Universidade de Évora - Escola de Ciências e Tecnologia

Mestrado Integrado em Medicina Veterinária

Relatório de Estágio

Equine clinics

Annette Christiane Roider

Orientador(es) | Susana Monteiro
An Sleeckx
Elisa Maria Bettencourt

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O relatório de estágio foi objeto de apreciação e discussão pública pelo seguinte júri nomeado pelo Diretor da Escola de Ciências e Tecnologia:

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Évora 2021

Acknowledgement

To my supervisor at the University of Évora, Professor Dr. Susana Monteiro who was able to transmit the fascination of equine medicine with an incredible amount of knowledge in her classes. Her contagious enthusiasm for equine medicine is a living example for me.

To my external counselor, Dr An Sleeckx for the opportunity to do the training in the Greater Lisbon / Ribatejo area, for the discussions, laughter and patience with me. Thank you for your inspiring friendship.

To all my friends Andreia, Raquel, Sandra, Patricia, Inês, Marina, Sara, Cátia and Laura who supported me during this time, I know it's not always easy. I wouldn't have survived the course without you.

To Joana Reis who opened a new passion for internal medicine in me. To Isabel Valencia and José Manuel Correia Lopes, my faithful riding companions, whose keen intellect and inspirations I greatly admire.

To Willi who supported me during this time, taking care of our animals and our Quinta.

To my dad, who would have been proud.

Finally, to all the animals that accompanied me, in Africa, in Portugal and in Germany. All this is for the passion for you.

Abstract

Equine Clinics and Surgery

The present final report concluding the degree of the Integrated Master in Veterinary Medicine at the University of Évora is based on the curricular externship in an outpatient clinic with Dr. An Sleeckx in the Greater Lisbon / Ribatejo area.

This report is divided into two parts. The first part presents the casuistic of the externship and describes clinical cases like abdominal pain, lameness, pre-purchase exam, intoxication with monensin, insect bite hypersensitivity and castration which were followed during the externship. As painful events like lameness and colic are very common in equine clinics, a literature research on pain assessment in horses was made and presented in the second part as a monography. The focus was on new composite pain scales including behavior and facial expressions which seem to be the most reliable to detect pain according to the newest publications.

Keywords: equine, clinics, pain diagnostic and management in horses

Resumo

Clínica e Cirurgia de Equinos

O presente relatório de conclusão do curso de Mestrado Integrado em Medicina Veterinária da Universidade de Évora é baseado no estágio curricular realizado em clínica ambulatória com a Dra. An Sleeckx na zona da Grande Lisboa/ Ribatejo.

O relatório é dividido em duas partes. A primeira parte apresenta a casuística do estágio e descreve casos clínicos como dor abdominal, claudicações, acto de compra, intoxicação com monensina, hipersensibilidade à picada de insectos e castração, que foram acompanhados durante o estágio. Uma vez que eventos dolorosos como as claudicações e as cólicas são muito comuns nas clínicas equinas, foi feita uma pesquisa bibliográfica sobre avaliação da dor em cavalos, que foi apresentada na segunda parte como uma monografia. O foco foi em novas escalas composta de dor, incluindo comportamento e expressões faciais que parecem ser as mais fiáveis para detectar a dor de acordo com as mais recentes publicações.

Palavras-chave: equinos, clínica, diagnóstico e tratamento de dor em equinos

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Abbreviations

AAEP — American Association of Equine Practitioners

AP — antero-posterior

AVMA — American Veterinary Medical Association

BALF — bronchio-alveolar lavage fluid

BEVA — British Equine Veterinary Association

BID — twice a day

bwt — bodyweight

CAS — Equine Comfort Assessment Scale

CRI — continuous rate infusion

DDFT —deep digital flexor tendon

DMSO — Dimethyl sulfoxide

DP – digital palmar

DP – dorso-palmar

DV – dorso-ventral

EAAPS — equine acute abdominal pain scales

ELISA— enzyme-linked immunosorbent assay

EQUUS-FAP — Equine Utrecht University Scale for Facial Assessment of Pain

G — gauge

HR — heart rate

IASP — International Association for the study of pain

IBH — Insect-bite hypersensitivity

i.e. — it est

IM — intramuscular

IV — intravenous

LM — lateromedial

ml — milliliter

NSAID — nonsteroidal anti-inflammatory drugs

P2 — middle phalanx

P3 — distal phalanx

PCR — polymerase chain reaction

PCV — Packed cell volume

PO — per os (by mouth)

p.r.n. — Latin "pro re nata“: as needed

PSGAGs — polysulfated glycosaminoglycans

RR — respiratory rate

SC — subcutaneus

TID— three times a day

TP — total protein

1. Introduction

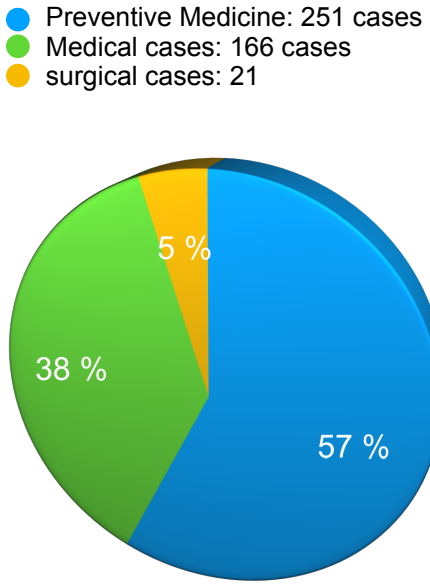
This report describes the activities during the curricular externship of the Integrated Master in Veterinary Medicine of the University of Évora. The externship took place from 2nd of September till the 31th of December 2019, at an ambulatory clinic for horses in the Greater Lisbon and Ribatejo area. It aimed to consolidate theoretical knowledge and its application in practice. With the monitoring of the daily routine with a vast variety of activities in outdoor equine practice, it was intended to develop practical and theoretical skills to deal with future work. The intern had the opportunity to accompany Veterinarian An Sleeckx in ambulatory veterinary service, having at her disposal the necessary materials to perform diagnostics in medical clinic including digital X-ray and ultrasonic device.

The monography of this externship report is about pain detection and pain management in horses.

2. Casuistic

2.1. Broad Classification of Cases:

The following chapter will describe the clinical cases observed during the externship, highlighting the most relevant in each area, whether by frequency, uniqueness or scientific interest. The choice of the developed cases was made based on their relevance and on uniqueness. The total number of patients followed over the four months of externship was 438, with a wide range of different case. To facilitate the presentation and analysis, the casuistry was grouped into three areas of veterinary medicine: preventive medicine, medical clinic (including locomotor disorders) and surgical clinic.



Graph 1 - Different areas of veterinary medicine: Preventive Medicine, Medical cases (including locomotor disorders), Surgery. (of 438 horses treated in the externship in ambulatory equine practice)

The analysis of graph 1 shows that the vast majority of cases accompanied were preventive medicine with 57%, which corresponds more exactly to 251 cases, medical cases in 38% and surgery in 5%. The horse breeds seen during the externship were mainly lusitanos and some lusitano crossbreeds and a few thoroughbred arabians and angloarabians of all ages.

In preventive medicine, numerous consultations for identification and placing of microchip (electric transponder) were carried out, for the subsequent registration and inscription and request for identification document. The most common cases were pre-purchase exams for horses sold within the European Union, X-rays of the large joints, deworming, Influenza and Tetanus vaccinations for competition horses as well as basic İmmunization for foals and routine teeth control and dentistry with sedation. Horses going to the US required additionally blood collection for diagnosis of Piroplasmosis.

In medical clinic different types gastrointestinal afflictions like esophageal obstruction and colic, respiratory diseases, dermatologic allergic reactions, intoxications, infectious diseases were seen. Numerous consultations also concerned locomotor disorders like different forms of lameness in leisure horses, competition horses and bullfighting horses. Many lameness test were made in sales horses in the context of pre-purchase exams. Emergency calls were often related to abdominal pain with 25 cases of colic, esophageal obstructions (4 cases) and various wounds (5 cases), and intoxication (4 cases of intoxication with monensin) and acute infection (3 cases with Piroplasmosis). Affections of the respiratory system also were a common reason for ambulatory veterinary consultation (6 cases). In dermatology, insect-bite hypersensitivity was frequently seen (7 horses) apart from wounds, other allergic reactions and dermatophilosis and melanomas. Reproductive cases where nearly non-existent, as the externship took place late in the year after the end of breeding season.

The surgical clinic had a smaller number of cases due to the ambulatory character of the externship. The treatment and suture of more extensive skin injuries often as a result of accidents with barbwire fence and hoof kicks, and castrations where the surgical intervention most frequent in the field. The most common planned procedure was orchiectomy (16 horses).
A description of some of the cases integrated in the areas of intervention will be made below.

2.2. Preventive Medicine

In preventive medicine, numerous consultations for microchips and requests for inscription in the Blue Book (48 cases), deworming (63 cases) and vaccination (82 cases), annual dental check under sedation (5 cases), and 53 pre-purchase examinations for horses of all ages were performed during the externship (Table 1).

Table 1 - Casuistic in preventive medicine

Preventive Medicine	Number of cases
Vaccination (Tetanus/ Influenza)	82
Microchip / inscription	48
Deworming	63
Pre-puchase exam	53
Dentistry	5
TOTAL	251

2.2.1 Vaccinations

The most common visits in stud farms were made to perform for vaccinations against tetanus and influenza mostly for yearling foals but also for adult horses like pregnant mares and competition horses.

The vaccination of all animals with tetanus/ influenza was recommended, although this is not obligatory in Portugal. Only those who participate in international equestrian competitions have to present updated vaccination records for equine influenza, following the rules of the International Equestrian Federation (FEI) (FEI, 2019). Clients were informed that sports horses are not allowed to compete within seven days of influenza vaccination. Most of the vaccines available in the market provide protection against the Influenza virus from the Orthomyxoviridae family and for exotoxins produced by the gram-positive anaerobic bacillus *Clostridium tetani,* agents of equine influenza and tetanus, respectively (MacKay, 2014).

The vaccine used by the ambulatory horse clinic of this externship was Equilis Prequenza-TE®. It consists of two strains of Influenza and tetanus toxoid (MSD Animal Health Portugal, 2020). With this active immunization of equines, first dose at 6 months of age, immunity for both - tetanus and influenza - established approximately 2 weeks after the first dose (Heldens *et al.,* 2010; Kendall *et al.*, 2016). The dose of 1 ml must be administered strictly intramuscular, according to the scheme: first dose at six months of age and the second dose four weeks later. The third dose for tetanus is administered not more than 17 months after the basic immunization. Equine influenza vaccination should be repeated 5 months after the base vaccination and results in an immunity that is maintained for at least 12 months. For Tetanus, two years is the maximal time interval which should not be exceeded in horses (MSD Animal Health Portugal, 2020). A simultaneous emergency vaccination with Tetanus-Serum Intervet (passive immunization) was used in four injured horses that were not previously vaccinated. In these cases, the first dose of tetanus toxoid was administered at the same time as the prophylactic dose of tetanus antitoxin (Intervet Tetanus Serum 1000 I.E./ ml) using separate injection sites and different syringe and needle. This provided passive tetanus protection for at least 21 days after simultaneous administration (MSD Animal Health Portugal, 2020).

2.2.2 Pre-purchase Examinations

The performance of pre-purchase exams is a very explored area nowadays and represents, not only in sport horses of high-level competition, one task with great responsibility and demanding of expertise for the veterinarian who performs it (Werner, 2012).

Cases in the externship

The 53 cases accompanied during the externship were mostly pure Lusitanos aged one to fifteen years. They were sold for different purposes ranging from horses for hacking and leisure, to dressage, bullfight and breeding. Some were very expensive others not. Many were for horses intended for sale abroad. Cases consisted of general and clinical examinations, static and dynamic and 24 x-rays. Different projections were performed routinely to evaluate the limb: the latero-medial, dorso-palmar/plantar (coffin and pastern joints, fetlock, carpal joint and hock), and dorso-45° lateral palmar/plantar-medial oblique and dorso-45° medial palmar/plantar lateral oblique projections (fetlocks, hock) and Oxspring projection (P3 and navicular bone) and Skyline projection (navicular bone). In hind legs additional projections for the femuro-patelar joint were used (latero-medial, caudo-lateral 30°cranio-medial oblique). Young or unbroken horses were put in a round pen or presented on a lounge and observed for symmetry or lack there and for conformational defects. Older horses also were presented under a rider. The physical examination was performed methodically and according to body system. Informations, findings and every action taken by the veterinarian were recorded on pre-purchase examination worksheets. The client determines how exactly and in what detail the horse is to be examined in order to get exact statements about the functionality and health. Various complementary diagnostics and procedures can be performed depending, ultimately, on the will of the customer. Radiography is considered the method of choice in pre-purchase examination for osteochondral changes (van Hoogmoed *et al.*, 2003; Bastos *et al.,* 2017).

In the externship some examinations were performed without any x-rays, while in others there was a radiographic panel that amounted to more than 48 radiographs per animal, in addition to ultrasound scan of tendons and also blood samples to control for doping substances. The x-rays were performed with a portable direct digital X-ray machine. Where necessary the animals were sedated with Detomidine (0,01 mg/kg bwt) especially when they were young and not used to handling. The vast majority of equines present one or more radiographic findings because radiographic changes are very common in clinically healthy horses (Vos, 2008). It is essential to know the exact purpose for which the horse is intended to be able to assess whether or not the changes and anomalies found during the examination may limit the intended use.

The radiographic evaluation in a pre-purchase examination should describe the radiographic changes and prioritize the diagnoses so that a prognosis for the use of the horse can be concluded (van Hoogmoed *et al.,* 2003). From a certain age onwards, one should not expect a completely clean horses i.e. without any abnormalities. Some alterations (smaller joint space, subchondral signs of sclerosis, exosthosis) are age-appropriate and don't compromise the use of the horse (Vos, 2008). Existing technical devices and scientific knowledge can only indicate

some probabilities and possibilities of evolution of certain affections or anomalies found (Vaughan, 2007; Baxter and Stashak, 2011). Depending on the case, test for blood concentrations of performance-enhancing drugs should be considered, most notably phenylbutazone (commonly used to suppress locomotor disorders due to pain) as well as blood tests to exclude metabolic disease. It is important to be fully aware that this service is being rendered to the one paying for the exam which is usually the buyer. Frequent requests of sellers to have access to the pre-purchase report, especially when the horse is not sold, should not be allowed without the permission of the client who payed (Werner 2012).

Pre-purchase examination record

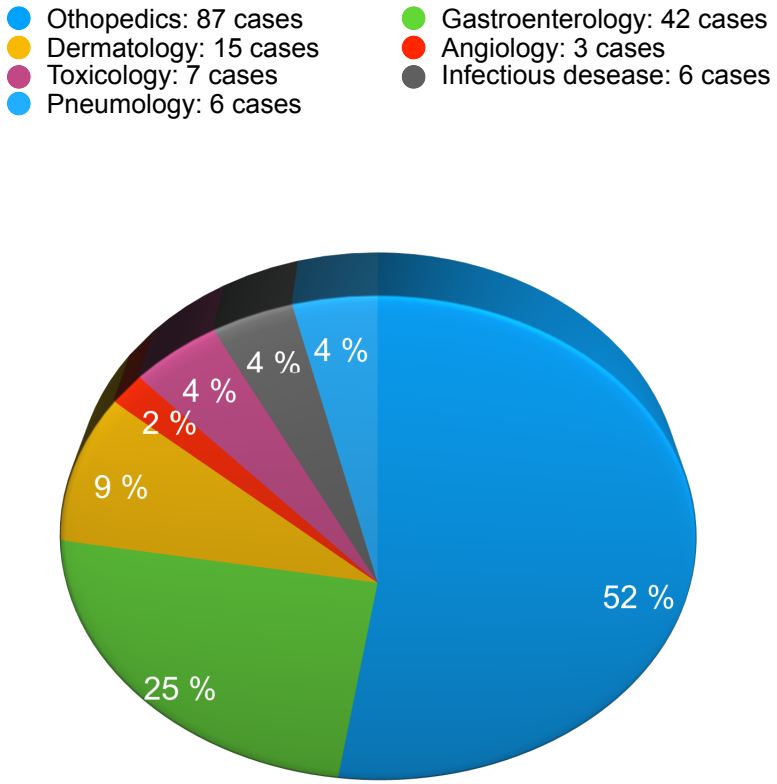
According to Vaughan (2007), the written pre-purchase examination record should contain the following facts: Complete identification is fundamental, including breed, sex, color and markings, brands, tattoos, microchips, and age, by registration papers and as much specific information as possible. The medical history should include documentation of any express and implied warranties against vices, illness, surgery, treatments, and all related incidents. All examination results of all organ systems, the oral cavity, the pelvic area, and the feet and limbs should be documented. It is of critical importance to the defense of a malpractice claim that records of all findings be complete and legible. Any finding that constitutes an existing unsoundness or predisposition to unsoundness should be clearly described. No attempt should be made to diagnose or treat a disorder. At the end of the examination the written report based on all the data collected must be signed and stamped with date, time and location.

Conclusion

Based on experience and knowledge and taking into account the purpose for which the horse is intended, the veterinarian gives no recommendation to buy but a medical description of the findings that can be easily understood by laypersons. The final decision rests solely and exclusively with the client, the potential buyer. The veterinarian is only responsible for providing all the data so that the buyer decides in full knowledge whether to go ahead with the business (Vaughan, 2007). The most common basis for finding a horse unserviceable in pre-purchase exams is lameness (Dart *et al.*, 1992). In the externship eight horses were obvious lame during the gait evaluation and the purchase examination was postponed to a later date. Horses used for pleasure riding (37 cases) tended to be considered serviceable more often than horses intended for completion and more athletic endeavors (16 cases).

2.3. Medical cases

Medical cases (including locomotor disorders), that is 38% (166 of 438 cases) seen in the externship included a wide range of different afflictions ranging from orthopedics (87 cases), gastroenterolgy (42 cases), angiology (3 cases), toxicology (7 cases) pneumology (6 cases), dermatology (15 cases) to infectious disease (6 cases) as seen in graph 2. Lameness due to orthopedic problems was the most frequent with 87 cases, followed by 42 cases of gastroenterology with abdominal pain.



Graph 2 - Medical cases seen in the externship according to the respective specialities.

Neonatology (3 foals with diarrhea, i.e. gastroenterologic case), oncology (2 cases with melanomas, i.e dermatologic case), neurology (1 foal with tetanus/ infection) and ophthalmology (one case of obstruction of the lacrimal duct discovered in prepurchase exam) were the areas with less relevance during the externship.

2.3.1. Orthopedics

Lameness was one of the most frequent reasons for consultation and had most relevance in the ambulatory clinic. A wide range of different disease processes including the hoofs, joint structures, bones as well as tendons, ligaments and muscle problems were seen in the course of the four months of externship (Table 2).

Lameness definition

Functional or structural pathologies of the musculoskeletal system can result in an abnormal gait and stance in equines.

While normal horses in general have a balanced and symmetric way to move, lame horses unconsciously shift their body weight to protect the afflicted part of the locomotor system and

therefore show an unbalanced asymmetrical body motion (Davidson, 2018). The basis for lameness diagnosis in horse clinic is the detection of pelvic hike and head nod.

Table 2 - Casuistic of orthopedic cases in the externship
(third metarcarpal bone MCIII, forth metacarpal bone MCIV, distal phalange P3)

	Number of cases
Osteoarthritis	23
Osteochondrosis dissecans	12
Subsolar hoof abscess	5
Fractures	6
Tendinopathy	4
Laminitis	6
Synovitis	4
Navicular syndrom	13
Hematoma muscular	3
Kissing spines (over-riding spinous processes)	2
Keratoma	1
Thrush	8
TOTAL	87

In the externship systematic lameness examination started with a detailed history followed by visual examination of the resting horse. The complete musculoskeletal system then was palpated with both the limb supported and suspended and application of the hoof tester. Next, followed an observation of the horse step by step in walk and trot in a straight line and circle on both sides, on hard and soft ground, and flexion tests. If necessary, perineural or intra-articular anesthesia from distal to proximal direction with 2% mepivacaine hydrochloride were performed. The degree of lameness was determined after the observation of the horse in movement using the lameness scale of the American Association of Equine Practitioners (AAEP) (Baxter and Stashak, 2011). After determining the region of origin of lameness, complementary diagnostic methods such as radiography or ultrasound were used to reach the diagnosis.

In the externship 35 horses had orthopedic disorders which affected the very distal part of the limbs. In the hoof / hoof joint area the differential diagnoses of acute severe lameness with origin in the hoof are numerous. It can classically be distinguished by hoof abscess, sole

bruises, septic arthritis, osteoarthritis, laminitis, navicular syndrome, distal phalanx fracture, navicular fracture, acute damage to the soft structures (e.g. often the deep flexor tendon) and diseases in the area of the processus extensorius.

2.3.1.1. Navicular syndrome

Navicular syndrome is one of the most frequent reasons of foreleg lameness in equines (Waguespack and Hanson, 2011) and a common cause of lameness in horses 6 to 10 years of age (Rose, 1996). It results of degenerative alterations of the navicular apparatus, which include the soft tissue structures as well as the navicular bone. The navicular apparatus is comprised of the distal sesamoid impar ligament, the navicular suspensory ligament, the deep digital flexor tendon (DDFT) and the associated bursa (Figure 1 and 2) (Waguespack and Hanson, 2011).

In a healthy horse, the navicular bone functions to equally distribute mechanical forces between the DDFT, the middle phalanx and the distal phalanx (pedal bone), keeping the insertion for the DDFT in an constant angle (Waguespack and Hanson, 2011).

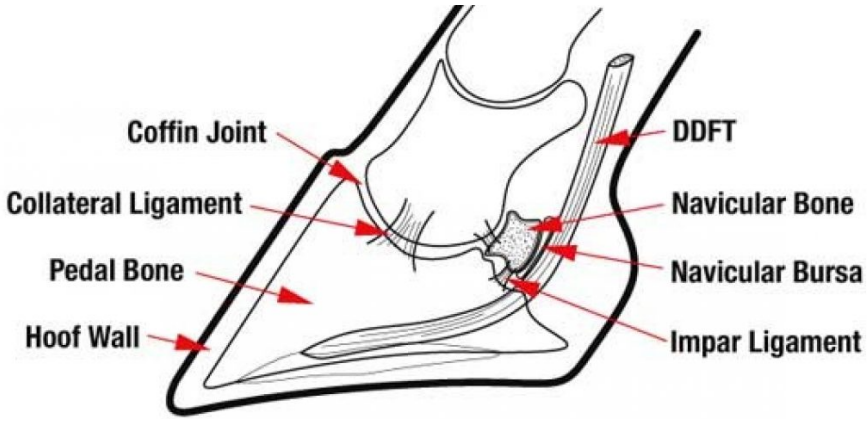


Figure 1 : Anatomy of navicular apparatus; drawing by Carole Herder (Equisearch, 2013)

Definition

By definition the navicular syndrome is a progressive affliction which affects the DDFT, the navicular bone, the associated bursa as well as its surrounding soft tissue structures which all together form the so called navicular apparatus (Rose, 1996; Stanshak, 2002). Other expressions used for this condition are “navicular bursitis“, “bursitis podotrochlearis“ and the Latin synonym “podotrochlitis chronica aseptica“ which means chronic aseptic podotrochlitis (Numans and van der Watering, 1973).

Clinical signs

Horses suffering from navicular disease typically present increasing unilateral or bilateral chronic forehand lameness, general stiffness, short strides, stumbling and unwillingness to

make short turns. In order to protect the palmar part of the foot, these horses try to land with toe first, which changes the aspect of the gait (Rose, 1996). This type of lameness is usually more evident on hard surfaces. Signs of pain exacerbate by trotting in small circles and usually increase when the lame inner leg has to bare more weight (Waguespack and Hanson, 2011).

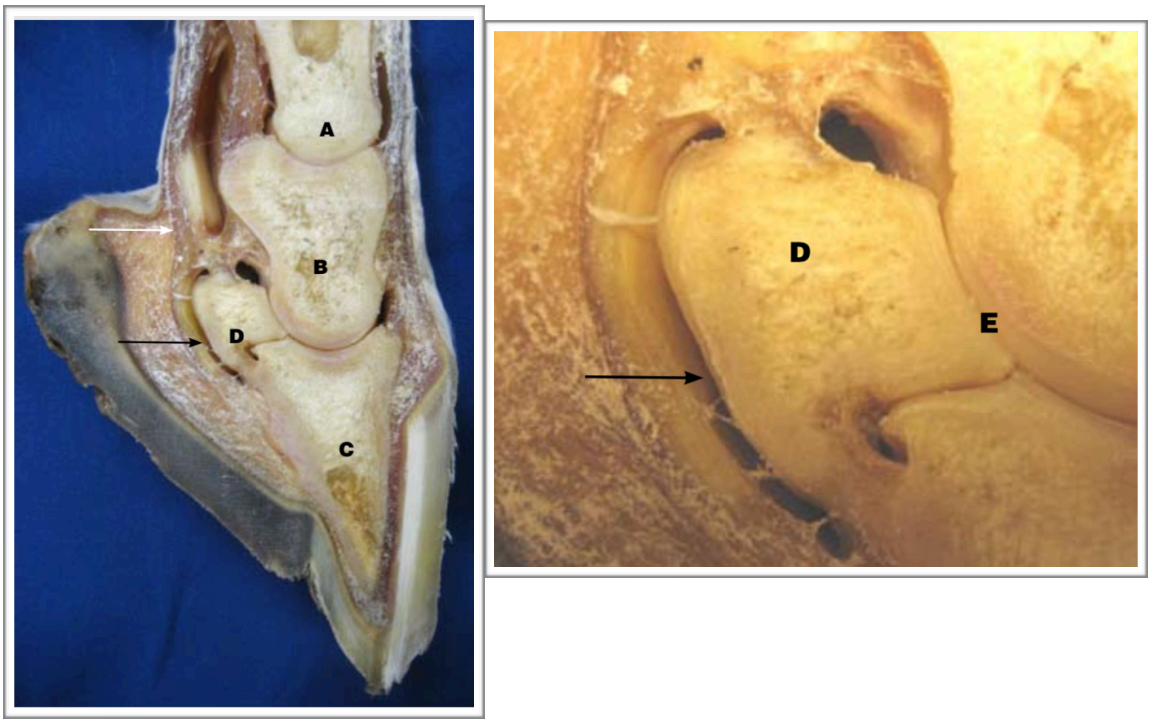


Figure 2 - Midsagittal section of of the distal phalanges, images from Waguespack and Hanson, 2011: (black arrows) navicular bursa, (white arrow) DDFT, (A) Proximal phalanx, (B) middle phalanx, (C) distal phalanx, (D) navicular bone, (E) distal inter-phalangeal joint.

