a few. For orthopedic purposes, clinically MSCs are most commonly sourced from adipose tissue (AD-MSCs) or bone marrow (BM-MSCs) and there is evidence in horses that BM-MSCs derived have superior chondrogenic potential compared to AD-MSCs.[40-41] Further, HA induces chondrogenesis of equine MSCs.[42]

The most impressive evidence for the use of MSCs in the treatment of joint disease comes from a study in goats that underwent a severe experimental model of stifle OA that included complete medial menisectomy.[43] Animals treated with BM-MSCs showed meniscus-like repair tissue that was hyaline in nature containing Type I and Type II collagen, and had better histologic scores and less disease progression compared to controls. Results in horses using the carpal chip OA model did not show a treatment effect with IA MSCs.[44] A few clinical studies in horses have shown favorable, though not overwhelmingly positive, results with IA MSCs. In 33 horses that underwent stifle surgery and subsequent treatment with BM-MSCs, 75% were able to return to some level of work 1 year post surgery which is better than previous reports of 60-64%.[45] Two other studies have shown positive results in horses with naturally-occurring fetlock OA.[46-47]

Generally speaking, in horses, the literature shows stronger support for the use of MSCs to treat soft tissue disease.[48-54] In particular, one fairly robust long-term study (2 years) in racehorses with superficial flexor tendonitis found a lower reinjury rate (27.4% of 113 horses) in MSC-treated horses compared to historical controls.[54] Taken collectively, the research supports the use of MSCs, particularly BM-MSCs, in the treatment of musculoskeletal disease.

For IA use, the author typically administers 10 to 20 million MSCs per joint. Better results may be obtained if MSCs are combined with HA[55] as HA may extend the lifespan of the MSCs.[56] Particular indications for IA MSCs may include treatment of meniscal injuries[43, 45], joint disease in which there is an incongruent joint surface[43], and/or in high motion joints[46, 47]. For intra-lesional use in soft tissue injuries

the author typically uses 10 million MSCs. Treatment with MSCs may be especially warranted when there is a high risk of reinjury. One advantage to MSCs is the variety of ways in which they can be administered. Experimental studies have shown that MSCs can successfully be delivered to a soft tissue injury via regional venous or arterial perfusion.[57] A typical dose for regional perfusion is 20-30 million MSCs; this technique is useful when there is no core lesion in which to inject MSCs and/or when there is concern about iatrogenic needle injury to a structure. Finally, because bone marrow contains MSCs, some practitioners use concentrated bone marrow aspirate (BMAC) in a similar fashion to MSCs. While still likely a useful treatment option, BMAC contains magnitudes lower concentrations of MSCs and higher concentrations of red and white blood cells compared to its culture derived counterpart.

4. Polyacrylamide Gels

There are two commercially available polyacrylamide gels (PAAGs): a 2.5% and a 4% concentration. Interestingly, it appears that the mechanism of action may be different depending on the PAAG concentration with the 2.5% PAAG integrating into the synovial lining[58] and the 4% adhering to articular cartilage in increasing the coefficient of friction of the cartilage surface.[59] While proposed mechanisms of actions range from an increased elasticity of the joint capsule to a cushioning effect, ultimately, the mechanism of action of PAAGs is not yet well understood.

There are a few small clinical studies demonstrating efficacy of IA administration of 2.5% PAAG in horses with naturally occurring OA. These studies (ranging from 33 to 43 horses) reported an improvement or resolution of lameness in the majority of horses and a tendency for improving success over time (IE increasing proportion of horses obtaining soundness at 3 months vs. 1 month).[60-62] Similar improvements have been reported in two small clinical trials (n=12 and 28) with use of 4% PAAG.[63,64] Overall, the existing literature lacks robust double-blinded controlled studies and while initial reports are promising, the scientific literature is well behind the clinical use of these products.

5. Conclusions

When it comes to intra-articular medications, there are a plethora of products to choose from. While the use of orthobiologics is growing exponentially, the scientific support for their use is still somewhat lacking. Many studies are small, not blinded, and/or lack control groups. There is a desperate need for head-to-head studies in order to be able to evaluate the efficacy of one product compared to another. In the meantime, practitioners must rely on personal experience and extrapolation of data from other species.

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Declaration of Ethics

The author adhered to the AVMA Principles of Veterinary Medical Ethics.

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Advances in Performance Horse Imaging:
Computed Tomography and Positron Emission Tomography

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Take Home Message: Although diagnostic imaging has always played a vital role in the care of equine athletes, advances in the practical use of computed tomography (CT) and positron emission tomography (PET) over the past five years have added to the diagnostic arsenal. Corresponding and presenting author: Rood and Riddle Equine Hospital, Lexington, Kentucky. Email: kgarrett@roodandriddle.com

1. Introduction

Computed tomography (CT) scan times are very short, generally ranging from 1-3 minutes. Computed tomography uses x-ray radiation and a detector to acquire images along the axis of the bore of the machine. In a practical sense, that generally translates to the transverse (axial) plane of the anatomy scanned. The x-ray generator and the detector rotate around the area of interest in a synchronized manner, creating multiple projections of the anatomy from different angles. These data are processed to create thin slice images which can be viewed and reprocessed using tools like multiplanar reconstruction and volumetric reconstruction. Although not a perfect description, CT can be thought of as a "3D radiograph" in the sense that information about the radiodensity of a tissue is reflected in the resultant cross-sectional images.

Positron emission tomography (PET) involves injecting the patient with a radionuclide that combines a radioactive fluoride molecule (fluorine-18, ^{18}F) with a carrier molecule that localizes to different tissues based on their metabolic activity. In horses, ^{18}F-NaF is typically used to evaluate bone metabolism and fluorodeoxyglucose (FDG, also known as [^{18}F]FDG) is typically used to evaluate soft tissue metabolism (based upon glucose metabolism). After the radionuclide has been injected intravenously and allowed to accumulate in the target tissue for 30-45 minutes, the horse is scanned. The ring-shaped scanner surrounding the anatomy of interest detects the gamma radiation emitted from the areas of radionuclide accumulation and the data are processed by a computer to create thin slice images depicting the metabolic activity of the target tissue. Like CT, these data can be reprocessed using tools such as multiplanar reconstruction and maximal intensity projections. PET scan can be thought of as a "3D bone scan" in the sense that information about the metabolic activity of a tissue is reflected in the resultant cross-sectional images. Scan times typically range from 3-8 minutes, depending on the length of scan required.

CT and PET are both cross-sectional imaging modalities. One of the major advantages of cross-sectional modalities is the lack of superimposition of anatomy, which is an inherent limitation of two-dimensional imaging modalities like radiography and nuclear scintigraphy. Computed tomography and PET are generally considered to be superior imaging modalities as compared to radiography and nuclear scintigraphy. It is important to note that "superior" in this case refers to the imaging test itself and does not consider other important factors such as availability, cost, and practicality.

2. Practial Use for Horses

A significant challenge in equine imaging is solving the problem of taking technology originally designed for use

in human medical imaging and adapting it for use in the horse. Small animal practitioners are generally able to use human imaging technologies for their patients with minimal to no modifications required. Unfortunately, that is rarely the case in equine imaging, and CT and PET have been no different.

CT

Most CT scanners manufactured for humans use a stationary gantry with an integrated, indexing patient table. The patient table translates through the bore of the gantry, moving the anatomy of interest through the scan plane at quantifiable, controllable intervals and speeds (indexing). Although foals can be easily positioned on the patient table and scanned like a human in these systems, adult horses are too large and heavy. As a result CT scans for horses initially involved manufacturing specialized tables that could accommodate a horse in lateral and/or dorsal recumbency and allow the table to dock with the built-in patient table of the CT unit. The docking mechanism allowed the horse table/patient table combination to translate through the gantry of the CT scanner to adequately support the horse while permitting the required indexing. Unfortunately, these types of modified systems were challenging to use and prone to malfunction.

Some CT scanners developed for human use do not rely upon the use of an integrated patient table. Instead, the scanner itself translates along the floor, moving the gantry over the anatomy of a stationary patient. These scanners can be moved between rooms in a clinic setting, for example, from an imaging room to a surgical suite. This scanner design has inherent practical advantages for equine imaging. A docking mechanism for a patient table is not required, removing one possible point of failure. The patient can be supported on a more typical patient table with the anatomy of interest supported on a radiolucent stand if needed. Skulls can be imaged in the standing, sedated horse. The ability to perform intra-operative CT in the surgical suite is more efficient than needing to transport a large equine patient into a different room.

More recently, CT scanners modified specifically to accommodate horses have become commercially available. One design uses a traditional human scanner with a specialized platform for the CT scanner. With this system, the CT scanner is "tricked" into thinking the patient table is translating through the gantry, but instead, the platform holding the CT scanner is translating over the patient anatomy. The platform holding the CT can also raise and lower above floor level, allowing imaging of distal limbs and skulls in the standing horse. To image the cervical vertebral column, stifle, or pelvis, general anesthesia is required.

Cone beam CT systems have more positioning flexibility in a standing horse as cone beam CT systems do not utilize a toroidal gantry.[1-3] Instead, the x-ray source and the detector operate on separate, but synchronized arms and make one rotation around the region of interest. There are additional differences between cone beam and fan beam CT systems. In a basic sense, fan bean CT collects thin slices of information and cone beam CT collects a volume of information. In both types, the information is then processed into axial slices within operator-selected parameters. However, the differences in how the systems acquire and process data have practical implications that must be considered. Image quality is generally superior with fan beam CT as compared to cone beam CT with fewer artifacts, better signal to noise ratio, better contrast resolution, and lower scatter.[1, 2] The amount of anatomy that can be captured in a single scan is limited to the size of the detector in a cone beam system, so multiple separate scans may be required to fully image an anatomic region.

PET

In human imaging, PET scanners are often combined with CT scanners in a single unit, although they are also manufactured as stand-alone units. Regardless, the typical scanner design is similar to a standard human CT unit, with a toroidal gantry and a horizonal patient table. For horses, this design has all the disadvantages of a standard CT unit and requires general anesthesia.

Recently, a PET scanner specifically designed for standing, sedated horses has become commercially available. This unit has a ring-shaped detector module (like all PET scanners), but the ring is oriented with the bore vertically and the ring opens to allow positioning around the limb of a standing horse. During scanning, the ring moves along the axis of the limb. An important safety feature of this design is that if the horse moves to escape the ring, the ring opens easily, allowing the horse to exit without being trapped. Motion correction software is used to correct for small limb movements (swaying) during the scan. Currently, this design permits imaging up to the carpus and tarsus.

3. Use in Sport Horses

The importance of a thorough lameness examination prior to diagnostic imaging cannot be overstated. Palpation of the limb, flexion tests, and response to regional/intra-articular anesthesia are vital in localizing the source of lameness. Diagnostic images are best interpreted within the clinical context of an individual animal, considering the horse's history and the results of the lameness examination. One important confounding factor is that the specificity of

various regional or intra-articular analgesic techniques is much lower than we would like (and lower than we used to believe).[4–8]

When considering how to most effectively use CT and PET for a particular case, a useful framework is to consider the difference between structural and functional imaging modalities. Structural imaging modalities provide information about the anatomic structure of tissues whereas functional imaging modalities provide information about the metabolic activity of the tissue. Functional imaging modalities may identify problems at an earlier stage than structural imaging modalities. Radiography, ultrasonography, and CT are structural imaging modalities, whereas nuclear scintigraphy and PET are functional imaging modalities. Magnetic resonance imaging (MRI) can be considered to have features of both structural and functional imaging modalities. Both types of imaging modality have strengths, and in an ideal situation, structural and functional imaging would often both be used in an individual case, as they complement one another nicely. For example, a combination approach can help determine if a structural abnormality is metabolically active and likely clinically relevant. However, economic realities often play a role in how a diagnostic imaging strategy is determined. As a result, the clinician needs to determine the most efficient way to arrive at a diagnosis (which is not always the least expensive way).

As is typical when imaging technology advances, our ability to identify abnormalities or individuation variation has outpaced our knowledge of what some of the abnormalities mean clinically. With additional experience, this knowledge gap will narrow, but for now, we must recognize this gap and interpret findings considering the gap. Luckily, there is substantial ongoing research directed towards these efforts.

Cervical Vertebral Column

Until the recent advent of wide-bore and cone beam CT scanners, clinical cross-sectional imaging of the entire cervical vertebral column of a live adult horse was not widely available. Instead, we were restricted to radiography (limitations: lateral and oblique views only, inherent superimposition of anatomy), ultrasonography (limitations: evaluation of the superficial aspects only of the vertebral column and associated soft tissues), and nuclear scintigraphy (limitations: lateral and oblique views only, inherent superimposition of anatomy). Unfortunately, PET of the cervical region of adult horses is still not currently possible, but CT has become not only possible, but widely available. As such, our structural imaging abilities have increased dramatically. An important limitation of CT is that it has a more limited ability to directly the spinal cord as compared to its ability to directly assess bony structures of the vertebral column. In many cases, MRI would provide a more complete evaluation of the cervical vertebral column. Unfortunately, due to available scanner designs, MRI of the cervical region is not possible in a live adult horse.

Computed tomography of the cervical vertebral column is generally indicated for cases with neurologic signs localized to the cervical region, neck pain/stiffness, or unblockable/obscure forelimb lameness. Adding myelography to a CT scan protocol enhances the ability to evaluate spinal cord compression. Although there is one cone beam system currently in use at one location that accommodates imaging of the entire cervical vertebral column in the standing horse, general anesthesia is required for all other systems. Scans are typically performed in a neutral neck position in lateral recumbency, although dorsal recumbency is sometimes used. Some large bore systems permit scanning in extended and flexed neck positions as well. However, flexion of the caudal portion of the neck can be challenging to achieve within the confines of the scanner geometry. As a result, radiographic myelography is a useful adjunct for the flexed neck position.

Computed tomography is useful for the diagnosis of a variety of conditions in the neck. Although radiographic myelography has been considered the gold standard for the diagnosis of cervical vertebral compressive myelopathy, its sensitivity, specificity, and observer agreement are not particularly high.[9–12] Although similar studies with post-mortem confirmation of pathology have not yet been published for CT myelography, the hope is that CT myelography will be more accurate than radiography. As a cross-sectional modality, CT also permits the diagnosis of lateralizing compression as radiographic myelography is limited to compression that involves a dorsoventral plane component.[13–15]

Osteoarthropathy of the cervical synovial joints is a common finding in sport horses. Unfortunately, there is a wide variation in the interpretation of radiographic images between veterinarians (including radiologists), and it can be difficult to assign clinical significance to radiographic findings.[16–18] Computed tomography has the potential to help remove some of the gray area, but this remains to be proven.[19]

Intervertebral foramen narrowing is a potential consequence of articular process enlargement and can be readily observed on CT.[20–22] The spinal nerves exit the vertebral canal through the intervertebral foramina to supply the

musculoskeletal system. These nerves carry both afferent and efferent fibers, so pathology can manifest as pain, lameness, or neurologic deficits. It is possible that narrowing of the intervertebral foramina can cause pathology of the spinal nerves, either due to compression or due to local inflammation. This is an area of ongoing investigation, as the clinical relevance of the degree and location of intervertebral foramen narrowing is unclear.

Although intervertebral disc disease was long assumed to not be clinically relevant in the horse, more recent work has shown that intervertebral disc disease not only occurs in the horse but can cause neurologic disease.[23, 24] As with many of these conditions, additional work is needed to define the clinical relevance of various findings.

Joints

The development of CT and PET scanners that can evaluate the distal limb in a standing, sedated horse has opened new avenues in equine imaging. Although CT is superior to radiography to evaluate the subchondral bone,[3, 30–32] high-field MRI is generally considered to be the modality of choice for whole-joint evaluation but requires general anesthesia. Although low-field standing MRI has been available for the distal limb for two decades, the relatively low resolution and susceptibility to motion artifact of standing MRI limits its ability to identify subchondral bone and articular cartilage pathology.[25–29] In sport horses, the metacarpo/tarsophalangeal joint and distal tarsal joints are common areas for evaluation, and many lesions involve the subchondral or periarticular bone.[33, 34]

Computed tomography, due to rapid acquisition times, is generally able to be obtained without motion artifact in standing horses. It has inherently high spatial resolution (including excellent thin-slice images) and lends itself well to multiplanar reconstruction, allowing detailed evaluation of bony pathology, including subchondral bone pathology, which is particularly important in our equine athletes. Although articular cartilage cannot be directly evaluated using CT, the use of CT arthrography permits detection of articular cartilage defects or tears in intra-articular soft tissue structures, such as menisci or intra-articular ligaments.[35–37]

Positron emission tomography also excels at evaluation of subchondral and periarticular bone pathology, but from a functional, rather than structural perspective. Areas of increased radioavidity indicate increased bony modeling/remodeling activity. Although we expect some degree of bone turnover in athletes as their skeleton adapts to training demands, persistence or higher levels of radioavidity may indicate an area of concern, particularly if these lesions are the region that a lameness has been localized to. Much of the early research on PET has been performed on Thoroughbred racehorses, which tend to have a different spectrum of pathology than do sport horses. In Thoroughbred racehorses, lesions of the palmar/plantar condyles of MC/TIII and the proximal sesamoid bones are common.[38] In sport horses, more chronic, lower-grade subchondral bone injury is often the clinical concern.[39, 40]

Subchondral bone pathology in sport horses is an area in which the combination of structural (CT) and functional (PET) imaging can increase our diagnostic capabilities synergistically . Determining the significance of an abnormal area on CT scan can be challenging, as some abnormalities may not be clinically relevant. However, if the same area has increased radioavidity on PET scan, it is more likely that area is undergoing active remodeling, thus representing a clinical problem.[40] PET scan is a useful tool to monitor lesions over time.[41] Since functional abnormalities often precede structural abnormalities, PET scan may identify a lesion sooner than it is apparent on CT scan.

Tendons and ligaments

Although CT is often thought of as a tool for bone imaging, it provides very good images of tendons and ligaments in the distal limb.[42–44] It does not have the high contrast resolution of MRI, but the high spatial resolution is helpful, as is the thin-slice, cross sectional nature of the images. Pathology at entheses can generally be very well evaluated for hyper/hypodensity within the bone or avulsion fragments. The use of intravenous or intraarterial contrast can improve soft tissue lesion detection.[45–49]

The use of FDG in PET scan can identify areas of increased glucose metabolism within tendons or ligaments suggestive of lesions undergoing active repair.[50] This is useful in cases with ultrasonographic abnormalities that that may represent scar tissue from previous injury that is not a current clinical problem. Increased radioavidity at these locations supports the presence of an active lesion. Adding an NaF scan can identify areas of increased radioavidity at tendon/ligament entheses. The suspensory ligament is a good example of how NaF/FDG PET scan provides useful functional information to complement ultrasonographic examination.

4. Conclusion

The increased availability of CT and PET for horses has increased our diagnostic abilities for the sport horse. . Further work is needed to determine the clinical significance of many of these findings.

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Declaration of Ethics

The author adhered to the AVMA Principles of Veterinary Medical Ethics.

Disclosure of Financial Interests

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Neurologic Causes of Poor Performance Parts I and II

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Take Home Message: Successful performance in the horse depends on the normal function and integration of several body systems such as the musculoskeletal, neurologic, cardiovascular, and respiratory systems. Therefore, it is important to obtain a complete medical history and perform a full physical examination to start directing the next steps of performance evaluation and ruling out the involvement of specific body systems. Integration of the musculoskeletal and neurologic systems is essential for successful movement and performance. Corresponding and presenting author: University of California-Davis, Davis, California. Email: mraleman@ucdavis.edu

1. Introduction

Neurologic causes of poor performance can be of central origin (e.g., brain and spinal cord), peripheral (e.g., nerve rootlets, roots, plexuses (brachial, lumbosacral), nerves, neuromuscular junction), or a combination of both. Clinical signs vary according to location of disease and will be explained with examples of specific diseases in the following sections. A coordinated integrated movement depends on the function of all the components and pathways originating at the brain, going through the spinal cord and nerves ending at the limbs with feedback to the brain. Disease of any part of this pathway loop will result in alterations of gait and performance. Breeding practices for desirable traits such as specific gaits by breed have also inadvertently bred for undesirable traits. Cases of poor performance and gait deficits of neurologic origin affecting performance will be presented during the session. This manuscript will focus on neurologic causes of poor performance.