Horses may exhibit sensitivity over the frog of the foot when hoof testers are applied. In eighty percent of equines with navicular syndrome, flexion tests of the fetlock and the pastern show intensified pain with pronounced lameness (Rose, 1996).

Pathophysiology

The source of pain is multifactorial ranging from the bone itself to components of the navicular apparatus (DDFT and the corresponding bursa, navicular bone, distal sesamoid impar ligament, the navicular suspensory ligament). The exact pathogenesis of the navicular disease is still unclear. Three theories exist which try to explain the etiology: vascular compromise to the foot, chronic inflammation, and repetitive biomechanical forces (Waguespack and Hanson, 2011).

The most accepted mechanism is that biomechanical abnormalities of the foot alter the normal forces present on the navicular apparatus leading to tissue degeneration. Alterations in the biomechanical forces can be due to poor conformation of the foot and pastern, hoof imbalances, improper shoeing or trimming, excessive weight bearing and exercise on hard surfaces. Factors

which predispose to this affliction are large body size, small hoofs, bad shoeing with long toe and short heel, and upright conformation (Waguespack and Hanson, 2011).

Diagnostic

Navicular disease can occur in equines of all ages and breeds. The most susceptible breeds are Quarter horses, Thoroughbreds and Warmbloods, where it occurs most in geldings (Dyson, 2003). Hind limbs can be affected, although it has rarely been described in literature. This syndrome commonly affects showjumping, western, and polo horses (Wollenman *et al.*, 2010; Murray, 2014; Holbrook, 2014).

A complete history of the horse, as well as thorough physical and lameness examination with additional diagnostic anesthesia, are essential to diagnose navicular syndrome. According to Rose (1996) the following characteristics should be present: a recurrent or chronic increasing bilateral or unilateral lameness of the forelimb, exclusion of other hoof diseases (e.g. laminitis), radiological alterations in the navicular bone and significant improvement due to deep palmar nerve anesthesia.

Radiography can support clinical diagnosis of navicular syndrome. The most common finding are signs of osteolysis and cysts as well as changes of the distal foramen in the size and shape. This can be evaluated on x-ray on special navicular view or upright pedal view (Rose, 1996; Waguespack and Hanson, 2011). Further radiographic changes are evident sclerosis of the navicular bone medulla, nearly no cortex-medullary demarcation in the palmaroproximal–palmarodistal oblique view, medial to lateral imbalance in the dorsopalmar weightbearing view and palmar processes of the distal phalanx project in a position lower than the toe in the lateralmedial view (Waguespack and Hanson, 2011). Unfortunately, none of the changes seen on x-rays are definitively pathognomonic for navicular disease. It also occurs that horses with pronounced clinical signs of navicular syndrome may have no radiographic changes at all associated with the navicular bone. Further imaging techniques are ultrasonography, nuclear scintigraphy, computer tomography and magnetic resonance. Intrabursal anesthesia with 4 ml of 2% mepivacaine of the navicular bursa (Figure 3) can help to differentiate the source of pain. A positive response to this type of diagnostic anesthesia is a strong hint for the existence of painful pathologic alterations of the navicular bone, its bursa, soft tissues structures and ligaments (Dyson and Kidd, 1993).

Treatment

Treatment of navicular syndrome comprises three main options like pain management, the use of drugs to promote blood circulation, or alterations of the limbs biomechanic (Rose, 1996). Due to the multiple etiologies that may contribute to any case, treatment and management of the condition is rarely straightforward and often requires a combination of strategies. There is not a gold standard as it is not curable. Treatment centers around managing the level of pain present through multiple, different techniques, such as medical or surgical therapy.

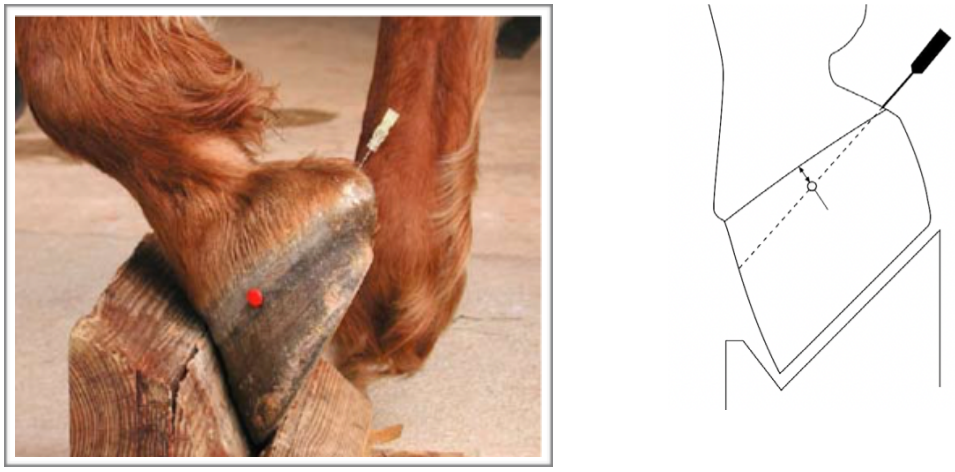


Figure 3 - The palmar midline approach for centesis of the navicular bursa (Image from Waguespack and Hanson, 2011; drawing from Schumacher *et al.,* 2004)

The basic treatment of navicular disease comprises rest, a corrective hoof trimming to improve hoof balance and shoeing with elevated heels using egg-bar shoes. Heel elevation decreases the tension placed on the DDFT to allow better weight distribution and reduce the pressure applied to the navicular apparatus. The application of systemic and intra-articular anti-inflammatory medication is the initial medical therapy for navicular syndrome. Patients with degenerative radiographic signs within the navicular bone can be treated with bisphosphonates, like clodronate disodium or tiludronate disodium. These drugs work to inhibit bone resorption, potentially slowing the progression of the disease. Medications injected directly into the bursa or coffin joint decrease inflammation and support joint health. These medications include corticosteroids, polysulfated glycosaminoglycans (PSGAGs), biologics (autologous conditioned plasma PRP or autologous conditioned serum IRAP®) and hyaluronic acid (Bogers, 2018).

When medical therapy is ineffective, a surgical palmar digital neurectomy might be indicated. Surgical therapy can also include navicular bursoscopy with debridement and desmotomy of the navicular suspensory ligaments (Waguespack and Hanson, 2011). Probably one of the most established surgical treatments of navicular syndrome is the neurectomy of the lateral and medial palmar digital nerves. Cryoneurectomy and alcohol block can also help to relief navicular apparatus afflictions by blocking pain pathways of the caudal foot permanently or half-permanent (Rose, 1996).

Anyhow, treatment of navicular syndrome stays challenging due to the wide variety of pathologic changes which can occure. Diagnosis is complex with no existing reliable diagnostic technical to proof the disease. Unfortunately there is also no therapy that guarantees a definitive cure (Rose, 1996; Waguespack and Hanson, 2011). Treatment of the individual horse therefore should focus on each individual case using technique to reduce pain, reduce stress on the navicular apparatus and to slow down degenerative processes.

2.3.2. Gastroenterology

Besides locomotor disorders and respiratory issues, intestinal diseases are a frequent reasons for the presentation of horses in the veterinary practice. In the externship 42 animals with gastroenterology cases were treated (Table 3), ranging from choke, gastric ulcer, diarrhea, impaction, different types of colic and neoplasia. Three needed surgical treatment. A two and a half year old foal with nephrosplenic dislocation and a 10 year old arabian gelding with suspicion of neoplasia were transferred to the hospital for surgery. One horse, where a big intraabdominal tumor was localized had to be euthanized during surgery (Histologic differentiation of the type of tumor was not made). Another horse with a large colon torsion was euthanized for financial reasons as the owner decided against surgery. The other 38 cases were resolved with medical treatment. Table 3 shows the distribution of the observed gastrointestinal casuistic. Surgical cases were the 2 horses with neoplasia.

Table 3 - Gastrointestinal casuistic seen in the externship

Gastrointestinal cases	Number of cases
Esophageal obstruction (Choke)	4
Gastic ulcers	3
Diarrhea	10
Impaction colic	6
Spastic colic	5
Tympanism colic	2
Sand colic	5
Dislocation nephrosplenic	1
Neoplasia (surgical cases)	2
Unknown cause for colic	4
TOTAL:	42

2.3.2.1. Esophageal obstruction or “Choke“

In the externship 4 cases of esophageal obstruction were accompanied and successfully resolved.

Etiology

Esophageal obstruction is the most frequent affection of the esophagus and can result in life-threatening complications (Chiavaccini and Hassel, 2010). It occurs as a consequence of physical obstruction of the oesophagus with food or foreign bodies (Camacho-Luna and

Andrews, 2015). Primary obstruction can occur by ingestion of food that is eaten too hasty (e.g. apples, carrots), of poor quality or poorly chewed. Teeth in poor condition, especially in older horses, or the presence of oral ulcers may be the main cause. Other reasons which can lead to choke are eating under sedation, insufficient drinking quantity, and a variety of esophageal disease like stenosis or strictures, cysts, neoplasia, diverticula, inflammation with abscesses and other functional disorders (Feige *et al.*, 2000). In cases of simple esophageal impaction, the prognosis is good (Whithair *et al.,* 1990; Wintzer and Kraft, 1997).

Clinical signs:

Diseases concerning the horses cervical esophagus often show very identical clinical signs in cases of acute, chronic or recurrent obstruction (Sutton, 2015). The most commonly observed clinical signs are nasal discharge containing ingesta, coughing, gulping and excessive salivation. Lesser frequent signs are extensions of the head, showing no interest in food, apathy or restlessness and sweating (Feige *et al.*, 2000; Camacho-Luna and Andrews, 2015). The distal thoracic and proximal cervical part of the esophagus are the most common sites for obstruction (Chiavaccini and Hassel, 2010).

Diagnostic

Diagnostic is based on clinical signs, history and medical examination. The passage of a nasogastric tube, esophagoscopy and contrast radiography are diagnostic aids, which can elucidate the etiology of the obstruction (Feige *et al.*, 2000). If the nasogastric tube resolves the situation immediately, the diagnosis of an uncomplicated “choke“ is confirmed (Sutton, 2015).

Treatment:

Basic treatment of esophageal obstruction consists in withholding feed and water, induction of smooth muscle relaxation, tranquilization, analgesia, anti-inflammatory treatment, nasogastric intubation and lavage. Numerous cases of esophageal obstruction may subside spontaneously if water and feed are withheld. An IV administration of sedatives like xylazine 0,4 mg/kg bwt (Feige *et al*., 2000) can enhance the process by relaxing the horse. Sedation makes these animal lower their heads into a position where it drains the nasopharynx, and therefore reduces aspiration (Sutton, 2015). To relax intestinal smooth muscle, Oxytocin in a dose of 0.1–0.22 mg/kg, IV, can be quite effective. When horses do not respond adequately to withdrawal of water and feed, oxytocin and sedation, an esophageal lavage should be the next step. Soft pressure with a nasogastric tube is often required to restore passage into the stomach (Sutton 2015).

Endoscopic evaluation after successful obstruction resolution should be performed in all chronic cases (>24 hr). To reduce pain and inflammatory reaction of the esophageal mucosa, anti-inflammatory medications like flunixin meglumine or phenylbutazone can be used (Feige *et al.*, 2000; Knottenbelt and Malalana, 2015; CliniPharm, 2020).

Mucosal impairment

Endoscopic examination is highly useful in the evaluation of mucosal impairment (Chiavaccini and Hassel, 2010). Circumferential mucosa damage may provoke obstructive esophageal

strictures, foreign bodies can produce marked pressure necrosis. Complications depend on the extension of damage caused. The three main anatomic abnormalities encountered in endoscopic exam after esophageal obstruction are ulcers, strictures, and esophageal diverticula.

Aspiration pneumonia

According to a study of Chiavaccini and Hassel (2010), an indicator of early pulmonary impairment is the respiration rate (RR) of the horses. There is evidence of a six-fold risk having a pneumonia when the respiration rate exceeds 22 breaths per minutes. Commonly used antimicrobials to treat aspiration pneumonia are procaine or potassium penicillin G, trimethoprim sulfamethoxazole and gentamicin sulfate (Knottenbelt and Malalana, 2015). For management of anaerobic pulmonary infection Metronidazole in a dose of 15 mg/kg PO is a good option (Camacho- Luna and Andrews, 2015).

Case seen in the externship

In the ambulatory equine practice an esophageal obstruction was treated in a 19-year-old Lusitano stallion that presented cough, bilateral nasal discharge of food and saliva, and ptyalism, already for several hours. The horse was sweating and appeared to be anxious, extending his head and neck, showing frequent attempts to swallow, all typical clinical signs of this affection (Camacho-Luna and Andrews, 2015). The impaction was easily palpated at the distal to medial third of the neck and had the form and the size of a mango seed. The owner reported that the stallion had the habit to eat mango fruits from a tree on his paddock. The horse was sedated with xylazine (0,4 mg/kg bwt) and an attempt was made to clear the esophagus cautiously trying to pass a nasogastric tube, but without success. As the swallowed foreign body obviously was solid, no try was made do solve it with warm water via the nasogastric tube. Oxytocin (0.10–0.22 mg/kg, IV) in order to relax the smooth muscles was given and another attempt 10 minutes later to push the seed downwards into the stomach was successful. The animal was put into a box for four days and antibiotic therapy with penicillin G procaine (300,000 International Units (IU)/mL, injectable solution), a bactericidal antibiotic effective in the treatment of aerobic and anaerobic Gram-positive bacteria (Plumb, 2011), intramuscular (IM) dose 22,000 IU/kg twice a day for the risk of aspiration pneumonia (Camacho-Luna and Andrews, 2015) was given prophylactically. A single shot of phenylbutazone (2,2 mg/kg bwt IV) was given to reduce/ prevent inflammatory reaction of the esophageal mucosa. After one day of fasting, a liquid food consisting of mash and soaked hay pellets was reintroduced to facilitate swallowing and minimize trauma to the esophagus. The oral cavity was inspected to assess the state of the dentition which was acceptable for the horses age and had no need of further intervention.

Complications

Esophageal obstructions can lead to a variety of complications like ulceration of the mucosa, local inflammation and pressure necrosis, development of strictures due to cicatrization, aspiration and consecutive pneumonia, pleuritis, recurrent obstructions, paralysis of the

larynges and laminitis (Craig *et al.*, 1989). The incidence for aspiration pneumonia after esophagus obstruction is rather high. In 44% of all cases studied by Chiavaccini and Hassel (2010) it has been confirmed radiographically. If the period of obstruction was longer than two days the risk increased additionally and the observed horses showed an even higher degree of tracheal contamination as well as an elevated respiratory frequency at consultation (Chiavaccini and Hassel, 2010).

Prognosis

Two aspects have an important impact on how fast a relieve can be achieved. The type of swallowed feed and the pre-existence of esophageal pathologies. Directly after an episode of choke, reduced motility of the smooth muscles on the oral site of obstruction can be observed for further 48 hours (Sutton, 2015). In cases of simple esophageal impaction, the prognosis is good (Wintzer and Kraft, 1997). However, with obstruction due to functional or morphological abnormalities, the prognosis is poor. Horses with extended or recurrent damage of the mucosa due to chronic obstructions have a definitively higher risk, with mortality going up to 22% according to Craig *et al. (*1989).

2.3.2.2. Colic

Emergency calls in the ambulatory clinic of the externship were often related to abdominal pain (25 cases).

A number of international studies show that acute abdominal pain is rather frequent in equine emergency consultations. It seems to be one of the main reasons why horses die or are euthanized (Tinker *et al.*, 1997; Archer and Proudman, 2006; Egenvall *et al.,* 2006). Visceral pain can affect all types horses and all ages (Robertson and Sanchez, 2010). The majority of colics resolve with medical treatment (Hines, 2018). In ambulatory equine clinic, 7% to 10% have afflictions which need surgery (Proudman, 1992).

Systematic approach for abdominal pain in the externship

In the externship the systematic approach of the outdoor clinic to all cases of acute abdominal pain was more or less identical. It began with questioning the owners, to collect the history of the animal, giving more importance to information about the clinical signs demonstrated, of the appearance of the feces and of the last time that the animal defecated, abdominal surgeries or previous colic occurence, any type of alteration in the management or feeding, as well as about eventual medications or pre-treatment given by the owners or other veterinarians.

At the same time the horse's behavior was observed. Signalment and history provide informations that may hint at a specific reason for colic and rule out false colic which does not originate from the intestinal tract. Sedation can have a decisive influence on vital parameter. Therefore the physical examination (heart and respiratory rate, auscultation of gut sound and rectal temperature) should be performed before any medication is administered. Some horses showed more signs of colic than others, with intense sweating, restlessness, looking at the

flank, scraping, kicking against the abdomen or attempts to lie down.

In order to find a primary differential diagnosis in the horses seen in the externship, additional parameters were evaluated. The degree of pain and the general condition of the horse was assessed by rating vital parameters, alteration in behavior, abdominal distention, a basic evaluation of cardiocirculatory status with staining of mucous membranes, peripheral perfusion by hydration capillary refill time, digital pulse, jugular fill, gastrointestinal motility, gastric reflux, findings on rectal palpation, characteristics of peritoneal fluid collected by abdominocentesis, echographic findings and fecal analysis for sand and parasites.

In horses with moderate to severe signs of abdominal pain, or recurrent signs of mild colic despite initial treatment, rectal palpation was alway performed in order to reach out a diagnosis. Afterwards a nasogastric tube was placed (evaluation of the gastric content - quantity, color and pH - and decompression of the stomach) if necessary.

Further test were hematology/biochemistry with total protein (TP) and packed cell volume (PCV) as well as ultrasound scan for a base assessment, evaluation of inguinal region, ventral middle line for small intestinal distention and motility, large colon distention and thickness, and excess peritoneal fluid.

Definition of colic

Colic is an unspecific clinical syndrome which describes abdominal pain regardless of the cause (Hines, 2018). Colic can be triggered by many different affliction of the abdominal organs. However, acute gastrointestinal disease is the most frequent cause for equines to suffer visceral pain (Curtis *et al.*, 2015; Hines, 2018). To reach out a diagnosis for colic is challenging and sometimes nearly impossible (Moore and Moore, 1994). Most cases of colic in fact, are due to gastrointestinal tract conditions but may also originate from the liver, spleen, kidneys, uterus, bladder or peritoneum (Coté, 2005; Hines, 2018).

Pathophysiology

The clinical syndrome of colic is multifactorial and has a vast variety of underlying conditions (Archer and Proudman, 2006). Pathophysiologic mechanism of true colic with gastrointestinal tract origin can be divided broadly into several categories (Graubner, 2017; Hines, 2018).

Visceral pain in a horse with gastrointestinal disease can come from mucosal inflammation, generalized or regional ischemia, tension on the blood vessels of the mesentery, heightened intra-mural tension, spasm of smooth muscle combined with hypermotility or a combination of some of these reasons **(**Archer and Proudman, 2006; Graubner, 2017). The pathophysiological mechanisms variy due to the numerous causes of colic (Table 4).

Table 4 - Pathophysiologic mechanisms of abdominal pain, adapted from of Graubner (2017).

Pathophysiologic mechanism	Reasons for visceral pain in gastrointestinal disease
Mucosal inflammation	Enteritis/colitis/ duodenitis/ ulceration/ necrosis
Increased intramural tension	Gas, impaction, sand, feed, intraluminal obstruction, foreign body, parasites, enteroliths,
Regional / generalized ischemia	Torsion, volvulus, strangulation, displacement, herniation, intussusception, incarceration
Smooth muscle spasm/hypermotility	Toxines, ileus, spasmodic colic

True colic with gastrointestinal tract origin can be classified by the site (gastric, small intestine, large intestine, cecum, small colon), by the appearance acute, chronic, recurrent, whether non-strangulated lesions or a strangulated lesions, whether obstructive or non obstructive (Hines, 2018). There are a variety of physical and functional changes which can provoke abdominal pain ranging from intraluminal lesions (i.e. impactation, foreign body), extraluminal lesion (i.e. adhesions, strictures), mural lesions, intestinal displacement, inflammatory bowel disease, spasmodic colic, torsion, incarceration and necrosis (Hines, 2018; Graubner, 2017; Worku, 2017).

Fortunately the majority of colic cases seen in field practice resolve with medical treatment. Anyhow, the real incidence of specific causes of visceral pain in equines still remains unclear (Worku *et al.*, 2017).

Clinical signs

Horses have many ways to express abdominal pain (Moore and Moore, 1994; Orsini and Divers, 2008). Inappetence or restlessness and getting up and down repeatedly, are often first obvious early signs. Vocalization (groaning), flank watching , Flehmen reaction, kicking at the abdomen, rolling on the back (Robertson and Sanchez, 2010), sweating profusely and straining as if to urinate are obvious behaviors associated with colic (Ashley *et al.,* 2005; Hines, 2018). The higher the heart rate the more severe is the pain and/or circulatory compromise (Cook and Hassel, 2014). Tachycardia also can hint on endotoxemia. If the heart frequency exceeds 80 beats per minute, a severe illness is likely (Moore and Moore, 1994)

Pain perception and the reaction to it is very individual and varies from horse to horse. The severity of the pathologic changes therefore often may not correlate to the severity of clinical signs. The stress of pain itself can cause paralytic ileus. Further negative consequences are electrolyte dysbalances and dehydration due to fluid losses and reflux (Robertson and Sanchez, 2010).

A detailed description of the assessment of abdominal pain is listed in detail in the following monography - Pain diagnostic and management in horses - in the second part of this report.

Medical versus surgical colic treatment

The medical exam and process of pain evaluation ought to begin with the precise history of the horse. A detailed physical examination then should be followed by rectal palpation and placement of a nasogastric tube (Cook and Hassel, 2014, Hines, 2018). Key components of a physical examination are the general condition of the horse, vital parameters and pain level with pulse and respiration rate, temperature, as well as auscultation of gastrointestinal peristaltic and evaluation of perfusions/hydration index with refill of capillaries and jugular veins, mucous membrane color and moisture and temperature und pulse quality of the horses extremities. When it was not possible to find a precise diagnosis during the check and the response to analgesics was inadequate or recurrence of colic occurred even after analgesic treatment has been issued needs to be perceived as a severe case that requires surgical method of treatment (White *et al.*, 2005).

In the case of horse presenting with acute forms of colic, timely identification and differentiation of surgical and medical lesions at the earlier stages of the condition is associated with improved prognosis (Burke and Blikslager, 2018). According to Nikvand *et al.* (2019) there exists limited data regarding the essence of clinical examination methodologies as far as the determination of the most effective therapeutic intervention that can be applied in the treatment of colic among horses is concerned. Abdominal sounds (i.e. no gut sounds), an elevated heart rate over 45 bpm and a capillary refill time over two seconds are the most sensitive parameters for the prognosis. Rectal palpations (in 57.1% of the horses) and nasogastric reflux findings (in 28.6%) were least sensitive determining survival (Nikvand *et al.*, 2019). Horses presenting with reduced or no detectable borborygmic have an increased probability of needing surgical intervention when compared to horses whose intestinal sounds are within the required ranges (Cook and Hassel, 2014). Other extended diagnostics, such as abdominocentesis (to confirm perforation, peritonitis), abdominal scan (to evaluate peristaltic, detect edema of the intestinal mucosa, form of the duodenal loops) assessment of glucose and lactate, can help to find the decision how to proceed (Cook and Hassel, 2014).

Even though there exist a variety of advance methods of diagnosis (blood analyses, abdominal scan etc.), the most reliable indication for surgery are the presence of mild to serious signs of abdominal pain, reemergence of pain after the right analgesic treatment, and lack of intestinal borborygmic (White *et al.*, 2005; Burke and Blikslager, 2018).

In general, signalment and history combined with basic physical examination will usually reveal the data to decide, whether surgical or medical treatment is indicated (Cook and Hassel, 2014).

Types of colic

Certain horse and management factors increase the likelihood of particular types of colic (Cook and Hassel, 2014, Graubner, 2017). The most common gastrointestinal colic is spasmodic and tympanic, followed by impaction and major colon displacement. The determination of the segments of the bowel indicated that afflictions of the larger colon were more frequent, the small intestine, caecum, followed in that order (Hines, 2018). The main

reason for strangulation and consecutive obstruction was the large colon torsion. Whereas obstructions of the small intestine significantly lead to a linear increase in the fatalities (Proudman *et al.,* 2002).

Diagnostic and medical treatment

When the underlying pathology is identifiable, treatment is focused on its correction (Robertson and Sanchez, 2010), including supportive therapy and dietetic management. Supportive treatments consist of analgesia, fluid therapy to restore hydration (sufficient tissue perfusion, pH, and electrolyte balance) regulation fo intestinal motility, avoidance of gastric perforation and control of endotoxemia. A few specific lab tests can provide data regarding the extent of water loss/ hydration, imbalance of electrolytes, and acid-base status in order to ensure an adequate fluid management as well as hinting at a possible prognosis (Moore and Moore, 1994).

A definitive diagnosis is difficult to find and in many cases the reason for colic remains unclear. Before starting the initial treatment, the decision has to be made whether the horse can be treated medically, if surgical intervention is required or whether euthanasia is indicated.

Analgesia

In general pain assessment consists of observation and interpretation, especially when we evaluate it in animals or nonverbal human beings (Robertson and Sanchez, 2010). If several administrations of analgesics are necessary in the control of pain, this is usually attributed to the need for intervention that is mainly surgical. In horses, the numbers of analgesics that can be used for severe pain is relatively limited. Opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and alfa-2-adrenergic agonists are the main medications (Robertson and Sanchez, 2010).

The treatment of a mild to moderate colic without shock symptoms consists of the administration of spasmolytic and analgesic drugs (Graubner, 2017). Initial therapeutic options are medication with metamizol or combination of butylscopolamin/ metamizol in mild colics to relieve pain and reestablish a physiologic peristalsis. When more moderate signs of colic are evident alpha2-agonist like detomidine-butorphanol combinations can be considered.

Xylazine is often effective in the sedation of horses presenting visceral pain. It makes faster pain relief for moderate to severe pain and is characterized by a shorter effect (15-30 minutes) (Moore and Moore, 1994; Knottenbelt and Malalana, 2015). The limitation of the use of xylazine entails reduced cardiac output, slower heart rate, and deterioration of gastrointestinal ileus.

Detomidine is effective pain-relieving and sedating and has a relatively prolonged effect (90 minutes). Since the pain induced by ischemia could be blocked and disguised for an extended duration, detomidine should only be applied when the equines experience extreme levels of abdominal pains (Kohn and Muir ,1988). Detomidine also prevents the occurrence of self-induced mutilation, it facilitates exam, analysis, treatment and transport to referral hospital for surgery.

Flunixin meglumine, a powerful NSAID for colic, is more suitable for the management of mild to moderate visceral pain and provides a pain-relieving characteristic for up to 24 hours. Limitation of flunixin meglumine entails issues that may revolved around delayed relief of pain (30 minutes), low heart rate and improved nature of the mucous membranes, and often prevents the detection of the abdominal pain, and thus impair surgery in horses presenting intestinal strangulations (Moore and Moore, 1994). The use of Flunixin must therefore be considered carefully due to its potent analgesic and particular endotoxic properties which can delay identification of the need for surgery. Acepromazine is contraindicated in horses with colic as it provokes hypotension and vasodilation.

The colic therapy should be monitored via pain behavior, progression of clinical signs, and should be repeated and adapted to the findings.

Fluid therapy

Almost all horses presenting with any case of abdominal distress are expected to have total body fluid deficits and are bound to experience some benefit of the administration of fluid. Intravenous infusions may save the lives of the horses dealing with cardiovascular challenges (Moore and Moore, 1994). Depending on the cause sufficient hydration with either intravenous fluid therapy, or oral electrolyte solutions of 5-6 liters via stomach tube can be performed (Fielding, 2014). In cases of mild forms of dehydration, oral fluids can be administered. However, such therapeutic measures could be contraindicated with nasogastric reflux (Moore and Moore, 1994). Laxatives (i.e magnesium sulfate) can effectively resolve impactions due to feed. Anyhow they should be used with caution as they can lead to irritation of the mucosa. In horses with nasogastric reflux or small intestine distension laxatives are obsolete .

Decompression: Nasogastric tube and enterocentesis of the cecum.

The horses experiencing sudden onsets of abdominal pains should be subjected to nasogastric intubation to prevent rupture (Moore and Moore, 1994). Aside from the therapeutic benefits, the procedure equally provides data in addition to other essential treatments (Cook and Hassel, 2014) showing the nature of gastric content. Large volumes (>4 liters within 5 minutes) hint at a serious affliction and appropriate referral should be taken into account. An increase pH (>5) indicates liquid from the small intestines. Strong foul odor with red/orange color is often linked to proximal enteritis (duodenitis/proximal jejunitis). Pronounced distention of the large colon and/or cecal inflammation in horses where surgery is not a choice, cecal enterocentesis can be done. Cecal or colonic thympany decompression by trocharization may also reduces death during transport especially among horses suffering severe respiratory distress (Moore and Moore, 1994).

Temperature

Before performing rectal palpation, body temperature should be obtained, as this could reveal insights concerning the cause. Subnormal temperature can have origin in cardiovascular problems. Colics with fever are often combined with infections and inflammations such as colitis,

jejunitis and duodenitis (Cook and Hassel, 2014).

Gastrointestinal motility

Horses experiencing spasmodic visceral pain or colitis may have increased gastrointestinal motility, whereas animals with mechanical obstructions, strangulations, or non stangulations show decreased or absent borborygmic. If continuous intestinal peristaltism is confirmed and feces is produced, surgical intervention is often not required.

Rectal palpation

Rectal palpation is an essential aspect of diagnosis which can identify many pathologies: nephrosplenic entrapment, right dorsal colon displacement, impactions of the cecum and the pelvic flexure (Cook and Hassel, 2014), small intestine distention, tumors, inguinal hernias and gastrointestinal ruptures.

Abdominocentesis

Peritoneal fluid needs to be examined in terms of color and consistence, differential cell count and concentration of total protein (Moore and Moore, 1994). Usually peritoneal fluid of healthy horses is transparent and has a yellow color (Cowell *et al.,* 1987). Alteration in the peritoneal fluid usually occurs faster as a result of its close proximity to the viscera. Therefore obtaining peritoneal fluid helps to detect pathology in the abdomen cavity.

According to Cook and Hassel (2014), color, clarity and total protein concentration (measured with refractometer) guide the decision for referral. Blood stained fluid findings are a 98% proof of surgical lesion. Total protein in horses without intestinal pathology is less than 2,5 g/dl (Cook and Hassel, 2014). An elevation shows a pathologic progression of visceral permeability, which facilitates rapid leaking of the plasma proteins. Equines with intestinal surgical lesions as well as peritonitis will therefore show high levels of total protein.

Lactate (measured by portable lactate meters)

In a healthy horse there should be an equilibrium in terms of the concentration of blood and peritoneal lactate. Lactate elevation in episodes of abdominal pain confirms hypoxia and anaerobic metabolism as a result of compromised intestinal perfusions and hypovolemia (Burke and Blikslager, 2018). A blood lactate over 3 mmol/L is often linked to ischemia (Cook and Hassel, 2014).

Ponies are an exception. They show elevated levels of lactate even without surgical lesion. When peritoneal to blood lactate ratio is higher than “1“ , equines are expected to have intestinal strangulations. Moreover, elevation in peritoneal lactate against time is essentially linked to the occurrence of strangulation. This phenomenon was particularly higher among equines that had admission peritoneal fluid lactate over 4 mmol/L (Burke and Blikslager, 2018).

Glucose

Elevated glucose level is predominant among horses presenting with colic and is often characterized by a poor prognosis. It may indicate non-vital intestine and necrosis. Around 50% of the hospital cases have glucose level above 135 mg/dl. Pronounced hyperglycemia (>180 mg/dl) in adult equines indicate surgical colic and a poor prognosis (Hassel *et al.*, 2009). With the help of a glucometer, the level of glucose in the peritoneal fluid can also be checked. (Van Hoogmoed *et al.*, 1999). Reduced glucose level below 30 mg/dl in the peritoneal fluid is a proof for infectious peritonitis.

Given the outpatient nature of the externship, this was the possible approach in a case of colic. If it was suspected that the horse would need extensive continuous medical care or surgery, it was immediately referred to the next hospital.

Referral reasons in the externship

Large colon displacement diagnosed via transrectal palpation, palpable tumor, persistent pain lacking effect to analgesic, recurrent unresolved colic signs in 24 to 48 hours after onset, persistently elevated heart rate, signs of shock, suspicion of endotoxemia with impaired cardiovascular status including weak pulse and abnormal color of the mucosas and delayed refill time of the capillaries were the basis referral reasons in the externship.

Clinical case: medical colic

The owner of an 18 year old quarter horse stallion called at night, stating that his horse had mild signs of abdominal pain with anorexia, looking at his abdomen, repetitive Flehmen, lying down frequently and was gradually worsening. He had no fever. A small amount of dry feces has been found on his sandy paddock. The stallion had no change in feed prior to these attacks and had no previous history of colic. He was in fit body condition and had been performing well within the last 4 months, being ridden at least four times a week and used regularly for cow work. He lived 24 hours outdoor in a big field together with a number of geldings. All horses were fed from the ground as in late September there was not enough grass left on the paddocks. The owner confirmed routine vaccination, annual teeth control and a twice a year deworming program with Ivermectin/ Febendazol and Dectomax.

Signalment and diagnostic in the accompanied case

That evening the horse was examined. He appeared depressed with his head lowered down, looking in one corner of the paddock, not interested in the veterinarian entering the paddock. He now and then kicked against his abdomen and lowered his head indecisive to lie down. There where no signs of sweating. He was normothermic and slightly tachycardic (HR = 48 bpm) and tachypneic (RR= 30), mucus membranes were pink with rapid refill and strong pulse. Abdominal pain was evident about every fifteen minutes and the stallion postured as if he wanted to

urinate. Borborygmic were frequent and present in all auscultation areas.

Rectal abdominal palpation revealed a dry and sandy manure with signs of pelvic flexure impaction, no further abnormalities. Naso-gastric intubation showed no reflux. Auscultation at the deepest point of the abdomen could not confirm sounds of moving sand. According to the clinical and historical findings the working hypothesis of this case of acute abdominal pain was colon impaction with sand, due to high uptake by feeding from the ground, low quality hay and presumably not sufficient water supply.

Treatment

After clinical examination, medical multifactorial therapy was started. Treatment of sand colic includes withholding feed until the impaction passes, rehydrating the ingesta, and administering analgesic drugs. In this case seen in the externship, an intravenous catheter was placed to institute fluid therapy with isotonic fluids (Fielding, 2014), using 20 liters of isotonic crystalloid solution (Ringer Solution). Intravenous fluids and withholding food are mainstays of treatment. Intravenous fluids for dehydration and sufficient hydration help to soften up the intraluminal impaction of the manure and sand. Oral fluid and electrolytes via nasogastric tube also soak the sandy manure and restores electrolyte balance preventing paralytic ileus. Metamizol IV was given to reduce pain and achieve and maintain orthograde peristalsis of the intestinal wall. As the intestine tries to move the impaction, severe pain may ensure. Psyllium mucilloid (1g/kg bwt q 24 h) and MgSO4 (1 g/kg bwt) were given by nasogastric tube for 4 days in order to remove the intestinal sand accumulation (Knottenbelt and Malalana, 2015; Niinistö *et al.*, 2018). Pain signs improved significantly after Metamizol IV and oral fluids. His posture was more relaxed, with no more sign of abdominal discomfort. After three hours he developed diarrhea and excreted a huge amount of sandy manures. No further treatment was necessary.

Sand colic

Etiology

A geographically specific problem of horses is the oral uptake of sand with its accumulation in the abdomen. This may provoke serious life-threatening intestinal obstructions especially in horses which are living in regions with sandy grounds (Niinistö *et al.,* 2018). Sand is a frequent reason of colon impaction, especially where horses are kept in sandy paddocks and fed on the ground. Some horses may develop pica, or curious foals may ingest large amounts intentionally (Sanchez, 2018).

Following ingestion, sand becomes sedimented by gravitational forces. It then causes irritation to the colonic mucosa and impaction when there is enough sand built up within the lumen (Mair, 2002). The distention by sand and gas then causes abdominal pain and motility disorder. Chronic irritation of the colonic mucosa may reduce the absorptive capacity of the mucosa and lead to diarrhea and protein losing enteropathy (Mair, 2002). The sediment usually accumulates in the ventral colon. Rough sand on the contrary can also accumulate in the transverse and dorsal part of the colon. Intra-intestinal sand may dry out, becoming a concrete-like consistency and provoke impaction or cause a displacement or torsion (Sanchez, 2018). The lower the

impaction in the gastrointestinal tract, the less intense will be the colic. (Udenberg, 1979). Colic associated with torsion, volvulus or intussusception has more acute and violent clinic signs.

Clinical signs of sand colic

A higher amount of sand ingestions provokes clinical signs of acute or recurrent abdominal pain. The horses loose weight, suffer from chronic diarrhea and have a bad body condition with reduced performance (Bertone *et al.,* 1988; Ruohoniemi *et al.*, 2001). Generally, symptoms are alike to many other causes of colic. Initially the signs may be mild and intermittent, with diarrhea or soft feces. The horse may show signs of catabolic imbalance, losing weight with a good appetite. With more sand accumulation the clinical signs will progress (Mair, 2002). The horse may become anorexic, dehydrated, lethargic and have abdominal distention from gas and sand. Auscultation of the ventral abdomen can reveal sandy sounds, as if hearing waves on a beach. Massive sand accumulation may be palpated per rectum and effect impaction.

Diagnostic

Abdominal auscultation, trans-rectal palpation, fecal sand sedimentation test using a glove, ultrasonographic assessment of the ventral colon, and abdominal radiographs are some of the methods that can be used to diagnose sand accumulations (Ragle *et al.*, 1989b; Ruohoniemi *et al.,* 2001; Keppie *et al.,* 2008). However, positive identification of sand during trans-rectal palpation or by fecal sedimentation is only possible in 22% of the cases (Kilcoyne *et al.*, 2017). An inconclusive transrectal palpation diagnosis of the existence of sand impaction can be due to the fact that impactions often occur in areas that are out of reach (Colahan, 1987). Also, sand auscultation is only possible in 21% of the cases, reinforcing the importance of using abdominal radiography to reach the clinical diagnosis of sand impaction (Kilcoyne *et al.,* 2017). However, it is not easy to perform a radiograph on an adult equine abdomen. For those motives, sand enteropathy relies upon a diagnostic of exclusion.

Sand impaction often can be found in anatomically predisposed regions like the large colon pelvic flexure, the cecum, the transverse colon and the ileum (Granot *et al.,* 2008).

Treatment of sand colic

Slow progression of colic symptoms is typical for impactions of the lower digestive tract due to sand. The treatment should aim towards relieving pain and supporting normal body functions including normal water intake, lubrication and break down of the obstructive sandy mass. Intravenous or oral fluids can support to rehydrate the digestive tract. Laxatives can assist the sand removal and help to prevent recurrence (Mair, 2002; Kilcoyne *et al.,* 2017). In order to remove intestinal sand an attempt with psyllium, magnesium sulfate or mineral oil, can be made.

The effects of several conventional treatments to manage a medical colic due to sand accumulation in equines are discussed controversy. Newer clinical studies however, show that feeding or its administration via nasogastric intubation of magnesium sulfate, psyllium mucilloid, dioctyl sodium sulfosuccinate and their combinations (Kaikkonen *et al.,* 2016; Niinistö *et al.,* 2018) can have a significant effect. Magnesium sulfate works like as an osmotic cleaning agent

accumulating water in the intestines lumen and additionally improving intestinal motility (Freeman *et al.,* 1992). Psyllium has cathartic effect (Boothe and Jenkins, 1995) associated to its fiber content, and promotes intestine peristaltic by activation of its 5-HT4 and muscarinic receptors (Mehmood *et al.*, 2011; Niinistö *et al.,* 2018). According to Niinistö *et al.*, (2018), sand impaction in the colon of equines can be medically treated with daily administration of a combination of Magnesium sulfate (1 g/kg bwt) and psyllium (1 g/kg bwt) via nasogastric tubing. A four-day treatment reduces the relative sand quantity significantly compared to no treatment. It might also resolve the sand accumulation by complete evacuation.

Having no access to soil, some horses can spontaneously clear their intestines of the ingested sand. Mineral oil should not be used as it causes granulomatous inflammation to denuded mucosa, worsening already irritated intestinal lining and if surgery was to be needed, and an enterotomy performed to empty the colon of sand, mineral oil would escape into the abdomen with consequences of granulomatous inflammation and peritonitis.

In horses with large sand accumulations with intractable pain, surgery may be necessary. These horses may have colon displacement, gas accumulation, reflux, or sudden worsening of clinical signs. As with any colic surgery, there are possible complications, including bowel rupture and peritonitis (Plummer *et al.*, 2007).

Prevention

After initial treatment and recovery, continued daily use of psyllium for 10-14 days can continue to remove remaining sand (Niinistö *et al.,* 2018). Continuous feeding is not advisable as microbes will begin to digest the psyllium, and its effect will be lost. Other preventive methods include removing horses from sandy areas, rotation of pastures to prevent overgrazing, and avoiding ground feeding. Sand accumulation can be found in small amounts even in equines of well-managed horse farms as horses are grazing naturally form the ground. (Husted *et al.,* 2005). Constant access to fresh water, and plenty of exercise to stimulate gastrointestinal motility is essencial. Most horses recover from sand impactions over several days. In general medical cases of sand impaction have better prognosis than surgical cases (White and Dabareiner, 1997). Those that require surgery have a survival rate approaching 90% (Ragle *et al., 1*989a; Granot *et al.*, 2008).

Second case: surgical colic

One of the outstanding cases occurred in a 12 year old Arabian gelding, who was found by abdominal surgery to have an obstructive neoplasia in the ileum. The mesenteric lymph nodes seen during laparotomy had a non pathologic aspect, histology of the neoplasia later confirmed adenocarcinoma.

The animal exhibited multiple bruises, abrasions all over the body and the head, resulting from self-inflicted trauma, which indicated severe pain. Physical examination was nearly impossible because he was violently rolling on the ground and nearly refused all methods to stand him. He presented a heart frequency of 75 beats per minute, respiratory rate of 38 breaths per minute, pale and dry mucous membranes, capillary repletion time of four seconds, slow jugular filling

and intestinal motility absent in all quadrants. Transrectal palpation was not possible. Nasogastric intubation achieved reflux of 5 liters. The ultrasound scan presented distended loops of small intestines with increased luminal diameter and thickness of the bowel wall. The patient showed nearly no response to analgesic medication. Clear clinical signs with the presumptive diagnosis of an obstruction in the small intestines made referral to hospital for abdominal surgery urgent. The gelding was stabilized for transportation and anesthesia. The objectives were pain control and hydration. In order to get sufficient analgesia and sedation xylazine (0.3-1 mg/kg, IV), butorphanol (0.02-0.04 mg/kg, IV) and NSAID flunixin meglumine (0.25-1 mg/kg, IV) were used. The fluid therapy consisted of an initial bolus of 1L of hypertonic solution (NaCl 7.5%; 4 mL/Kg/0.5h) to restore the dehydration deficits, followed by 10 L of isotonic solution of Ringer's lactate (8-20 mL/kg/h) and 5 L of 0.9% NaCl with the addition of 100 mL of calcium (2-4 mL/kg/h).

The horse was immediately taken to the reference hospital for surgery. In exploratory laparotomy an induration of 8 cm length at the distal jejunum and some adherent intraluminal turmors were found. Approximately 20 cm of jejunum were resected. Postoperative histological examination revealed an adenocarcinoma. The partial luminal obstruction of the jejunum caused by the adenocarcinoma presumably was responsible for the appearance of the clinical signs of colic. The main risk in this disease are recurrence of adenocarcinomas from transformation of remaining adenomas (Taylor *et al.*, 2006). The gelding recovered from surgery without any complications and was discharged after 14 days. According to his owner he never had a colic before and had been alway healthy and shown good performance as a distance horse.

Nine months after the surgery, the horse improved body condition with normal appetite and no further signs of abdominal pain. He has been already ridden for three months and starts to show good performance.

Only few case reports are published about intestinal ademomas and adenocarcinomas in horses. This type of neoplasm seems to be rare in this species (Baker and Ellis, 1981). Lymphoma is the most frequently diagnosed intestinal neoplasm, others include, leiomyoma, leiomyosarcoma, neurofibromas and metastatic neoplasia. The most commonly affected segment is the small intestine. A breed predisposition exists for Arabian horses. Intestinal neoplasia appear 4.5 times more often in Arabians than in any other breed (Taylor *et al.*, 2006). Arabian horse also are predisposed to impaction of the ileum and small colon as well as to formation of enterolith (Dart *et al.,* 1992; Moore and Moore, 1994). This makes them twice as likely to colic in comparison to other breeds.

Intestinal neoplasia do not have specific clinical signs and unfortunately clinical signs often only become evident when the tumor growth is already advanced. Therefore an early diagnosis of intestinal neoplasia is challenging. The most consistent clinical signs are poor body condition, weight loss, tachycardia, tachypnea, colic, inappetence, diarrhea and fever (Taylor *et al.,* 2006). Moreover, a number of diseases with similar clinical signs complicates the diagnosis such as intestinal ulceration, helminthosis, inflammatory bowel disease, liver and kidney afflictions, and different types of neoplasia which originate identical symptoms from outside the intestinal tract.

2.3.3. Angiology

In the externship, numerous catheterizations - mostly of the jugular vein - were performed in horses of all ages. Although strictly aseptic technique was applied, three cases of jugular thrombophlebitis were seen during the course.

Thrombosis and thrombophlebitis after intravenous catheterization

Jugular thrombophlebitis is very common affliction in equines. Its origin is usually iatrogenic, due to inadequate and traumatic venipuncture procedures and intravenous application of medications with irritant tissue effect (Schoster, 2017).

Introduction

Vascular disorders are relatively common in humans (Sprynger, 2018), but are less common in horses. Veins may be damaged by blunt or sharp force trauma but often needles and local irritation by intravenous catheters can cause intravascular complications in equine practice.

Intravenous administration of drugs, taking blood samples and intravenous fluid treatment is a very essential component of treatment of sick horses (Geraghty *et al*., 2009a; Gehlen and Stadler, 2010). Catheter placement in equine clinic is often performed and usually straight forward. On the other hand, it naturally always has the risk of iatrogenic complications (Schoster, 2017).

Certain complications may occur: They range from thrombosis and thrombophlebitis to intravascular or intracardiac catheter pieces and bacteriemia. Thrombophlebitis is usually reported the most among these mentioned complications (Lankveld *et al.,* 2001), with a high incidence in equines with systemic disease and endotoxemia.

Case report

In the externship a ten month-old Lusitano colt was treated with IV fluids via jugular catheter and sucralfate oral for gastric protection because of intermittent clinical signs of diarrhea and anorexia. Gastric ulcers were suspected after possible stress of post-weaning. The somewhat skinny horse was alert, normothermic and vital parameters were normal. Vaccine and deworming programs were complete. After 30 hours, the foal developed clinical signs of thrombophlebitis at the catheter in the left jugular with local increase in temperature, signs of pain on palpation, exudation and thickening of the venous wall and subcutaneous perivenous tissues. Ultrasonic scan revealed a partial thrombosis with phlebitis of the jugular vein.

The catheter was removed, local treatment with cold water and hot pack was applied to reduce the edema, as well as local Dimethyl sulfoxide (DMSO). With pyrexia (39,3°C) a broad spectrum antimicrobial treatment with ceftriofur IM was started and maintained for three days. The colt recovered fast and after 24 hours no fever occurred.

2.3.3.1. Thrombophlebitis in Horses

The use of intravenous catheters into the horses usually makes it possible for the caregivers to have an easy time accessing the veins. It facilitates continuous administration of intravenous fluids, therapeutic or anesthetic drugs and reduces discomfort and other forms of complications that may arise from frequent punctures (Geraghty *et al.*, 2009a).

Catheter-associated venous diseases are a common complication with multifactorial etiology in equine medicine particularly during intensive care (Spurlock *et al.,* 1990). It can lead to a circulatory impairment of the horses neck and head with systematic as well as local signs of inflammatory reaction (Spurlock *et al.,* 1990). Beside the frequently seen thrombophlebitis (occurrence rate 1-29% according to Geraghty *et al*., 2009a) others complications like venous air embolism, blood loss via catheter, catheter rupture may also occur (Schoster, 2017).

Definition: Thrombosis, Thrombophlebitis, Septic thrombophlebitis

Thrombosis is characterized by the clotting of blood inside a vein thus impairing the continuous flow of blood along the vessels which can lead to mural inflammation (Spurlock *et al*., 1990; Divers, 2003). By definition, thrombophlebitis describes inflammatory alterations in the vessel wall that usually occurs from accumulation and formation of septic or aseptic thrombogenic material (Schoster, 2017). The majority of thrombophlebitis in hospital set ups are often non-septic (Geraghty *et al.,* 2009a). Local skin bacteria colonize the thrombus more likely than hematogenous infections (Geraghty et al., 2009a).

Pathophysiology

The formation of a thrombus originates from the association of multiple factors. Vascular injury with endothelial wall lesion, hyper-coagulability of the blood and reduced intravascular flow / venous stasis, the so-called Vichow´s Triad, can cause thrombus formation (Bagot and Arya, 2008). Reasons which predispose horses to this disease are chemical or mechanical irritation of the veins caused by factors such as poor hygiene, injecting irritating drugs without flushing the catheter, traumatic venipuncture and prolonged catheterization.

The site of the venipunture and the catherter's tip are the most usual site where the thrombus is often initiated (Divers, 2003). In horses, local distress is the most essential aspect of the Virchow triad in the progression of thrombosis of the jugular (Lankvelt *et al.,* 2001). The onset of thrombosis is usually characterized by the attachment of platelets in the exposed subendothelian part around the lesion leading to the formation of fibrin clot which facilitates the coagulation process (Hopper and Bateman, 2005).

The coagulation system in horses is very prone to hypercoagulability. When they get sick they tend to have exaggerated coagulation and impairment of the anti-coagulation pathway as well as fibrinolysis which then predispose to thrombosis (Dunkel *et al.*, 2010).

Every venipuncture causes a kind of mechanical trauma in the endothelium of the vein resulting in impairment of the blood flow, due to altered surface texture and the complete or incomplete occlusion of the vascular lumen.

The jugular veins are mostly affected as they are the preferred picture sites in equine practice. Every insertion site may allow bacteria to gain access to local or deeper tissues, leading to infection (Geraghty *et al*., 2009a).

Risk factors

The development of thrombophlebitis following catheterization depends on a variety of factors like catheter-associated factors, patient factors and medication given (Traub-Dargatz and Dargatz, 1994; Divers, 2003; Geraghty *et al*., 2009a; Schoster, 2017) (Table 5):

a) Catheter-associated factors:

Technique of catheter placement, cannula size, catheter material, catheter maintenance, and dwell time are crucial for this undesirable iatrogenic complication (Aksoy *et al*., 2008; Schoster, 2017).

Catheters that are short tend to induce more trauma to the endothelium as they are prone to some mild movement. The catheter material also is decisive (Spurlock *et al.,*1990; Divers, 2003). Over-the-wire catheters made of polyurethane are known to present minimal risk. Polyurethane over-the-needle catheters on the contrary seem to provoke more complications whereas polytetrafluoroethylene or teflon catheter have the greatest probability of unwanted side effects (Aksoy *et al.,* 2008). The stability of a catheter and the duration equally influence the risk of developing thrombophlebitis.

b) Medication-associated factors:

The type and quantity of intravenous fluid therapy determines the extent of caused blood flow turbulences and consecutive irritation of the local endothelium especially at the tip of the catheter (Geraghty *et al*., 2009a). Other crucial factors are the pH of the IV fluid used, duration of infusion and applications of pharmaceuticals which have irritating effect on the vessels. The drugs associated with thrombophlebitis include the frequently used phenylbutazone, oxytetracycline, thiopental and calcium gluconate (Edens, 1999). Phenylbutazone for example, when accidentally injected extra-vascular has a strong tissue irritating effect leading to thrombophlebitis (Thomassian, 1996). Parenteral nutrition is also more damaging to blood vessels, owing to its hyperosmolarity. Bacterial contamination of applied substances can also be a cause (Divers, 2003).

c) Patient factors:

There are patient risk factors (Table 5) that can lead to thrombosis as well. These include age, systemic disease, fever, large intestinal disease with diarrhea, hypoproteinemia, endotoxemia, debilitation and lowering of the head for prolonged periods (Divers, 2003). Fillies and colts have an elevated probability to develop catheter side effects compared to adult horses (Ettlinger *et al.,* 1992). Icelandic horses seem to have at significantly higher risk for venous pathology compared to other breeds (Aksoy et al., 2008).