2. Neurologic Examination

This section will focus on the examination pertaining to gait and performance. In brief, the neurologic examination must include evaluation of behavior, state of consciousness (normal: bright, alert, responsive; abnormal: obtunded [quiet, dull whether standing or recumbent and responsive to non-painful stimuli], stuporous [recumbent and exclusively responsive only during painful stimuli], comatose [recumbent and not responsive to any stimulus]), cranial nerves (responses, reaction, reflexes), segmental (spinal) reflexes, posture and postural reactions (includes proprioception), palpation (detection of asymmetry, muscle mass and tone, pain), gait evaluation, and nociception (checking for conscious perception of pain) only in patients that are non-ambulatory and on which voluntary movement is not observed or is questionable.[1] This section will concentrate in the evaluation of segmental reflexes, posture and postural reactions, and gait.

Posture and postural reactions

Posture of the head, neck, trunk, tail, and limbs is important. Head tilt, neck turn, whole body leaning or drifting, trunk turn or scoliosis, lordosis, or kyphosis, wide- or narrow-based stance, tail down or up or pulled to the side could be ob served with neurologic disease. Postural reactions (proprioceptive placing and hopping tests) can be performed in the horse, but the examiner must practice caution due to safety concerns.

Proprioception is knowing position in space and can be evaluated by simply observing foot placement of the horse without intervention of the examiner or positioning the limb in different positions by the examiner (placing one limb far apart from the other or crossing one limb in front of the other) and observing when and how the horse replac-

es the limb. A repeated series of maneuvers followed by rest for several seconds to minutes to note foot placement provides reliable information of proprioception without exposing the handler and/or examiner to be crushed by a potentially collapsing horse. Horses with painful limbs might stand in unusual or abnormal position to protect the affected limb. Also, compliant or trained horses might hold an abnormal stance and complicate interpretation of limb placement. It is important to mention that proprioceptive deficits alone are not a localizable neurologic deficit to a specific area of the nervous system since these can be seen with brain, spinal cord, and peripheral disease. Therefore, the examiner should determine what other concurrent signs are present to further localize disease.

Segmental (spinal) Reflexes

Evaluation of segmental reflexes is limited in the standing horse. Segmental reflexes that can be evaluated in the standing horse include thoraco-laryngeal ("slap test"), cervicofacial/auricular, cutaneous trunci (panniculus), perianal, and perineal. Other segmental reflexes can only be evaluated in the recumbent relaxed (no increased tone) animal and include triceps, biceps, patellar, gastrocnemius, and withdrawal (flexor) reflexes. However, evaluating these reflexes in the recumbent adult horse can be challenging to perform and interpret.

Gait Evaluation

Causes of lameness or irregular gaits could be due to orthopedic, muscle, and neurologic disease. More than one system could be involved which complicates gait evaluation and interpretation. Lameness and neurologic examinations are a must in the horse presented for gait deficits or poor performance, especially if other body systems have been ruled out. The examiner must be familiar with various gaits depending on breed to avoid misinterpretation of gait alterations. There could be a "fine line" between what is considered a desired ("normal") and undesired gait when breeding horses for specific gaits (e.g., "floaty" gait in Warmblood breeds, hyperflexion gaits in Paso Fino and Peruvian Paso, pacing in Standardbreds).

Movement abnormalities include dysmetrias (abnormal range of movement: hypermetria, hypometria), ataxia (incoordination), paresis (decreased voluntary movement) or paralysis (no voluntary movement), weakness (lack of strength), hyperextension/hyperflexion, and specific gait deficits associated with nerves deficits (i.e. radial, femoral, sciatic, peroneal, tibial). Horses can be evaluated at the walk, trot and canter when safe. Helpful maneuvers include the following: walk and trot in straight-line, walk-in serpentine (zig-zag), walk with head elevated, walk while pullingtail in each direction, spin in tight circles, walk on uneven ground (back and forth over curb or cavaletti, up and down hill), and walk backwards. Using different surfaces (soft, hard, uneven, colors) can be very helpful to challenge locomotion skills especially in horses with subtle deficits. Flexion and extension of neck and limbs and repeating gait evaluation can be very helpful to detect deficits not previously seen or worsening of deficits that might suggest a dynamic (i.e., intermittent impingement or compression of spinal cord or nerves) component of disease.

2. Spinal Cord Disease

Motor or sensory deficits or both can be seen and depend on lesion localization within the spinal cord (Figure 1A). Motor deficits include paresis, paralysis, dysmetrias (hypermetria, hypometria), and weakness (often confused with paresis). Sensory deficits include ataxia, posture and postural deficits, proprioceptive deficits, and alterations in sensory input. Important to note the distinction between spinal cord segments (C1-C5, C6-T2, T3-L3, L4-S2, S-Caudal) versus cervical vertebrae articulations (C1-C2, C2-C3, C3-C4, C4-C5, C5-C6, C6-C7, and so forth) which are different. Horses have 8 cervical spinal cord segments and 7 cervical vertebrae. In this text, the distinction will be made when referring to spinal cord segments versus cervical vertebrae. Compressive myelopathies such as cervical vertebral compressive myelopathy, intervertebral disc disease, compressive soft tissue anomalies (e.g., synovial cyst, hypertrophy of ligamentum flavum), extradural or intradural masses (e.g., abscess, neoplasia), intramedullary masses (e.g., abscess, neoplasia), intramedullary anomalies (e.g., syringomyelia, syringohydromyelia) will result in both, sensory and motor deficits ***(Figure 1A)***. Equine protozoal myeloencephalitis usually causes a combination of motor and sensory deficits. Equine motor neuron disease affects lower motor neurons within the spinal cord resulting in motor deficits, whereas in neuroaxonal dystrophy the afferent proprioceptive tracts in the spinal cord are affected resulting mainly in sensory deficits. Note that areas within the brain (nuclei and tracts) can also be affected resulting in gait alterations. Neuroaxonal dystrophy (NAD) and equine degenerative myeloencephalopathy (EDM) are examples of neurodegenerative disease on which the lateral (accessory) cuneate, medial cuneate, and gracile nuclei of the medulla oblongata, and afferent proprioceptive tracts in the spinal cord are affected resulting sensory deficits such as proprioceptive ataxia, proprioceptive and postural reaction deficits ***(Figure 1A)***.

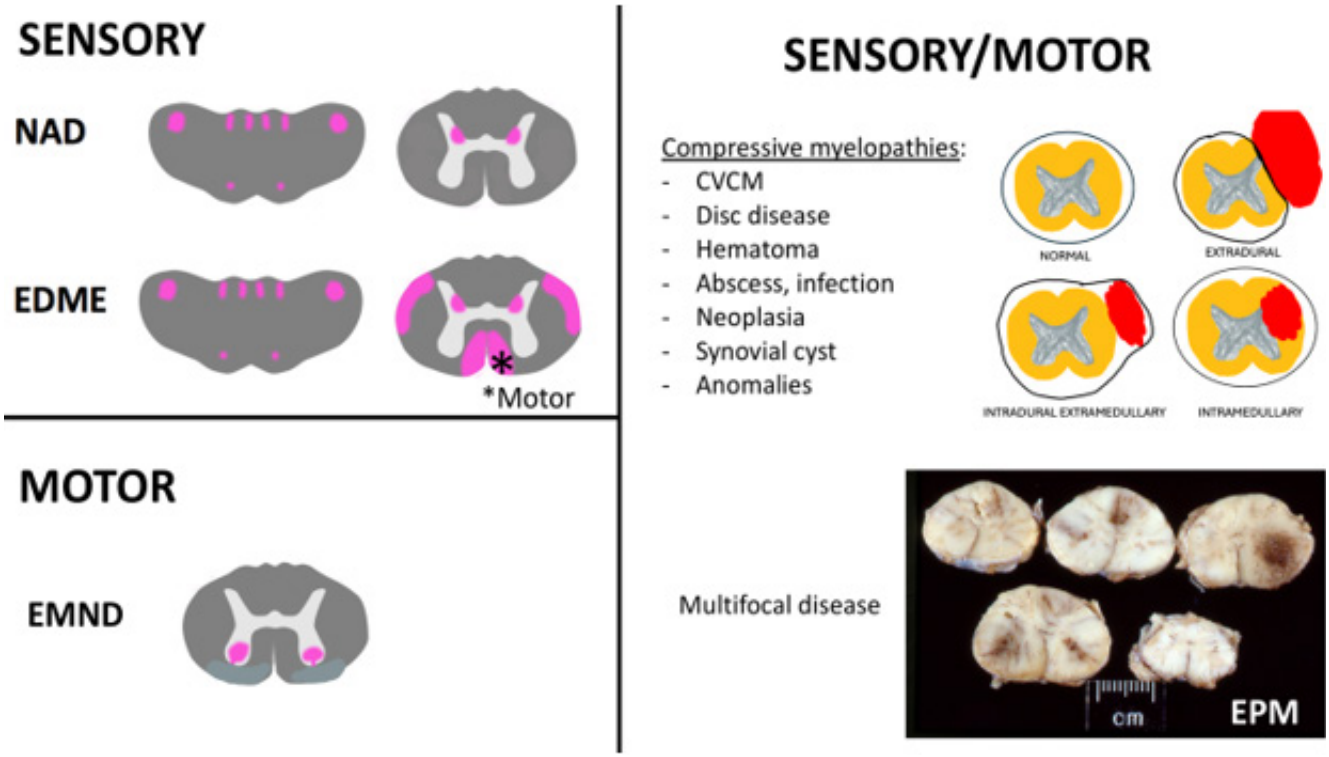


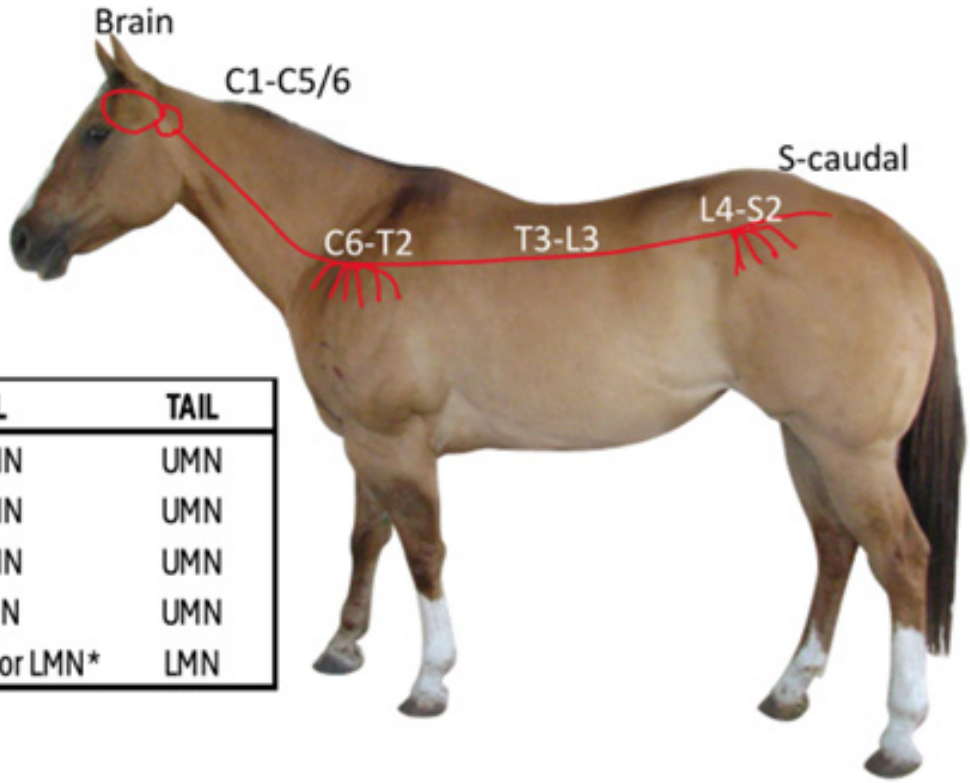
Figure 1A. *Spinal cord sensory and motor deficits (mapping of lesions). Examples of diseases causing sensory, motor, or both deficits are provided. NAD = neuroaxonal dystrophy, EDME = equine degenerative myeloencephalopathy, EMND = equine motor neuron disease, CVCM = cervical vertebral compressive myelopathy, EPM = equine protozoal myelitis (myeloencephalitis).*

To determine if ataxia is due to cerebellar (cerebellar ataxia), vestibular (vestibular ataxia) or spinal cord (general proprioceptive [spinal] ataxia), the examiner must assess if other signs of cerebellar or vestibular disease are present. These include for cerebellar disease: hypermetria, intention tremors, +/- lack of menace response; vestibular: pathologic nystagmus, positional ventrolateral strabismus, head tilt, body lean, circles in the direction of the head tilt; or none of these which supports spinal cord disease. Other neurologic deficits that can be seen with spinal cord disease include toe scuffing, dragging of the feet, delayed protraction, knuckling over, crossing over, stepping on itself, pivoting (leaving the foot stationary), circumduction ("swinging" of the limb), uneven/ irregular stride length.

In addition to ataxia with spinal cord disease, paresis and upper motor neuron (UMN) or lower motor neuron (LMN) deficits depending on location within the specific spinal cord segments can be seen ***(Figure 1B)***. With UMN involvement, the gait/stride could be exaggerated ("upper" hyper, exaggerated, elongated); whereas with LMN, the gait/stride is short, choppy with weakness that can result in a base-narrow stance and muscle fasciculations if severe. With LMN lesions, muscle atrophy happens earlier and faster in the course of disease than with UMN lesions, and usually more profound with LMN than with UMN disease. In chronic cases, the presence of muscle atrophy alone cannot help in distinguishing UMN versus LMN injury. Figure 1B summarizes UMN versus LMN signs depending on affected spinal cord segments. Note that urinary and rectal function might be abnormal depending on specific sacral spinal cord segments with cases of cauda equina commonly suffering from urinary and rectal retention and incontinence.

3. NEUROMUSCULAR SYSTEM DISEASE

The neuromuscular system has central (lower motor neurons influenced by both excitatory and inhibitory interneurons) and peripheral (nerve rootlets, nerve roots, ganglia, nerves, neuromuscular junction) components. The neuromuscular junction consists of the presynaptic (i.e., terminal axon and its membrane), synaptic space, and postsynaptic (i.e., myofiber membrane innervated by specific motor neuron) areas. Neuromuscular disorders can be diffuse or involve a single nerve. Diffuse neuromuscular disease induces generalized weakness, difficulty supporting weight, base-narrow stance, paresis or paralysis, muscle fasciculations, and tendency to become recumbent. Segmental reflexes can be decreased or absent in neuromuscular disease. The two most common diffuse neuromuscular diseases of horses are equine motor neuron disease and botulism. Fo-



LESION	TL	PL	TAIL
C1-C5	UMN	UMN	UMN
C6-T2	LMN	UMN	UMN
T3-L3	NORMAL	UMN	UMN
L4-S2	NORMAL	LMN	UMN
S-CAUDAL	NORMAL	NORMAL or LMN*	LMN

Figure 1B. *Spinal cord segments. Depending on neuroanatomical localization of disease within the spinal cord, upper (UMN) or lower motor neuron (LMN) signs will be observed. TL = thoracic limbs, PL = pelvic limbs, * = normal or abnormal depending on specific location (example: sciatic nerve originates from cranial sacral spinal cord segments).*

cal LMN disease or neuropathies lead to specific signs pertaining to the region affected, such as specific gait deficits and focal muscle atrophy.

4. DISTINCTION OF GAIT DEFICITS FROM NEUROLOGIC VERSUS ORTHOPEDIC DISEASE

Distinction of gait abnormalities from neurologic versus orthopedic origin is essential to formulate a list of possible causes, direct diagnostic plan with the goal of providing a clinical or definitive diagnosis, provide appropriate therapy, and possible outcome. However, making this distinction could be challenging in some cases and often both neurologic and orthopedic disease present concurrently.

It is especially challenging diagnosing gait abnormalities that are intermittent. Cases with a history of intermittent thoracic limb lameness or lameness which origin cannot be determined through perineural or intra-articular anesthesia at multiple locations, should raise the suspicious of possible lameness of neurologic origin such as nerve root or nerve impingement or compression as the nerve exits the intervertebral foramen. Detection of pain in these cases is also important as nerve compression is painful. This compression could be intermittent when the horse move, specially upon flexion or extension of the neck; usually upon extension when the intervertebral foramen of the caudal cervical vertebrae normally narrows down. Complete lack of extension the carpus, knuckling, tripping, stumbling, and fasciculation of the affected thoracic limb are signs of weakness which could be of neurologic origin as in nerve compression. The following section will provide examples of neurologic causes of gait abnormalities.

Gait alterations can be consistently regular or irregular in terms of pattern. Limb movement and foot placement is going to vary according to underlying origin of lameness. The following is a guideline that have been useful for this author:

- **Consistent regular gait abnormality.** This is more likely to be observed with lameness from orthopedic or muscle origin. The gait usually follows a regular abnormal pattern. In other words, the lameness does not change in terms of arch of flight and foot placement. The exception of neurologic disease would be causes affecting specific nerves, on which the gait abnormality will be more consistent and regular in its pattern. For example, horses with femoral nerve paresis are going to drop their stifle in a consistent way because of the lack of dysfunction of the nerve exerting normal innervation to the quadriceps muscle supporting the stifle

and therefore drop. Shivers and stringhalt are also examples of neurologic disease on which the gait abnormality presents a consistent pattern (discussed in following sections).

- **Consistent irregular or inconsistent gait abnormality.** The pattern of the abnormality, whether the arch of flight or foot placement will vary in an inconsistent manner. Horses with spinal cord disease are an example of limbs moving in various ways whether motor (e.g., hypermetric, hypometric, paresis, weakness) or sensory (e.g., proprioceptive ataxia, abnormal postural reactions, and proprioceptive deficits when standing still) deficits. Horses might interfere with their limbs their own gait, step on themselves, knuckle, trip, stumble, drag, circumduct, pivot; all varying and manifesting in an inconsistent way.

4. NEUROLOGIC CAUSES OF GAIT ABNORMALITIES

Following teaching practices for enlisting possible causes of disease based on a classification scheme: DAMNIT-V approach, examples will be provided where D = degenerative, A = anomaly, M = metabolic, N = nutritional, neoplasia, I = inflammatory, infectious, immune-mediated, T = trauma, toxic, and V = vascular. Examples of disease are provided below. Some diseases might fit into more than one category. Of note is that neurodegeneration can occur with aging, therefore not a disease.

Degenerative disease: Cervical vertebral compressive myelopathy, neuroaxonal dystrophy/equine degenerative myeloencephalopathy (NAD/EDM), equine motor neuron disease, intervertebral disc disease.

Anomaly: Axial skeletal malformations such as vertebral malformations, synovial cyst (could also be acquired), syringomyelia, syringohydromyelia.

Nutritional: Vitamin E deficiency.

Neoplasia: Primary (e.g., lymphoma), secondary (e.g., melanoma).

Inflammatory, infectious, immune-mediated: Equine protozoal myelitis, viral encephalomyelitis (e.g., herpes virus, West Nile virus, other equine encephalitis), *Anaplasma phagocytophylum*, parasitic, fungal.

Trauma: Self-explanatory.

Toxic: Ingestion of plants, drugs, chemicals, toxins, toxico-infectious (e.g., botulism). Note: Toxic causes usually involve more than one body system such as ionophores toxicity which affects cardiovascular, muscle, and nervous system.