Main source of bacterial catheter infections are either nosocomial hospital pathogens or the animals own skin (Schoster, 2017). Foals, seriously sick and exhausted animals and colic patient which spend a long time in recumbency therefore run an elevated risk to develop septic thrombophlebitis.

Table 5 - Risk factors which can lead to thrombophlebitis
(Ettlinger *et al.*, 1992; Traub-Dargatz and Dargatz, 1994; Lankveld *et al.*, 2001; Divers, 2003; Dolente *et al*., 2005; Geraghty *et al*., 2009a; Dallap-Schaer and Epstein, 2009; Schoster, 2017)

	Risc factors			
Drugs - associated	Irritating substances (i.e.Phenylbutazon, Thiopenthal, calcium gluconat)	Anesthesic induction technique	Total parenteral nutrition	Bacterial contamination of needle, medication
Patient factors	Systemic disease, Fever, Endotoxemia	Systemic inflammatory response syndrome	Gastrointestinal disease, Hypoproteinemia Coagulopathies	Foals Recumbent horses
Catheter-associated factors	Local trauma, improper placement, hygiene	Diameter, Flexibility composition	Dwell time	Maintanance Monitoring

Severely sick equine patients that are often at risk for coagulopathy entail septic foals, animals with severe systemic inflammatory response syndrome and those with serious forms of gastrointestinal afflictions (Traub-Dargata and Dargatz 1994; Lankveld *et al*., 2001). These patients often have excessive coagulation activation, and impairment of coagulant pathways as well as of the fibrinolysis (Dolente *et al.,* 2005; Dallap-Schaer and Epstein, 2009).
Serious implications such as the strangulation with ischemia and necrosis and enteritis often cause disseminated intravascular coagulation (Divers, 2003). Genetic coagulation defects, protein-losing enteropathy, neoplasia and protein-losing nephropathy can equally pose a serious problem to the horses (Dolente *et al.*, 2005). Horses that exhibit depression from any disease, and that stand with their heads down, cause venous stasis and are more likely to have catheter thrombus formation (Divers, 2003).

Clinical signs of catheter thrombosis and thrombophlebitis

Symptoms often appear while the venous catheter is still in situ or 24–48h after it has been removed (Lankveld *et al.*, 2001). The puncture site and the catheter tip are often the start point for adhesion of clotting material. Clinical sign thrombosis is a localized cord-like firmness of the vein which resist compression. When there is complete occlusion of the vessel proximal to the thrombus site a marked distention can be seen. Usually it is not painful. Clinical signs of pain on palpation as well as an increase in local tissue temperature with a visible thickening of the subcutaneous perivenous area are typical for thrombophlebitis (Divers *et al.* 2003). Bacterial infection of the thrombotic material leads to septic thrombophlebitis. These horses then appear

depressed, have a stiff neck and intermittent episodes of pyrexia. In blood analysis, leukocytosis with neutrophilia, acute-phase proteins, fibrinogen and elevated serum amyloid A are present (Westerman *et al.*, 2016).

Diagnosis

The diagnosis of thrombosis, phlebitis or thrombophlebitis is made based on the horses history, the shown typical clinical signs at the catheter site as well as examination of the affected vein by duplex Doppler ultrasonography (Edens, 1999; Dias and de Lacerda Neto, 2013). Ultrasonic scan of the vessel and local tissue can help to estimate the extension and type of the thrombus and the lesions progress (Gehlen und Stadler, 2010). A homogenous hyperechoic mass which is connected to the wall protruding into its lumen confirms the thrombus confirmation in ultrasonografic scan. Approximately 1- 29% of horses with IV catheters develop subclinical small, mural thrombi (Aksoy *et al.,* 2008). Venous occlusion provokes distention and subcutaneous edema by leakage of fluid from the blood vessel (Dias and Lacerada-Neto, 2010). A thickening of the vessel wall may be seen in phlebitis (Eden, 1999). Perivascular swellings with liquid retention might also reveal an abscess. Cavitation and septation in the middle of a thrombus is suspicious for bacterial infection (Dias and Lacerada-Neto, 2010).

Complications

There are many known serious secondary complications of thrombophlebitis: Bacteremia, septicemia, thrombus loosening from the vessel wall with consecutive thromboembolism into the lungs and right heart failure, pleuropneumonia and endocarditis (Tan *et al.*, 2003; Ryu *et al*., 2004; Aksoy *et al.,* 2008). Horses with endocarditis may show signs of congestive heart failure, ventral and brisket edema or jugular vein pulsation, along with exercise intolerance. Rarely septic thrombi may result in pulmonary thromboembolism and pleuropneumonia. These horses may have trouble breathing, are usually febrile, often endotoxic, and are depressed.

Treatment

First of all prevention of thrombus formation is essential. The choice of local and systemic thrombosis treatment depends on the severity of the case. It consists in decreasing the present inflammation, preventing the increase of an existing thrombus, encouraging its dissolution and preventing and treating secondary bacterial infections (Divers, 2003; Schoster 2017). Any thrombotic vessel should no longer be used for injection or taking blood samples. An alternative site for drug and fluid administration in horses can be the lateral thoracic vein. A less thrombogenic catheter (over-the-wire polyurethane) should be used in these patients. Hydrotherapy and hot packs applied over the swelling four times daily, local treatment with dimethyl sulfoxide (DMSO) solution and heparinized creams can be attempted (Dargatz and Dargatz, 1993).

NSAID may help to reduce inflammation reaction and pain. In sepsis IV antibiotics are needed (Schoster 2017; Schwarzwald, 2018). In severe cases with generalized coagulopathy, the administration of heparin [unfractionated, 40 to 100 IU/kg BW, IV or SQ, q6h or low molecular

weight (Dalteparin), 50 to 100 IU/kg BW, SQ, q24h], as it is traditionally performed in human medicine, may be a good prophylaxis (Orsini and Divers, 2008).

In case of thrombophlebitis with an inlying catheter, it should be taken out in a sterile way and the tip should undergo microbial testing (aerobic and anaerobic culture) and sensitivity profile for antibiotic treatment (Schoster, 2017). Bacteria isolated from the catheters seem to be predominantly commensal bacteria of the adnexal tissues (Micrococcus and Staphylococcus species), fecal contaminants (enterobacteria) and fungi (Geraghty *et al*., 2009a).

Horses which present clinical signs of a septic thrombus, treatment with NSAID and broad-spectrum antibiotics should be instituted. According to Divers (2003) the choice of antimicrobials (penicillin, trimethoprimsulfa-methoxazole,gentamicin, metronidazole) is based on the result of sensitivity testing, prize, toxicity, and how they can be given (IV, oral, IM).

In ultrasound check the size of the inlying thrombus should not increase over several days. Systemic treatment of the patient should be maintained till the signs of inflammation subside and the differential blood count is in normal range (Schoster, 2017). Depending on the size surgical removal of the thrombus via phlebotomy or thrombectomy and drainage of abscesses can be considered.

Certain medications can be used to prevent further clotting and to help break down the clot directly, such as aspirin, heparin, and recombinant tissue plasminogen activators. The effects of low-molecular-weight heparins in equines resemble those in humans (Schwarzwald *et al*., 2002). Once-daily SC administration of enoxaparin or dalteparin can be an effective anticoagulatory prophylaxis in horses. For thrombophlebitis prevention a better clinical effect (compared with heparin 40-100IE/Kg, IV or SQ q6h) was proved for low molecular weight heparin which additionally had less adverse side effects (Schwarzwald *et al.,* 2002).

Acetylsalicylic acid (20mg/kg PO q48h) reduces thrombocyte aggregation. Aspirin as well as heparin can inhibit further growing of the thrombus. Anyhow, there is no licensed thrombolytic drug for horses on the market. Unfortunately thrombophlebitis often has a long-term history.

Medications such as streptokinase are cost-prohibitive in horses and are off-label use (Schoster, 2017). The correction of any cardiac arrhythmias which cause turbulent blood flow can be preventive.

Prevention

Preventing of jugular thrombophlebitis includes mitigating any risk factors mentioned above. Many factors have to be considered: type of catheter, chosen site, technique and catheter management are decisive (Divers, 2003). The number of puncture of the designated vein should be reduced. Before placing the venous catheter, the site should be shaved (Geraghty *et al.,* 2009b) and thoroughly pre-cleaned with chlorhexidine or iodine soap. Disinfection, first with iodine followed by alcohol should be performed.

Decisive for the potentially vein-irritating properties of a catheter are above all the materials used. Catheters made of polypropylene can be used without any problems in horses with good general condition. However, the maximum vein retention time of six hours specified by the manufacturer (B. Braun Melsungen AG, Germany) should not be exceeded. It is recommended

not to leave Polytetrafluoroethylene (Teflon) catheters in the vein for more than three days (Hardy, 2010).

If there is an increased risk of thrombosis or a vein retention period of more than three days, fewer thrombogenic materials such as polyurethane or silicone should be used (Schoster, 2017). In addition to vein-friendly materials such as polyurethanes and silicone, some manufacturers also offer an antimicrobial catheter coating of chlorhexidine/silver sulfadiazine or minocycline/rifampicin (Barakzai, 2003). This impregnation can be applied to the outside of the catheter only or additionally in the lumen. Coated catheters are especially intended for intensive care patients who have an increased risk of thrombophlebitis due to sepsis, endotoxemia and coagulopathies.

The size of the lumen of the catheter used should be suitable for planned fluid volume but not too thick as increased diameter causes a bigger lesion in the vessel endothelium (Traub-Dargatz and Dargatz, 1994). A 14G catheter is suitable for a large to middle size horse, whereas 8G–12G can be used if large volumes have to be given. For ponies and foals 14G or 16G can be used. Catheters should be monitored frequently and flushed regularly to keep them open. In order to avoid constant contact and manipulation at the catheter, an extension should be connected permanently. In horses at high risk, aspirin may be used as prophylaxis.

Good alternatives for intravenous catheters are the cephalic vein, lateral thoracic vein and the saphenous vein (Divers, 2003). For parenteral nutrition a large vessel (jugular vein or lateral thoracic vein) should be chosen to reduce endothelial irritation. Irritating drugs have to be limited and diluted adequately according to their properties (especially caution with acidic or alkaline or hypertonic fluids) (Hardy, 2006). The best choice are commercially prepared fluids. When supplements are added the physiologic tonicity should be maintained (Divers, 2003; Schoster, 2017). Especially equines with gastrointestinal pathologies have to be monitored closely as these disorders provoke a marked prothrombotic state. Proper treatment to minimize the imminent systemic inflammation reaction is important.

Prognosis:

The site of the thrombosis or thrombophlebitis due to catheterization may be jugular, cephalic vein or at the saphena. The thrombus can suffer recanalization and a sufficient blood flow may be obtained. In cases of total obstruction, collateral vessels might develop. Recanalization of the blood vessel usually takes between four and eight weeks. Long-duration thrombophlebitis can cause total fibrous blockage of the blood vessel, impeding the return of blood to the heart, limiting performance. Horses tolerate unilateral thrombophlebitis well as there is still another jugular vein. Bilateral jugular thrombophlebitis may result in swelling of the neck, poor performance, dysphagia, and airway obstruction that may be life-threatening (Schwarzwald, 2018). Cellulitis and limb edema and are possible complications when the cephalic vein was used.

Conclusion

Jugular intravenous catheterization in horses are common in equine practice and complications can occur frequently in 1-30% (Aksoy *et al.,* 2008; Schoster, 2017). The risk of

thrombosis and thrombophlebitis may be reduced by careful choice of material, site and technique and catheter management.

2.3.4 Toxicology

In intoxication case, the equine veterinarian usually experience extreme diagnostic and treatment problems as far as the etiology of the disease is concerned (Talcott, 2018). Such a problem may be experienced when a particular horse becomes extremely ill after the consumption of what was assumed to be ordinary normal healthy feed. It is difficult to figure out the toxic substance responsible for presented clinical signs and treatment can only be symptomatic as in most of the cases an antidote does not exist (Talcott, 2018).

The potentially toxic agents can range from drugs (e.g antibiotic like Monensin), acaricide and insecticide (e.g. Amitraz), to plants (Yellow Star Whissel, Oleander, Ragwort), molds with mycotoxins (e.g. Aflatoxind, Fumonisin), lead intoxication by industrial pollution of the environment near rivers (Talcott, 2018). They can manifest themselves in a variety of clinical conditions.

2.3.4.1 Intoxication with Monensin

Fortunately, not many toxicological cases were observed during the externship. The only four clinical cases of intoxication observed where caused by feed contamination with the ionophore antimicrobial Monensin, a food additive intended for poultry. Monensin is found as coccidiostat in chicken food and a growth promoter used in cattle (Talcott, 2018).

Case report

Four Lusitano horses (age 4-12 years) were presented to the emergency service over a 6-hour period for evaluation of acute signs of mild abdominal pain, depression, profuse sweating, and anorexia. The four horses were all in the same stud farm, which had 25 horses outside in the field and only those 4 horses were kept in boxes for training purposes. All animals had been in apparent good health at the time of that morning's feeding. The 25 horses outside were kept on grass pasture with additional hay feeding, the four horses in the box stayed in the barn and were fed hay and grain two times daily, in the morning and in the evening. All had access to well water via dispense in water troughs. The corn was a commercial feed mix prepared especially for horses from a local provider.

In the 6-hour period all four animals presented identical clinical signs and peracute progression to prostration, anorexia, profuse sweating and marked colic signs with tachycardia (range from 48-55 bpm), tachypnea (from 25 - 36 breaths per minute) and weak pulse. They were all normothermic. Oral mucosa of all 4 horses where light pink and dry with capillary refill time over three seconds showing signs of hypovolemia. All horses had no reflux via nasogastric tube, no feed concentrate could be obtained from the stomach, rectal palpation revealed no pathologic findings. Gut movement was reduced but present. Hay was removed.

To prevent cardiocirculatory depression and further development of colic signs due to intestinal hypoperfusion a supportive treatment with sufficient intravenous volume substitution

was started: Two liters of hypertonic saline IV, 20 liters of polyionic intravenous fluids with calcium, thiamine, selenium, and vitamin E was given IV via jugular catheter. For general anti-inflammatory and analgesic therapy flunixin meglumine in the dose of 1,1 mg/kg IV was given once a day for three days in order to reduce gut inflammation and abdominal discomfort. With no reflux via nasogastric tube, activated charcoal followed by 3 liters of mineral oil 20 minutes later, were administered twice with four hours apart in order to avoid further absorbtion.

They all had problems to do the suction movement in order to drink. Therefore for ten days the nasogastric tube was maintained and the owner applied 30 liters of water daily. One horse got worse very fast and died within 24 hours, the other 3 showed milder signs but it still took six weeks to return to normal. After two days, the surviving horses showed interest in food and hay was supplied, which they managed to chew in sufficient quantity. Their only neurological problem was to fulfill the suction movement, making drinking impossible. Only after 10 days they were able to drink and the nasogastric tubes were removed. Six month later the owner reported that all horses had returned to their normal performance. Further tests to evaluate myocardial damage (i.e. blood test Troponin T in the first day after intoxication, repeated ECG after some weeks) were not made due to monetary reasons.

In this situation, the only plausible explanation for the simultaneous occurrence of identical symptoms in four horses in the same stable, was a kind of toxic effect most probably caused by feed. As the farm had no chicken and no cattle, a grain contamination with feed additive with Monensin was suspected. The local feed manufacturer also produced grain for cattle and poultry.

Ionophore toxicity in horses

Ionophores are natural or synthetic substances which modify the permeability of biological membranes toward certain ions. By forming reversible lipid-soluble complexes with specific metal cations, ionophores enable an elevated ion transport across the cell membranes (Huge *et al.,* 2009). This effect leads to a decrease of ion gradients and loss of membrane potential, most obvious in the function of skeletal muscles and neurological tissues (Novilla, 1992; Huge *et al.,* 2009).

Many antibiotics, particularly macrolide antibiotics, are ionophores. Some have a selectivity for cations or anions, some exhibit a high affinity for Na+ and others a high affinity for K+. In veterinary medicine ionophores are utilized as antibiotics as well as growth-enhancing feed additives for cattle and chickens. The most commonly applied are monensin, lasalocid, and salinomycin. Monensin and salinomycin are the most toxic to horses. In industrial poultry production they are needed as a feed additives for the treatment of coccidiosis and histomoniasis (Castanon, 2007), in cattle they were used to improve feed efficiency and increase the rate of weight gain (Butaye *et al.*, 2003).

Monensin

Monensin is an antibiotically active substance from the group of polyether antibiotics and is metabolized by the actinobacteria Streptomyces cinnamonensis (Agtarap *et al*.,1967). It only

transports potassium and sodium between extracellular and intracellular spaces and shows toxic ionophoric activity in mammalian cells. The loss of the Ione gradients across the membrane prevents oxidative metabolism and reduces the energy production of the cell significantly. Increases in intra-cellular sodium provokes water influx in the cell and consecutive mitochondrial swelling. Loss of energy, ion imbalance, loss of membrane potential and cell edema contribute to cell death (Lowicki and Huczyński, 2013).

Equines are highly sensitive to the toxic effect of ionophores compared to other species. In cattle and poultry, the median lethal dose (LD50) of monensin is 80 mg/kg btw and 200 mg/kg btw respectively. At these levels, a safe and effective use in order to prevent Coccidiosis in these species is possible (Novilla 1992; Huge *et al.,* 2009). Horses in contrast, have an extreme low tolerance with 1–2 mg/kg bwt, making it especially dangerous for them (Matsuoka 1976; Doonan *et al*. 1989; Peek *et al.* 2004, Divers *et al.*, 2009; Huge *et al.,* 2009).

Intoxication of horses by accidental contact with contaminated feed, feed intended for chicken or cows, has led to several deaths in the past (Doonan *et al*., 1989; Peek *et al*., 2004). The contamination of the feed occurred in most known cases when feed batches for poultry, cattle and horses were prepared simultaneously in the same time at the same facility.

Severity of effects and the speed of onset is proportional to the level of feed contamination (Doonan *et al*., 1989).

Clinical signs of toxic effects of monensin

Horses that have eaten feed with monensin can show a variety of signs. Clinical effects and case-fatality rates are influenced by individual factors (bodyweight, health, vitamin E and selenium deficiencies) and the quantity of ionophore ingested (Doonan *et al.*, 1989). The diagnosis of ionophore intoxication is challenging as symptoms are not pathognomonic.

Signs of peracute/acute intoxication:

At the beginning, that is 24-48 hours after the ingestion of monensin, horses show anorexia and variable signs of colic. Clinical signs rapidly progress including general muscle weakness and heart failure and death (Muylle *et al.,* 1981).

Early signs of feed related monensin intoxication include depression, anorexia, diarrhea, sweating, weakness, ataxia with staggering and falling, hypermetric gait, abdominal pain, tachyarrhythmias, tachypnea, pyrexia, dark discolored urine (myoglobinuria), recumbency, paddling movements with the limbs before death, seizures and sudden death (Matsuoka 1976; Bezerra, 1999; Boemo *et al.*, 1991; Peek *et al.,* 2004). Electrolyte imbalances as well as direct damage to the myocardium itself lead to pronounced arrhythmias. Blood biochemistry shows signs of dehydration with increased packed cell volume (PCV) and high protein levels as well as renal damage (increased blood urea nitrogen and creatinine) (Peek *et al.,* 2004).

Repeated ingestion of sublethal doses can lead to a chronic form of intoxication. Clinical signs are initially stiff movements, muscular weakness, poor performance and finally death due to congestive heart failure (Muylle *et al.,* 1981; Whitlock 1990; Boemo *et al*., 1991; Hughes *et*

al.; 2009). According to Talcott (2018) some horses die independently of the therapy, others may recover after a couple of weeks and even return to normal work. Some also maintain a permanent heart failure and never recuperate.

Vitamin E and selenium deficiency can predispose to more severe tissue damage, but adequate concentrations do not prevent toxicosis.

Pathophysiology

Monensin ingestion by equines can either lead to acute death due to induced electrolyte dysbalance and consecutive arrhythmia, or to a lagged congestive heart failure caused by degeneration of the myocardium (Muylle *et al.*, 1981). In animals which survive acute intoxication, connective tissue replaces necrotic myocardial cells, which can result in permanent myocardial dysfunction and cardiomyopathia.

The effects on the skeletal muscle are similar to the myocardial muscle, but the damage is frequently less severe. Ionophores alter nerve conducts and this results in altered reflexes and muscle coordination. Renal tubular damage can occur and is associated with myoglobin casts. Hepatocellular necrosis and decreased function can occur.

Death is caused by necrosis of the heart muscle and a resulting cardiac arrest. Other symptoms include circulatory disturbance with abnormal pulse, tachycardia and cardiac arrhythmia. A sublethal dose of monensin and its effect on the myocardium does not necessarily need to be permanent. In some horses return to normal performance in riding and reproduction (Hughes *et al.*, 2009).

A small number of horses that survived poisoning, observed by Peek *et al.* (2004) showed no more abnormalities after two months. Examination findings like heart rate, serum biochemical analyses (CK, CK-MB, Troponin T), echocardiography and ECG, were unremarkable after this period of time (Peek *et al.,* 2004).

Diagnosis

Diagnosis is confirmed by history, clinical signs, consideration of possible differential diagnoses and serum biochemical analysis to detect the possible intoxication caused by ionophore. Electrocardiography (ECG) can help in the assessment of arrhythmias and heart function but unfortunately abnormalities in resting ECG seem to be inconsistently present and are no reliable prognostic factor (Talcott, 2018).

Significant abnormalities in routine hematologic and biochemical variables include slight mature neutrophilia, hyponatriemia, hypochloremia, hypocalcemia, severe hyperglycemia, pre-renal azotemia and total protein increases consistent with dehydration. Metabolic acidosis with low total CO2 and low blood pH can be revealed in the venous blood gas (Peek *et al.*, 2004). Various abnormalities seen in biochemical analyses such as increased serum osmolarity, high levels of creatine kinase, aminotransferase, aspartate and urea, may help to identify the acute form of the toxicosis (Doonan *et al.*, 1989; Peek *et al.*, 2004). However it must be kept in mind, that even when these abnormalities are found, they are a generally poor predictors for prognosis (Doonan *et al.*, 1989; Talcott, 2018).

Main necropsy findings are in the skeletal muscles and myocardium. The presumptive diagnosis therefore is confirmed by necrosis of the skeletal muscle, focal degeneration of the myocardium and congestive heart failure (Matsuoka, 1976).

Differential diagnosis are acute gastrointestinal disease, acute neurologic disease, rhabdomyolysis, Vitamin E and selenium deficiency, viral, bacterial or other toxic forms of myocardial failure (Talcott, 2018).

Treatment

At the moment, there exist no antidote for monensin intoxication. The only treatment which can be provided is supportive (Talcott, 2018). Suspect feed must be removed immediately, but it should be saved for testing if needed. A quantitative analysis should be performed if a sample of contaminated feed is available.

If initial treatment is performed immediately after exposure, decontamination can be attempted. With the help of activated charcoal or mineral oil via nasogastric tube an attempt to evacuate some toxins from the gastrointestinal tract and delay its absorption can be tried. To alleviate gastrointestinal discomfort and reduce mucosal damage, gastric protectant can be used. Fluidtherapy IV to combat dehydration is indicated as well: supportive therapy with two liters of hypertonic saline, poly-ionic intravenous fluids, thiamine, selenium, and vitamin E can be applied.

For general anti-inflammatory therapy 1,1 mg/kg IV flunixin meglumine IV can be administered. DMSO 1g/kg diluted to 10% in fluids IV BID for 3 days is also recommended (Knottenbelt and Malalana, 2015). Prevention is the most important factor. Horses should not not have any contact with feeds prepared for cows and chickens. Feed and pre-mixes should only be bought from reliable producers that guarantee a professional practice with quality control.

2.3.5. Pneumology

According to Davis (2018), equine respiratory disease is the second most common disorder behind musculoskeletal disease, reducing the horses performance and use (Perkins *et al*., 2005, Davis, 2018). In the externship 15 cases concerning the respiratory tract were seen. Infectious disease of the upper airway was rare. Only one younger horse with rhinitis and one horse which developed a bronchopneumonia with septicemia after long distance transport were presented to consultation. Noninfectious inflammatory cases of the lower airway were more frequent (13 horses) during the 4-month period in the ambulatory clinic (Table 6).

Table 6 - Casuistic of Pneumology seen in the externship. (Recurrent airway obstruction RAO, equine asthma syndrome EAS, inflammatory airway disease IAD)

Disease	Numbers of cases
Rhinitis	1
Severe EAS (RAO)	11
Mild-moderate EAS (IAD)	2
Bronchopneumonia	1
TOTAL	15

In the ambulatory clinic, the owners main complaint was reduced exercise tolerance of their horses and coughing during exercise as well intermittent at rest. On all horses an examination of the general condition including heart and lung auscultation, rectal temperature measurement and respiratory and heart rate count was performed. At clinical examination of 13 horses with coughs, two showed expiratory dyspnea at rest, all 13 had expiratory dyspnea when being ridden and all of them had bilateral serous nasal discharge. The horses had both inspiratory and expiratory wheezing at tracheal auscultation with reproducible cough when making pressure on the trachea. Diagnostic was based on physical examination and typical respiratory pattern and BALF.

Horses with RAO and IAD seen in the externship were all treated with modification of their environment, putting them out in the pasture and giving them watered hay or pellets. The owners were informed that there was no cure for the disease and that the horses needed to be managed rigorously, avoiding as much as possible exposure to any type of dust.

Two animals presented clinical signs that implied an emergency treatment with IV administration of corticosteroids such as dexamethasone at dose 0.05 - 0.1 mg/kg (Wilson and Robinson, 2015) for dyspnea attack. All horses were treated with β2 clenbuterol adrenergic Ventipulmin® granulate PO (16 µg clenbuterol hydrochloride per g) at dose 0.8 µg/kg BID for its bronchodilator effect and with prednisolone PO (2 mg/kg SID), for the anti-inflammatory effect, until clinical signs disappeared. In one 11 year old Lusitano stallion who never had shown clinical signs of RAO or IAD before an endoscopy was made to confirm diagnosis. The presence of more than 20% of non-degenerative neutrophils in the cytological examination was indicative for RAO (Ainsworth and Cheetham, 2010; Wilson and Robinson, 2015) in this case.

Respiratory disease in equines can be subdivided into upper or lower airway disease and in infectious and noninfectious, contagious and noncontagious, and inflammatory or other independent disorders (Davis, 2018).

2.3.5.1 Noninfectious inflammatory conditions of the lower airways in horses: Recurrent airway obstruction (RAO), Inflammatory airway disease (IAD)

There are many terms that describe noninfectious inflammatory conditions of the lower airways in equines: " Heaves" or " recurrent airway obstruction", or " severe equine asthma", summer pasture-associated RAO, and inflammatory airway disease IAD or " mild to moderate equine asthma" cause a typical clinical signs in affected horses (Davis, 2018).

It has been proposed that RAO and IAD should be reassigned as "equine asthma", as they resemble human asthma in many respects (Leclere *et al*., 2011).

Prevalence:

Inflammatory afflictions of the lower airway are frequently seen nowadays in domestic horses. In the Northern Hemisphere RAO is often encountered especially when horses are mainly indoors most part of the year due to climatic reasons and where drying of hay is difficult. According to several studies the prevalence varies from 2% to 80% depending on which parameters and criteria were included (Bracher *et al., 1991;* Traub-Dargatz *et al.,* 1991; Léguillette, 2003).

Definitions of IAD and RAO

According to Mazan (2015) recent research supports the concept, that - even though considered separate diseases - there exist a kind of range or graduation, with low-grade IAD on one end and RAO on the other end (Mazan, 2015; Couetil *et al.,* 2016).

IAD (or mild to moderate equine asthma)

By definition IAD is an inflammatory condition of the lower airways characterized by recurrent and reversible airway obstruction caused by accumulation of inflammatory cells leading to excess mucus production and airway hyper-responsiveness. Pathologic changes occur in the small airways (bronchioles), the alveoli are not affected. IAD shares similar features with RAO but the signs are less severe and may also affect young horses (Couetil *et al.*, 2016) .

RAO (or severe equine asthma)

RAO is an environmental inflammatory disease affecting the lower part of the airway (Davis, 2018). Clinical signs are bronchospasm, dyskrinia, and airway remodeling which is leading to a partial or totally reversible airway obstruction with variation of crisis and symptom-free periods resembling human asthma (Léguillette, 2003). The spasm seen in RAO affects the whole lung parenchyma and is not restricted to a circumscribed area of the lung (Bracher and Fellenberg, 1991). RAO manly affects animals over seven years and the incidence increases with age (Couëtil and Ward, 2003). Islandic ponies and warmblood horses seem to have a hereditary component to develop this pathology more often, but in general there exist no breed or gender predilection for RAO (Davis, 2018).

It is common in countries with temperate and cold climates, where horse are stabled for

prolonged periods. Most typical for RAO is, that clinical signs disappear when horses are turned out to pasture (Couëtil and Ward, 2003).

Clinical signs

Clinical signs of " equine asthma" are frequent coughing, episodic respiratory distress due to variable airflow obstruction, excess mucus production with serous nasal discharge, airway inflammation/remodeling, chronic innate immune activation and reduced exercise intolerance (Mazan, 2015; Sheats *et al.*, 2019). During clinical exacerbation of RAO flared nostrils, and an increased respiratory rate with augmented effort during expiration, and a so called " heave line" on the lateral abdomen may be visible. During the attacks of dypnea the clinical signs vary in severity, appearance and duration. The affected horses are alert and afebrile (Couetil *et al.*, 2016).

Differentiation between the two forms of respiratory disease can be made by on the one hand severe exercise tolerance in RAO, and an the other hand the non-existence of impaired breathing at rest in IAD. The grade of bronchopulmonal remodeling due to chronic inflammation in RAO requires time to develop. Horses with IAD recover without residuals (Couëtil *et al.*, 2016). An excessive production and accumulation of mucus (dyskrinia) in the airways is typical for both RAO and IAD (Koblinger *et al.*, 2011).

Pathogenesis:

The most important risk factor to develop a lower airway inflammation are repetitive or constant exposure to mold spores (i.e. *Aspergillus fumigatus*, *Saccharopolyspora rectivirgula*, and *Thermoactinomyces vulgaris)* found in hay dust (Mazan, 2015). It leads to hypersensitivity reaction with inflammation in susceptible horses. Released cytokines enhance the inflammation and lead to excessive mucus production, coughing, airway spasm and consecutive respiratory distress (Davis, 2018).

Hypoxemia is common, presumably resulting from ventilation and perfusion inequalities and inefficient gas exchange with high shut fraction as some parts of the lungs are not ventilated adequately. Hypoxemia with normocapnia in RAO-affected equines is resulting from a lower solubility of oxygen compared to CO2. The exchange rate of oxygen therefore is reduced to such a greater extent that leads to hypoxemia without any retention of carbon dioxide (Léguillette, 2003). The role of viral infections and nonspecific environmental dust particle (i.e. endotoxins) on the induction and maintenance of heaves is currently ill-defined.

The causes of IAD and RAO share similarities. Airborne environmental allergens and high concentration of irritants like molds, endotoxins and dust from hay, bedding, noxious gases such as ammonia form stagnant bedding and prolonged stabling are believed to be the primary causative agent, especially for an animal which by origin is supposed to live outdoor as migrating mammal. Both are diseases of domestic equines as these animals are more exposed to dust from hay and stable environment. Nevertheless it remains unclear if the difference of RAO and IAD lies in its severity or if pathogenesis itself it totally different (Mazan, 2015).

The pathogenesis of IAD remains incompletely defined (Couetil *et al.,* 2016) but its etiology is multifactorial. IAD is often considered to be an allergic disease, but an IgE mediated inflammatory reaction till now has not been found yet (Wagner, 2009). Constellation which can contribute to of IAD are viral disease, bacterial infection, air pollution and genetic predisposition (Wagner, 2009).

Diagnostic:

Diagnostic of inflammatory airway disease is based on history and physical examination and airway endoscopy (Robinson, 2000; Davis, 2018)). The respiratory pattern of affected horses shows pronounced expiratory effort due to air trapping and emphysema. In auscultation wheezes and mild crackles can be heard, and the field of the lung is larger due to the emphysema (Mazan, 2015). Analysis of serum chemistry and blood count usually are normal and there is no indication for thoracic x-ray in routine diagnosis. Bronchoalveolar lavage cytology is the method of choice for diagnostic (Robinson, 2000; Davis, 2018; Couëtil and Thompson, 2020).

Endoscopy

Based on clinical signs, bronchoscopy with bronchoalveolar lavage fluid (BALF) cytology can be used in practice to confirm a presumptive diagnoses of IAD / RAO (Robinson,2000; Couëtil and Thompson, 2020). In healthy horses the percentage of neutrophils in the total nucleated cells present in the collected mucus varies between 5 - 10% . A cytology of the bronchoalveolar lavage with neutrophils over 10%, more than 5% of mast cells and more than 5% of eosinophils confirms IAD (Ainsworth and Cheetham, 2010; Wilson and Robinson, 2015). In RAO, after being exposed to aeroallergens, a high percentage of neutrophils (>25%) can be found.

The role that neutrophil play is relatively known to be controversial even though their mechanism of recruitment is still being studies. Neutrophils tend secret high volumes of cytokines such as the IL-8 which are profoundly beneficial in RAO (Lavoie *et al.*, 2001). Horses with chronic cough over more than 3 weeks usually show an increase of neutrophils in BALF, which can be used as a prove for pulmonary inflammatory reaction (Bedenice *et al.,* 2008).

Cytology in IAD horses on the contrary often show only a light elevation of eosinophils, neutrophils and mast cells (Fogarty and Buckley, 1991; Couëtil 2001).

Treatment:

Therapy for RAO and IAD are nearly identical (Mazan, 2015; Couëtil *et al.*, 2016): control of the inflammatory reaction, reduction of the hyper responsiveness of the bronchial wall, and decrease of airway obstruction are the decisive actions to improve pulmonary function in the long term.

Environmental modification

The crucial factor for controlling these airway disease is a significant reduction of allergen exposure by environmental alterations. Affected animals should be kept in a dust-free place

reducing the organic dust particles from moldy hay and straw. Keeping the horse outdoors, preferably on pasture and offering soaked hay is paramount for a successful long-term treatment (Couëtil *et al.*, 2016). New exacerbation can be triggered by indoor training, seasonality, infectious agents and genetic predisposition. When the disease progresses and turns chronic, the frequency and the severity of coughing episodes increase with time (Mazan, 2015). Reduced exercise capacity often persists even if the horse is in clinical remission.

Anti-inflammatory therapy and bronchodilator therapy

Systematic or inhaled corticosteroid can effectively aid in the treatment if taken in an environment that has allergens reduced conditions; bronchodilators can help as a short-term relieve to reduce clinic signs of bronchospasm.

Systemic administration of corticosteroids is the traditional approach.

Studies have revealed that oral prednisone is a short term aspect does not have any profound benefit as far as the clinical presentation, pulmonary functioning and BAL cytology in RAO is concerned (Traub-Dargatz *et al.*, 1992; Jackson *et al.*, 2000). The lack of efficiency might be explained by reduced absorption in the gastrointestinal tract and conversion of prednisone to prednisolone (Robinson et al., 2000).

When given on a long-term basis, prednisone might improve pulmonary function in some equines (Robinson et al., 2002). In consideration of the bioavailability of oral prednisolone, a dose of 1 to 2 mg/kg PO every 24 hours might be effective but this has not been proven yet by clinical studies.

Systemic triamcinolone and dexamethasone are clinically tested and have shown to be effective in the treatment of RAO but have an increased risk of side effects like laminitis. A single dose of triamcinolone can bring relief for up to 28 days, but has side effects like adrenal suppression, hyperglycemia and hyperglyceridemia following administration (Lapointe *et al.*, 1993).

Dexamethasone reduces airway obstruction alleviating clinical signs for up to 10 days and can be given PO, IM or IV (Robinson *et al.,* 2002; Davis 2018). If the change in management is not possible or insufficient to control symptomatology, treatment with corticosteroids such as fluticasone at the dose of 4 µg/kg, BID and/or bronchodilators such as ipratropium bromide at the dose of 0.5 - 1 µg/kg, TID or four times a day via inhalation (Lavoie and Divers, 2007) is also a good choice, decreasing the necessary dose and consequently the risk of laminitis.

Inhalation of aerosolized beta2-adrenergic-agonist or anticholinergic agents, in order to relieve the smooth muscle contraction, reduce excessive respiratory effort and cough, are indicated. They also improve delivery of inhaled corticosteroids to the distal airways (Couëtil *et al.*, 2016). Effective alternative therapy for mild to moderate affected animals is the inhalation of corticosteroids via inhalation mask for horses (Figure 4).

Beclomethasone is the most common aerosolized corticosteroid used in allergic airway disease in humans with a delayed onset after 24 hours. Fluticasone can also be used for inhalation purpose and it is the most expensive and potent (Davis, 2018). Rapid effective

bronchodilators like aerosolized short-acting beta2-adrenergic-agonists are used for rescue therapy in human and horses. Rapid relief of bronchospasm is indicated in RAO when horses are demonstrating respiratory difficulties at rest and hypoxemia is marked (Davis, 2018). Long-acting bronchodilators are ineffective for rescue therapy, as they have a delayed onset of activity (i.e. Salmeterol).

Oral clenbuterol has an extended effect of 12 hours and is indicated for temporary smooth muscle airway relaxation and not for prolonged therapy. As bronchospasm is a consequence of inflammation (Derksen, 1993), a monotherapy with bronchodilators is not appropriate (Davis, 2018).

Figure 4 - Use of inhalation mask in a horse with RAO

An alternative to salbutamol or clenbuterol with bronchodilatory effect are Buscopan (N-butylscopolammonium bromide), a peripherally acting muscarinic, antichokinergic agent and Atropine. Due to several adverse effects (i.e. paralytic ileus, central nerve toxicity, tachycardia) this drug is only recommendable as rescue therapy for sever and life-threatening situations (Davis, 2018).

In horses with profound hypoxemia (Pa O2 under 60 mmHG) inhaled oxygen supplementation via a nasopharyngeal tube may be required until ventilation is improved. Exercise level should be adjusted according to the degree of respiratory dysfunction (Davis, 2018).

Table 7- Summary of therapeutic goals for treating RAO: Control of the inflammation and decrease airway obstruction. (Robinson *et al*., 2000; Robinson *et al.,* 2002; Lavoie and Divers, 2007; Knottenbelt and Malalana, 2015; Couëtil *et al*., 2016; Davis, 2018)

Treatment			
Environmental modification to reduce allergen exposure	Outdoor living, maximize fresh-air periods, maintain environment dust free, maintain an up to date vaccination schedule for influenza and herpesvirus	Change diet: Pasture instead of hay	Pelleted food or soaking/ watering hay
Corticosteroids (Antiinflammatory therapy)	Dexamethason 0,05 mg / kg IV or IM for severe attacks	Single dose of Triamcinolone 20-40 mg IM reverses signs for 3-5 weeks (increased risk of side effects)	Prednisolon PO 1-4 mg /kg, for mild cases (often recommended but efficacy not documented)
Inhaled Corticosteroides	Beclomethasone 250 mu/ puff 12 puffs BID for 2 weeks	Metered does inhaler: Fluticasone 250 mu/ puff, eight puffs BID for 2 weeks	
Bronchodilator beta2-adrenergic-agonist or anticholinergics	Clenbuterol 0,8-3,2 mu/ kg BID PO	Metered dose inhaler : Ipratropium bromide 0,4-1 mu/kg q 6h	Salbutamol 100 mu/puff, given 10-15 minutes before exercise

Conclusion:

The ancestors of our contemporary horses were steppe animals and confining them into boxes made them susceptible to diseases of civilization (Mazan, 2015). The diagnosis and differentiation of IAD and RAO can be made based on clinical signs, BALF cytology and lung function. Therapy as summarized in Table 7, consists of systemic or inhaled pharmacologic treatment and environmental reduction of antigenic agents (Marzan, 2015). In competition horses, clenbuterol is obsolete due to doping regulation.

Despite the fact that individuals presenting with mild forms of respiratory inflammations have an elevated risk of RAO development (Bosshard and Gerber, 2014) there is no peer- reviewed literature which can support the rational behind the change from IAD to RAO.

2.3.6. Dermatology

During the externship, consultations in 15 cases with dermatologic disorders were made, as represented in table 8. Traumatic wounds (4 horses), insect-bite hypersensitivity (7 horses), dermatophilosis (2 horses), allergic exanthema (1 horse) and equine sarcoid (1 horse) were seen.

Two horses were treated with dermatophilosis or “rain scald“ at all four limbs at the pastern and fetlock. “Rain scald“ is a condition generally found during autumn and winter month and affects the skin of the horse, usually at the back and flanks and legs (“mud fever“), which occurs most commonly in horses kept outdoor in wet and muddy conditions. The two horses showed clinical signs of dermal infection (*Dermatophilus congolensis*) with a moist erythema partially covered with crusts and sensitive to palpation on the palmar/plantar side of the pastern and distal part of the cannon bone.

The treatment consisted of daily washing with liquid antiseptic soap with Betadine® Foam (iodopovidone 4%). The crusts were removed, the wounds desinfected, and antibiotherapy with Ulfaprisol® powder, (trimetoprim 30 mg/g, sulfadiazine 150 mg/g PO at the dose 30 mg of the combination)/kg, BID) started. The owner were informed to wash grooming brushes in disinfectant and avoid sharing tack and equipment with other horses. Bacterial growth can be prevented through the action of putting the horses in an environment that is dry, has proper circulation of air, and free from wet conditions (Rosser, 1995). Possible relapse of the clinical signs can be prevented through the management of the environment, underlying etiology as well as application of effective control measures (Weese and Yu, 2013).

Table 8 - Cases of Dermatology seen in the externship

Diseases	Number of cases
Traumatic wounds	4
Insect-bite hypersensitivity	7
Allergic exanthema	1
Dermatophilose	2
Equine sarcoide	1

Skin affections due to insect-bite hypersensitivity, was a frequent complaint, seen in the externship. In seven severe cases the ambulatory practice was called for consultation.

2.3.6.1. Insect-bite hypersensitivity (IBH)

Around the globe, equine pruritus is commonly caused by the hypersensitivity that results from insect bites (Pilsworth and Knottenbelt, 2004). About 10% of the horses in the entire world tend to have IBH (Marti *et al.*, 1992). Severe unrelenting pruritus is a frequent medical issue that can be linked to equine dermatoses. However, the condition is known to manifest in the form of alopecia, crusting, excoriations and scaling and due to self-mutilation (Figure 5 and 6).

Severe unrelenting pruritus is a common complaint associated with equine dermatoses and manifests in self-mutilation with alopecia, excoriations, scaling, and crusting (Figure 5 and 6). The aspect of such a horse is often deteriorated hence it is usually not used for riding or

showing (Fadok, 1995).

Figure 5 — Mare with IBH seen in the externship: self-mutilation with alopecia, excoriations, scaling, and crusting.

Definition of IBH

IBH of horses, also called allergic dermatitis, summer eczema or sweet itch, is a seasonal dermatosis of extreme pruritus which is caused by salivary antigens of biting insects (Kurotaki *et al.,* 1994). The best documented is Culicoide hypersensitivity, but horses also can develop hypersensitive reactions to stable flies, black flies, mosquitoes and horse and deer flies (Fadok, 2013). The hyper-responsiveness of the immune system manifests clinically as severe, unrelenting pruritus. The principal clinical sign of IBH is a severe skin pruritus especially at the site of the insect bites.

Pathophysiology

IBH is an immune system disorder that results from an exaggerated immune response to the presence of an antigen from biting midges (Ferroglio *et al.*, 2006). The disease is known to be contributed by genetic and environmental factors making it multifactorial in onset and perpetuation (Steinmann *et al*., 2003). Many research conducted within the last 10 years have proven that antigenic proteins produced by the salivary glands of Culicoides are identified as allergens by IgE of IBH-affected horses (Hellberg *et al*., 2006). The reaction to allergen can be divided into immediate (5-10 minutes), late phase (2-5 hours) and delayed type of hypersensitivity (Zhu and Paul, 2010).

In terms of classification, IBH is a IgE-dependent type I allergy (Hellberg *et al.,* 2006), involving as well a type IV allergic hypersensitivity reactions (Kurotaki *et al.,* 1994)

Clinical signs of IBH

Typical clinical signs of IBH are severe pruritus and secondary lesions of alopecia and crusting.

Initially it begins with skin sensitization to insect bites, horses start to scratch the itching papulas by rubbing mane and tail (stufted hair) and develop a consecutive hyperesthesia on the biting sites (Brostrom *et al.,* 1987; Fadok, 2013). The distribution of the horses skin lesions shows the preferred feeding sites of the species of Culicoides. The „sweet itch“ or summer eczema classically distributes dorsally on the middle line with lesions found on the face and ears, the base of the mane and tail, withers and rump (Fadok, 2013). There exists some variation in the nature of the insect species responsible for the conditions making the clinical presentations to equally vary with time (Greiner, 1995).

Equines with IBH show clinical symptoms when biting insects are more active depending of the time of the year. The hypersensitivity unfortunately suffers gradual progression over time (Broström *et al.,* 1987). Secondary infections (with bacteria, mites and fungi) of self inflicted wounds by scratching contribute to the disease progression as they cause further local irritation (Riek, 1953).

Clinical signs of IBH with chronic progression are permanent alopecia of the mane and tale thickening of the skin, fibrosis, marked hyperkeratosis and lichenification (Figure 6), fold and formation of transverse ridges (Riek, 1953; Schaffartzik *et al*., 2012).

Figure 6 - Mare seen in the externship with chronic IBH: Secondary lesions of alopecia and crusting; hypertrophy of epidermal tissue, and marked hyperkeratosis and lichenification.

Prevalence

About 10 % of the horses in the globe tend to suffer from IBH, and that kind of allergic predisposition can occur in all breeds (Marti *et al.,* 1992). There is a huge variety in prevalence. According to McCraig (1973) this allergic disease is found in 3% of all horses in Great Britain

(McCaig, 1973) whereas Riek (1953) describes in his study that 60% of all equines are affected in Australia. The climate profoundly influences the occurrence of the IBH. Factors such as areas with low wind speed, forests as well as a dry a warm climate are relatively favorable for the growth of blood feeding insects (Steinman *et al.,* 2003). Colts and fillies, which are often kept in the same environment together with affected older animals, only begin to develop clinical signs above the age of 2–4 years (Steinman *et al.*, 2003).

Predisposition

Horses that have originated from Iceland and living in the European region are usually affected by the condition at a rate of >50% (Björnsdóttir et al., 2006). Generally, the disease is known to affect all the breeds of horses. The clinical presentation only appear after horse has passed 2-4 years (Wilson *et al*., 2001; Schaffartzik *et al.,* 2012)).

Diagnostic

History, clinical signs, the horses response to the control of insects (use of blankets, repellents), as well as serology (ELISA) and intradermal testing confirms the insect bite hypersensitivity. As endoparasites influence the total IgE levels, IgE therefore can not be used as indicator of an allergic predisposition in equines (Scharrenberg *et al.*, 2010).

Treatment

Effective therapeutic intervention is still a challenge even though IBH is one of the best studied form of allergic dermatitis (Schaffartzik *et al*., 2012; Fadok, 2013).
Steroid-based immune-suppression and hypsosensitisation still yield unreliable outcomes as the success rates is still below 50% making the attainment of high efficacy to be relative elusive. Prevention by avoiding insect bites is therefore essential. Reducing the exposition to blood sucking insects by stabling the horses during time when insects prefer to feed, use fans to guarantee a good ventilation (small flies are bad flyers), use repellents (i.e. Permethrin) or protective blankets (Olsen *et al.*, 2010), might reduce the severity of the clinical signs (Fadok, 2013).

The application of insecticides on a regular basis can be a good choice in the management of the disease, and permethrin seems to be the most effective (de Raat *et al.,* 2008). Several products like spot-on treatments, sprays or liquid (i.e. „Wellcare“) as repellent do exist on the market. Sometimes even a product for dogs (Vectra 3D) its used off-label by some specialist of dermatology (Fadok, 2013). Vectra 3D is a mix of the drugs pyriproxyfen, permethrin and dinotefuran (Fadok, 2013; Emmerich, 2015). In Portugal and Spain the off-lable use of Arpon G (Cipermetrina), a product legalized for cows and sheep, is often used as repellent for horses by privat owners. A new vaccine for horses to reduce the itch may be on the marked soon.

2.3.6.1.1. New vaccination against IBH

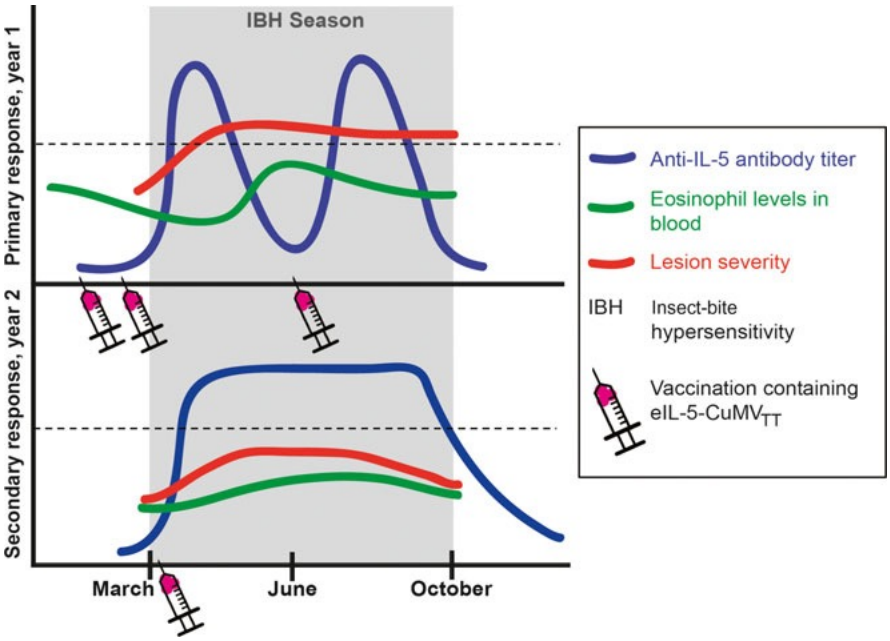
Immunotherapeutic approach with cytokine-blocking anti-bodies

Since 2018 a new immunotherapeutic approach with an active vaccine against interleukin

IL-5 is tested on Islandic ponies in Switzerland. Allergic skin afflictions of equines are related to a pronounced type-I/type-IV allergic reactions with eosinophil infiltration especially at the insect bite site. The principal cytokine for eosinophils is the Interleukin-5 (IL-5). A significant reduction of pruritus can be achieved by decreasing IL-5 level via vaccination (Fettelschoss-Gabriel *et al.,* 2019). According Fettelschoss-Gabriel *et al. (*2018) the basic vaccination are three vaccine injections in the first treatment year. This already induces sufficient antibody titers against self IL-5 (Graph 3). It is given SC without any added adjuvants.

In the second treatment year a single booster dose amplifies anti−IL−5 antibody titers, reducing the pruritus in these horses even more (Graph 3). From then on, an annual vaccination is necessary. After this form of vaccination the blood eosinophil levels significantly dropped in this study. Regarding infestation of helminths there was no difference found, indicating that effector function of eosinophils deteriorated due to the vaccines effect (Fettelschoss-Gabriel *et al.*, 2018).

This vaccine is the first approach of immunotherapy for a chronic allergic disorder in horses (Fettelschoss-Gabriel *et al.,* 2018). Maybe it is an option for a long-term solution in treating IBH and other eosinophil-mediated diseases in equines to vaccine yearly agains IL-5. Clinical trials have been made and a commercial vaccine is supposed to be on the market in 2021.



Graph 3- Basic vaccination regime for IBH according to Fettelschoss-Gabriel *et al.(* 2019).

Conclusion

There is still limited knowledge concerning allergies among horses as it lags behind that of the dogs. However, there is a lot of progress in this levels of understanding as far as insect hypersensitivity is concerned (Fadok, 2013).

Immunotherapeutic Cytopoint „lokivetmab" a monoclonal antibody targeting against activity of interleukin IL-31, which is responsible to induce pruritus in dogs, is already successfully on the marked since June 2017. The immunotherapeutic approach in horses with yearly active vaccination against IL-5 seems to be a possible longterm solution und effective treatment (Fettelschoss-Gabriel *et al.*, 2019).