Vascular: Primary (anomalies) or acquired vascular injury.

5. DISORDERS CAUSING GENERAL PROPRIOCEPTIVE (SPINAL) ATAXIA

The top two most common causes of spinal ataxia in horses are cervical vertebral compressive myelopathy and neuroaxonal dystrophy/equine degenerative myeloencephalopathy.[2] Other common causes include trauma and infectious causes such as equine protozoal myelitis, and viral myelopathies such as those caused by equine herpes virus and West Nile virus.[2] Ruling out equine herpes virus in horses with fever and acute onset of ataxia is a priority due to its highly contagious nature.[3] Depending on geographic location, *Anaplasma phagocytophylum* infection should be a consideration for cases with fever and acute onset of ataxia.[4] Overall, signs of spinal cord disease will vary depending on disease process and lesion localization (motor: UMN versus LMN, sensory; ***Figure 1A***).

Cervical vertebral compressive myelopathy (CVCM)

Cervical vertebral compressive myelopathy is the most common cause of proprioceptive (spinal) ataxia in the horse which neurologic signs been recognized since 1860 and termed as "Wobbler syndrome" in 1938.[5] The disease is also known as cervical vertebral stenotic myelopathy (CVSM), cervical vertebra malformation (CVM), and cervical vertebral instability.[6] Both symmetrical and asymmetrical ataxia, hypermetria, paresis, and proprioceptive deficits can be observed depending on the site of compression. The pelvic limbs (PL) are commonly more severely affected by 1 grade (Mayhew grading scale[7]) than the thoracic limbs (TL) due to the more superficial location of the proprioceptive tracts of the PL compared to those of the TL, or similarly affected TL and PL. Acute, subacute, or chronic onset of signs can happen and progression of disease is usually slow but acute exacerbation of signs is not uncommon. Progression results from ongoing spinal cord compression or repeated trauma as in the case of "dynamic" compression (compression exacerbated by neck flexion or extension). Compression of C1-C5 spinal cord segments results in UMN signs to all limbs, whereas compression in caudal cervical spinal cord segments causes LMN to TL and UMN to PL. A mixed disjointed gait with UMN and LMN can also be observed with spinal cord compression at the caudal neck region.

The disease has been reported in various breeds including Warmblood, Thoroughbred, Tennessee Walking Horse, Quarter Horse, Arabian, and Morgan, among others. Males are more likely to be affected than females (ratio of 3 to 1).[6] Horses less than seven years of age likely to be affected. CVCM has been classified into two main categories as: Types I and II.[6] Type I CVCM usually affects young horses most commonly Thoroughbreds on which multiple factors such as genetic, sex, rapid growth, diet, and trauma contribute to development of disease. Developmental abnormalities include cervical vertebral malformation, stenosis of the vertebral canal, enlargement of physes, extension of the vertebral arch, malalignment of vertebral bodies, and malformation of articular processes. Type II affects older horses of all breeds causing osteoarthritic (OA) changes resulting in spi-nal cord compression. It is important to mention that not all older horses with OA will result in spinal cord compression.

Diagnostic modalities include imaging: Plain radiographs (lateral, oblique, neutral, flexion, extension of the neck), myelogram (neutral, flexion, extension), CT myelogram (neutral, flexion, extension). Depending on equipment availability, size of equipment (large enough to fit a horse's neck and perform dynamic views), size of animal, time of anesthesia or other concerns might dictate which imaging modalities will be performed. Evaluation of spinal cord injury in live horses would require an MRI. Currently, there are several studies on imaging to study neck pathology. Other modalities that would be helpful in the diagnosis of spinal cord disease, such as electromyography (mapping spinal cord segments by muscles innervated by specific segments), nerve conduction studies, transmagnetic stimulation (study motor pathway), and transcranial electrical stimulation (motor pathway), are being underutilized.[8,9] Important to note is ruling out other causes of proprioceptive (spinal) ataxia. For more in-depth information about CVCM, medical management, ground exercises and physical therapy to maintain muscle tone, and surgical options, the reader is referred elsewhere.[6]

Neuroaxonal dystrophy/equine degenerative myeloencephalopathy (NAD/EDM)

Equine neuroaxonal dystrophy/equine degenerative myeloencephalopathy is an inherited neurodegenerative disease associated with vitamin E deficiency in the first year of life.[10, 11] This disease is the second most common cause of proprioceptive (spinal) ataxia.[2] Ataxia is usually mild to moderate.[10] The disease has been reported in various breeds such as Quarter Horse, Warmblood, Thoroughbred, Lusitano, Standardbred, Morgan, and Gypsy Vanner, among others.[11, 12] Manifestations of disease can occur as early as two months of age which can be missed because of gradual subtle onset.[10] Most often signs are noted at 6 to 24 months of age. Signs can range from impaired performance to obvious neurological signs such as symmetrical proprioceptive ataxia, proprioceptive and postural reaction deficits, and wide base stance at rest.[11] Deficits are similar in thoracic and pelvic limbs or worse in the pelvic limbs.[10] Tetraparesis is also a common sign with involvement of ventromedial tracts.[10] Other spinal cord diseases with similar signs must be ruled out such as CVCM and EPM.[11] Quarter Horses might have a calm quiet demeanor, whereas aggression has been reported in some Warmbloods with EDM.[10, 13]

The definitive diagnosis is currently determined by histopathological evaluation.[10] There are no macroscopic lesions.[10] The lesions consist of bilateral symmetrical neuronal degeneration and vacuolation with neuronal loss and axonal spheroids in the caudal brainstem and spinal cord.[10] The nuclei affected within the brainstem include the nucleus gracilis, cuneatus medialis, and cuneatus lateralis.[10] In the spinal cord, symmetric degeneration within the nucleus thoracicus, dorsolateral, and ventromedial white matter tracts can be observed.[10] Phosphorylated neurofilament heavy chain (pNfH), a protein released after axonal damage, can be measured in serum (reference range 0-1 ng/mL) and cerebrospinal fluid (0-3 ng/mL).[14] This protein has demonstrated specificity for NAD/EDM (serum > 1 ng/mL) but with an overall low sensitivity.[14] This protein can also be elevated with other neurologic diseases on which axonal damage occurs. It is also important to mention that pNfH within reference range does not rule out disease.[14] This reinforces the need for ruling out other diseases.

Primary source of vitamin E includes fresh grass. Environmental conditions such as drought, farming and harvesting management, bailing of hay, and others can substantially alter the content of vitamin E in forages.[11] Pregnant mares during the last trimester of pregnancy and foals from families with a known history of NAD/EDM should be supplemented with natural α-tocopherol at 10 IU/kg once daily to prevent development of clinical or severe manifestations of disease in individuals at risk.[10 11] Daily administration of 10,000 IU of natural α-tocopherol to adult horses crosses the blood brain barrier, reaching the brain and spinal cord.[15]

Equine protozoal myeloencephalitis (EPM)

Several studies including consensus statements are available on EPM and readers are referred elsewhere.[16] A few points here for clarification. Testing should be reserved

for those horses with neurological signs. More commonly, signs consist of asymmetrical multifocal central nervous disease such as brain and spinal cord, multifocal within the brain and spinal cord, multifocal within the spinal cord, or combinations. However, symmetrical unifocal or diffuse spinal cord disease is also seen and diseases such as CVCM and NAD/EDM (the top two most common spinal cord diseases in horses) must be ruled out. Large scale study on seroprevalence for antibodies for *S. neurona* and *N. hughesi* demonstrated antibody titers in a high percentage of horses even in the absence of neurologic disease across the United States with some regions as high as 84% of horses tested.[17] Validated serologic tests in serum and CSF in support of antemortem clinical diagnosis of EPM include immunofluorescent antibody test (IFAT) and *S. neurona* surface antigen (SnSAG) immunosorbent assay (ELISA).[18-20] Both, serum and CSF samples must be tested concurrently for antibodies to determine if antibodies in CSF are higher in proportion and relation to those of serum antibodies (intrathecal production). Serum to CSF ratios of < 64 and < 100 in IFAT and SAG ELISA, respectively, are supportive of clinical disease. More recently, *Toxoplasma gondii* has been suspected to be a causative pathogen of EPM.[21] However, IFA titers for *T. gondii* have also been identified in horses with no neurologic disease.[22]

6. DISORDERS ASSOCIATED WITH NECK PATHOLOGY

Various phenotypes have been associated with neck pathology involving the vertebral column (cervical vertebrae, first thoracic vertebrae), soft tissues, or combinations. Phenotypes include: neurologic, thoracic limb lameness, neck pain, neck stiffness, altered behavior (e.g., unpredictable, explosive, aggression, seizure-like), poor performance, head shaking, sensory deficits, patchy sweating, and combinations of these.[9] Neurologic manifestations include proprioceptive (spinal) ataxia, tetraparesis, dysmetria, UMN or LMN or combination depending on lesion location (spinal cord segments: C1-C5, C6-T2, or C1-T2). Intervertebral foramen disease of the caudal cervical vertebrae and C7-T1 such as that secondary to severe osteoarthritis with obliteration of the foramen resulting in nerve impingement or compression has been recognized as a cause of nerve pain, intermittent lameness, stumbling, tripping, knuckling at the carpi, weakness, and collapse of the thoracic limbs.[9] Similarly, abnormalities of the junction of the first thoracic vertebrae and its corresponding ribs contributing or causing disease such as brachial plexus disease and neuropathies have been recognized.[23, 24] Studies on imaging modalities describing the various pathological entities of the neck with focus on the caudal cervical vertebrae, first thoracic vertebrae, and ribs in association with clinical disease is underway by various groups.[9, 23-29]

7. MOVEMENT DISORDERS

Movement disorders (dyskinesias) are a heteroge nous complex group of disorders that result in recurrent episodes of involuntary movement without changes in consciousness.[30] Definition and classification of specific disorders in horses like those in human medicine are not available due to their complexity, and differences in locomotion. In horses, movementdisorders are termed by their clinical manifestations such as “stringhalt” and “shivers”. In stringhalt, horses present as if they have a string halting their pelvic limbs into a predetermined gait consisting of hyperflexion of one or both pelvic limbs towards their abdomen while horses are walked or trotted. Horses with shivers “shiver” in their pelvic limbs and sometimes tail as they walk backwards without affecting forward gaits until advanced progression of disease.[31] These horses exhibit abduction of one or both pelvic limbs in either hyperflexion or hyperextension when walked backward.[31] Studies by Valberg and collaborators have identified that selective cerebellar Purkinje cell axonal degeneration is associated with shivering resulting in abnormally elevated muscle recruitment of the pelvic limbs, particularly the biceps femoris and vastus lateralis during backward walking.[32, 33] For in-depth information about these two disorders, the reader is referred elsewhere.[31]

Stiff horse syndrome is a rare disorder characterized by muscle rigidity, episodes of severe muscle contractions, stretched-out or camped posture, apparent muscle cramps, and prolonged recumbence.[34, 35] These episodes of stiffness are often induced by startling or excitement. Glutamic acid decarboxylase (GAD) antibodies have been identified in CSF from horses with this rare syndrome.[35] This enzyme produces the active form of the inhibitory neurotransmitter gamma amino butyric acid. Spontaneous electrical activity of muscles based on electromyography is seen during episodes. Other less defined patterned involuntary movements have been observed in the horse and manifested as paroxysmal movement with or without tremors and alterations in muscle tone.

Neuromyotonia is a rare progressive nerve disorder characterized by hyperexcitability that causes muscle twitching at rest (myokymia), cramps, impaired muscle relaxation, and spontaneous abnormal activity on electromyography.[36, 37] Myokymia is manifested as a continuous undulating or wave-like movement of the overlying skin.[36] Long term follow up of suspected horses is not available.

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Declaration of Ethics

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Percutaneous Single Portal Endoscopic Foraminotomy:
Indications, Outcomes and Case Examples

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Take Home Message: Endoscopic foraminotomy is a novel minimally invasive surgery for treatment of cervical radiculopathy in the horse. Corresponding and presenting author: Ocala Equine Hospital, Ocala, Florida. Email: travistull@gmail.com

1. Introduction

Cervical radiculopathy is defined as cervical spinal nerve injury at the intervertebral foramen.[1] The condition has been recognized in horses and is a contributor to forelimb lameness and cervical pain/dysfunction.[2–7] In humans, it is most commonly associated with disc disease, spondylosis, cysts, tumors, or vascular anomalies.[1] In the horse it appears to be primarily caused by articular process joint osteoarthropathy and enlargement.[2, 8, 9] Previous medical treatments include ultrasound guided cervical spinal perineural corticosteroid injection, rehabilitation, or complementary medicine.[3, 10–14] Recently, a novel minimally invasive surgical approach was published, allowing the widening of the intervertebral foramen through a single incision.[2] The author adopted the technique after training with Dr. Swagemakers in Germany and performed the first foraminotomy in the United States. Subsequently, the author has performed thirty-one procedures to date.

2. Case Selection for Edoscopic Foraminotomy

Case selection for endoscopic foraminotomy (EF) is complex. Currently, the author identifies horses with cervical pain by ruling out other possible causes of the clinical signs and performs computed tomography (CT) or CT dynamic myelogram. Perineural cervical spinal nerve diagnostic analgesia can lead to recumbency and is not recommended. (personal communication Dr. Jan-Hein Swagemakers). Intra-articular analgesia of the articular process joint can be performed but is not specific for cervical radiculopathy. If there is evidence of mild to moderate intervertebral foraminal stenosis (IVFS) then either medical treatment or surgery is recommended. Ultrasound guided perineural cervical spinal nerve injection with corticosteroids can be utilized to gauge response to therapy. A positive response reinforces the diagnosis, although a negative response does not mean surgery would be inappropriate. Although a computed tomographic grading system for IVFS does not exist, surgery is often recommended for horses with more severe computed tomographic findings. Many horses with IVFS will have multiple areas of cervical spinal pathology. The best candidate has two or fewer sites of IVFS, no evidence of spinal cord impingement/compression, and minimal ataxia on clinical examination. Further complicating treatment options are horses with negligible clinical signs or signs that don't correspond to the most significant pathology. The author is currently exploring the use of electromyography to help determine if there is a dysfunction of the specific cervical spinal nerve in question.[15–19]

3. When Surgical Intervention is Recommended

When surgical intervention is recommended horses are placed in lateral recumbency under general anesthesia with the affected side up. The surgery site is identified with fiduciary markers and lateral to lateral cervical radiographs.

Richard Wolf Spine's instruments, specifically the Vertebris lumbar set, are utilized. A guide pin is placed under ultrasound guidance dorsal to the intervertebral foramen (IVF) on the ventral aspect of the articular process. A small 2-3 cm skin incision is made, and graduated dilators that slide over the guide pin are used to bluntly dilate a path through the cervical musculature. A cannula is then advanced over the dilators, which are then removed. The endoscope is placed in the cannula, and dissection commences through the musculature using radiofrequency and hand instrumentation. Once the ventral edge of the articular process is identified varying size rotary burrs are used to enlarge the foramen. A postoperative CT is performed immediately after the procedure and the horse is placed in a padded recovery stall and hand assisted to stand with a rope secured to the halter and tail.

• **Intra-Operative Complications** include those that accompany any anesthesia, hemorrhage that obscures the surgical field, and disorientation due to inadequate landmarks/patient positioning. Immediate post operative complications are prolonged recumbency, neuropathy, ataxia, pain. Short to long term complications are increased ataxia that usually resolves in 4-8 weeks, local muscle atrophy, localized sweating, and failure of resolution of clinical signs.

• **Postoperative Care** includes three days of stall rest and then a rehabilitation/controlled exercise schedule that progresses to ridden work six weeks after surgery ***(Figure 1).*** The author believes rehabilitation is as important as the surgical procedure.

OCALA EQUINE HOSPITAL

Neurologic Disorders -Controlled Exercise Program

With any neurologic disorder, the rehabilitation goal is to retrain the neurologic and musculoskeletal system through neuromotor training. This involves exercises designed to encourage proprioception, sensory input, and motor control to aid balance, strength, and coordination.

- Note: Day 0=day of surgery.
- 0-3 days
  - Strict stall rest
  - No hand walking
- 3-14 days (day 3-2 weeks after surgery)
  - Small paddock turnout (no larger than 30' X 30') or round pen turnout is ok provided the horse remains calm and the incision stays dry and clean.
  - Start small paddock turnout for small amounts of time and slowly increase duration up to 8-10 hours per day
  - Hand walking 2-3 times daily (twice is better than once)
  - Begin with 5 minutes 2-3 times daily slowly increase the amount of time on each walk.
  - Do not exceed a total of 45 minutes per day
  - While remaining in a safe environment walking over differing surfaces, textures, elevations, and even ground poles is encouraged.
  - Walk in a serpentine or figure of 8 patterns for part of the time.
  - You can also walk up and down small hills if available/safe for horse and handler.
  - Incorporate active and passive range of motion exercises for the neck (flexing the neck to the right or left by pulling on the halter with the horse standing square up front or encouraging the horse to bend to the right and left and up and down with treats.)
  - Holding up a leg for a short duration can also improve balance and proprioception.
  - Any passive/active stretching of the limbs is also beneficial.
- 14-28 days (2 weeks to 4 weeks after surgery)
  - Continue small paddock turnout
  - Begin lunging (walk, trot, canter) slowly in a halter or bridle whichever yields more control (no riding), 10 minutes once daily for the first 5 days increasing to twice daily after that timeframe.
  - After 3 days of twice daily lunging for 10 minutes increase the amount of time for each lunging session gradually not exceeding 25 minutes twice daily
  - When lunging apply support boots or wrap the lower limbs as this helps stimulate proprioception
  - You can also utilize Thera-Bands or body wraps to encourage core strength and proprioception while lunging.
  - Continue the range of motion exercises mentioned above.
- 28-42 days (4 weeks to 6 weeks after surgery)
  - Have your veterinarian re-evaluate your horse.
  - If cleared for continued work:
  - Small paddock turnout (no larger than 30' X 30') for as many hours in the day as possible
  - Increase the lunging walk, trot, canter to 2-3 times daily for up to 25 minutes a session.
  - You can add tack during the lunging and consider incorporating equine balance band system (equinebalancebands.com)
  - At this point long lining under tack would also be appropriate provided it is safe to do so.
  - Continue with recommendations for proprioception and range of motion mentioned above as well
  - Six weeks from surgery begin work under tack slowly under the guidance of your veterinarian and return to routine care/turnout

Figure 1. *Recommended rehabilitation schedule post-operatively.*

4. Conclusion

To date the author has performed 36 surgeries on 28 horses. Clinical signs include refusal to go forward, behavioral changes (bucking, rearing, bolting), intermittent forelimb lameness, multiple limb lameness, and inability to raise the head. Complications have included 2 horses whose intra-operative bleeding required early cessation of surgery (they were successfully operated one week later), one fatality that appeared to have cerebral/hindbrain ischemic injury (pathology pending), one horse that had hindlimb ataxia that resolved in 2 hours, and one horse with minor forelimb neuropathy (resolved in 2 weeks) and hindlimb ataxia (resolved in 4 weeks) and subsequently developed supraspinatus and infraspinatus atrophy, and one horse that had worsened ataxia in the hindlimbs that resolved in 6 weeks post-operatively. Currently, 21/28 horses are back in ridden work 5/28 are still in rehabilitation; one horse did not recover, and one horse died in a paddock accident after it had commenced riding again. Surgical sites included twenty-six C6-7, seven C5-6, and three C2-3. Four horses had two bilateral C6-7 surgeries, and 5 horses had unilateral surgeries at C5-6, and C6-7. Dr. Swagemakers has performed 256 procedures on 170 patients, with 72.2% back in ridden work and over 80% having significant improvement, with half of those back to pre-performance levels or better (personal communication Jan-Hein Swagemakers).