2.3.7. Other

This chapter includes areas that have been grouped together because they are less common procedures or diseases, or precisely because they occur with some frequency in horses, but their approach is somewhat simple or limited. However, these topics - Piroplasmosis (3 cases) and euthanasia (5 cases; Table 9) are not without significant relevance in equine practice and are therefore represented here in the following.

2.3.8.1. Piroplasmosis

In the externship, three cases of acute Piroplasmosis were seen. All horses were lethargic with high fever (39,0 - 39,8 Celsius). They presented hyperemic and icteric mucous membranes, an increased heart rate (44 - 52 bpm) and respiration rate, intermittent gastrointestinal signs of colic and showed evidence of coagulopathy with some oral petechiae. One horse also had pronounced subcutaneous edema at all limbs and a visible icterus of the mucosas. Diagnose was solely made on the clinical signs by elimination of other causes, since at the moment of the consultation it cannot be confirmed immediately wether the horse is suffering from Piroplasmosis.

Treatment with Imidocarb 2mg/kg bwt IM (i.e 2 ml/ 100kg bwt) was performed, 5 ml per injection site for a 500 kg horse, as deeply as possible into the neck or semitendinosus/ semimembranosus muscles. The injection of Carbesia™ (Imidocarb) into the pectoralis muscles should be avoided (CliniPharm, 2020). Twenty minutes before Finadyne® (Flunixine meglumin, 50 mg/ml) 1.1 mg/kg btw. IV was given to diminish reaction to Imidocarb and reduce frequently seem side effects like abdominal pain. Imidocarb 2mg/kg bwt IM was repeated after 72 hours if the horse had not significantly improved within 24 hours. The owners were asked to take temperature in the morning and in the afternoon for several days after the first injection of Imidocarb. If they showed fever again 20 mg/kg bwt IV (i.e.20 ml for a 500kg horse) of Vetalgin® (Metamizol 500mg/ml) was administered (Knottenbelt and Malalana, 2015; CliniPharm, 2020). One horse needed supportive treatment with 20 liters of poly-ionic intravenous fluids. The horses received routine care, normal diet and restricted activity for 3 weeks. According to the owners, one month later they all had returned to normal activity.

Pathogenese

Equine piroplasmosis is an infectious cause of hemolysis provoked by one or both erythrocytic parasites *Babesia caballi* and/or *Theileria equi,* dual infections occur. Similar pathogenesis includes transmission by ticks and an intravascular erythrolysis leading to the main clinical symptom of anemia (Wise *et al.,* 2013). The hemolysis is caused by replication of

the erythrocyte-stage parasites.

Equine piroplasmosis is a globally important disease (Wise *et al.,* 2014). In Southern Europe, including Portugal, it is considered endemic (CFSPH, 2018). Tick vectors include species of *Rhipicephalus, Dermacentor, Haemaphysalis, Hyalomma* and *Boophilus* (Mehlhorn and Schein, 1985). Iatrogen transmission and intra-uterin transmission to fetus have been reported. Equine piroplasmosis that is linked to Theileria equi has an incubation period that ranges from 12 to 19 days and may take up to between 10 to 30 days when the cause is associated with Babesia caballi (OIE, 2009).

In practice its is often challenging to diagnose piroplasmosis as the clinical signs are nonspecific. The disease can often be confused with other hemolytic conditions presenting as well jaundice, fever and anemia (Wise *et al.*, 2013). *Theileria equi* has more severe courses of Piroplasmosis than Babesia caballi.

Acute, subacute and chronic form

Four different forms of piroplasmosis can be characterized by its progression: peracute, acute, subacute and chronic forms. Piroplasmosis has a case fatality rate that falls between 10% to 50%. The survival of animals is usually higher in the endemic areas. Cases of peracute piroplasmosis are uncommon with equines encountered dying or already dead.

The onset of the acute cases is usually characterized by a set of non specific presentations which include febrile illness, congested mucus mebranes, labored breathing, and malaise. The affected animals usually shows clinical symptoms ranging from cases are often transient and mild in nature to cases of severe illness (Wise *et al*., 2014; CFSPH, 2018). A vast majority of the horses presenting with piroplasmosis usually develop pale or in some cases icteric mucous membranes, anemia, elevated breathing rates, general fatigue, among other signs. Signs of hemoglobinuria or bilirubinuria can be observe and in some severe cases thrombocytopenia leads to bleedings (petechia) in mucous membranes, such as the ones in the eyes (Zobba *et al*., 2008; Wise *et al*., 2013).

The existence of non-specific clinical presentations is still a common challenge in the chronic cases and usually occurs in the form of loss of body mass, poor performance, and in some case inappetence. In chronic carriers, disease recrudescence can occur during instances of increased stress or intercurrent infection (Leblond, 2019).

Blood smears collected from the superficial capillaries, when subjected through intense microscopic examination, can demonstrate the parasite within the erythrocytes when the blood was taken exactly during the acute phase with appearance of fever (OIE, 2009; Coultous *et al.,* 2018). Identifying piroplasmosis in the carriers examination of blood smear is extremely time consuming and definitively not practicable when done in many animals.

Polymerase chain reaction (PCR) and serological methods are preferred. The serologic tests cELISA for equine piroplasmosis measure antibodies to an erythrocyte stage protein epitope of *Babesia caball*i and *Theileria equi* (OIE, 2009) while PCR detect the parasite itself. Horses that test positive on cELISA are restricted from entry into the United States, Canada, Australia and Japan and New Zealand (Knowles, 1996; CFSPH, 2018).

Imidocarb is the most effective and safest chemotherapy to date. According to Frerichs and Holbrook (1974) the recommended dose for *Theileria equi* is 4 mg/ kg bwt, every third day for a total of 4 treatments. For *Babesia caballi* it is 2 mg/kg btw for 2 consecutive days for a total of two treatments. Each dose is given IM and divided among at least four injection sites. Local injection site swelling and muscle inflammation are very frequent, especially since the administration is repeated (Leblond, 2019). Adverse reactions with agitation, diarrheia, sweating or colic are frequent. However, the last can be prevented with the administration of anticholinergic drugs such as n-butylscopolamine. Atropin sulfate at 0,01 mg/kg bwt IV or Glycopyrrolate at 0,0025 mg/kg bwt has been recommended for colic associated with imidocarb treatment.

In the externship, the main objective was to reduce the symptoms in the acute piroplasmosis and its pathogenic effect. Eradication of the parasite is not advisable. Portugal is endemic for Piroplasmosis and the majority of horses living in the field had contact with this disease developing protecting antibodies. Repeated contact with infected ticks normally keeps the level of immunity high. Horses with no previous contact, like horses imported from Piroplasmosis free countries, get more seriously ill.

For export to Piroplasmosis free countries an eradication of *Babesia caballi* can be tried. *Theileria equi*, on the contrast, can not be eliminated totally.

2.3.8.2 Euthanasia

In the externship five horses had to be euthanized for various reasons (Table 9). There were emergency calls for two foals, two month and five month of age, with open comminuted bone fractures. They were euthanized on humane grounds as open multiple long bone fractures are nearly incurable in horses and exceed the financial limits of the owners. One 13 year old stallion with signs of severe colic and confirmed colon dislocation (transrectal palpation) was euthanized as the owner refused surgical intervention. A 25 year old mare with laminitis and solar prolapse of the tip of the distal phalanx was put down for no more treating options.

Table 9 - Casuistic of euthanasia in the externship

Reasons	Numbers
Open long bone fractures	2
Progressed neurologic symtoms of Tetanus	1
Laminitis with solar prolapse	1
Colic	1
TOTAL	5

Tetanus and decision for euthanasia

A two year old horse, with no vaccination record of Tetanus, was presented (Figure 7) with signs of ataxia, facial muscle spasm with lockjaw, prolapsed third eyelid and obvious erect ear

carriage. A rigid extension of neck, back and legs wit an elevated tail, reluctance to move, stiff gait and fever confirmed the suspected diagnosis of Tetanus. As the neurological symptoms were already very advanced the horse was euthanized immediately to prevent further suffering.

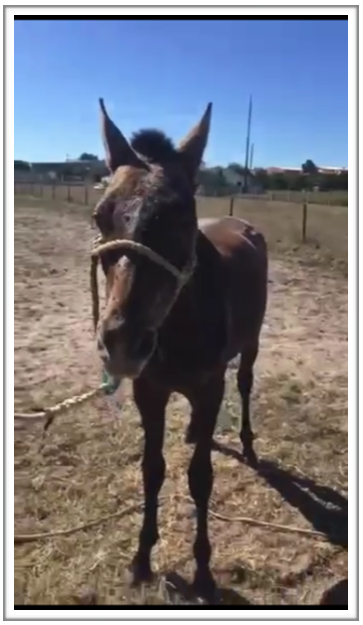


Figure 7 - Tetanus in a 2 year old horse seen in the externship; ataxia, facial muscle spasm, prolapsed third eyelid and obvious erect ear carriage, rigid extension of the neck.

Horses are particularly sensitive to the effect of *Clostridium tetani* and it is a major cause of mortality in areas, where vaccination is not routinely performed. Spores of the bacteria *Clostridium tetani* are commonly found in the environment. They may gain entry into the body via wounds, via the umbilicus in foals, and in mares via the urogenital tract immediately after foaling ((Nout-Lomas, 2018). The produced toxin tetanospasmin, prevents neurotransmitter release resulting in higher muscle tone and spasm. Tetanospasmin also affects both the sympathetic and parasympathetic nervous systems which might lead to elevated heart rate, cardiac arrhythmia and peripheral vasoconstriction. Parasympathetic hyperactivity can result in bradyarrhythmias and sinus arrest (Nout-Lomas, 2018). Tissue necrosis is caused by the toxin tetanolysin and promotes the bacterial growth.

Diagnosis is obtained by history (wound 1-4 weeks earlier, lack of vaccination) and clinical signs like generalized hypertonia of the striated muscles, hyperesthesia, sawhorse stance, painful reflexes, trismus, prolapse of the nictitans membrane and extended rigid tail. All signs are exacerbated by stimulating and excitement (van Eps, 2008a; Nout-Lomas, 2018).

Wounds of unvaccinated horses should be cleaned thoroughly if it can be located. Necrotic tissue should be removed. In order to eradicate vegetative forms of *Clostridium tetani. H*igh dose of Penicilline is recommended to prevent continuous production of tetanospasmin. For deep and penetrating wounds Metronidazol should be administered, as it can enter necrotic tissues without loosing efficacy (Nout-Lomas, 2018). In order to neutralize unbound toxin and

stimulate immune reaction tetanus antitoxin can be applied locally, and IM, but this has no effect on already bound toxin. Tetanus toxoid vaccine should be given at separate sites to minimize risk of serum hepatitis (Van Eps, 2008a).

Analgesia can be provided with Flumixine meglumine in the dose of 1,1 mg/kg every 12 hours IV. Supportive care, placing the horse in a calm, quiet area with well-bedded stable with feed and easy water access, is advisable.

The success of the therapy depends on the speed of the disease progression and its severity. However, horses with imminent neurologic symptoms have a poor prognosis with mortality rates over 60%, with a long and costly treatment (Nout-Lomas, 2018). The suffering of the animal must also be taken into account when deciding on euthanasia.

Guidelines for euthanasia

The BEVA Guidelines for the destruction of horses states that “the horse sustains an injury or manifests an illness or disease that is so severe as to warrant immediate destruction to relieve incurable and excessive pain and that no other option of treatment are available to that horse at that time“ (BEVA Guidelines, 2020). Currently there are three methods of humane euthanasia, as outlined by the American Veterinary Medical Association’s (AVMA) 2020 Guidelines for the Humane Euthanasia of Animals, being used. The approved methods are gunshot, high-dose barbiturate lethal injection and potassium chloride overdose of an anesthetized equine. All of these methods meet the requirements for humane euthanasia (American Veterinary Medical Association, 2020).

Death is caused by the euthanizing agents through three basic criterions that ranges from suppression of neuron activity necessary for basic life functions, hypoxia and the mechanical impairment of brain activity.

The process of euthanasia should be done in a manner that does not expose the animal through intense pain, distress, or high levels of anxiety hence it is often carried out when the animal is unconscious (American Veterinary Medical Association, 2020). Unconsciousness, is often defined as a situation when the brain lacks the capacity to integrate and process information thus leading to the absence of self-awareness about the surrounding. Thus, appropraite euthanasia needs to be guided by these critical aspects of unconsciousness which often cardiac and respiratory functions leading to the death of the brain.

Pentobarbital (i.e. Release® 500 mg/ml) is the most effective drug that can be used for equine euthanasia (AVMA, 2020). Barbiturates have a depressing effect of the central nerve system starting in the cortex with unconsciousness progressing to loss of pain perception. When given in higher doses the induced deep anesthesia subsequently leads to depression of the respiratory center causing apnea and cardiac arrest due to hypoxia.

Apart from pentobarbital, T-61® can be used (i.e. 85 ml of T61® for a horse of 500 kg) . The injectable drug T-61® is a mixture of embutramide, mebozonium (mebenzonium) iodide, and tetracaine hydrochloride (Giorgi and Bertini, 2000). Embutramid, a derivative of γ-hydroxybutyric acid, produces deep anaesthesia and paralysis of the brain stem. Mebezonium iodide has a

curare-like effect on the neuromuscular endplate and leads to relaxation of the skeletal and respiratory muscles. The local anaesthetic tetracaine is administered intravenously and, depending on the dose, has a central excitatory effect first, then a cardiac depressive effect and finally a central depressive effect. The combination of all three drugs leads to death due to cerebral depression, circulatory collapse and asphyxia (Giorgi and Bertini, 2000). The use of T-61® is contraindicated in pregnant animals. In the externship in case of planned euthanasia an intravenous catheter was placed into the jugular vein. A long extension tube of 50 cm was added so that injection could continue as the horse moved backwards during euthanasia. Sedation was only needed once in the nervous colic horse in oder to facilitate catheterization. It was performed with 20ug/kg of detomidine (i.e.1 ml for a 500kg horse). Multiple syringes of Release® 500 (pentobarbital) were drawn up, adjusted to the body weight of the horse. The volume needed was intentionally overestimated. Once the horse had the catheter, was sedated (if needed) and in a safe location, the full dose required was administered as quickly as possible. Collapse was seen within 35-40 seconds. If necessary, it was continued to administer further pentobarbital solution until the horse died, which occurred around 1,5 minutes after the collapse. The vital parameters were checked to confirm that brain-death was final and complete and were re-checked again five and ten minutes afterwards. It included lack of pulse, absence of reflexes (eyelash and corneal reflex), no respiratory sounds/ breathing and cardiac activity by use of a stethoscope, as well as graying of the mucous membranes.

2.4 Surgical cases

2.4. 1. Reproductive system in stallions: Castration

The externship took place between September and December when the breeding season was over and the mares were in transitional or anestrus phase. Therefore there were no consultations for reproduction, only four pregnancies were supposed to be confirmed via ultrasound scan. The mares were already covered during summer, and three of them were actually confirmed pregnant. In late autumn castrations of the stallions were carried out (Table 10). The climate in Portugal then is usually less straining on the cardio-circulatory system and less flies contaminate the surgical wounds than in high summer. The surgical removal of the male gonads (orchiectomy) is called castration of the stallion. By weaning both testicles, the primary source of androgen is removed. *C*astration is probably the most frequently performed routine operation in equine practice (Trotter, 1988; Trotter, 1993; Schumacher, 1996).

Table 10 - Surgical cases in the externship related to reproductive system of the horse

Reproductive organs		Case numbers
Castration	Standing	16
	Recumbent	0
Total		16

Orchiectomy

In this externship all 16 orchiectomies in stallions were performed in the field, at the owners' house or in public stables in local anesthesia and sedation with the horse standing. The ages of the 12 animals were between two and sixteen years. The owners were informed about the procedure and the risks of surgery and anesthesia. All horses were classified as 1 according to the criteria of the American Society of Anesthesiologists. Tetanus vaccinations were confirmed and when necessary boostered. According to Schumacher (2019) horses whose tetanus vaccination has been done for more than six months should be given a vaccination booster.

Prior to surgery, a physical examination was done. Special attentions was payed to locating both testicles in the scrotum and identifying any local irregularities such as hernias (scrotal or inguinal), different size. The material for surgery was prepared first. A sterile basic surgical box, surgical gloves, scalpel blade, a Reimer emasculator, sterile field cloths, an absorbable suture yarn (Surgicryl® PGA 3.5), syringe flush with injectable isotonic solution, iodopovidone 4% foam solution and ethyl alcohol 70% for asepsis and a spray of oxytetracycline.

The castrations were performed with the animals in sedation, under neuroleptoanalgesia: They were sedated with detomidin (Hypnoton®) 0,04 mg/ kg bwt IV and butorphanol (Butomidor®) 0,01 mg/kg bwt IV in the jugular vein. Flunixin meglumine (Flunixin® 50 mg/mL) was then administered at 1.1 mg/kg IV and ceftiofur (Ceffect® 25 mg/mL) at 2.2 mg/kg IM, providing peri- and postoperative analgesia and antibiotic protection. Prior to local anesthesia, the region was washed with alternatively, iodopovidone 4% foam solution and 70% ethyl alcohol in extrinsic circles to get aseptic conditions. Local anesthesia of the skin and the spermatic cord was performed with Lidocaine 2% (Anestesin®) using a 18-gauge needle. Five to ten milliliters were deposited subcutaneous under the scrotal skin on either side of the median raphe along the proposed incision line and 15 ml each side intratesticular/parafunicular.

In 14 cases, the orchiectomies were made according to the closed technique (Schumacher, 2019) via scrotal approach: The parallel scrotal incisions were made one at a time, eight to ten centimeters apart, two centimeters from the raphe. Then the scrotal skin, the tunica dartos and fascia spermatica was pushed back, the testicle and distal part of the spermatic cord was exteriorized by the incision. The parietal vaginal tunic was not opened and stayed intact and the structures inside were not exteriorized, with the exception of two cases in which the semi-open technique was applied. In the latter, the parietal vaginal tunic was opened with a cut and the structures inside were exteriorized, but at the moment of emasculation, the tunic was also covered, constituting the most external layer of tissue (Schumacher, 2019). The emasculator was applied as proximal as possible, for at least eight minutes, depending on the size of the structures to be emasculated. Proximal to the emasculator a suture was placed ensuring a closed parietal vaginal tunic as well as a vascular ligation. After excision of the testicles, the incisions were left open and healing was done by second intention (Schumacher, 2019).

In the post-surgical period antibiotic coverage with ceftiofur (Ceffect® 25 mg/mL) was maintained at 1 mg/kg IM every 12 hours for two days and analgesia with flunixin meglumine

(Flunixin® 50 mg/mL) at 1.1 mg/kg IV every 24 hours for three days (Knottenbelt and Malalana, 2015). Twenty-four hours after the procedure, the equines started working by hand to stimulate the drainage and keep the incisions clean and open and received cold water showers three times a day, to minimize the formation of edema of the preputio and scrotum. There was no knowledge of any post-surgical complication in the accompanied cases.

Indication for castration

There are numerous reasons why to castrate a horse like avoiding unwanted covering of mares, easy handling, and aggression reduction and possible group housing when castrated. Removal of the testicles can also be a therapeutic measure in the case of testicular tumors, trauma in the genital area, inguinal hernias, inflammation of the testicles, torsion of the spermatic cord or cryptorchidism (Schumacher, 2019). Annually, approximately a quarter of a million horses are castrated in Europe (European Horse Network, 2010; Dalla Costa *et al.*, 2014). In these particular 16 cases of the externship the main reasons mentioned by the clients were management decisions like behavioral problems with competition horses, too energetic for inexperienced riders in riding schools and safety reasons (children), as well as a lack of interest in using these animals for reproductive purposes.

Surgical techniques: open, half-closed and closed castration

Castration of the normal equine can be performed in two set ups: using sedation and regional anesthesia while the horse is firmly standing, or in a surgical facility recumbent with general anesthesia which is especially indicated for cryptorchid horses. There are several surgical procedures that can be used in the removal of the testes and include open, closed or half-closed castration techniques (Searle *et al.*, 1999; Schumacher, 1992; Schumacher, 2019).

Schumacher (2019) describes the open technique as follows: Two skin incisions of 8-10 cm length are made at a distance of about 2 cm parallel to the raphe scroti. After the skin incision, the tunica dartos, the fascia spermatica and the tunica vaginalis parietalis are cut through from the outside to the inside. By opening the Processus vaginalis a direct connection to the abdominal cavity is created. The ligamentum caudae epididymidis is exposed and bluntly cut through. After the testicles, epididymis and spermatic cord have been completely isolated from the tunica vaginalis parietalis by the removal of the mesofuniculum and mesorchium, these structures are removed with the emasculator.

In the procedure of a closed castration the tunica vaginalis parietalis is not incised in contrast to the open technique. It is clamped together with the testicles, epididymis and part of the spermatic cord and is separated as a whole. Since the processus vaginalis is not opened in this method, there is no direct communication between the surgical wound and the abdominal cavity (Schumacher, 1992).

In the half-closed technique, the tunica vaginalis parietalis is incised vertically at a length of 2-3 cm proximal to the testis. The structures located in the processus vaginalis can then be inspected and moved through the incision. The ligamentum caudae epididymidis, which connects the epididymis with the tunica vaginalis parietalis, causes a part of the processus

vaginalis to be turned inside out. The testis and the epididymis is then separated with the emasculator proximal to the opening incision. The method is therefore described as semi-closed, as the testicles and epididymis are uncovered, but the spermatic cord is deposited covered with the tunica vaginal parietal (Wriedt *et al*., 1979; Schumacher, 1992; Schumacher 2019). Scrotal wounds of castrations, traditionally allow for second intention healing. Primary closure may be done in select cases where castration is performed aseptically in a surgical facility. Surgical techniques for cryptorchid animals comprises an inguinal approach, a para-inguinal approach, or less frequently via laparoscopy. They are performed at a recumbent horse in general anesthesia in an operating theatre, laparoscopy can also be done with the horse standing.

The choice of the castration method is influenced by several factors. Personal experience and preference of the surgeon, age and temperament of the horse, owners wishes, regional tradition and also the existing environment are important decision criteria (Mason *et al*., 2005).

The success of the surgical intervention largely depends on a number of factors which include the skills of the surgeon, equipment and assistence, as well as the size and behaving of the animal.

Complications

There are numerous complications of castration can occur: excessive bleeding, postoperative swelling, hydrocele, eventeration, peritonitis, funiculitis, penile damage, inflammation with fever and continued stallion-like behavior (Searle *et al.,* 1999). In some cases, the horse may remain with the stallion behavior, which may be due to the persistence of already acquired behavior or a bad castration (Searle *et al.,* 1999). To minimize the risk of general anesthesia and trauma on recovery, standing castrations without primary suture nowadays are performed routinely in the field (Mason *et al*., 2005). Complication rates of approximately 23% in closed castrations (Racine *et al.,* 2019) consisted in excessive swelling (29,9%), surgical site infection (27,9%) and severe hemorrhage (3,1%). Another publication of 2019, a prospective multicenter survey of complications associated with equine castration (Hodgson and Pinchbeck, 2019) reported a complication rate of 11,2% in 495 castrations. The high variability of complication rate in different studies might be due to different techniques used, experience of the surgeons, environment (castration in the field or hospital) and individual components of the equines (i.e. age, size, used to handling).

3. Monography: Pain assessment and management in horses

3.1 Introduction:

As observed in the externship, a high number of consultations in ambulatory equine practice are related to pain like lameness or colic. A literature revue was made for how to assess pain in horses according to the newest publications about pain scales.

Animal pain relief has become increasingly important in veterinary medicine. Driven by greater emphasis on animal welfare, public ethical awareness, increased knowledge and changing attitudes, modern veterinary medical practice increasingly aims to reduce patient morbidity, enhance recuperation and effectively manage pain (Bisgaard *et al.,* 2001; van Loon and Van Dierendonck, 2019). The feeling of pain it is a highly subjective experience that animals and some human (i.e. newborn babies) are inable to communicate (Anand and Craig, 1996). It encompasses emotional as well as sensory components (IASP, 2018; van Loon and Van Dierendonck 2019),

This has resulted to substantial argument on the utilization of the concept of pain when it is referenced to animals (Molony and Kent, 1997; Taylor *et al.,* 2002). The evolutionary view suggests that animals are absolutely capable to differentiate stimuli that cause tissue damage, and that they in fact perform activities to evade further damage (Molony, 1992). Judging from anatomical and physiological similarities in vertebrates structure and function of nerves and CNS (Robertson 2002), pain should be taken for an existing sensation in animals (Molony, 1992; Anand and Craig, 1996; Molony and Kent, 1997; Taylor *et al.,* 2002), but it is difficult to assess.

Among sport and companion animals, horses occupy historically an important place in human society. Horses don't cry or scream. As they suffer silently, this makes them victims of neglect and insufficient pain treatment. Being a prey animal it evolutionary was an advantage not to make noises of pain, show no weakness by pain behavior, as this would make them easy victim for predators (Ashley *et al.*, 2005). Horses even have the tendency to suppress pain to escape from imminent danger which makes assessment of pain in horses especially challenging. The only tool presently at our disposal is the recognition of their behavioral and physiological responses.

A systematic approach with objective and subjective measurements, including the development of pain scales within the last years (Bussières, 2008; Sutton *et al.*, 2013; American Association for Equine Practitioner, 2014; Dalla Costa *et al.*, 2014; Gleerup *et al.,* 2015; Taffarel *et al.,* 2015; Van Loon and van Dierendonck, 2015; Mullard *et al.*, 2017), improve the accurate evaluation of pain in this species and help to find the appropriate multimodal treatment (Taylor and Senior, 2018). The existing options for pain assessment in equines will be presented in this monograph.

3.2 Pain definition

A significant multidisciplinary global relationship in the domain of human pain, known as the International Association for the Study of Pain (IASP), has explained pain as displeasing sensorial and psychological feelings connected with existent or possible tissue lesion or explained in reference to the kinds of damage (IASP, 2018).

Pain is a subjective feeling which is altered and shaped to various extents by biological, psychological, and social issues or reasons.

However, the inability to verbalize pain does not mean that it does not exist: it should not be overseen when a non-verbal human or animal is in need of appropriate pain relief treatment (Merskey and Bogduk, 1994; Anand and Craig, 1996; IASP, 2018). This definition of the IASP is also recognized in veterinary medicine. It is supposed that animal pain basically provides similar function as in humans and that pain perception is similar, though they are not undisputedly identical. (Molony, 1992; Molony and Kent, 1997).

Pain is a complex phenomenon of perception consisting of sensory, cognitive, affective, motor and vegetative components (Merskey, 2007). Scientific evidence supports that horses can witness pain which may not be identical to human's experience. Anyhow, we even do no know if two humans experience the same pain sensation after an identical injury. However, the anatomic, nerve endings and nerve pathways, and chemical components needed for nociception are common to humans and all fellow vertebrates (Robertson, 2002).

3.3. Physiology of pain

The pain perception relies on a highly differentiated transduction and transmission of a noxious stimuli by pathways which include specialized neurons. It is a highly complex and multifaceted process which varies according to the type and intensity of signal (Daglish and Mama, 2016). Principally, four anatomic structures take part in the pain establishment: nociceptors (thermal, mechanical, chemical, or polymodal), primary afferent neuronal pathways (ascending nerve fibers), the spinal cord, and the brain (Driessen, 2007). Stimulation of nociceptors, inflammations and consecutive activation via chemical mediators or direct lesion of neural tissue can lead to pain (Guedes, 2017).

3.3.1. Physiology of nociceptive pain

Pain is triggered by actual or imminent tissue damage due to stimulation of nociceptors and is therefore classified as so-called nociceptive pain (IASP, 2018). Nociception is the neural process of encoding noxious stimuli from thermal, chemical, and mechanical sources (Kandel *et al.*, 2000; Dubin and Patapoutian, 2010;IASP, 2018). High threshold receptors (nociceptors) are located all over the body (i.e. skin, muscles, joints, internal organs) with alternating density (figure 8). They can be either unimodal and detect a single form of irritation or polymodal. A stimulation of nociceptors starts an action potentials within afferent neurons of C-fibers or A-delta-fibers whose cell bodies are located in the dorsal root ganglia (Molony and Kent, 1997;

Meyer *et al.*, 2006; Daglish and Mama, 2016). The primary afferent neurons, whose cell bodies lie in the dorsal horn, synapse with local interneurons (inhibitory or excitatory type) that leads to signal modulation (figure 8) and synapse with second-order projection neurons that transport the stimulus to the brain (brainstem and thalamus) via the spinoreticulothalamic and spinothalamic tracts, respectively. Third-order projection neurons in the brainstem and thalamus transmit the information to the somatosensory cortex, where intensity and location of the stimulus are identified (Meyer *et al.*, 2006; Driessen, 2007; Guedes, 2017). Neuropeptides like inhibitory GABAergic receptors and excitatory Glutamate receptors and glycinergic receptors modulate the transmission (figure 8) of the signal in the spinal cord and brain (Zhang and Bao, 2006; Daglish and Mama, 2016). The A- delta fibers ensures more efficient discriminating positioning of noxious evocations and are basis for the distinct traits (sharp pain) of various kind of pain perception. The C-fibers relay to pain which is more diffuse in localization, and which is normally identified by a burning, aching traits preceded by the first insult (secondary numb pain) (Guedes, 2017).

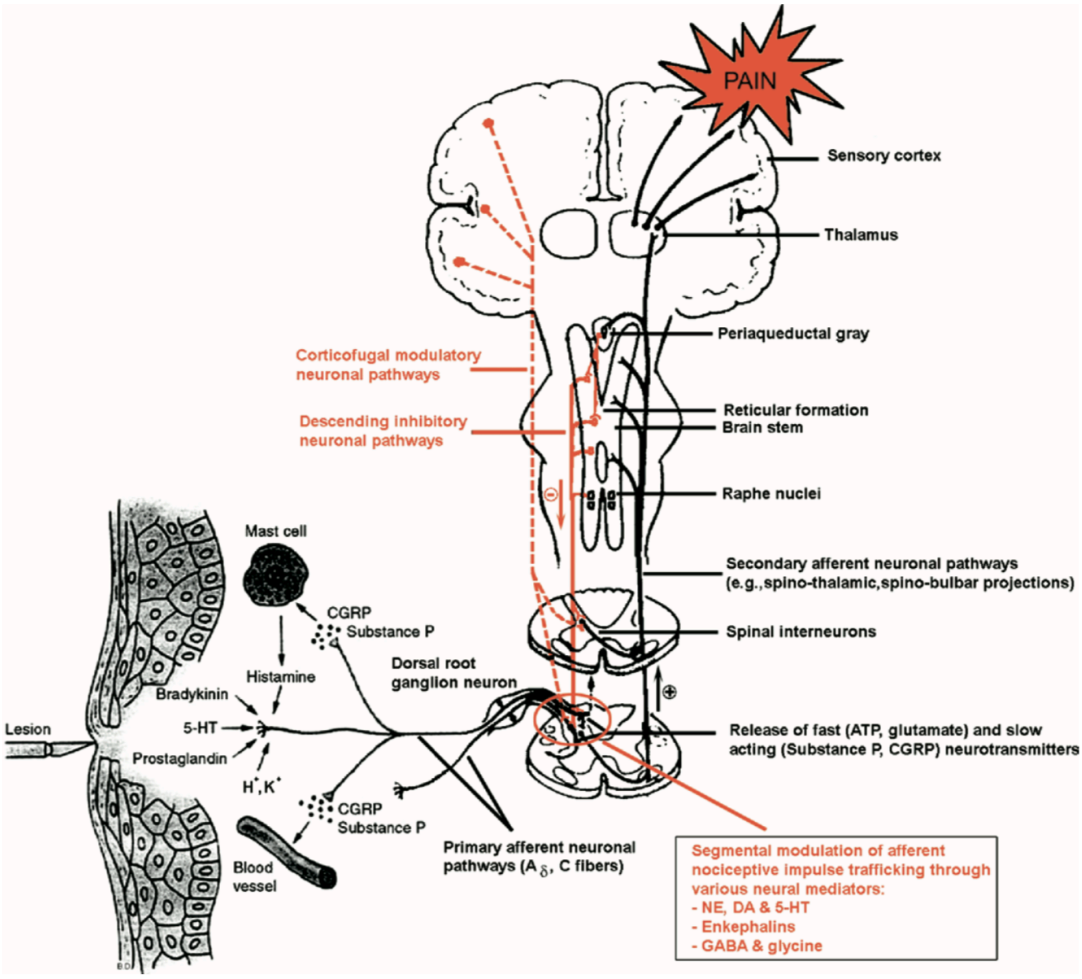


Figure 8 - Pain pathway, figure from Driessen (2007) (Norfenephrin NE, Dopamin DA, Calcitonin Gene-Related Peptide CGRP).

3.3.2. Physiology of neuropathic pain

An injury or disease of the nerve system itself causes neuropathic pain (Gilron *et al.*, 2015), with can originate from the peripheral nerves and the central nerve system, brain and spinal cord. There is a variety of neural affections that can be classified either by etiology (eg, infectious, toxic, metabolic, degenerative and traumatic) or by anatomic structure (central or peripheral) (Gilron *et al.,* 2015). Therefore, neuropathic pain is mainly diagnosed based on clinical findings (Gierthmühlen and Baron, 2016).

Neuropathic pain research emphasizes several additional effects of pain modification: central and peripheral sensitization, dysbalance of inhibitory modulation, nociceptive nerves ectopic stimulation, as well as pathological stimulation of microglia (Gilron *et al.*, 2015). The development of peripheral neuropathic pain includes alteration in ion channels (i.e. sodium, potassium and calcium), increased production of mediators like protones, cytokines and nerve growth factor, sprouting of nerves endings, phenotypic switches and participation of the vegetative nerve system (Vranken, 2012). The reduced effect of inhibitory spinal pathways is due to activation of N-Methyl-D-Aspartate receptors, microglia, astrocytes, oligodendrocytes, elevated synthesis of brain-derived neurotrophic factor as well as nerve growth factor which leads to a pronounced hyperexcitability of central neurons and preservation of neuropathic pain (Vranken, 2012).

All this leads to neuroplasticity including changes in chemistry (mediators), in structures of neurons and changes in function, resulting finally in highly modified sensitivity.

3.3.3 Inflammatory process after tissue or nerve injury

In both nociceptive and neuropatic pain, neural local reactions lead to the release of inflammatory mediators (Bradikinin, 5-HT3, Prostaglandin, Potassium, Histamine) that activate and sensitize nociceptors (figure 9) (Meyer *et al.*, 2006). The inflammation linked with tissue lesion results to acid pH and electrolyte alterations in the injury site, with activation of silent peripheral nociceptors, up- regulation of pro-inflammatory enzymes, all of which turn nociceptors more reactive to noxious and non-noxious stimuli (Driessen, 2007).

The release of substance P and calcitonin gene-related peptides causes pain modulation via retrograde activation of nerve terminals. Substance P and CGRP induce degranulation of mast cells with consecutive edema and vasodilation and further sensitization (Kandel *et al.*, 2000). Leukotrienes, prostaglandins, and Nerve Growth Factors will additionally activate silent nociceptors at the terminal ends of C and A deltas.

Central sensitization can be provoked by the cumulative effect of repetitive nociceptive input as well as neuropeptide secretion of neurokinin A and substance P that directly stimulate NMDA-receptors (Zhang and Bao, 2006; Dubin and Patapoutian, 2010; Hector and Mama, 2018). These NMDA receptors located in the dorsal horn neurons are responsible for a long-lasting central sensitization for pain (Vranken, 2012).

Endogenous opioids, alpha2-adrenergic agonist, serotonin, acetylcholine and cholecystokinin concentrations can also modulate the descending pathway and can transmit an inhibitory signal form higher centers to the peripheral tissues, reducing the pain (Zhang and Bao, 2006).

3.3.4 Pain regulation

Pain pathways underlie an active control by inhibitory and excitatory circuits in the CNS. Additionally to the nociceptive ascending pathway, animals contain anti-nociceptive nerves that descend and deliver impulses to modulate nociceptive input at the supra-spinal and spinal positions. Active pain regulation is mainly performed by the brainstem nuclei that can either exaggerate or diminish pain depending on attitude, cognitive function and past experience (Ossipov *et al.*, 2010). Endogenous opioids, alpha2-adrenergic agonist, serotonin, acetylcholine and cholecystokinin concentrations can modulate the descending pathway and can transmit an inhibitory signal form higher centers to the peripheral tissues, reducing the pain (Zhang and Bao, 2006). Opioids alter nociceptive transmission at spinal and supraspinal niveau. Each of the three opioid receptors, μ, κ, and δ can be found on nociceptive afferents of the CNS. The neurotransmitter released by the descending pathways can have either a pain reducing or pain increasing effect. A disbalance in this descending system provokes chronic pain (Ossipov *et al*., 2010; Guedes, 2017).

3.3.5. Chronic pain regulation

Untreated acute pain after a trauma or postoperative can induce chronic pain (Akkaya and Ozkan, 2009; Grubb, 2010). When molecular characteristics of spinal nociception are altered, a normal peripheral stimuli can then lead to the perception of pain (Zhang and Bao, 2006). A wind-up phenomenon by persistent activation of nociceptors leads to pain increase due to threshold lowering for its special signal (Zhang and Bao, 2006). Additionally it may cause silent nociceptors and non-nociceptive nerve fibers produce pain signals. The C-fibers are believed to be responsible for this effect since they have a slow conductivity (Merskey and Bogduk, 1994; Vadivelu and Sinatra, 2005).

In the last ten years, studies have shown that chronic pain is linked with apparent organizational adjustments in the brain, backing the idea of chronic pain as a disorder of the nerve system (Schweinhardt and Bushnell, 2010). The consequence was, that in 2018 the IASP extended the taxonomy to the new concept of "neuroplastic pain“ (IASP, 2018).

Generally, chronic pain seems to be grossly underdiagnosed and undertreated in both human and veterinary patients (Muir and Woolf, 2001; Gaynor, 2008). It is likely that this type of pain is greatly overlooked in animals as verbal communication is impossible and it may explain why some animals become aggressive for no apparent reason**.** In horses, chronic pain is recognized in musculoskeletal diseases like laminitis, navicular syndrome and osteoarthritis (van Weeren and Back, 2016) and trigeminal nerve neuropathy (Guedes, 2017).

3.4 Classification of Pain

Traditionally pain has been classified and described either by its anatomic location (visceral or somatic), by its mechanism (nociceptive, inflammatory, neuropathic), by its intensity (mild, severe) or by its duration (acute, chronic, recurrent) (Scholz and Woolf, 2002; Driessen, 2007; Guedes, 2017; Orr *et al.,* 2017). In 2018 the IASP defined a new taxonomy of pain (IASP, 2018):

3.4.1. Latest pain Taxonomy: nociceptive, neuropathic, nociplastic pain

The Pathophysiological Pain Classification System is founded on the type mechanism that actually leads to the injury. The two main explanations are nervous tissue damage/pathology and nociception (Orr *et al.,* 2017). The latest pain taxonomy of the IASP defines nociceptive pain, neuropathic pain and includes the new concept of nociplastic pain (IASP, 2018):

Nociceptive pain

Nociceptive pain arises from impulse transduction in nociceptors localized all over the body and its viscera. It is caused by tissue injury and is usually associated with inflammation (Scholz and Woolf, 2002).

Traumatic skin injury, castration, hot branding are examples where this type of pain is predominant.

Neuropathic pain

Neuropathic pain is a pain due to a dysfunction of, or damage to, a nerve or group of nerves (IASP, 2018). It is frequently induced by direct nerve lesion in the peripheral nervous system or CNS. In horses, conditions which can be related to neuropathic pain are headshaking (ie, trigeminal nerve neuropathy), laminitis, surgical trauma and arthritis (Schaible, 2012; Borsook *et al.,* 2013; Aleman *et al.*, 2014; Guedes, 2017).

Nociplastic pain

According to definition of the IASP (2018), nociplastic pain is pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. Till now no literature about nociplastic pain in horses can be found. Musculoskeletal diseases like laminitis, navicular disease and osteoarthritis cause chronic pain in horses (van Weeren and Back, 2016). According to the definition of nociplastic pain, an involvement in these equine diseases is conceivable.

However, a simultaneous experience of neuropathic, nociceptive, and nociplastic pain can lead to mixed pain (Freynhagen *et al.,* 2019) as illustrated in figure 9 .

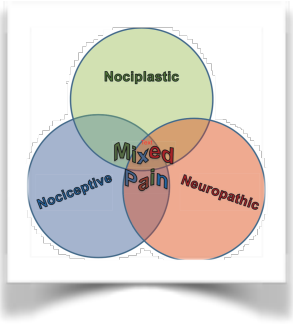


Figure 9 - “Mixes pain“ is the result of the overlap of the three different types of pain according to IASP (Freynhagen *et al*., (2019).

3.4.2. Classification by duration: Acute and chronic pain

The amount of time since onset determines the distinction between acute and chronic pain (IASP, 2018). Alternatively, chronic pain does not implies fixed duration, it is "pain that extends beyond the expected period of healing“ (Turk and Okifuji, 2001).

Definition of Acute pain

Acute pain, according to the IASP, is the physiologic response to and experience of noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviors to avoid potential or actual tissue injury. In the present taxonomy, acute pain is considered to last up to seven days, with prolongation to 30 days being common (IASP, 2018).

Definition of Chronic pain

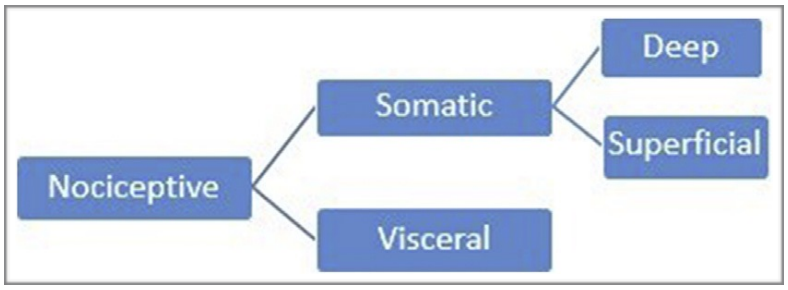
Chronic pain is defined by IASP as pain that persists or recurs for more than 3 months (IASP, 2018; Treede *et al.,* 2019).

3.4.3. Classification by anatomic location: Somatic and visceral pain

Somatic pain

Somatic pain in horses is also called musculoskeletal pain and its most common clinical sign is lameness (Davidson, 2018). Nociceptive receptors in the skin and mucous membranes are responsible for superficial somatic pain sensation (graph 4), while deep somatic pain originates from structures such as joints, bones, tendons, and muscles (WHO, 2012). Nociceptors are located in almost every tissue of the body and they react according to the type and the intensity of the received stimuli. Visceral tissues have fewer pain receptors and larger receptive fields, whereas somatic tissues have more nociceptors and smaller receptive fields. These differences in receptor distribution account for some of the qualitative differences between visceral - diffuse, poorly localized pain - and somatic - discrete and well localized (Coda and Bonica, 2001).

Therefore, the location of somatic pain is easier to find than visceral pain as extended innervation with sensory receptors supplies muscles, bones, as well as the skin and other soft tissues (Meyer *et al.*, 2006).



Graph 4 - Nociceptive pathway (WHO, 2012)

Visceral pain

Visceral pain per definition comes from internal organs. This type of pain is triggered by various processes like organ hypoxia and ischemia, hollow organ stretching, mesentery traction, and inflammatory processes which release endogen mediators, a chemical stimuli for visceral nociceptors (Robertson and Sanchez, 2010; Gebhart and Bielefeldt, 2016). Structural changes in internal organs or dysfunction may also be a cause for visceral pain (Robertson and Sanchez, 2010). Nociceptors present in every tissue, have two basic traits. They encrypt evocation degree into the noxious expanse as they stimulate.

Nociceptors in all tissues are characterized by two common properties. They traduce the stimulus according to its intensity and the they sensitize (Gold and Gebhart, 2010). In internal organs, mechano-sensitive endings tend to have low thresholds for pain.

According to the IASP (2018) visceral pain is vague, diffuse and difficult to localize due to the the low density of nociceptors and the extensive distribution of visceral afferent nerves within the CNS.

Gastrointestinal dysfunctions and pathologies in equines are the most frequent reason for visceral pain (Mair, 2002).

3.4.4. Classification by pain mechanism

Pain can characterized by three different mechanism of origen (Figure 10), which helps to specify their pharmaceutic treatment: nociceptive pain, inflammatory pain and pathologic pain (Woolf, 2010). The underlying pathophysiologic mechanism was already described in paragraph 3.3.1. and 3.3.2. above.

a) Nociceptive pain:

Based on the definition of the IASP (2018), “nociceptive pain is the pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors“ localized in the skin, muscles, joints, viscera and other organs (Merskey and Bogduk,1994). It can be physiologically protective (i.e. promotes withdrawal reflex) and is associated with the detection of noxious stimuli like an early warning system with a high-threshold (Woolf, 2010) as explained in figure 10, “A“ Nociceptive pain. Nociception triggers metabolic response (hyperglycemia), neuroendocrine response (increase in catecholamines, and cortisol), and physiologic response (tachycardia, tachypnea) and pain perception can lead to behavioral responses like avoidance or lameness (Hector and Mama, 2018).

b) Inflammatory pain**:**

Inflammatory pain is spontaneous pain, adaptive with a low threshold and is linked to tissue lesion and accumulation of immune-active cells like granulocytes, macrophages, neutrophils and mast cells (Woolf, 2010). It can induce healing by causing hypersensitivity and consecutive protective posture until healing occurs (Figure 10, “B“ Inflammatory pain). The inflammation process may initially intensify pain but then is followed by the removal of the cause. In order to reduce a lasting discomfort it is essential to limit this inflammatory response (Daglish and

Mama, 2016).

c) Pathologic pain (neuropathic and dysfunctional):

Pathological pain is caused by direct injury to the nerve system (neuropathic) or by its dysfunction and can cause an anomalous central processing (Woolf, 2010), as illustrated in the figure 10 (“C“ Pathological pain) below. It is caused by the destruction of nerve fibers through trauma, inflammation or infection. The healing of these nerve damages changes the sensory information in the affected region. The originally damaged nerves develop a momentum of their own and send nerve impulses without actual information to the central nervous system, thus leading to a spontaneous pain reaction that is not related to a lesion (Grubb, 2010). Pathologic pain can induce neuroplasticity, resulting in alterations (metabolic, physiologic, immunologic) that threaten the animals homeostasis and enhance sickness (Merskey and Bogduk,1994; Maier and Watkins,1998; Muir and Woolf, 2001).

Clinical signs of pathologic pain continue after cure is anticipated. Special clinical signs are allodynia (i.e. pain triggered by normal stimuli) and hyperalgesia which refers to a heightened pain response to noxious stimulus (IASP, 2018).

The subjective pain intensity does not correspond with the dimension of tissue damage, but with changes of central processing.

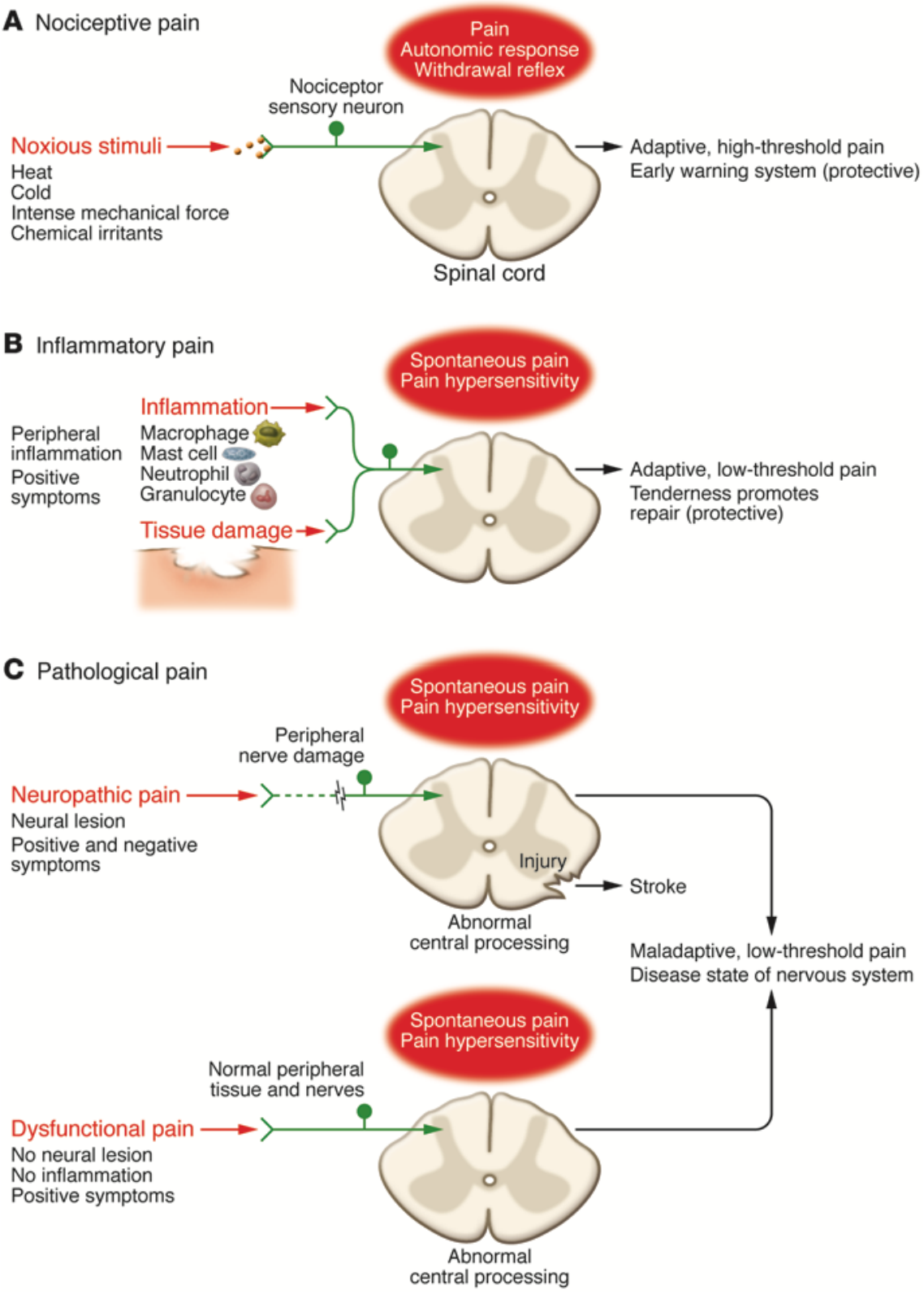


Figure 10 - Pain classification by mechanism; figure from Woolf (2010).

The main characteristic of pathological as well as inflammatory pain is that stimulation of nociceptors are no longer necessary for pain sensation as pain surges spontaneously without stimuli (Woolf, 2010).

3.5 Clinical signs of pain

Pain detection in the horse is based on subjective observation and examination as well as objective measures: animal behavior, reaction to environment, vital parameter, responding to palpation, lameness grades, responding to intra-articular medication, gait analysis technology, pain scales; all this is used by veterinarians to detect and evaluate pain in equines (Daglish and Mama, 2016).

3.5.1. Non-specific signs:

There are many non-specific signs of pain in horses: Tachycardia, tachypnea, profuse sweating, agitation or depression, anxiety, altered interaction, anorexia, fixed stare, reluctance to move, muscle tremors, weight shifting, lowered head position, clenched jaw, tail twitching and aggression (Bussières *et al.*, 2008). Vital parameter as well as levels of beta-endorphins and endogenous corticosteroids were taken in an attempt find a correlation to the corresponding pain level (Raekallio *et al.*, 1997; Daglish and Mama, 2016). Although these parameters are easy to achieve and to validate, they unfortunately have turned out to be less sensitive and specific mainly due to numerous factors (eg fear, exercise, stress, shock, temperature of environment, medication) which influence these responses (Taylor *et al.,* 2002; Wagner, 2010).

3.5.2. Specific clinical signs

Behavior assessment, facial expression patterns, lameness grading, functional tests (flexion tests), pain scales, biomechanical analysis (kinetic analysis) response to treatment (diagnostic anesthesia, diagnostic medication) can be used to describe more specific clinical signs (Table 12) in horses (Bussières *et al.*, 2008, Hector and Mama, 2018).

In the past years the attention has turned towards investigating the behavioral changes which can be very subtle like facial expression, posture, gait and alterations in stance (van Loon and Van Dierendonck, 2018). These changes in behavior can be more specific according to their origin and can confirm the existence and hint at the origin of pain.