The author is in the process of gathering information via anonymous surveys on owners' opinions of outcomes. Based on initial feedback from referring veterinarians and trainers, the outcomes have been similar to those in Germany.

There are still many questions about the procedure and information to be learned. It is currently unknown if the IVFS will return and, if it does, how long post-procedure. Identifying clinically affected horses remains a challenge. Many patients have multiple areas of pathology and varying clinical signs, which often don't correlate with the imaging findings. Preliminary results have been very encouraging, and the author strongly believes these horses have reduced signs of clinical pain often several days postoperatively. Seven institutions across the country offer the procedure, with several more in the process of acquiring equipment. More information should be available for case selection, prognosis, and long-term outcomes as more surgeries are performed.

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Declaration of Ethics

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Frontiers in Pituitary and Metabolic Dysfunction:
Updated Diagnostics and Current Treatments

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Take Home Message: Endocrine and metabolic disorders have wide-ranging effects. Not only problematic by themselves, as comorbidities they provide a diagnostic challenge as their combined clinical appearance can be at times confusing. Current concepts in diagnosis and management of both pituitary ***pars intermedia*** dysfunction and insulin dysregulation are ever evolving with realization of the challenges of definitive diagnosis in the live horse and inadequacies of many treatment options. Corresponding and presenting author: Rood and Riddle Equine Hospital, Lexington, Kentucky. Email: pmorresey@roodandriddle.com

1. What is Going on with Pituitary *Pars Intermedia* Dysfunction (PPID)?

Pituitary *pars intermedia* dysfunction (PPID, Cushing's syndrome) is a common condition of aged horses and ponies in which inhibition of the intermediate lobe of the pituitary is lost due to degeneration of hypothalamic dopaminergic neurons. During the initial stages of this syndrome, cellular hyperplasia of the intermediate lobe results in increased levels of pro-opiomelanocortin (POMC), α precursor molecule cleaved into many peptides including α-melanocyte stimulating hormone (α-MSH), adrenocorticotropic hormone (ACTH), β-endorphin and corticotropin-like intermediate lobe peptide (CLIP). As the syndrome progresses, the *pars intermedia* enlarges to a degree that a singular intermediate lobe adenoma develops that compresses adjacent pituitary and hypothalamic structures.

2. What is Going on in Equine Metabolic Syndrome/ Insulin Dysregulation?

Insulin dysregulation (ID) was first proposed as a cause of glucose intolerance, elevated insulin concentration, dyslipidemia, and hypertension in humans over 30 years ago.[1] Metabolic syndrome has developed from this concept, being defined as a combination of cardiovascular risk factors including such diverse components as visceral adipose accumulation, insulin resistance, hyperinsulinemia, hypertension, chronic inflammation, microalbuminuria, and a prothrombotic state leading to endothelial cell dysfunction and atherosclerosis.[2] This concept has been extensively reviewed in horses[3], and a parallel increase in pro-inflammatory compounds concurrent with insulin insensitivity has been demonstrated. Fasting hyperinsulinemia, an excessive insulinemic response to oral carbohydrates, and tissue insulin resistance can be considered hallmarks of equine ID.

Adipose tissue is not simply a store of excess energy but is rather an organ of diverse functions which plays a pivotal role in development of metabolic syndrome.[4] Adipokines, biologically active hormone secretions of adipose tissue, may play a role in the pathogenesis of insulin resistance as some have been shown to have effects on insulin sensitivity and signaling.[5] It is the resulting hyperinsulinemic proinflammatory state that is thought to drive the laminitis seen in affected horses.

Considerable debate exists regarding the etiology and pathogenesis of metabolic syndrome as no single unifying mechanism has yet been elucidated.[6] A complex interaction between genetics, hormonal status and nutrition is most likely. It is most instructive to consider ID as the salient underlying risk factor for the clinical syndrome.

Other markers of obesity and ID have been investigated. The entero-insular axis consists of incretins released by the intestine following carbohydrate ingestion. The two most

prominent incretins are glucagon-like polypeptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).[7] Adiponectin is an anti-inflammatory adipokine produced by adipocytes affecting glucose regulation. Levels are negatively correlated with body mass index in some studies. In other studies where obesity was absent, reduced adiponectin concentrations were associated with ID and laminitis risk.[8] Leptin has been associated with decreased insulin sensitivity however increased leptin appears associated with increased body condition.[9]

3. Is Pituitary Dysfunction Related to Insulin Dysregulation?

Phenotypically, horses with ID or PPID may be indistinguishable in the initial stages of either condition as both may display abnormal adiposity and hyperinsulinemia with hyperglycemia. A relationship between the onset of metabolic syndrome and PPID is anecdotally reported, although it is not clear how PPID induces ID. Both conditions increase in prevalence with age, therefore they may be coincidental.[10, 11] However, one study determined that horses with PPID were 2.7 times more likely to display hyperinsulinemia compared with aged-matched controls.[10] Increased ACTH secretion can lead to hypercortisolemia which has profound effects on metabolic and immune function. There is evidence that pituitary peptides such as CLIP may disturb insulin regulation.[12] Yet another recent study found no influence of PPID or pergolide on the levels of insulin or cortisol, and no effect on reduced immune function in PPID horses was seen with pergolide treatment.[13]

4. Pituitary *Pars Intermedia* Dysfunction (PPID, Cushing's Syndrome)

In PPID, following loss of hypothalamic dopaminergic inhibition acting on the *pars intermedia*, increased synthesis of POMC peptides and proliferation of melanocytes occurs. Hypertrichosis, chronic infections, loss of muscle mass, abnormal fat deposition, slow wound healing, polyuria and polydipsia, and lethargy are common clinical signs. It is thought that altered secretion of prolactin and the gonadotrophic hormones may potentially influence reproductive function. A significant proportion of PPID affected horses are concurrently afflicted with ID.

5. Diagnosis of PPID

No existing ante-mortem diagnostic technique can be completely relied upon for confirmation of PPID. The presence of hypertrichosis in an aged horse is strong evidence to make a presumptive diagnosis of PPID.[10] Subclinical cases are more difficult to detect and diagnose, with screening for subclinical disease of debatable value. However, initiating treatment prior to progression to end-stage seems desirable. Untreated PPID cases (possibly resulting from false-negative test results) can lead to issues with thermoregulation, loss of muscle mass, and opportunistic infections. False positive test results are also financially burdensome if accompanied by unnecessary treatment.

Seasonal variations in *pars intermedia* secretion are well-known, with a seasonal rise in ACTH concentrations naturally occurring in the fall in preparation for winter. Of interest, basal and thyrotropin-releasing hormone (TRH)-stimulated ACTH concentrations in late summer/early fall identify horses that transition to clinical PPID over the next few years in one study.[14] While results may be equivocal, this suggests early diagnosis may be possible.

Basal ACTH Concentration

This test is easy to perform with only a single sample required at any time of day. Basal ACTH concentration follows a circannual rhythm in all horses with a peak concentration occurring in the autumn months. Seasonally adjusted diagnostic cut-off values have been suggested to improve detection of early PPID when clinical appearance is considered. Assessment of basal ACTH concentration is excellent for ruling out PPID, but less accurate for detecting the condition prior to the horse displaying overt clinical signs. Therefore, basal ACTH concentrations are not recommended as a screening test or for horses early in the disease, however basal ACTH concentrations appear more sensitive for detection of the condition in autumn. Some breed differences occur in late summer and early fall. Once collected in an EDTA tube, the sample should be centrifuged, refrigerated at 4°C, then assayed within 24 hours. Freezing beyond this period is necessary to avoid heat degradation of ACTH, however multiple freeze-thaw cycles should be avoided. Equivocal results should prompt a TRH stimulation test due to greater accuracy of this test.

TRH Stimulation

Provocative dynamic testing improves diagnostic accuracy when signs are mild or PPID is early in the course of disease and perhaps subclinical. Thyrotropin-releasing hormone increases ACTH and α-MSH concentrations in plasma via TRH R1 receptor stimulation within the pituitary *pars intermedia* and *pars distalis*. In horses affected by PPID, TRH stimulation results in proopiomelanocortin (POMC)-derived peptide secretion by melanotrophs of the *pars intermedia*. This excessive ACTH secretion by hyperplastic melanotrophs is unaffected by the usual negative feedback loop involving glucocorticoids.

Measurement of ACTH concentration 10-minutes post TRH administration is widely practiced. There is a large variation in ACTH levels one minute either side of the 10-minute time point in one study[15] leading some researchers to suggest assay at 30 minutes post TRH maximizes accuracy especially when testing is repeated.

To investigate whether horses with pain presented a challenge regarding the utility of the TRH-stimulation test, ACTH and cortisol concentrations were assessed in horses with colic, orthopedic, and laminitis post TRH administration using standard testing protocols. No differences were found between groups with respect to pain and disease status, however response to TRH may have been attenuated. The authors concluded horses in mild to moderate pain remained candidates for TRH-stimulation testing in the diagnosis of PPID.1[6]

Side effects occur in some horses with flehmen response, yawning, coughing, and muscle fasciculations noted. These are mild and self-limiting. Available TRH is synthetic thyrotropin releasing hormone and commercially available from chemical suppliers and some compounding pharmacies.

Other Testing

The dexamethasone suppression test requires two samples (pre and 18-20 hours post 0.04mg/kg dexamethasone IM). Normal horses display suppressed cortisol secretion due to negative feedback diminishing ACTH production by the corticotrophs of the *pars distalis*. In PPID, this suppression of cortisol production is lost as melanotrophs of the *pars intermedia* continue excessive ACTH secretion.

6. Treatment of PPID

Treatment involves control of resultant clinical signs, and this is achievable by attentive management practices. Medical treatment cannot cure the underlying hypothalamic and pituitary pathology.

Pergolide Mesylate

Pergolide is the treatment of choice and only medication registered for use in PPID. Pergolide is a synthetic D2-dopamine agonist with high affinity for the inhibitory receptors on the *pars intermedia* melanotrophs. Production of POMC is rapidly reduced, diminishing clinical signs and limiting PPID-induced morbidities within a short time of initiating treatment.[17, 18] This exogenous dopamine agonist replaces that which would usually be provided by the hypothalamus, promoting more appropriate pituitary *pars intermedia* function via provision of dopaminergic inhibition. Hypertrichosis, hyperhidrosis, lethargy, regional adiposity, and laminitis are often demonstrably reduced. Insulin dysregulation, however, has not been consistently improved[19], and immune function improvements are equivocal.[13] Subjectively muscle atrophy is diminished. Pituitary size has not been demonstrated to decrease with treatment.

An initial dosage of 0.002mg/kg PO once daily is recom-mended. Dosage can be adjusted in 0.001mg/kg increments following reassessment at monthly intervals until an effective dosage is determined. Thereafter, monitoring every 6-12 months should be sufficient, preferably with consistency in testing methods. The level of ACTH may not consistently fall within seasonal reference ranges while on treatment however results must be taken in conjunction with the appearance of the horse and achieving freedom from the worst of the deleterious effects of PPID. Pergolide has been shown to reduce POMC production within hours of oral administration. Terminal half-life was reported to be less than 12 hours suggesting that twice daily dosing may be more effective.[17]

Side effects include neurological signs, somnolence, sweating, inappetence, and colic. These can be addressed by temporary reduction in dose rate prior to increasing to effective levels although intolerance can rarely occur.

While commercially available in an approved tablet form, compounded liquid medications are available. Stability of liquid preparations is inconsistent.[20]

Cyproheptadine

The serotonin antagonist cyproheptadine has been widely used as a treatment for PPID although proof of clinical efficacy is lacking, or it is shown non-superior to pergolide.[21, 22] The mechanism of action of cyproheptadine on the *pars intermedia* is unknown, and concurrent administration with pergolide appears to be well-tolerated and may be dose-sparing with respect to pergolide.

Trilostane

Trilostane is a 3-hydroxysteroid dehydrogenase competi-tive inhibitor. Widely used in canine medicine to reduce adrenal cortisol production, reports of clinical efficacy in the horse are limited. Reductions in lethargy, polyuria-polydipsia, and recurrent laminitis have been reported in PPID affected horses with prolonged treatment.[23] Twice-daily dosing is required, with 0.4-1mg/kg PO twice daily reported as a recommended dose.[23]

7. Insulin Dysregulation

Insulin dysregulation is a consistent feature of the equine metabolic syndrome (EMS), a collection of genetic and environmental factors linked with hyperinsulinemia-associated laminitis along with other morbidities. Obesity tends to be an overt association with this condition. Prolonged hyperinsulinemia is associated with a significant increase in the production of proinflammatory cytokines in the digital lamellae.[24] While genetic tendency varies between horses, any horse can develop components of EMS if exposed to sufficient inciting factors, chiefly a diet high in non-structural carbohydrates (NSC).

8. Diagnosis of Insulin Dysregulation

Basal insulin concentration assessment in isolation is an insensitive detector of ID and can often result in a misdiagnosis.[25] Therefore, low basal insulin concentrations do not exclude a diagnosis of ID; therefore, a dynamic test, like the oral sugar test (OST) is recommended.[26]

Oral Sugar Test (OST): Standard Dose (SD) and High Dose (HD)

The OST is in wide use as it can be conducted conveniently in a field situation. The advantage of an oral sugar challenge over intravenous glucose administration to measure insulin responses is the inclusion of the entero-insular axis in the response to the test protocol. The entero-insular axis includes components of the gastrointestinal tract cell secretome that directly or indirectly affect insulin secretion.[7]

A single dose oral of 0.15 ml/kg corn syrup (Karo Light Corn Syrup®[a]) has been standard (SD-OST) for the OST with insulin measured at baseline and 60 minutes later. An additional 90-minute insulin sample has also been reviewed. Studies have investigated the use of a higher dose (0.45ml/kg) (HD-OST) to improve sensitivity.[27] Results suggest SD-OST is appropriate for diagnosing ID in horses, but the HD-OST could improve detection of subclinical horses and provide superior monitoring of borderline cases. Currently it is recommended to perform the OST after fasting however one study comparing horses at pasture to those fasted found no significant difference in OST outcomes.[27]

Seasonal Variations in OST

Seasonal variations in insulin concentrations have been linked to fluctuations in forage composition resulting from seasonally driven changes in soluble carbohydrates and starch content, with intake rates also being variable. Seasonal fluctuations in metabolic activity predominately in the summer and fall are also reported.[28] Seasonal insulin and adiposity fluctuations with ID horse are therefore not surprising in response to the feeding a diet of variable carbohydrate content. In a study across all four seasons involving ID and normal horses, condition score and cresty neck score were higher in ID horses Spring through Fall. Also, OST results varied seasonally, with normal horses having higher 60 minute samples in Spring, and ID horses having elevated baseline and 60-minute samples. For ID horses baseline insulin was confirmatory in 56% whereas 60 minute samples confirmed status 94% of the time regardless of season.[26]

Concurrent PPID and ID Testing

It is often clinically relevant to test for both PPID and ID in the same horse, and convenient to perform the procedures concurrently. However, conducting the OST prior to TRH-stimulation testing has been shown to blunt the response of ACTH resulting in false negative results for the diagnosis of PPID.[29] It appears performing testing for PPID prior to the OST does not alter diagnostic ability of the combined testing, enabling accurate testing to be per- formed with one clinical evaluation of the suspect horse.[30]

9. Treatment of Insulin Dysregulation

Levothyroxine

The use of levothyroxine in cases of ID and/or obesity is widespread. Administration is proven to favorably alter plasma lipid concentrations and improve insulin sensitivity.[31]

Metformin

Metformin counters hyperglycemia in Type 2 diabetes human patients, appearing both safe and affordable. Limited oral bioavailability in horses has led to mixed effects on insulin sensitivity in experimental studies. Metformin is thought to facilitate a reduction of glucose absorption from the gastrointestinal tract, this being the primary mechanism through which it is thought to exert its effects in the horse.[32] This is supported by superior effects on ID with oral sugar challenge compared to intravenous testing of insulin sensitivity. In other species, a reduction in glucose production by the liver contributes to the mechanism of action.

Caloric Control and Exercise

Weight loss attempts in horses typically center around dietary restriction, but exercise has been demonstrated to provide additional benefits. A study was conducted where obese horses were matched on signalment and breed, then fed either 85% of requirements or 100% with

15% expended during exercise essentially making caloric intake equivalent for both groups.[33] Bodyweight, regions of abnormal adipose tissue accumulation, and insulin concentrations were recorded. An OST was conducted at initiation of the study and 28 days later. While bodyweight and abnormal fat distribution decreased similarly in both groups, insulin:glucose ratio and insulin sensitivity were significantly improved in the exercise group. Therefore, the effects of a diet and exercise protocol with comparable caloric restriction to a sedentary lifestyle in obese horses can be considered superior.

Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibition

It is considered the development of insulin resistance may be in response to prolonged hyperinsulinemia, not the opposite. Insulin-sensitive glucose transporters (GLUT4) responsible for glucose uptake into peripheral tissues are therefore overloaded. When peripheral GLUT4 transporters are overwhelmed, this leaves only the kidney as a route of significant excretion when excessive glucose absorption cannot be avoided.

By blocking SGLT2 transporters, renal glucose reabsorption is severely reduced. Filtered glucose is usually reabsorbed in the proximal tubule by high-capacity SGLT2 transport proteins. Any remaining glucose not reabsorbed by SGLT2 is reabsorbed in the distal proximal tubule by SGLT1 proteins. In metabolically sound horses, glucose loss via the kidneys is negligible. Glucosuria only occurs when the capacity of the renal glucose transporters is saturated because of plasma glucose concentration exceeding the renal threshold for glucose excretion. Use of SGLT2 inhibitors lowers the renal threshold allowing glucose loss via the urine, reducing blood glucose and reducing stimulus for pancreatic insulin secretion.[34]

The SGLT2 inhibitors have demonstrated the ability to limit post-prandial insulin responses and prevent the development of diet-induced laminitis. No medications are currently registered that target hyperinsulinemia in the equid.[35] Ertugliflozin has been shown effective in reducing insulin concentrations in horses and ponies with EMS, and recovery from laminitis associated with hyperinsulinemia was advance.[36] In a study of the effects of ertugliflozin on the OST in horses and ponies with ID, basal insulin concentrations and the insulin response to sugar challenge were measurably reduced.[37] Triglyceride levels were transiently increased.

10. Conclusion

Endocrine and metabolic derangement of the equid present significant diagnostic and therapeutic challenges to the clinician. Early signs of disease are non-specific and may be subtle. While age-related onset of PPID varies, the interplay of genetics and environment shape the onset and severity of ID. While PPID and ID are separate conditions, they can occur as comorbidities with PPID—driven hypercortisolemia contributory to hyperglycemia and ID. Chronic hyperinsulinemia is proinflammatory, this being manifest through the digital lamellae precipitating laminitis which is the most devastating consequence of ID. Control of PPID rests upon restoration of dopaminergic inhibition and management of the systemic sequelae of excessive pituitary peptides. Dietary control, exercise, and restoration of insulin sensitivity are the mainstays of ID management.

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Footnotes

[a] Karo Light Corn Syrup® ACH Food Companies, Inc. Oakbrook Terrace, IL 60181

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Muscle Causes of Poor Performance

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Take Home Message: Muscle conditions leading to poor performance are many and varied. They may involve genetic, nutritional, or exertional causes. Pathology may be subtle or extensive. Diagnosis requires a systemic approach, consideration of signalment, and a sound knowledge of muscle pathology.

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1. Introduction

Successful performance in the horse depends on the normal function and integration of several body systems. Optimal locomotion depends on the initiation and coordination of movement controlled by the nervous system over skeletal muscles. Signs of muscle disease can vary from rhabdomyolysis (muscle necrosis), myalgia (muscle pain), myasthenia (muscle weakness), myotonia (persistent muscle contraction), alterations in muscle mass (atrophy, hypertrophy), tone (hypotonia, hypertonia), muscle fasciculations, stiffness, myoglobinuria, poor performance, exercise intolerance, camped stance, gait alterations, colic-like signs, and recumbence. It is important to rule out other causes that might present with similar signs such as colic-like, poor performance, gait alterations, and recumbence. Alterations in skeletal muscle will impact performance and desire to work.

Myopathies can be associated with exercise (exertional) versus no exercise (non-exertional), with rhabdomyolysis versus no rhabdomyolysis, inflammatory (presence of inflammatory cellular infiltrates) versus non-inflammatory.[1] Exertional myopathies such as polysaccharide storage myopathy type 1 (PSSM1), PSSM2 in Quarter horses, malignant hyperthermia (MH), recurrent exertional rhabdomyolysis (RER), and myofibrillar myopathy (MFM) in Arabians are characterized by rhabdomyolysis and increased muscle enzyme activities.[2-7] Increased muscle enzyme activities (creatine kinase [CK], aspartate transaminase [AST]) support muscle disease and are seen in myopathies characterized by rhabdomyolysis.[2] Lack of increased muscle enzyme activities such as in those myopathies with no rhabdomyolysis does not rule out muscle disease. As an example, hyperkalemic periodic paralysis (HYPP) usually does not present with rhabdomyolysis.[8] Other exertional myopathies characterized by exercise intolerance, reluctance to move forward, collect, and engage the pelvic limbs with normal muscle enzymes include PSSM2 and MFM in Warmbloods.[2, 9]

Causes of exertional myopathies could be sporadic or chronic.[2] Sporadic causes include deficient diets (e.g., electrolytes, vitamins, minerals), over-exertion, lack of proper training, and environmental stress (heat, high humidity).[2] Whereas chronic causes can present with or without rhabdomyolysis.[2] Those with rhabdomyolysis include RER, MH, PSSM1, PSSM2, and MFM in Arabians; and without rhabdomyolysis PSSM2 and MFM in Warmbloods.[2]

Myopathies resulting in poor performance and weakness can be challenging to diagnose because often muscle enzyme activities are normal.[2] Muscle atrophy can be subtle and therefore, not recognized as such. However, reduction in muscle mass will impact performance. Muscle atrophy can be focal or generalized.[2] Both neurogenic (e.g., equine

motor neuron disease, neuropathies) and non-neurogenic causes can result in muscle atrophy.[10] Non-neurogenic muscle atrophy includes myopathic processes (e.g., vitamin E deficient myopathy, immune-mediated myositis), disuse, metabolic, endocrine, malnutrition, sarcocystosis (S. fayeri), and corticosteroid-associated, among others.[2,11,12] This section will focus in myopathic processes.

2. Diagnostic Workup

The diagnostic approach for each case must be done on an individual basis. Basic blood work for the investigation of the overall health status of the horse is recommended. To determine if muscle damage is part of the disease process, evaluation of muscle enzymes activities is essential. Evaluation of electrolytes including ionized calcium and magnesium which are essential for normal neuromuscular function is recommended.[10] Determination of lactate concentrations can be helpful in the investigation of poor performance and stiffness as the result of lactic acidosis and impaired oxidative energy metabolism during exercise as in rare cases of mitochondrial myopathy due to deficiency of mitochondrial complex I respiratory chain enzyme Arabian mares.[13] Presence of myoglobinuria is supportive of muscle leakage or damage.[14] An exercise challenge (tolerance) test can be performed on which the horse is worked at a walk, trot, and canter for a few minutes (10-15 minutes). Serum creatine kinase concentrations are measured before and 4 to 6 hours post-exercise; whereas plasma lactate concentrations before and immediately after the end of exercise. Muscle biopsy for the characterization of a myopathic process is essential.[15] Electromyography (EMG) is a useful diagnostic aid to characterize myopathic processes such as those with myotonic discharges that support a myotonic disorder (e.g., myotonia congenita, myotonic dystrophy, tick myotonia). Imaging and thermography can be used to investigate focal myopathic processes such as trauma.[2]

Lastly, breeding practices for desirable traits such as specific muscle mass, tone, strength, and gait have also resulted in inadvertently breeding for undesirable traits.[16, 17] Therefore, genetic testing is also recommended. Examples of myopathies with a known genetic cause include HYPP, glycogen branching enzyme deficiency (GBED), MH, myotonia congenita (MC; reported in a single New Forest Pony), myosin heavy chain myopathy (MYHM), and PSSM1.[3, 12, 17-20] Co-mutations can occur in Quarter horse breeds. The following sections will briefly describe muscle causes of poor performance. For detailed description of various muscle disorders, the reader is referred elsewhere.

3. Muscle Disorders

Polysaccharide Storage Myopathy

Presence of amylase-resistant polysaccharide in myofibers of skeletal muscle is termed polysaccharide storage myopathy (PSSM).[21] High muscle glycogen concentrations and high insulin sensitivity are found in horses with PSSM. A dominant gain of function mutation in the glycogen synthase 1 gene (GYS1) was identified in a subset of horses with PSSM, therefore termed PSSM1.[3] Whereas, muscle disease with abnormal amylase-sensitive or resistant poly saccharide within myofibers and lack of the GYS1 mutation was termed as PSSM2.[4]

Polysaccharide Storage Myopathy Type 1

Several breeds of horses derived from the continental Belgian breed have been reported to have the GYS1 mutation that causes PSSM1. Some examples of breeds include Percheron, Belgian draft and crosses, Clydesdale, Breton, Quarter horse, Paint, Appaloosa, Warmblood breeds, Tennessee Walker, and Gypsy Vanner, among others. Thoroughbred, Standardbred, and Arabian do not have the GYS1 mutation. Clinical signs vary from subclinical to rhabdomyolysis, poor performance, exercise intolerance, muscle pain, atrophy, and recumbency. Regular controlled exercise, access to a paddock, and dietary management (low starch, high fat) are recommended to prevent clinical manifestations of disease (>75% of horses stopped tying-up; https://ker.com/nmdl/resources/pssm-1). For further information, the reader is referred elsewhere.

Polysaccharide Storage Myopathy Type 2

This myopathy has been reported in Quarter horses and related breeds predominantly of barrel racing and working cow performance and presents with exertional rhabdomyolysis and high serum muscle enzymes concentrations.[4] Other signs seen include low-grade lameness, stiffness, muscle fasciculations and atrophy.4 Glycogen concentrations in muscle are high but not as high as in PSSM1.[4]

Myofibrillar Myopathy

Myofibrillar myopathy has been reported in Arabian horses with exertional rhabdomyolysis and Warmblood breeds with exercise intolerance (no rhabdomyolysis)[7, 9]

- **Arabian breed. A**ggregates of glycogen within myofibers led to a diagnosis of PSSM2 in Arabian horses with exertional rhabdomyolysis.[7] However, muscle glycogen concentrations are comparable to control horses, and therefore not supportive of a glycogen storage disorder. Desmin aggregates and Z-disc degeneration with myofibrillar disruption and accumulation of

B-glycogen are identified within myofibers of affected horses.[7] Recommendations to manage these cases include regular daily exercise, turnout, and diet management. Diets with high quality amino acids, higher protein (12-14%), moderate levels of non-structural carbohydrates (20-30%), and fat (4-8%). A commercial pellet diet for MFM is available (KER.com).

- **Warmblood breeds.** Desmin aggregates in type 2A and 2X myofibers have been identified in Warmblood breeds previously diagnosed with PSSM2.[9] Affected horses display exercise intolerance, reluctance to move forward, stiffness, and lameness.[9] Rhabdomyolyis is not a feature of this myopathy in Warmblood breeds.[9] Transcriptome studies found a protein that degrades the cysteine-based antioxidant glutathione in affected horses and is believed to play an important role in disease.[22] Exercise protocol for these horses consists of 2 days off following exercise, followed by 3 days of work.

4. Malignant Hyperthermia

In horses, both anesthetic- and non-anesthetic-triggered forms of MH can occur.[5] Anesthetic triggers include halogenated anesthetics such as halothane (no longer under routine use and not commercially available) and isoflurane, and depolarizing muscle relaxants (succinylcholine).[5] Non-anesthetic triggers include stress including environmental stress (heat), exercise, breeding, and concurrent illnesses and myopathies.[5] Clinical and laboratory abnormalities are similar in both forms.[5] Triggered clinical manifestations include rapid progressive hyperthermia, hyperacute rhabdomyolysis, muscle rigidity, stiffness, sweating, recumbency, and death.[5] Historically, some fatal cases had intermittently or persistently mild elevations of creatine kinase activity.[5] Non-fatal episodes can include intermittent elevations of muscle enzymes activities and mildly increased rectal temperature.

5. Vitamin E Deficient Myopathy

With domestication, horses' natural diet has been modified from grass to processed hay, grains, and pelleted diets. Lack of fresh green grass, a primary natural source of vitamin E, can result in or contribute to vitamin E-associated disease such as equine motor neuron disease (EMND), neuroaxonal dystrophy/equine degenerative myeloencephalopathy (NAD/EDM), and vitamin E deficient myopathy (VitEM).[23] Equine motor neuron disease is characterized by weakness and diffuse irreversible muscle atrophy. Whereas horses with VitEM display weakness and reversible diffuse muscle atrophy when treated with daily natural α-tocopherol orally at 10 IU/kg for at least 1 month.[24]

6. Myosin Heavy Chain Myopathy

An autosomal missense codominant E3321G mutation in the myosin heavy chain 1 (MYH1) gene encoding the fast-twitch type 2X myosin heavy chain causing myosin heavy chain myopathy (MYHM) has been identified in Quarter horses.[12] This mutation confers susceptibility of disease manifested as immune-mediated myositis (IMM), non-exertional rhabdomyolysis, or systemic calcinosis.[12,25-27] Because of MYH1 dominant mode of inheritance with variable penetrance, susceptibility of disease is conferred with one or two copies of the mutated allele.[12] The allele frequency of this mutation in the general QH population in the United States was found to be 0.034 with variable frequency among the different exercise disciplines with the highest frequency in reining QH.[26]

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Lower Respiratory Tract Inflammation:
Current Concepts in Management and Therapy

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Take Home Message: The importance of small airway health for the equine athlete cannot be overstated. Inflammatory changes are insidious yet widespread in the performance horse population. Understanding of inciting events, pathophysiology, diagnostic methods, and tenets of rational management are ever evolving. Along with medications to ameliorate inflammation, environmental improvements are necessary to effect long term control. Corresponding and presenting author: Rood and Riddle Equine Hospital, Lexington, Kentucky. Email: pmorresey@roodandriddle.com

1. Introduction

Lower airway disease is the second most common cause of wastage amongst performance horses behind musculoskeletal disease. A single inflammatory episode may resolve without problem; however repeated or continuous exposure to insult may result in structural changes to the airway including mucosal hypertrophy and increased airway smooth muscle. Historically a plethora of terms have been applied to lower airway diseases depending on the degree of inflammation present. Recently, the term equine asthma has been introduced, being classified as mild-moderate or severe based upon clinical and diagnostic findings.

While pathogenesis of airway inflammation and hyperactivity is incompletely understood, non-infectious agents (dust, molds, pollen, fungi, endotoxin) have been incriminated. Dysregulation of the pulmonary immune system is present with increased expression of genes encoding for the potent immune stimulators TNF-α, IL-1β and IFN-γ.

2. Importance of Airway Inflammation

Inflammatory conditions of the lower airway have been shown to be widespread in the racing Thoroughbred population.[1] Non-infectious inflammatory conditions are considered to affect 25–80% of stabled horses. Studies show stabling leads to pulmonary neutrophilia in both affected and control horse populations. While these conditions represent a continuum of airway inflammation, this does not imply that mild asthma leads inevitably to severe, and horses with similar presentations can vary widely in significance of the disorder. Numerous antigens have been incriminated in the onset of equine asthma, and synergism between multiple allergens renders some horses uniquely sensitive to disease.

The major differential diagnosis for inflammatory conditions of the airway is infectious respiratory disease. Infectious agents can cause airway inflammation and mucus accumulation. Fever, inappetence, abnormal thoracic auscultation, and lymphadenopathy suggest a primarily infectious cause rather than inflammation alone. However, retrospective studies have shown that a large number of horses treated with antimicrobials for apparent bacterial infections in fact have inflammatory pulmonary disease that remains persistent due to inappropriate treatment.[2]

3. Categories of Asthma

Mild-Moderate Equine Asthma

Less severe airway inflammation was once classified as inflammatory airway disease (IAD), now mild-moderate equine asthma (MEA). Horses of any age can be affected, although the condition is more common in younger individuals. These horses, while showing no overt respiratory distress, have evidence of increased tracheal mucus,

inflammatory cells within the airways, and decreased exercise tolerance. Signs of systemic illness are not present; however, cough may occur. Breathing at rest is unaffected, and thoracic auscultation can be unremarkable without rebreathing examination, at which time subtle abnormalities may be present. Signs can be non-specific, and diagnosis can be challenging. Horses with MEA tend to recover with medication and environmental modification.

Severe Equine Asthma (SEA)

Severe equine asthma affected horses present with cough, nasal discharge and increased respiratory effort all at rest in contrast to MEA. This condition occurs when individuals with genetic predisposition are exposed to environmental aeroallergens including particulates with resulting synergistic effects.

Most often associated with hay feeding, summer pasture may also induce signs. Widespread in the environment of the horse, fungal spores, bacterial endotoxins, microbial toxins, pollen and plant debris, bacterial peptidoglycans, proteases, and inorganic particles initiate disease. Exposure results in significant airway inflammation, profound mucus accumulation, and widespread bronchial constriction.

4. Pathophysiology of Lower Airway Inflammation

Genetics

Several horse breeds have shown heritability or at least a familial tendency towards equine asthma. This illustrates a complex genetic heterogeneity resulting from the interaction of different genes. Due to the variety of genetic background mechanisms contributing to the disease and external factors such as environment, application of these findings to the general equine population is severely limited.[3, 4]

The Respiratory Epithelium

The airway epithelium is integral in the defense of the lung and as part of the regulatory mechanisms that drive lung inflammation.[5] Epithelial cells are a protective barrier and secrete mucus that is a mixture of proteins, lipids and glycoproteins which actively contribute to this protection. The cell population is dynamic (secretory cells increase in asthmatic horses) and mucus composition changes. Also present are a large and diverse population of immunologically active cells.

Neutrophils

Neutrophils play a significant role in SEA, therefore limiting their activation and increasing their attenuation can ameliorate disease severity and limit downstream morbidities resulting from tissue injury. Airway infiltration by neutrophils is a hallmark of EA, where they contribute to the innate immune response via phagocytosis of pathogens and cytokines and protease, and reactive oxygen species (ROS) production.[6] Aeroallergen and irritant exposure activates the resident pattern recognition receptors increasing cytokine and chemokine production promoting the migration of neutrophils into the airways. Neutrophil apoptosis appears to be a method of attenuating the inflammatory response.[7]

Alveolar Macrophages

Alveolar macrophages are the most common immune cells found in the lungs of healthy horses. By releasing cytokines and chemokines, they act as first respondents in the host's defense and therefore contribute to the pathophysiology of EA.[8] They can be responsible for neutrophil recruitment influencing the inflammatory pathways associated with equine asthma. Depending on local microenvironment, macrophages can modify their phenotype with a pro-inflammatory phenotype (M1) induced by pathogen-associated molecular patterns (PAMPS) and IFN-y, while the anti-inflammatory (M2) phenotype participates in wound healing and tissue repair.[9] It appears EA-affected horses may lack this dynamic modulation, and the M1 alveolar macrophage may contribute to the dysregulation of neutrophil apoptosis necessary for attenuation of inflammation described in EA horses.

Reactive Oxygen Species (ROS)

A large quantity of ROS are formed by inflammatory cells and contribute to cell injury and airway remodeling. They are responsible for transcription factor activation and inflammatory cytokine production. To counter oxidative injury, cells produce antioxidants. With EA, horses show signs of an imbalance between oxidants and antioxidants.[10] This oxidative stress may precipitate the corticosteroid insensitivity associated with intractable asthmatic horses who maintain significant neutrophilic inflammation despite corticosteroids, which may be caused by the expression of the chemoattractant IL-8.

Inflammatory Response

Severe EA is characteristically a neutrophilic response and does not appear typical for type 1 hypersensitivity.11 A T_h2 cytokine profile has been described in SEA-affected horses, a late phase response leading to neutrophilic bronchiolitis with CD4+ T cells in the bronchoalveolar lavage fluid (BALF), has been described.[12]

Inflammation is mediated by a suite of T-helper cells (T_h1, T_h2, and T_h17) with persistence driven by significant neutrophilic inflammation. The cytokine profile involved in

SEA is heterogenous implying different disease endotypes, reflecting the inflammatory response of the examined cells but also differences between local and systemic inflammatory responses.[11]

The expression of IL-17 has been associated with severe neutrophilic asthma in humans, and in horses this cytokine causes activation and persistence of neutrophils in the airways by increasing viability and decreasing apoptosis.[13] The presence of IL-17 has been associated with a reduced response to corticosteroids in severe cases via induction and persistence of IL-8.[14] Several studies report increased IL-8 in asthmatic horses during disease exacerbation[6, 8, 15, 16], however IL-17 whose role is upstream in the cytokine cascade appears to have a more significant impact on neutrophil recruitment during chronic EA.

5. Pulmonary Microbiome

It is suggested that the microbial flora of the lower respiratory tract plays an important role in modulating the innate immune response of the host and contribute to the immunology of equine asthma.[17] This difference, seen mainly when airway inflammation was present in horses with asthma but not in control animals, suggests that the altered lung microbiome in asthma might not be inherent but coincident with inflammation. Pulmonary, oral, and nasal microbiomes have been shown to be influenced by environmental conditions, but only the pulmonary microbiome was demonstrated to differ between horses with and without asthma. Compared to non-affected healthy horses, the pulmonary microbiome of asthma-affected horses is distinct with respect to the relative abundance of bacterial families. This distinction is not present within the oral and nasal microbiomes. This bacterial dysbiosis in EA-affected horses has potential to induce a disproportionate response of the immune system promoting a self-reinforcing inflammatory loop where activated pulmonary inflammatory cells alter the bacterial population via secreting inflammatory cytokines to which bacteria may adapt.[18]

Interestingly both healthy and asthma-affected horses in situations of high antigen exposure (where healthy horses also have some degree of pulmonary inflammation) have altered microbiomes suggesting the immune system is important in regulating the lung microbiome.[18] Therefore it is difficult to separate the effect of the environment and the effect of inflammation induced by inhaled antigens, because both seemingly have an effect on the local environment of the lungs.

Corticosteroids can influence the diversity of the pulmonary microbiome[18], meaning differences found experimentally in some studies could be secondary to therapeutic corticosteroid exposure. However, the altered microbiome of chronic pulmonary inflammation may occur in patients receiving no inhaled or oral corticosteroids while cohabiting with experimental non-affected controls.

Mildly affected EA horses also have altered lower airway microbiomes. Similarly to severely affected horses, this may be due to persistent inflammation or chronic corticosteroid usage.[19] Of note in mildly asthmatic horses the relative abundance of *Streptococcus* was increased suggesting this as a risk factor for development of mild/moderate EA.[20]

6. Gut-Lung Axis

The gut microbiome of humans with respiratory disease has been shown to differ from that of healthy individuals.[21] This suggests an immunological linkage between the pulmonary and gastrointestinal systems. This interaction is termed the gut-lung axis. Locally the gut microbiota interacts with the mucosal immune system producing both pro and anti-inflammatory metabolites.[22] These may have effects both within the gut and at remote sites.

Where dysbiosis of the gut occurs, decreased production of short-chain fatty acids (SCFAs) may result because of alterations in the relative populations of various bacteria. Lymphoid cell secretion of interleukin (IL)-5 and IL-13 along with dendritic cells differentiation can initiate and promote allergic airway inflammation. Dysregulated IgA secretion, T1/T2 inflammation imbalances, and increased T17/Treg responses downstream from these changes promote airway inflammation consistent with asthma.[23] This appears to be gut to lung, although it is possible systemic inflammation resulting from pulmonary changes could feed back to gut dysbiosis and inflammation.

Microbiota research in horses is mostly descriptive and has focused on the gut and respiratory populations separately. However, one study found intestinal microbiota differed between healthy and asthmatic horses.[24] Healthy horses transitioning from pasture to hay diets had increases in fecal *Fibrobacter* and this did not occur in EA horses. A smaller difference was seen in asthmatic horses in remission and controls suggesting gut changes are most prevalent during clinical exacerbations. Similar changes occur in adult humans with asthma. As asthma is associated with changing to a hay diet, it is difficult to decide if the gut microbiota transitioned due to the disease or to the diet modifications.

Asthma onset in the absence of dietary change with microbiota change concurrently would be strong evidence for causality of the gut alterations in EA onset/worsening.

7. Mechanical Irritants and Pathogens

Pollens and mold spores are highly irritant. Numerous allergens of these groups are found in hay, as are mechanical irritants such as dust (silicates, organics). Ammonia in poorly ventilated and cleaned barns is directly irritant to the airway epithelium.[25] Bacterial endotoxin is plentiful in the stable environment. Fungal and plant cell walls contain β-glucan, which can be considered an indicator of fungal exposure and has been associated with increased BALF mast cell presence.[26] Mites and other insect antigens are also present. Even hot or cold air temperatures can initiate significant pulmonary inflammation.

Infectious agents are widespread in the equine environment with potential to invade devitalized pulmonary epithelial defenses. In one study equine respiratory virus genomes (Equine rhinitis B, Equine herpes virus (EHV)-2, EHV-5) were frequently recovered from upper airway samples, however they were rarely detected in BALF. Neither respiratory virus detection nor load was associated with clinical signs or performance.[27]

8. Presentation

Respiratory

Horses experiencing SEA have a history of recurrent respiratory difficulties often triggered by environmental provocations or seasonal exposures. Coughing, mucoid nasal discharge, increased respiratory effort may initially be seasonal in onset but progress to continuous occurrence exacerbated by environmental triggers. The onset of clinical signs may be induced by exposure to hay, dust, or poor air quality and inadequate ventilation. Pasture-derived pollens and fungal spores may also induce difficulties. Exercise tolerance is markedly reduced. Respiratory distress at rest may become prominent with nasal flaring and an abdominal lift. Horses afflicted with MEA may have few signs at rest, or minimal difficulties with reduced exercise performance being the only consistent signs.

Systemic

Asthmatic horses have been shown to have greater infiltration of B and T lymphocytes and other immune system cells into the duodenal and rectal mucosa when compared to unaffected horses. This is thought to be part of a systemic reaction or the result of provocation by ingested dietary hay antigens.[28] The allergic asthma phenotype would be characterized by a T_h2 mediated response, and this may be a comorbidity with other allergic diseases such as insect bite hypersensitivity or atopy in horses with SEA.[29, 30] Interestingly, type 1 hypersensitivity occurs in response to intradermal allergen testing in SEA-affected horses which supports the hypothesis of an allergic EA phenotype.[31]

In older horses, immunosenescence and inflammaging (proinflammatory phenotype associated with advancing age) occur both systemically and locally and are most likely involved in the immunology of SEA[32] although age-associated changes and how they affect airway inflammatory response require more research. The alveolar macrophage may be the key cell in aging and disease.

9. Diagnosis

Disease diagnosis is mostly based on history, clinical signs, and bronchoalveolar lavage fluid (BALF) differential cytology. Although lung function testing can accurately detect SEA, such equipment is unavailable to most field practitioners.

Clinical Signs

Cough is often the first reported sign; however, exercise intolerance usually precedes its onset. That said, with low grade airway inflammation less exertional activities may not uncover a loss of performance. As the disease progresses, the severity of cough increases, and prolonged bouts may occur. A short inspiratory phase followed by an extended expiratory phase of breathing becomes apparent, with hypertrophy of the abdominal musculature developing. Nasal flaring, an attempt to reduce upper airway resistance, becomes prominent.

As mucus production and accumulation is increased, a tracheal rattle may be present. Swallowing secretions regularly occurs so they may not be seen externally. If secondary bacterial infection occurs, nasal discharge will be present.

Thoracic auscultation reveals increased broncho-vesicular sounds, wheezes at end-expiration due to airway narrowing/collapse, and crackles upon inspiration as due to snapping open of collapsed airways. As air is trapped, the lung fields may appear audibly increased in size. Paradoxically, as air movement can be severely curtailed, pulmonary sounds can be near absent in severely affected EA horses.

Bronchoalveolar Lavage Fluid Cytology

Neutrophilia of the BALF is a hallmark of severely asthmatic horses. Cutoff values have been established and are

commonly used in everyday diagnosis, however some variation specific to population and geography is present.

Tracheal Aspiration Cytology and Culture
Inflammation of the lower airways may be sterile, however secondary bacterial infection is commonplace due to compromise of the respiratory tract defenses. Bacterial growth in its own right has the potential to be inflammatory therefore sterile aspiration of tracheal mucopus, cytology of the recovered fluid, and culture/sensitivity of the resulting microbial investigation is prudent, especially with recurrent cases.

Ultrasonography
Examination by ultrasonography allows visualization of the lung surface, pleural space, and pleural fluid if present. Changes are not pathognomonic for EA but allow assessment of other differentials. Comet tail artifacts (B-lines) are the most common SEA findings. In mild cases comet-tail artifacts may be only seen in limited areas over the lung surface as isolated or small grouping. In SEA coalescing comet-tail may occur over significant amounts of the lung surface, shadowing out deeper regions of the lung fields.

Radiography
Radiographic findings correlate with disease severity in SEA.[33] Peribronchiolar interstitial lung patterns with tracheal and bronchial wall thickening are noted.[34] In severe cases, when disease progression leads to lung remodeling, interstitial infiltration, increased lung radiopacity, and bronchiectasis can also be observed.[35]

Endoscopy
Mucosal hyperemia may be noted with EA. Direct visualization is of benefit where alternate differential diagnoses are present. Most endoscopic scoring systems assess the quantity and quality of tracheal mucus[36] with mucus accumulation correlating with clinical scores[37], cough frequency[38], and cytological indicators of airway inflammation.[39] During disease remission, tracheal secretion volume of EA horses can reduce markedly with endoscopic mucus scores unable to differentiate EA from unaffected horses.[40]

As tracheal secretions may pool at the thoracic inlet sterile endoscopy using double-guarded aspiration catheters is a convenient way to obtain microbiological and cytology samples.

Tracheal Fluid
A relationship between tracheal fluid cytology and poor performance has not been demonstrated.[41] Also, there is a poor correlation between tracheal fluid and BALF cytology rendering tracheal fluid a poor substitute for BALF in the diagnosis of small airway inflammatory diseases. [42, 43]

Bronchoalveolar Lavage Fluid (BALF)
Macrophages and lymphocytes make up the majority of cells in BALF from normal horses. Regional and management variation in cell populations exists. An appropriate differential count is considered to be 40-70% macrophages. 30-60% lymphocytes, <5% neutrophils, 2% mast cells and <1% eosinophils. Inflammatory changes within the BALF are found with cough, poor exercise tolerance, and environmental changes. The presence of inflammation and abnormal BALF cytology is correlated with decreased aerobic performance, airway obstruction and airway hyper-reactivity.

Mild asthma cellular changes are relatively minor. An increased neutrophil percentage, sometimes with the presence of eosinophils or mast cells is seen. Variations due to sampling techniques and volume are reported, however neutrophils >10%, mast cells >5% and eosinophils >5% are consistent with a diagnosis of mild asthma.[44, 45]

Severe equine asthma (heaves) is identified by more profound cellular changes. Neutrophilia (>25% of total cells) with reduced lymphocyte and alveolar macrophage percentage is characteristic.

Hemosiderophages suggest pulmonary hemorrhage even though no signs of bleeding may be seen following exercise. Absence of overt hemorrhage may be due to a low quantity of blood loss, regionality of the area of hemorrhage being relatively remote, and timing of evaluation (endoscopy) prior to blood traversing to the tracheal enabling it to be visualized. Occasional hemosiderophages are noted in airway cytology and do not indicate a problem. Where bleeding is significant, free erythrocytes and varying maturities of hemosiderophages may be noted (whole erythrocytes phagocytosed, biliverdin, hemosiderin).

Allergen Evaluation
Immunoglobulin E (IgE) involvement in EA remains controversial however allergen-specific IgE concentrations in the sera and BALF differ between healthy and SEA-affected horses.[46, 47] Intradermal tests (IDT) assess the patient's reaction to an allergen by injection of specific allergens intradermally. If the horse is sensitized, a wheal (local allergic reaction) occurs. In SEA-affected horses the use of IDT allowed the identification of allergen sensitization.[31, 48] As a subjective method, IDT assesses grade of reaction based on the wheals' size, discomfort, thickness, erythema and turgidity.[39, 49] By using multiple specific antigens, sen-

sitization profiles can be determined allowing development of individualized allergen-avoidance protocols. Identification of responsible antigens enables specific immunotherapy.

10. Therapeutics

Severely asthmatic horses are usually managed through antigen avoidance, corticosteroids, and bronchodilators. The aim is to reduce airway inflammation and bronchoconstriction with resultant improvements in lung function. Not all horses are responsive to corticosteroid administration complicating management.

Antimicrobials (if indicated)

The use of systemic antimicrobial therapy may be of benefit in inflammatory conditions where bacterial infection is contributing to the inflammation seen and should be based upon the results of sensitivity testing. Culture and sensitivity testing should be performed on tracheal aspirates and thoracentesis fluids (if present). Studies have shown many horses are needlessly treated with antimicrobials when the underling condition is purely inflammatory, therefore strong indications for their use should exist.[2] Antibacterials may also be administered by the aerosol route.[50]

Corticosteroids

Combined with a change in the horse's environment, corticosteroids are the drugs of choice, with systemic administration the mainstay of most therapeutic regimens due to financial efficacy and convenience. Inhalant corticosteroids provide a long-term management option.[51]

The immunomodulatory effect of corticosteroids allows dysbiosis of the microbiome. Systemic and inhaled dexamethasone alters the microbiota of the lower respiratory tract of healthy and asthmatic horses, with systemic increasing the abundance of *Streptococcus spp.* in the asthmatic group.[19]

Oral dexamethasone (0.05mg/kg q24h) and prednisolone (2mg/kg q24h) have both been demonstrated to improve pulmonary function during continuous antigen exposure, with dexamethasone being more efficacious.[52] Dexamethasone has been administered by the inhalant route. While oral dexamethasone is efficacious, nebulized dexamethasone (5mg q24h) did not improve pulmonary function and as with the oral route inhibited the HPA axis.

Triamcinolone acetonide administered intramuscularly at (0.08-0.09 mg/kg IM) improves lung function for approximately 4 weeks in SEA.[53]

Ciclosenide is a prodrug which is de-esterified in the lung to the active metabolite desisobutyryl-ciclesonide (des-CIC). Its glucocorticoid receptor binding affinity is 100- to 120-times higher than the parent drug ciclesonide, and 12 times higher than dexamethasone. The active compound des-CIC elicits glucocorticoid effects in the airways at the site of activation, significantly reducing the potential for systemic adverse effects, including HPA axis suppression.[54] Dose rate is 2700µg/kg q12h.

Budesonide 3µg/kg q12h effectively manages airway obstruction in severe equine asthma. At higher dosages, the improvement in lung function was of a similar magnitude as observed with systemically administered dexamethasone.[55]

Fluticasone 2-4µg/kg q12h has been shown to be more effective at preventing acute exacerbation of EA than treating episodes (where dexamethasone is superior).[56]

Bronchodilation

Airway obstruction is partly the result of bronchospasm. Bronchodilators provide symptomatic relief only, being an adjunct to the relief of inflammation which is the primary goal of therapy. Administration by the aerosol route is preferred, allowing higher concentrations of drugs without the risk of systemic side effects. Bronchoconstriction obstructs airflow obstruction in asthma and is the main cause of airway resistance. Bronchial tone is regulated by three systems: adrenergic sympathetic, cholinergic parasympathetic, and nonadrenergic/noncholinergic. These neural pathways can be modulated by bronchodilators including β2-adrenergic agonists and anticholinergic drugs, such as the muscarinic receptor antagonists. Concurrent administration can give additive effects.

- **Cholinergic**

  Atropine can cause bronchodilation (0.015mg/kg IV, SQ) however deleteriously also causes ileus and dry mucus membranes. N-butylscopolammonium bromide is a safer alternative for rescue situations[57] with 0.3mg/kg IV providing rapid bronchodilation for up to one hour.[58]

  Ipratropium bromide 0.4-0.8µg/kg q6h by aerosol has a 4–6-hour duration with slower onset than β-agonists, with effects tending to localize larger airways.

- **Adrenergic**

  Albuterol is classified as short acting but has a rapid effect that persists for only 1-2 hours. Dosed at 2µg/kg by aerosol this can be repeated every 2-4 hours.[59]

Albuterol absorption by the oral route is inconsistent, and clinical efficacy cannot be predicted with use by this route.

Long-acting inhalant salmeterol at 0.5µg/kg q12h may take 15-30 minutes for onset of action but can give up to 12 hours of useful bronchodilation.[59]

Clenbuterol at 0.8mg/kg PO q12h is the only Food and Drug Administration approved bronchodilator.[60] While effective, long-term usage can lead to cardiac issues and alter sweating. Multiples of the dose can cause weakness and muscle fasciculations.

- **Non-Cholinergic Non-Adrenergic**

Aminophylline is an effective bronchodilator thought to function via short-lived inhibition of phosphodiesterase which promotes smooth muscle relaxation. Mucociliary clearance is also increased, and mast cell degranulation inhibited. While toxicity can occur at higher dose rates, 1-2mg/kg IV/PO appears well-tolerated.[59]

- **Mast Cell Stabilizers**

Sodium cromolyn 0.04 to 0.06 mg/kg q12h has been administered by aerosol with the goal of reducing mast cell degranulation and the release of vasoactive mediators e.g. histamine. It is thought that leukocyte recruitment is also reduced.[59]

Other Treatment Options

Omega-3 fatty acid supplementation in conjunction with reducing environmental particulates has been shown to lead to more rapid improvement in clinical signs when compared to only a low-dust environment.[61, 62] In humans, the omega-3 fatty acid docosahexaenoic when supplemented in the diet reduced arachidonic acid metabolites, reduced macrophage recruitment, and increased pro-resolving mediators suggesting a role for dietary docosahexaenoic acid (DHA) supplementation as a potential therapeutic strategy for reducing dust-induced lung inflammation.[63] The omega-3 fatty acid DHA is metabolized by lipoxygenase, cyclooxygenase, and epoxygenase enzymes into various compounds which reduce pulmonary inflammation in the lung by regulating various processes including neutrophil and macrophage influx into the lung, and promoting tissue repair and immunity.[64, 65]

Mushroom and algal sources of DHA sources are considered preferable in horses having equivalent efficacy to fish-sourced products.[66]

Diminishing pro-inflammatory cytokine production by the usage of pentoxifylline has been shown to decrease the magnitude of inflammatory lung changes during challenge by irritants.[67] Human interferon-α has been shown to lower the total cell count in BAL fluid.[68]

Hyposensitization to allergens has also been suggested, however results are variable in the absence of removal of offending allergens where possible, and prolonged (up to two years) courses of desensitization are necessary.[69]

Herbal therapies are reported. *Allium sativum* has been shown to reduce tracheal mucus in equine asthmatic patients.[70] *Thymus vulgaris* also modulated mucus hypersecretion *in vitro*.[71] *Hedera helix* has been demonstrated to reduce cough[72] and has mucolytic activity similar to acetylcysteine.[73] *Glycyrrhiza glabra* is deployed for asthma in Chinese traditional medicine and is shown to reduce ROS production, bronchial inflammation, and mucus production in a murine model.[74]

Antioxidants vitamins C and E, also present in *Arthrospira platensis* herbal extract, have scavenging activity against ROS, and protect human bronchial tissue.[75] As high oxidative stress in the airways of the horse leads to neutrophil corticosteroid insensitivity, products with antioxidant properties may be useful in the treatment of equine asthma.[76]

- **Lidocaine**

Lidocaine nebulization 1.0 mg/kg q12h for 14 d significantly decreased ($P < 0.05$) clinical scores compared to control; the lidocaine cohort showed a significant decrease in bronchoalveolar lavage (BAL) neutrophil percentage and tracheal mucus score. Neither treatment resulted in significant changes in lung function parameters.[77]

- **Oclacitinib**

Janus kinase (JAK) inhibitors have enjoyed widespread usage since introduction for allergic conditions in small animals.[78] They target intracellular cascades responsible for production of cytokines contributing to allergic reactions. Use in the horse is extra-label with anecdotal reports of beneficial effects in insect allergies, atopy, and asthma.

- **Biological Therapies**

Immunomodulation via the use of cells and cell-derived biologics has been researched and reviewed.[79] Intratracheal therapy with autologous mesenchymal stem cells (MSCs) has been shown to reduce airway neutrophilia, increase anti-inflammatory cytokine lev-

els, and lead to improved clinical parameters.[80] It is now widely accepted that the secretome (cytokines, growth factors, and extracellular vesicles) is largely responsible for the regenerative properties of MSCs.[81] The plasma protein α2-macroglobulin is an acute phase protein that bind cytokines and inhibits proteases, thus downregulating inflammation and tissue destruction. It has been marketed as an orthobiologic to protect articular cartilage.[82] Nebulization has anecdotally been reported to have beneficial effects.

Specific mediator blockade is theoretically possible. Increased IL-17 is responsible for persistent neutrophilia in asthma and upregulates IL-8 providing an attractive target to inhibit this pathway.[14] The roles of individual cytokines are complex and require further study.

11. Management

Reduce Exposure to Airborne Allergens and Irritants

Improvement in the air quality in the horse's environment is arguably the most important step in prevention and management of lower airway disease. Minimize exposure to dust and other particulate irritants. Examine bedding and feed material. Remove hay from the barn where the horse is stabled and avoid using a hay loft. Increase ventilation in confined areas, and if this is not possible, remove the horse from confinement. Not only will this remove dust, but it will also decrease the build-up of ammonia from urine decomposition.

Steamed hay and haylage have been demonstrated to have significantly less respirable dust than untreated hay.[62] Neutrophil percentage in BALF was also reduced in the haylage group, with a more favorable plasma anti-inflammatory to pro-inflammatory lipid profile also seen only in horses fed haylage. Organic dust contains bacterial components, proteases, and particulates that generate pro-inflammatory responses, so removal from hay is indicated for the EA-affected horse. Soaked hay also markedly improved lung function in severe EA with some nutrient loss.[83]

12. Conclusion

Inflammatory changes of the small airways have varying effects on the horse, ranging from mild exercise intolerance to profound increases in respiratory effort, chronic cough, and severe exercise intolerance. While a continuum of clinical signs is present, progression from mild to severe asthma is not assured. Severity of disease is not necessarily correlated with the degree of airway inflammation. Diagnosis is based on clinical presentation, and most definitively categorized by cellular constituents of the BALF. Management is holistic in approach, centered upon environmental control to remove provocative allergen exposure, judicious use of corticosteroids both systemically and by inhalation, concurrent bronchodilation, and novel therapies aimed at beneficial immunomodulation.

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Declaration of Ethics

The author adhered to the AVMA Principles of Veterinary Medical Ethics.

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Sex and the Performance Horse:
Managing for Success

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Take Home Message: The high-level equine athlete faces many systemic challenges and stressors to the maintenance of high-level performance over prolonged periods. Often not considered are the impact of these stressors on reproductive function, amplifying inherent difficulties faced by any horse. Advanced reproductive techniques where permitted may provide an opportunity to carry on the legacy of the elite horse, but the basic tenets of sound reproductive practice must still be addressed. For the mare induction of cyclicity, manipulation of estrus, establishing conception, and maintenance of pregnancy are points of failure. For the stallion considerably less is known, however stresses inherent in athletic performance could reasonably be considered to have the potential to alter fertility. Corresponding and presenting author: Rood and Riddle Equine Hospital, Lexington, Kentucky. Email: pmorresey@roodandriddle.com

1. Introduction

Reproduction is a luxury bestowed upon the desirable or the lucky. Considerable resources are expended by all species to achieve it, and the horse is no different, albeit with opportunities dictated by human direction. For the athlete, time available separated from demands of competition for reproductive purposes may be limited necessitating application of advanced techniques to enable pregnancy to be established. While training, during transport, competing, or experiencing an altered social environment the performance horse is subject to stress which may compromise reproductive potential. To minimize the impact of these detractors the horse must be maintained in good health, preserve endocrinological and metabolic normalcy, and be managed to sustain anatomical and physiological reproductive soundness. In this review the potential effects of performance-induced stress on the equine athlete's reproductive system and selected diagnostic and therapeutic techniques will be reviewed. Routine management practices and pharmacological manipulation of the reproductive cycle will not be discussed.

2. What is Stress?

Stress can be considered the initiator of adaptive responses aimed at preserving homeostasis of the animal. Stress can take many forms, whether they are categorized as physical or perceived. To counter stress coordination of behavioral changes, nervous system activation, and neuroendocrine output occurs. Behavioral changes are overt and non-specific, starting with avoidance of the stressor. The nervous response initiates a diverse array of body system changes such as cardiovascular alterations in preparation for 'fight or flight', and metabolic changes under the influence of catecholamine release. Changes in neuroendocrine output, mediated by the hypothalamic-pituitary-adrenal (HPA) axis, can increase cortisol secretion sufficient to cause durable alterations in reproductive performance, immunity, and metabolism. The overall response to stress can therefore either enhance or detract from the performance and physiological fitness of the equine athlete. The breed and discipline can also affect response, as Warmblood breeds appear well-adapted for jumping and dressage activities in contrast to lighter breeds that are suited to flat surfaces at speed (e.g. Thoroughbreds).[1, 2]

3. Response to Stress

The changes induced by stress include a series of endocrinological modifications in two phases. An initial catabolic phase where biochemical, hormonal, and immunological changes cumulate in reduced athletic effort leading to immediate elevations of adrenocorticotrophic hormone (ACTH), catecholamines, and cortisol.[3] This is followed by an anabolic phase promoting adaptation and enhanced performance, and includes production of growth hormone-

-insulin-like factors.[4] Should these fail to retore balance endocrine activation ensues.[5]

The response to stress is activation of the HPA. Suppression of luteinzing hormone (LH) release can result, which can be long-term if stress is chronic. Exercise in horses has been shown to increase cortisol levels.[6] As suppression of gonadotrophin levels sufficient to suppress reproductive activity seems to require prolonged stress, acute stress may have limited yet uncertain effects on reproduction.

4. High Intensity Exercise

Intense training with insufficient opportunity for recovery can lead to a reduction in performance commonly referred to as overtraining syndrome (OTS). This syndrome is difficult to define but is thought to involve chronic energy deprivation curtailing repair of cumulative tissue damage. Expression of innate and adaptive immune genes are altered.[7] Acute, intense physical exercise has been demonstrated to alter T_h1 and T_h2 cell differentiation, nuclear factor kappa B (NFkB) intracellular signaling pathway, and chemokine production leading to activation of proinflammatory responses secondary to stress of acute exercise. This has been demonstrated to affect the environment of the oocyte.[8]

4. Insulin Dysregulation and Obesity

Metabolic syndrome/insulin dysregulation affects the insulin-like growth factor system, this being crucial to follicle selection and dominance in the mare, leading to disturbances of ovarian function.[9, 10] Affected mares have elevated concentrations of insulin, leptin, interleukin-1β, and tumor necrosis factor-alpha (TNF-α) with a concurrent decrease in adiponectin concentrations in follicular fluid correlated with systemic concentrations.[11] Numerous metabolite alterations in follicular fluid have been demonstrated with alterations in oocyte viability, ovulation dynamics, and fetal programming are possible.[12] Obese mares with reduced insulin sensitivity have been shown to have prolonged interovulatory and luteal phases, and to be more likely to form anovulatory follicles.[13]

There is an interaction between metabolic status and testicular function that is bidirectional in nature proven in other species. A comparison between fertile and subfertile human males found significant hormonal differences between subfertile obese and fertile males of normal body weight.[14] Obesity has been shown to affect sperm production. Sperm concentration was decreased in highly obese men, with a continuous decrease associated with advancing age.[15] Although total testosterone was decreased with obesity, estradiol was not affected leading to a decrease in the testosterone:estradiol ratio influencing the hypothalamic-pituitary axis.[16] Suppression of testicular function feeds back in a self-reinforcing cycle. A relative decrease in muscle mass and increase in body fat because of decreased testosterone encourages obesity, insulin resistance, and feedback to cause further pituitary depression.[17] In a study of low and high body condition score (BCS) stallions with normal oral sugar test (OST) results post thaw semen parameters were not different between groups.[18] This implies obesity alone is not responsible for deleterious semen parameters, rather other factors (potentially concurrent ID) are responsible. Unlike ruminant where adipose is deposited in the scrotal neck and semen quality is affected,[19] stallions deposit adipose along the prepuce which may avoid negative thermal effects on spermatozoa.

5. The Mare: Challenges of an Athletic Career and Enhancing Reproductive Potential

In other domesticated species short term stress elevates cortisol levels sufficiently to interfere with the follicular phase and delay ovulation by blunting LH pulses, reducing estradiol and the preovulatory LH surge. The production of GnRH is also reduced. In the mare plasma cortisol concentration increases with transportation[20, 21] and confining with new horses in a group.[22] While demonstrably stressful events, cortisol elevation was transient and no change were seen in estrus duration, ovulation, or resultant pregnancy rates between transported mares and non-transported controls with LH, estradiol, and progesterone release unchanged.[21] Transportation is often considered to be of concern in early pregnancy, however road transport of mares at 3 and 5 weeks gestation for 9 hours, while causing a transient increase in plasma cortisol levels, did not increase incidence of early embryonic death. Interestingly, plasma progesterone increased during transport then decreased thereafter but remained above a level that might endanger pregnancy.[20]

Mares retired from competition have lower pregnancy rates.[23] A retrospective study was performed on 189 retired sport mares in an attempt to assess reasons for lower-than-expected initial pregnancy rates often seen among older maiden mares recently retired from competition. This study included maiden, barren, and mares that had foaled. The incidence and severity of endometrosis (chronic degenerative endometrial changes) was associated with increased mare age, shown previously to decrease reproductive competency. Endometritis was least commonly diagnosed among unbred mares. Glandular differentiation disorders including endometrial inactivity and irregular

glandular differentiation were observed in 50% of mares biopsied during the breeding season, with the most frequent occurrence in maiden mares that were most recently retired from sports.[23]

6. Management of Mare Cyclicity for Breeding

Management of the transitional mare is multifactorial and includes the use of gonadotropin releasing hormone (GnRH) agonists, agents mimicking endogenous gonadotropins, progestogens, and dopamine antagonists. Cessation of cyclicity during the expected period of ovarian activity may occur for many reasons (physiological stressors including overtraining which alters HPA function,[24] concurrent medical conditions, pain from any source) with similar approaches used to induce cyclicity. Scheduling and inducing ovulation in the cyclic mare is also achieved by the same agents.[25] In the cycling mare, one commonly used program in the Thoroughbred industry is 150 mg progesterone and 10 mg estradiol-17β IM for 10 days, with prostaglandin $F_2\alpha$ administered on the tenth day.

Reliable induction of ovulation is essential to optimize scheduling of breeding to best use semen resources and veterinary time. Human chorionic gonadotrophin (hCG) and deslorelin acetate are commonly used, and ovulation within 48 hours reliably occurred with both however a higher percentage ovulated within 24 hours of hCG.[26] Additionally, progesterone concentration of 5 to 15 days post ovulation was higher in mares whose ovulations were induced with hCG compared to mares whose ovulations were spontaneous.[27]

7. Diagnostics: Mare

Microbiological Assessment of the Endometrium

Diagnosis of endometritis has routinely involved a uterine swab for microbial culture, an endometrial cytology swab to evaluate for the presence of inflammation and, where indicated, histopathology of an endometrial biopsy chiefly for prognostic information. Fitness of the reproductive tract is greatly aided by appropriate perineal conformation and systemic health of the mare which, while beyond the scope of this paper, must always be addressed. Bacterial uterine infections are associated with significant time and monetary loss in the equine breeding industry. The most prevalent uterine pathogen is *Streptococcus equi* subspecies zooepidemicus. Where an organism was recovered by swab culture β-hemolytic *Streptococcus* was recovered in 34% of samples with *Escherichia coli* the second most common isolate at 17%[28] Another study found the incidence of positive bacterial cultures among a population of mares presented for fertility assessment to be 39% with the majority β-hemolytic *Streptococcus*.[29]

Uterine swab culture, use of a cytology brush, and endometrial biopsy for cytological and bacteriological diagnosis of endometritis were investigated.[30]. This study concluded that uterine swab for microbial culture in isolation is insufficient to diagnose endometritis, rather endometrial cytology is essential for diagnosis. Use of a cytobrush technique has been demonstrated as superior in the support of a diagnosis of endometritis by cytology.[31]

Low volume lavage for culture and cytology has the advantage of sampling a larger surface area of the endometrium in comparison to relatively localized swab and brush techniques. Evaluation of cytology samples obtained via double guarded swab, double guarded brush and low volume lavage were compared. Swab samples were occasionally non-diagnostic, with brush samples yielding superior cytological samples.[32]

The stage in the estrous cycle that the sample is obtained is an important component of cytological interpretation. When compared to endometrial biopsy, sensitivity values were highest in the diagnosis of endometritis when samples with >2% neutrophils in a 300-cell count were compared to 2 neutrophils per high power microscope field collected during estrus using a brush.[33]

8. Selected Treatments: Mare

Control of Endometritis/Inflammation

The use of non-steroidal anti-inflammatories and corticosteroids for the control of inflammation is widespread in equine practice. However novel therapies have also been shown to be effective in the amelioration of endometritis.

Firocoxib has recently been reviewed in the periovulatory period.[34] As ovulation has similarities to inflammation[35] concerns are held with the usage of non-specific cyclooxygenase (COX) inhibition regarding delayed uterine clearance[36] and ovulation.[37] As a selective COX-2 enzyme blocker firocoxib was not shown to delay ovulation nor impede uterine clearance.

Corticosteroids have been reviewed for their utility controlling persistent post breeding endometritis. Dexamethasone at the time of breeding was shown to reduce the inflammatory response observed post-mating in treated versus control mares and mares with multiple risk factors for susceptibility to persistent mating induced endometritis, with improved pregnancy rates following treatment.[38]

Taking a different approach, mycobacterial cell wall extract (MCWE) was shown to modulate the immune response of the endometrium, promoting clearance of both *E. coli*[39] and *Streptococcus zooepidemicus*[40] experimentally. Clearance of uterine fluid was improved over control groups.

Biologicals have also shown efficacy in modulation of endometrial inflammation, improving pregnancy rates. Platelet rich plasma (PRP) used intraluminally has been shown to reduce endometrial inflammation, enhance uterine clearance, reduce endometrial infection rates, improve pregnancy, and increase embryo recovery rates.[41-43] Beneficial effects regarding endometritis, intraluminal fluid accumulation, and pregnancy have also been seen with infusion of stem cells prior to breeding.[44]

Stem Cell Therapy for Endometrosis

Endometrosis is a degenerative change of the endometrium secondary to senescence and cumulative cyclic insults. Chronic inflammation, vascular degenerative, and periglandulaar fibrosis occur. Stem cell introduction into the uterine lumen has experimentally shown distribution of instilled cells throughout the endometrium, glandular association, and favorable regenerative changes in endometrial structure.[45, 46]

Countering the Insulinemic and Oxidative Potential of Diet

In the mare systemic circulating markers associated with inflammation, oxidative stress, and altered lipid metabolism unfavorably alter the microenvironment of the *in vitro* oocyte. These changes potentially affect oocyte development and subsequent embryo quality.[8] Dietary supplementation is a feasible method to potentially improve oocyte function and developmental potential *in vivo*. A diet rich in antioxidants (vitamin E, vitamin C), replete in selenium, and favoring omega-3 over omega-6 fatty acids could therefore be of benefit.[47]

Assisted Reproductive Technologies

Artificial insemination (AI) has become the most common method of breeding in most domesticated horse species where not limited by breed regulations. Embryo recovery by uterine flushing 7-9 days after ovulation, followed by embryo transfer (ET) into a synchronized recipient mare is most commonly used to allow a mare to generate more than one offspring per year and also avoid the requirement of gestation. The *in vitro* production of embryos by ovum pick-up (OPU) followed by intracytoplasmic sperm injection (ICSI) has continued to increase in popularity The combination of OPU-ICSI was initially primarily for subfertile mares unable to conceive or produce a viable embryo by natural mating or AI. Reasons included irreparable damage to the reproductive tract due to chronic uterine infection or fibrosis, infertility of unknown origin, or to boost results from sub-fertile stallions. This has progressed to include usage in reproductively competent mares to enable more efficient use of limited semen from valuable stallions.[48] *In vitro* maturation and vitrification techniques have further enhanced embryo production.

Suppression of Reproductive Activity in the Mare

Should behavioral issues be suspected to be associated with estrus, it is important to document occurrence to compare to expected cycle intervals, and rule-out musculoskeletal pain, gastric ulceration, and any saddle-fit deficiencies.

Behavioral, Gonadal

Inconveniently displayed estrous behavior can be detrimental to competition activities necessitating attempts to suppress gonadal function. Several methods are available with advantages and disadvantages of each, however the primary aim for the performance mare is cessation of sexual behavior.

Natural and synthetic progestogens suppress gonadal function in the mare. These are the most widely used compounds. Injectable progesterone is effective, however daily injections lead to unacceptable local inflammatory changes. As altrenogest by oral application is widely available this is the most common treatment for suppression of ovarian function in mares with no ill-effects on future fertility noted. Daily long-term usage has however been implicated in an increased tendency for endometrial inflammation.[49] Injectable sustained-release formulations of altrenogest are available and convenient.

Progestogens and their metabolites exert a central nervous system effects. Altrenogest administration caused a demonstrably reduced stress response during training.[50] Compliance of mares during continuous altrenogest treatment may improve from both estrous suppression and central calmative actions.

Prolongation of the corpus luteum lifespan is also possible. Spontaneous ovulations day 9 post ovulation (day 0) generate luteal tissue non-responsive to the period of luteolysis (day 14) and the resultant corpus luteum can persist.[51] The use of hCG to induce a diestrus ovulation artificially induces the same response reported to last until day 58-82.[52]

Oxytocin at high doses early in the lifespan of the CL has been shown to inhibit endogenous luteolysis. Treatment of non-pregnant mares during mid-diestrus inhibited endome-

trial prostaglandin $F_2\alpha$ secretion.[53] Luteolysis was delayed experimentally in 60–70% of treated mares until approximately day 70 post ovulation.[54] To enable this protocol to be enacted efficiently the exact day of ovulation must be determined.

Mimicking Pregnancy

While the placement of glass balls in the uterus was successful experimentally in prolonging the diestrus period in many mares, field success was considerably less and complications including fracturing of the implant with subsequent endometrial damage were sufficiently common as to now preclude their usage.[55]

To address problems with marble placement a magnetically self-assembling device of inert material has been marketed.[56] Easy to insert and retrieve, effective suppression of estrous behavior is reported. Progesterone is maintained due to CL retention induced by the presence of the device. Effectiveness can only be expected during the predicted period of cyclicity and periodic assessment for the presence of uterine fluid is advised.

9. The Stallion

In stallions, while data is conflicting, exercise has been associated with reduced levels of testosterone between male racehorses in training and their untrained controls.[57] In another study, with regularly competition (weekly) plasma cortisol did not differ from control breeding stallions. Where competition was intermittent, marked fluctuations and elevation in cortisol were noted.[58] Stress can be accommodated over time. Experienced show horses had a less pronounced rise in cortisol and ACTH when compared to younger less experienced horses.[59] A rapid adaptation of horses has also been found to the stress of loading onto a trailer.[60]

Studies on the response of stallion semen to exercise are conflicting. In one study negative effects were not seen in stallion semen quality during competition. Interestingly, semen motility and total count were found to be higher in stallions taking part in equestrian competitions than in stallions used for breeding only at most times during the breeding season.[58] In another study, competition stallion semen was of significantly lower concentration and progressive motility than non-competing stallions. Semen volume was higher in competing stallions compared to non-competing stallions. Interestingly there was a significant difference in seminal attributes between disciplines and competition levels. This suggests there are endocrinological and physiological changes as a response to training intensity and competition dependent on discipline.[61]

Stallions share similar endocrinological responses to stress and have analogous hormonal changes to hypercortisolemia as mares. Thermoregulation of the scrotum during competition, which may induce significant hyperthermia, is potentially of concern. In one study measuring body temperature at remote sites and the scrotum during moderate exercise for a short duration extreme heat and humidity did significantly increase core body temperatures in stallions, however scrotal temperatures did not significantly increase, with sperm parameters unaffected.[62]

10. Selected Treatments: Stallion

Enhancement of sperm quality with antioxidant presence has been extensively reviewed.[63] As with the mare, it is reasonable to attempt dietary supplementation of antioxidants and favorable fatty acids to minimize the overall proinflammatory nature of the diet and any affect it may have on semen quality although studies are inconsistent regarding benefit.[64, 65]

Assisted Reproductive Technologies

Semen collection and cryopreservation are markedly more advanced than corresponding techniques for the oocyte in equids, the result of easier access and higher availability. Freezing and thawing of cryopreserved stallion semen has benefited from ongoing improvements in understanding leading to improved fertility. Deep horn insemination has allowed smaller doses to be administered. The increased availability of ICSI has further enabled success for the subfertile stallion or where semen is limited.

Preservation of epididymal semen from dead or recently castrated stallions allows salvaging of valuable genetics. Techniques have been reviewed, with the addition of seminal plasma shown to not have any damaging effect on sperm quality, rather it may also improve pregnancy rates with artificial insemination.[66]

11. Conclusion

Realizing the athletic potential of the horse creates difficulties providing opportunities for reproductive activity. While the timing of competition may restrict breeding attempts, assisted reproductive techniques enable pregnancies to be achieved within limited but schedulable windows. Inherent in competition are stresses including social, transportation, and intense exercise. Endocrinological changes may be suppressive to cyclic activity, chiefly increased cortisol

production. However, a commitment to sound nutrition, avoidance of overtraining, and diligent reproductive management will facilitate successful generation of progeny.

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Declaration of Ethics

The author adhered to the AVMA Principles of Veterinary Medical Ethics.

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The Athletic Hoof:
Conformation, Lamellar Strains and Pains, and Practical Management

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Take Home Message: Understanding the basic principles of podiatry and foot related lameness enables the veterinarian and farrier to unravel the complex mix of abnormalities, identify early warning signs, and manage existing problems more effectively. Hoof capsule distortions occur when the tensile, compressive, or shearing forces on the hoof exceed the capacity of the hoof capsule components to withstand them. We will focus on the principles of therapeutic shoeing based on the mechanical thought process of altering the internal forces as a means to aid preventing and/or treating the ill effects of capsule distortion that frequently occurs with the performance horse. Corresponding and presenting author: Rood and Riddle Equine Hospital, Lexington, Kentucky. Email: rbras@roodandriddle.com

1. Introduction

Regardless of the many variables, such as breed, limb conformation and environment that will change the overall shape of the foot, the ill effects from the demands of their athletic careers could result in compromised performance. More importantly we must remember that the foot is constantly changing due to growth, the rigors of training and farrier influence. External alterations of the hoof capsule can be evident to the astute eye. However, many crucial changes go unnoticed until lameness or other problems are evident. The key to understanding the mechanical thought process lies in the awareness that the forces within the foot have a direct influence on the shape, strength and durability of the hoof capsule, and likewise these forces are altered as the capsule changes.

A thorough knowledge of farrier science and mechanics within the foot provides a better understanding of how to change and improve abnormal foot conformation, and how to improve distal limb function. Recognizing subtle changes in hoof conformation and understanding what has changed internally enables us to preserve the integrity of the hoof capsule, along with the structures enclosed within, and thus prevent many of the associated lamenesses in the performance horse.[1] We will focus on the principles of therapeutic shoeing based on the mechanical thought process of altering the internal forces as a means to aid preventing and/or treating the ill effects of capsule distortion that frequently occurs with the performance horse.

Understanding the forces at play that underly the mechanical failure allows a more precise strategic management to be formulated. A key element relative to this discussion is the interconnectedness of all components of the digit. The interconnectedness of the digital structures allows the foot to function as an integrated unit, supporting the body and dissipating the forces of ground impact and loading to prevent overload and damage of any one particular component. Owing to the interconnectedness of the digital structures, when one component is weakened by genetic factors, overload, injury, disease, environmental factors, or human interference, the entire hoof capsule is weakened. A cascade of damage, altered growth, and hoof capsule distortion is inevitable, because all components are affected when one fails. As a result, the function of the entire digit is compromised.[2]

2. Demands on the Foot for the Performance Horse

Regardless of breed, once horses go into training, the ill effects of training and shoeing along with sudden changes in nutrition and the environmental demands on the foot quickly change the overall hoof capsule. More importantly, how long can the horse remain sound or how much can the hoof capsule change before lameness is evident? An increase in

training intensity often pushes the foot over the edge by significantly increasing the tensile, compressive, and shearing forces on the digital structures. A hoof capsule with adequate mass and resilience may be able to withstand these stresses without significant deleterious effects. A weakened hoof capsule has neither the strength nor the plasticity of a healthy horn. As a result, repeated compression during high-intensity exercise causes hoof capsule distortions.[3]

Once young horses go into training, most are confined to stalls or small pens and are inactive for most of the day. The germinal areas of the hoof capsule are dynamic tissues that respond and adapt to the forces placed on the horn; thus, inactivity can have a negative effect on the hoof capsule. The routine of most athletic horses is characterized by many hours of inactivity. This lifestyle has a negative effect on the foot. When the natural demand for toughness and durability of the protective capsule is not met, circulation of the foot is reduced due to inactivity and excessive moisture which contributes to horn distortion more than any normal activity. Subtle but steady deterioration may be occurring in the horn, soft tissue, bone, and circulation of the foot; all the while the horse is doing nothing. The weakened foot is then more susceptible to overload during athletic activity.[3]

The tough durable hoof capsule is relatively rigid with limited distortion and natural recall that occur with each step. Excessive moisture that may be due to environmental conditions or man-made with the practice of mudding feet to remove heat consistently weaken the horn integrity and makes it more vulnerable to distortion that is incapable of natural recall. The cumulative ill effects are precursors to the crushed heel syndrome.

Unlimited exercise during turnout or intense exercise during training and competition can become a major trigger for overload and, ultimately, for distortion of the weakened hoof capsule. The hoof capsule with adequate mass (sole and horn), durability, and resilience has a much-improved chance to withstand the stresses placed upon it without significant deformation. The downside of training a horse with steadily declining capsule strength is the risk of foot related lameness. Repeated compression and strain during strenuous exercise causes hoof capsule distortions. The stronger feet will have natural recall and recover while the weaker fall prey to the cumulative negative effects and soon lose the function of their natural shock absorbing, protective components.

3. Morphology of the Hoof

Although certain generalities can be made, it is important to realize that there is a range of normal for hoof characteristics that is dependent on the horse's breed, age, environment, and discipline of use regardless of sport, breed or discipline. The importance of understanding the variability in structure of the healthy foot lies in identifying subtle deviations from normal that are of clinical significance.

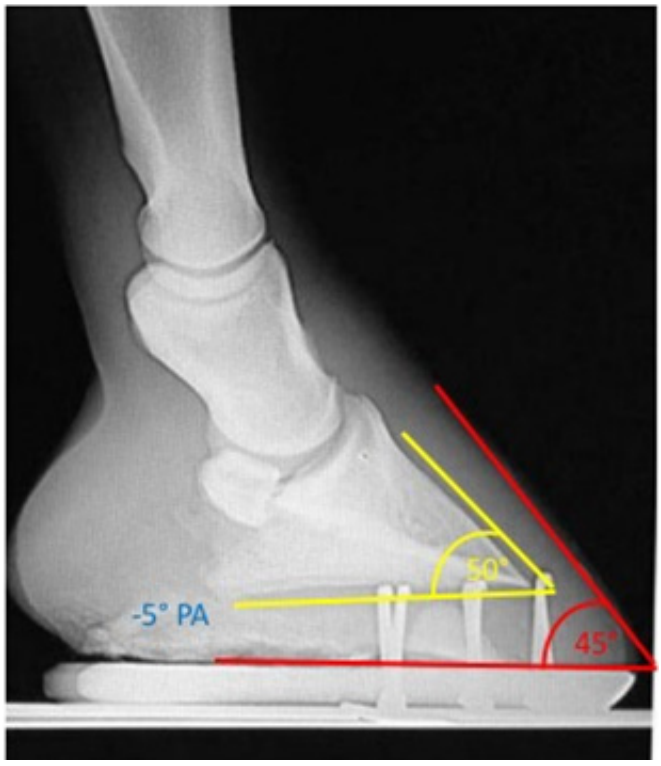

Figure 1. *Evidence of a 45 degree hoof angle with a 50 degree bone angle, which has a negative palmar angle of 5 degrees, crushed heel and broken-back pastern axis.*

We must overcome the "ideal" perception of the normal equine foot depicted in the veterinary and farrier literature for the past century as being symmetrical and matching the opposite foot as well as that of other horses of similar breed. Matching toe and heel angles simply do not exist on healthy feet. Toe angles, once idealized as 45º for front feet and 50º for hind feet, are a misconception as this combination only occurs with a very small population of horses that would have remarkably lower coffin bone angles than the average horse. The 45 º hoof angle with a 50-52 º bone angle would have a negative palmar angle (PA), crushed heel and broken back pastern axis, a far cry from the ideal healthy foot.[4] ***(Figure 1)***

A rigid set of toe lengths, toe angles and shoeing limitations can be problematic in disciplines that insist on recording toe angle measurements without regard to the coffin bone angle and shape that is the precursor of toe angles. It is also important to make the distinction between normal and healthy. Normal according to Webster is conforming to a standard, what is typical or expected, and it is this mind-

set that erroneously allows us to believe that normal and healthy are one and the same.

The majority of feet we see irrespective of breed with very similar shape are considered normal for that breed and discipline. However, this certainly doesn't mean the feet are healthy even though the horse appears sound and at the peak of their career. What we may commonly see can be far from what is healthy for the individual foot on the individual horse. This leads us to the key to understanding the mechanical principles of podiatry.

4. Mechanical Principles

The interconnectedness of the digital structures allows the foot to function as an integrated unit, supporting the body and dissipating the forces of the ground impact, and loading to prevent overload and damage of any one component. However, all components of the hoof capsule are connected to the muscles and tendons of the limb that are solely responsible for support and locomotion. Therefore, it can be said that without these controlling forces, the foot alone would be nonfunctional. Consistent and reliable clinical evidence supports the thought that the function of the deep flexor tendon (DDFT) plays a major role equalizing the relationship between digital load and the vascular supply that is vital for the overall health of the foot. It is only prudent that we consider the function of the DDFT when attempting to maintain a healthy robust foot, prevent the proverbial crushed heel, quarter cracks, thin soles, bruises, shelly walls and the associated ill effects. Distortion of one component is inevitably associated with distortion of adjoining components, albeit to a lesser degree in many cases.[4]

Breaking the complex foot model down into two basic zones with very different but complementing functions is a helpful means of developing the mechanical thought process for farriers and veterinarians. Visualizing the deep flexor muscle/tendon as a support component attached to the coffin bone that is statically attached to the laminae and the laminae in turn to the horn capsule completing the basic suspension of the digits. This unique arrangement makes the laminae and DDFT opposing antagonists. For every force, there is a resisting force, and these two very plastic but extremely strong components play a major role regulating the blood flow to this vital structure that is under constant alteration with the healthy foot as well as those suffering from a variety of conditions.[5] The support structures complement the suspension by acting as an energy sink as the digits descend under load and bottom out, so to speak, with ground contact. The support components consist of the digital cushion, frog, bars, sole, sole corium and ground surface wall. If we consider that a foot is balanced when the suspension and support components are in harmony and equilibrium, and have total recall following deformation from load, it changes our perspective of the real problem and greatly enhances our mechanical thought process as we contemplate therapeutic decisions.

Mechanics is a branch of science that deals with energy and forces and their effect on bodies or the functional parts of an activity. Considering the complexity of the equine foot it is only prudent that we understand the forces at play and their influence on all components. There are significant gaps in our knowledge regarding how therapeutic trimming and shoeing interventions affect the function of the structures of the foot. Fortunately, there has been considerable progress in the current understanding of the biomechanical basis underlying the function of the digit. Over the years, countless types of shoes and techniques have been developed not only as a therapeutic aid to treat lameness, but also to maintain or enhance functionality.[2]

5. Phases of the Stride

Understanding anatomy and physiology, form and function of the foot is imperative when examining the lame performance horse. The stride is divided into five phases: initial contact, impact, stance, breakover, and flight.[6] The foot moves in a sagittal plane parallel to the long axis of the horse. This varies among horses due to conformation.

Initial contact is usually made with the heels, although some horses land flat footed, some on the lateral side, and others land toe first.[7, 8] The propensity to land flat footed increases with speed. Toe-first contact is rare unless there is foot related lameness. The point of action of the ground reaction force is at the heels during initial contact, and its magnitude is low.

The impact phase is marked by rapid high frequency oscillations in the ground reaction force with a point of action toward the heels.[9] The oscillations are significantly reduced at the level of the first phalanx, indication that the soft tissues of the hoof, interposed articulations, and digital venous plexus are absorbing the energy impact. The vertical velocity and acceleration are greater in the forelimb than in the hind limbs, which may partially explain why the forefeet are more frequently injured.[10]

The stance phase extends from the end of impact until the beginning of breakover. The point of action of the ground reaction force is centered in the foot, slightly medial to the dorsal third of the frog.[10] During the first half of the stride,

the craniocaudal component of the ground reaction force of the foot is directed caudally, decelerating the limb; during the second half of the stride, it is directed cranially, propelling the horse forward. Toward the end of the stance phase, the point of action of the ground reaction force moves toward the toe.[7] With increasing speed, the ground reaction force increases and the strain in the hoof wall and tension in the tendons increases.

The breakover phase begins when the heels lift off the ground and ends when the toe leaves the ground. Once the heels are off the ground, the point of action of the ground reaction force is at the toe. The flight phase begins when the toe leaves the ground as the limb completes retraction and ends when the heel makes contact with the ground after protraction of the limb.

The way in which a horse breaks over is influenced by conformation of the limb and foot, shoe styles and trim, and the influence of pain throughout the phases of the stride. These variables also contribute to the flight path of the foot, and the flight path of the foot contributes to the way the foot lands. This relationship is used by farriers to correct interference problems and improve the appearance of the gait. Requesting radiographic information and input from the veterinarian teamed up with a farrier complements suggestions and recommendations that can often enhance therapeutic shoeing success.

6. Hoof Capsule Distortions

Many foot related lameness involve hoof capsule distortions. Hoof capsule distortions occur when the tensile, compressive, or shearing forces on the hoof exceed the capacity of the hoof capsule components to withstand them. There are three basic situations in which the loading capacity of a structure can be exceeded: normal load on an abnormal structure, abnormal load on a normal structure, and abnormal load on an abnormal structure. The latter is a more reliable recipe for distortion and perhaps outright destruction of the compromised component.[4]

Understanding the basic mechanisms of hoof capsule distortions and foot related lameness enables the clinician to unravel the sometimes-complex mix of abnormalities, identify early warning signs, and manage existing problems more effectively. Evaluating each of the components of the hoof capsule, both individually and as an integrated unit, allows the clinician to address the primary and secondary problems and come up with effective options for countering or attenuating the forces responsible for the distortion. The shape of the distorted hoof capsule reflects the distribution of loads across the foot. The severity of the defects thus depends on the severity and duration of the imbalance. We must bear in mind that the normal equine limb is not evenly loaded with the medial side normally bearing proportionately more load than the lateral side. This fact is reflected in the subtle but important differences in shape and density of the horn, soft tissues, bone, and vasculature between medial and lateral sides of the digit. These abnormalities compromise circulation to the germinal layers of the hoof capsule, thus retarding horn growth in affected areas, which further distorts the hoof capsule. A perfectly symmetric foot does not exist, and we should not be attempting to create such a foot with our manipulations.

Although we may be able to improve the condition, halt its progression, manage the secondary effects, and improve the appearance of the foot, we must accept that we cannot prevent or completely resolve the misunderstood distortion. Attempting to do so can have deleterious effects on other components of the digit. As we attempt to deal with one area of the foot, we must remain aware of the ill effects our manipulations may have on related structures. One must bear in mind that there is an interrelated network of structures involved: DDFT, P3, laminar attachment, solar corium, and hoof capsule. When altering one component, it is important to consider the effect that action is likely to have on the other structures.

Failure to understand the normal structure and function of the equine foot and to manage the foot and the horse accordingly have deleterious effects. With existing problems, developing these skills enhances the clinician's ability to interpret the degree of damage accurately and to devise mechanical solutions that create an environment in which healing, and restoration of function are maximized.

7. Influences of Shoeing

Shoeing horses has several influences on normal foot function. The weight of a shoe increases the moment about the distal joints of the limb.[3] In the performance horse, this increases animation, which is considered desirable in some disciplines. It increases stride duration, but does not increase stride length.[11] However, increasing the weight of the distal limb is likely to result in increased fatigue. The flat surface of a shoe can cause a horse to slide further after impact on a hard surface than if the horse was barefoot.[12] Also, the ability of the hoof to accommodate to an uneven surface because of its viscoelastic nature maybe reduced as a result of the rigid nature of the shoe.

The attachment of a shoe to a foot reduces expansion of the hoof capsule, but it does not prevent the heels from expand-

ing.[13] It also increases the maximum deceleration of the foot and increases the frequency of vibrations as the foot impacts the ground and the maximum ground reaction force.[14] This effect on reduced damping of impact forces by the hoof is negligible at the level of the metacarpophalangeal joint.[15] Shoes reduce the decrease in pressure within the digital cushion associated with weight-bearing during the stride and increase pressure on the navicular bone from the deep digital flexor tendon.[16] Interestingly, shoes do not change the point of application of the ground reaction force, nor do they change the stresses within the hoof wall, although they do cause some reorientation of these stresses.[17]

In addition to altering the kinematics of the distal limb and biomechanics of hoof function, shoes influence the rate of wear and growth of the foot. A shoe prevents natural wear from the weight bearing of the foot. Therefore, instead of maintaining a consistent length, the length of the foot fluctuates with the shoeing cycle, causing changes in the moment about the distal interphalangeal joint.[6]

The distal interphalangeal joint (DIP) is the major articulation of the digit. It is the center of articulation about which many structures of the distal limb act upon during locomotion. The DIP joint is therefore considered a focal point of the digit and is a major landmark when assessing hoof form, function, and balance. The DIP joint is primarily designed to move in flexion and extension; however, there are rotational/ transverse plane and collateral /frontal plane movements as well. These planes of motion allow the joint to tolerate uneven ground.

To limit the stress on the joint and maximize foot function, maintaining a balanced foot proportioned around the center of rotation of the DIP is necessary. The DIP joint, being the distal most joint of the limb, is most affected by asymmetrical loading patterns when ambulating on uneven terrain and is also greatly influenced by foot manipulations, such as trimming and shoeing. Special attention to trimming and shoeing is most likely to have the biggest impact, especially in cases with poor conformation or foot-balance issues. Trimming to establish even loading medial to lateral is the goal.

When shoeing, preserving the natural function of the foot is the goal. When the foot is loaded the elastic hoof capsule deforms, soft tissue is compressed and stretched, and the elastic/pliable lamellar interface allows the bone column to displace slightly within the hoof capsule. A well-formed hoof capsule with proper mass and shape are the foundation for a well-functioning foot.

8. Goals and Principles of Therapeutic Trimming and Shoeing

The function of the hoof can be affected by environment, discipline, exercise, and farriers to mention just a few. The hoof has the ability to respond relative to its structural characteristics, its natural tolerance of the mechanical challenges, or by adaptation with changes in growth rate and shape.[1] The stance phase is considered the most critical part of the stride for developing injuries of the musculoskeletal system.[18] The stance phase occurs while the foot is in contact with the ground and the limb is therefore subjected to an external impact force by the ground. This external impact is termed the ground reaction force (GRF), the magnitude of which depends on the horse's weight, speed of movement, and the surface on which the horse moves.[19] Lameness during the loading phase will alter the landing as well as breakover and influence the stride phase of the support limb as the horse becomes reluctant to load and prematurely unloads the painful foot. The horse must surely feel the discomfort from folded heel tubules, drastic loss of digital cushion, medial unnatural listing, joint imbalance, thin soles, and a negative PA long before showing detectable soreness. This may explain why these common signs of hoof distortion are often not taken seriously until it is obvious something is wrong with the foot.

Mechanical therapeutic trimming and shoeing techniques attempt to unload a specific painful or compromised area shifting the load to more healthy components. When considering therapeutic shoeing to enhance soundness or to prevent further capsule distortion hopefully warding off future problems, it is useful to keep in mind the type of horse, hoof, conformation, internal parameters, discipline, exercise regimen, environment, surface the horse works on, and extent of the distortion and associated unsoundness. The latter is important, because the therapeutic shoe-ground interaction is often at the heart of the success or failure of the intended treatment.

In general, most goals of mechanical therapeutic shoeing are based on the relationship of the suspension and support components. Remarkably reducing the tension of the DDFT relative to the intensity of the tissue lesion or hoof distortion using a variety of breakover enhanced trims and or shoes is a primary basis for mechanical shoeing. This can be broken down into 4 basic goals: (1) reducing concussion to the foot in general with focus on specific areas, (2) shifting load away from painful or compromised com ponents to healthier areas, (3) altering the distribution of force, and (4) changing the ease of movement about the distal interphalangeal joint. Preventive maintenance is the

key; however, there are many variables that we can't control that lead to foot injury despite having durable robust feet.

9. Prevention

Mechanical benefits that can produce medical benefits appear to be a major key to therapeutic and pathological shoeing. A well-made strategic plan based on the basic mechanical requirements of the foot can greatly improve the outcome and success of many podiatry cases. Understanding the basics principles of podiatry allows the veterinarian and farrier to manage the hoof in such a manner to aid the prevention of foot related lameness, maintain a sounder horse, and implement therapeutic shoeing when necessary.

As with many other types of foot related lameness, prevention is much more effective than treatment. Prevention begins with careful observation. It is important that detrimental changes in the foot be recognized early and dealt with appropriately while there is still a chance to preserve the integrity of the foot.

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Declaration of Ethics

The author adhered to the AVMA Principles of Veterinary Medical Ethics.

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