3.5.2.1. Specific clinical signs of predominant pain types in horses

In equines, the two dominant types of pain are somatic/musculo-skeletal and visceral pain (Clark and Clark, 1999, Driessen and Zarucco, 2007; Hector and Mama, 2018), which have totally different clinical signs (Table 11). Somatic pain refers to pain originating from the periphery, such as the skin, muscles and bones whereas visceral pain arises from the abdominal and thoracic cavities. In horses exists a third type of pain, laminitis, which does not belong in neither of these former groups (Hector and Mama, 2018).

Typical clinical signs of somatic, visceral or laminitis pain are listed in Table 11 below.

Table 11 - Summary of specific clinical signs in predominant types of pain in horses (Clark and Clark, 1999; Sutton *et al.,* 2003; Driessen and Zarucco, 2007; Bussières *et al.*, 2008; van Eps, 2008b; Hector and Mama, 2018)

Somatic pain Musculoskeletal cause	Visceral pain Hight number of underlying causes	Laminitis
Heat Swelling Digital puls Response to palpation Warm coronary band Hyperalgesia / Allodynia Biting Kicking Difficult to get settled down	Pawing Flehmen Looking back at abdomen Kicking at abdomen Rolling Grunting Trashing Walk in circuits Getting up and laying down frequently	Forelimbs protracted Both forelimbs affected Weight shifted back Hind limbs placed underneath Walks as if on eggshells Digital puls Warm hoof capsule Marked sensitivity to hoof tester Toe and apex of frog Refuse to walk Frequently shifting Recumbent
Reluctance to move Ill-defined stiffness Poor performance Non- weight-bearing	Not interested in food Attempt to urinate Attempt to defecate Play with water without drinking	Secondary pain in muscles
Alternate limb lifting Weight shifting Abnormal stance	Sweating profusely Shiver Abdominal circumference	Mental status: depression
Lameness		Reluctant to move
Facial expression Pain face	Facial expression Pain face	Facial expression Pain face

These three types of pain listed in table 11 have different qualities and may require different types of drugs for their treatment.

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3.5.2.2. Clinical sigs of somatic pain

The most sensitive and specific pain parameters for somatic pain are heat, swelling, digital pulse and response to palpation (Hector and Mama, 2018). Further clinical signs are a reluctance of the horse to move. It can be ill-defined, such as stiffness in the movement, shorter steps, poor performance, frequent leg lifting or non-weight bearing on one leg, shifting weight when standing, altered unnatural stance (e.g.“sawhorse stance”), unwilling to move in small circles, landing with the toe first during a step, and obvious lameness (Mitchell, 2012; Hector and Mama, 2018).

Balance and symmetry and subtleties of movement are altered. Back pain, bucking, cross cantering, difficulties in doing transitions, unwillingness to turn or bend, or untypical misbehavior when being saddled can appear as secondary symptoms to lameness.

Objective evaluation is often performed in combination with a variety of tests that can range from applying hoof testers, flexion tests, diagnostic regional block, x-ray findings and video gait analysis (Davidson, 2018).

3.5.2.3. Clinical signs of visceral pain (colic)

Abdominal pain is the most common form of visceral pain seen in equines (Mair *et al*., 2002; Hector and Mama, 2018). Clinical signs typical for abdominal discomfort (Sutton *et al.,* 2003), like curling up the upper lip (Flehmen), looking back, kicking against the abdomen, rolling, lying down repeatedly, walking in circles, lack of interest in eating, attempts to urinate and defecate, increased abdominal circumference, tremors or shivers, sweating profusely, tail swishing, grunting, restlessness, may be useful to identify abdominal pain form other types of discomfort (Ashley *et al.*, 2005; Hector and Mama, 2018).

However, visceral pain can have different underlying causes (Mair *et al.*, 2002; Robertson and Sanchez, 2010). In contrast to somatic pain, pain from intestines, spleen, liver, kidney, bladder and uterus, is conducted via pathways which belong to the parasympatic (vagal nerve) and sympathetic nerve system (i.e. afferent splanchnic nerves).

Discomfort originating from visceral organs have the tendency to show a rather unclear and diffuse location as their innervations overlap largely. Unfortunately this results in difficulties to relate pain to a certain organ (Hector and Mama, 2018).

3.5.2.4. Clinical signs of laminitis pain

Laminitis is a clinical syndrome linked with a huge variety of systemic afflictions (i.e. sepsis, endocrine disease, systemic inflammatory response syndrome, postoperative complication after colic operation) as well as alimentary mishaps or mechanical overuse of some limbs (Patterson-Kane *et al.,* 2018).

The pathophysiology is based on a failure of the hoofs-distal phalanx attachment apparatus which connects the hoof wall to P3. The lamellae suspend P3 within the hoof capsule, destroying the architecture which is required to withstand the forces of weight bearing and athletic performance (Patterson-Kane *et al.,* 2018).

Typical clinical signs of laminitis pain are lameness involving one or multiple hooves, stiffness, and weight shifting: Horses with laminitis assume a typical stance with their weight shifting to the back. They usually put their hind quarters directly underneath the body in order to relive the painful front legs(van Eps, 2008). They have warm feet, digital pulse, show a strong positive reaction to hoof tester especially at the front part of the hoof including toe and frogs apex. These horses are unwilling to walk, and avoid to lift a limp (Dyson, 2011b), stay recumbent and show compensatory pain in muscles like pectoral and gluteal, due to the unphysiologic posture (Hector and Mama, 2018).

Chronic laminitis might need lead to depression and assessment of mental status is essential. Clinical signs are usually diagnostic, except in very mild cases (van Eps, 2008). Laminitis is considered as an extremely painful state in horses and most often one or both front feet are affected (Hector and Mama, 2018).

Laminitis pain, visceral pain and somatic pain have different etiologies and also differ in their approaches of pain management.

3.6. Clinical assessment

The evaluation of horse pain is complex and dynamic, and the procedures used routinely to measure pain in humans and other animals are not easily translated to the horse (Taylor *et al*., 2002; Daglish and Mama, 2016). Being a prey animals, horses avoid to have a fragile and vulnerable aspect. Therefore they suppress pain signs in situation of danger or even in unfamiliar surroundings (Ashley *et al*., 2005; Hector and Mama, 2018). Lack of readily recognizable reactions to pain may also contribute to the belief that severe pain is not present. Therefore detection requires a multifaceted approach including consideration of probable cause (eg. visceral pain, musculoskeletal pain, laminitis, dental pain, infection). As in humans, objective measurement of pain is not possible. Important advances have been made through the development of horse pain scales which include behavior, vital parameters, posture and facial expression (De Grauw and van Loon, 2016):

a) Behavior assessment:

In general, horses should be evaluated under calm normal environment to identify abnormal posture, distressed activity or behavior, limb placement, appetite, sweating and its responsiveness to environment. Stress can modify behavior. After silent observation, the interaction with the veterinarian is evaluated and followed by examination of the physiologic parameters.

b) Vital parameter:

Temperature, HR and pulse, respiratory rate and borborygmic should be registered. Physiological parameters (Table 12) should be assessed in combination with situation, behavior and posture.

The usefulness of physiological assessments is mixed, because fear, exercise, stress, shock, temperature of environment medication etc. influence heart rate, respiratory rate, pulse and borborygmic as well as the level of stress hormones like cortisol, beta-endorphins and catecholamines.

Table 12 - Standard vital signs in the absence of pain (De Grauw and van Loon, 2016)

Standard vital signs	Adult horse	
Heart rate: 24-40 bpm	Respiratory rate: 10-15	Temperature: 37,5 -38,4 C

Although clinically easy to measure, vital signs unfortunately have low sensitivity as pain indicator as they are influenced by many other factors (Daglish and Mama, 2016)

c) Posture and facial expressions: In order to facilitate pain assessment and quantify pain in equine practice, different pain scales that incorporate objective clinical findings, facial expression, behavior and body posture have been developed within the past years.

3.6.1. Pain scoring systems

Various pain scales (Table 13) have been used to assess lameness, (eg. AAEP Guidelines for Lameness Evaluation), laminitis (Obel 1949), orthopedic (Bussières *et al,* 2008; Mullard *et al.,* 2017), abdominal (Sutton *et al.*, 2013; van Loon and van Dierendonck, 2015) and post-operative (Dalla Costa *et al*., 2014; Taffarel *et al*., 2015), pain in horses. They are either simple descriptive scales, composite pain scales or facial expression-based pain scales. All these scales differ in grade of validation, in evaluated pain type, and their applicability in practice (Taylor and Senior, 2018).

The problem with all these different existing subjective pain assessment scales is that they are difficult to validate because there is no gold standard for objective comparison.

Table 13 - Overview of simple descriptive, composite and facial expression pain scales for horses.

	Pain scales	
Simple descriptive	Composite pain scale	Facial expression
Obel Grades of Laminitis (Obel 1949)	Multifactorial Numeric Composite Pain Scale, orthopedic pain (Bussières, 2008)	Horse Grimace Scale; castration (Dalla Costa *et al.*, 2014)
AAEP Guidelines for Lameness Evaluation (AAEP, 2020)	Colorado State University Equine Comfort Assessment Scale (Hector and Mama, 2018)	Equine Pain face; (experimental with capsaicin) (Gleerup *et al.*, 2015)
	Equine acute abdominal pain scale EAAPS (Sutton *et al.,* 2013)	EQUUS-FAP for acute colic (Van Loon and van Dierendonck, 2015)
	Equine Utrecht University Scale for composite Pain Assessment EQUUS-COMPASS (Van Loon and van Dierendonck, 2015)	FEReq for orthopedic pain in ridden horses (Mullard *et al.*, 2017)

3.6.1.1. Simple Descriptive Scales

Lameness, while not strictly mechanical in nature, is a vital and readily identifiable sign of pain in horses (Hector and Mama, 2018), and the commonly used lameness classifications (i.e. AAEP or Obel) basically are pain scoring device. The AAEP lameness grading scale (0-5) described in Table 14, is an example for a simple descriptive pain scale commonly used by

equine veterinarians. In Grade 0, for example there is no perceptible lameness in whatever situation is, Grade 1 shows lameness which is not consistently apparent and difficult to observe, until in Grade 5 the animal nearly bears no weight when moving or is not able to walk. It is logical to assume that the pain increases in strength from 0 to 5.

Table 14 - AAEP Guidelines for Lameness Evaluation (AAEP, 2020)

AAEP Guidelines for Lameness Evaluation (AAEP, 2020)	
Grade 0	Lameness is not perceptible under any circumstances.
Grade 1	Lameness is difficult to observe and is not consistently apparent, regardless of circumstances (e.g., under saddle, circling, inclines, hard surface).
Grade 2	Lameness is difficult to observe at a walk or when trotting in a straight line but is consistently apparent under certain circumstances (e.g., weight carrying, circling, inclines, hard surface).
Grade 3	Lameness is consistently observable at a trot under all circumstances.
Grade 4	Lameness is obvious at a walk.
Grade 5	Lameness produces minimal weight bearing in motion and/or at rest or a complete inability to move.

Another very commonly used descriptive pain scale is the Obel Grades for laminitis (Table 15). The Obel Grades I to IV describes weight shift, observed lameness, willingness to walk, regularity of gait and resistance to lift one leg. At grade I, when the horse is resting it still passes weight between the legs and its lameness is not obvious at walk, but the trot appears stiff. Clinical pain symptoms are progressive until at grade IV the horse will not move unless forced (Obel, 1948).

Table 15 - Obel Grades (Obel, 1948)

	Obel Grades of Laminitis
Grade I	At rest, the horse frequently shifts weight between the feet. Lameness is not evident at the walk, but there is a short stilted gait at the trot.
Grade II	The horse is willing to walk, and there is no resistance to having a forelimb lifted. At a walk, the horse is lame, and the gait ist stilted.
Grade III	The horse resist having a forelimb lifted and is reluctant to move.
Grade IV	The horse will not move unless forced.

Although lameness scores might be the prerogative of orthopedic specialists (Dyson, 2011a), other behaviors and facial expressions have been studied by those with a particular interest in equine pain.

3.6.1.2. Composite pain scales

Unlike simple pain scales**,** composite pain scales take into account numerous parameters, frequently behavioral parameters and vital parameters (van Loon and Van Dierendonck, 2018). In literature of the past years several composite pain scales for different purposes can be found: A composite pain scale for abdominal pain (Sutton *et al.,* 2013), a composite pain scale for abdominal and musculoskeletal pain from the Colorado State University (Hector and Mama, 2018) and a composite pain scale for orthopedic pain (Bussière *et al.*, 2008).

Composite pain scale for abdominal pain

Abdominal pain emerges very often in equines (Cook and Hassel, 2014). For optimal management of colic however, there exists no standardized pain severity classification for clinical practice (Sutton *et al.*, 2013). Sutton *et al.*(2013), constructed behavior-related colic pain scales using a combination of subjective evaluation and mathematical approaches. They used 23 films of horses in colic and had the scenes evaluated by the expert opinion of 30 equine practitioners. Apart from the films, the vital signs, the applied medication, type of medical treatment or surgery, and outcome was documented. Pawing, flank watching, agitation and restlessness were seen extremely often (65 - 90%) in this study of abdominal pain, followed by behaviors like attempt to lie down (60%), recumbency (30 - 40%), rolling (35%) and kicking (20%) and Flehmen (10%). Collapse, as the most obvious sign of severe pain, was was seen in 10% of the cases. The two resulting equine acute abdominal pain scales (EAAPS) included 12 behaviors chosen by expert opinion (Table 16).

Table 16 - EAAPS -1: Frequency of pain behaviors seen in adult horses with colic; scoring according to expert opinion (Sutton *et al.,* 2013).

Behavior	Frequency of behavior median %	Weighting 1= mild pain to 5= severe pain
Attempting to lie down	60 %	4
Flank watching	65 %	2
Flehmen	10 %	1
Kicking	20 %	3
Lateral recumbency	30 %	4
Pawing	90 %	3
Rolling	35 %	5
Sternal recumbency	40 %	3
Streching	30 %	3
Agitation/restlessness/ continuous movement	65 %	3

Behavior	Frequency of behavior median %	Weighting 1= mild pain to 5= severe pain
Dorsal recumbency	15 %	4,5
Collapse	10 %	5

For pain classification Sutton *et al*. chooses the most severe behavior shown which leads to the corresponding score (Table 17). Vital signs were not taken into consideration since they are often unreliable (Ashley *et al.*, 2005).

Table 17 - Grading (1= mild pain to 5= severe pain) the severity of abdominal pain according to Sutton *et al.(* 2013), version 2 of EAAP.

Mild to severe	Behavior	1 Mild pain	2	3	4	5 Severe pain
Mild	Depression	1				
	Flank watching	1	2			
	Weight shifting	1	2			
	Pawing	-	2	3		
	Streching		2	3		
	Kicking abdomen		2	3		
	Restlessnes s		2	3		
	Sternal recumbency			3	4	
	Attempting to lie down				4	
	lateral recumbency				4	
	Rolling					5
Severe	Collaps					5

According the grading of Sutton *et al.,* (2013), the most severe manifestation of pain was collapse and rolling, followed by lateral recumbency, attempting to lie down and sternal recumbency. Restlessness, pawing, kicking to the abdomen and stretching were considered less severe and validated as expression of moderate pain. Depression, flank watching and weight shifting were taken as signals for mild pain.

Composite pain scales for abdominal and musculoskeletal pain.

The Colorado State University developed an Equine Comfort Assessment Scale (CAS) for use by faculty, shows a visual assessment scale including behavior, vital parameters, postural features (Hector and Mama, 2018). It contains a list of behavioral descriptors (general, musculoskeletal-specific, abdomen-specific, palpation reactions) and facial expressions (Table 8).

The list of behavioral descriptors used include general behaviors like pawing, stumping, tail switching without insects, circling in stall, frequently flaring nostrils, head shaking without obvious reason. Repetitive behaviors in this assessment were rubbing, grunting, difficulty to get settled down or getting up and laying down frequently, rocking to and fro on limbs.

Musculoskeletal-specific, like frequent weight shifting and grimacing, an abdomen-specific flank watching and flank biting, kicking at abdomen, are documented as well as palpation reactions and abnormalities, facial expression and body posture (Figure 11 and 12).

The second composite scale for all types of equine pain is the Equine Utrecht University Scale for composite Pain Assessment (CPS) (Van Loon and van Dierendonck, 2015). This scale consist of two parts: the first part helps to document and classify vital signs (heart rate, respiratory rate, body temperature, digestive sounds) and the second part evaluates and scales behavior and posture and reaction to palpation. Every parameter has four scores (0 = no pain/ normal behaviour, 1 = mild pain, 2 = moderate pain, 3 = severe pain) with a maximum score of 42.

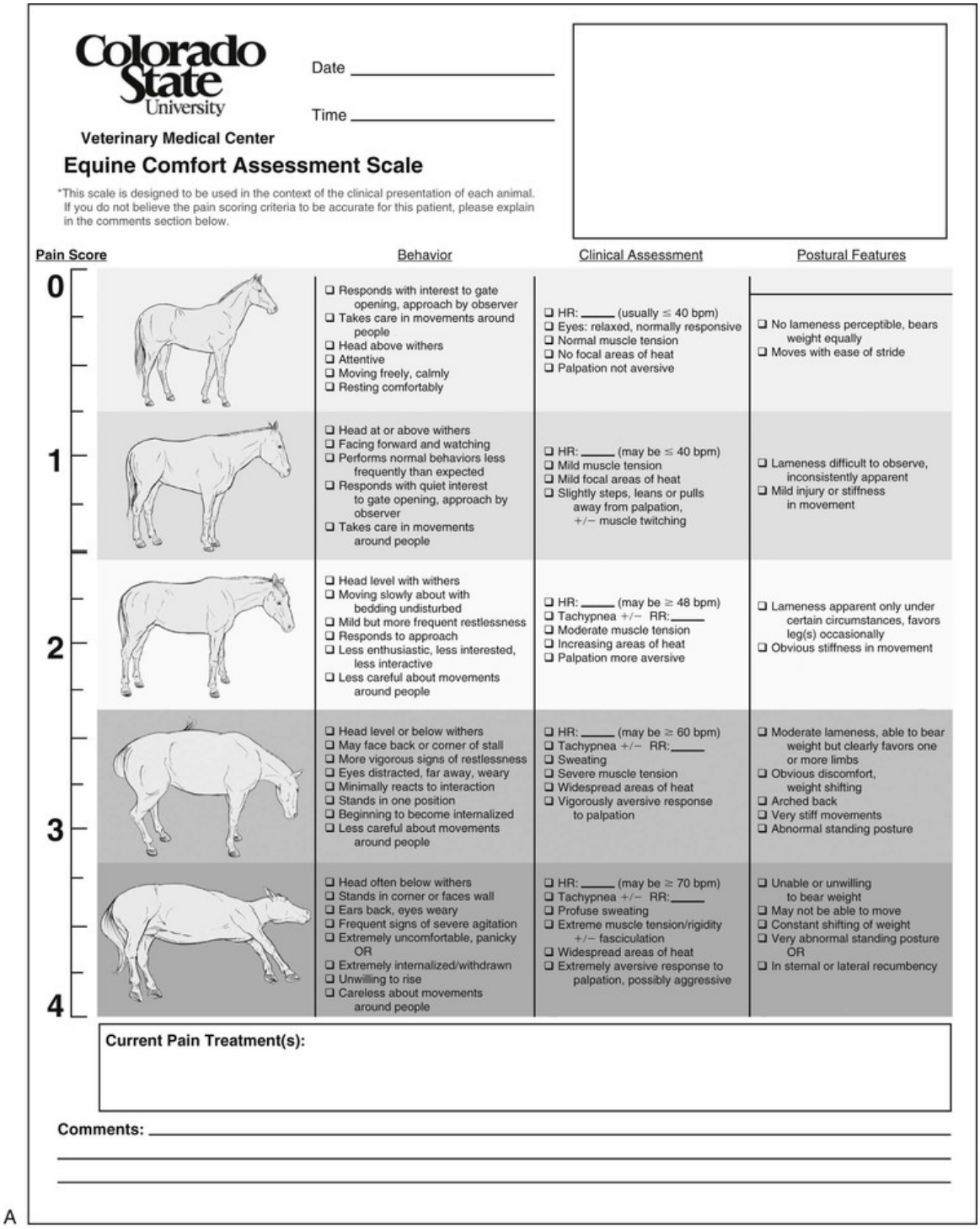

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Figure 11 - List of Behavioral Descriptors, Palpation Abnormalities, Facial Expressions, Equine Comfort Assessment Scale from the Colorado State University Medical Center (Hector and Mama, 2018)

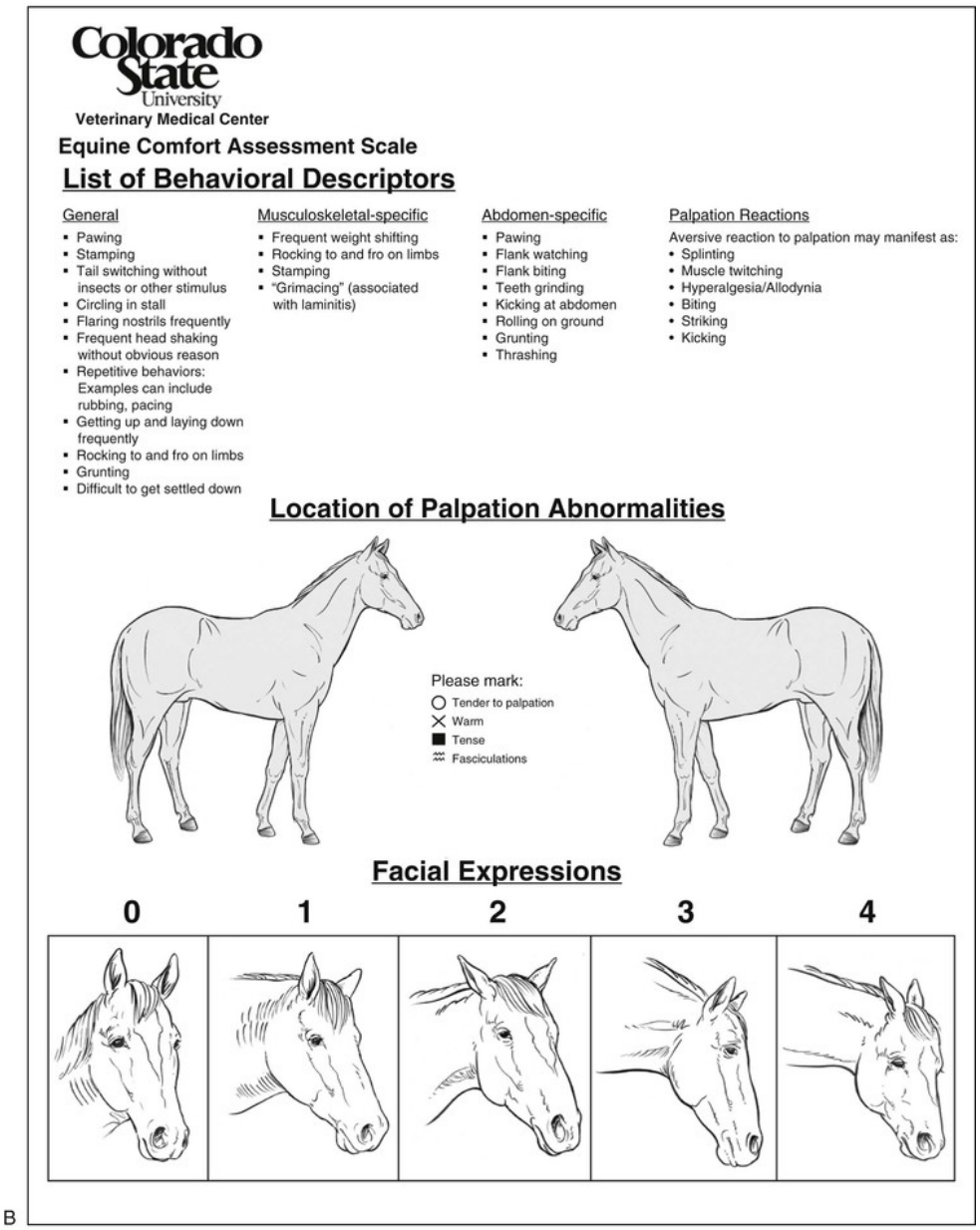

Figure 12 - Equine Comfort Assessment Scale from the Colorado State University Medical Center (Hector and Mama, 2018)

Composite pain scale for orthopedic pain

A further standardized pain scale designed for acute orthopedic pain, is the multifactorial numeric rating composite pain scale of Bussières (Bussières *et al.,* 2008). This scale was created in an experimental set up injecting amphotericin-B to induce synovitis. It is based on 13 items evaluated for five minutes including vital signs, reaction to stimulus well as behavioral components. Physiologic data like heart rate compared with baseline, respiration, peristaltic and rectal temperature get different numeric scores according to the respective criteria. Response to interaction, behavior, and palpation reaction of the sore region are evaluated. Each parameter

like unwillingness to move, excitation, fear, sweating, kicking or looking at the abdomen, pawing on the floor, the horses posture, head position in rest and movement, and interest in feed get different scores. The higher the score obtained the higher the probability of pain. Each of the 13 parameters can be scored on a scale of 0 to 3, ranging from 0 (no signs of pain) to 39 (maximal pain score).

The most promissing methods for pain evaluation in horses actually seem to be composite pain scales as well as facial expression pain scales. Several studies have been using these scales recently (van Loon and van Dierendonck, 2018). In the latest literature even pain scales for ridden horses were presented: Mullard *et al.* (2017) identified and analyzed the facial and body expressions of of mounted equines.

3.6.1.3. Pain scales based on facial expression

The composite descriptive Horses Grimace Scale (HGS) of Dalla Costa *et al.* (2014) was created to evaluate pain in castration on the basis of six facial parameters with specifically defined characteristics of 0 to 2 (signs of pain not existing, moderate or present): stiffly backwards ears, tension over eyes, jaw stresses, orbital restraint, tension in the masticatory muscles and nostrils, were some parameters (Figure 13).

Dalla Costa *et al.*, (2014) compared facial expressions from horses with surgery with a control group without surgery. For post-operational pain assessment after castration, the HGS was seen to be reliable, quick and repeatable based on results of 40 horse photographs (Dalla Costa *et al.,* 2014).

Figure 13 - Horse Grimace Scale (Dalla Costa *et al.,* 2014). The Horse Grimace Pain Scale with images and explanations for each of the six facial action units.

Van Loon and van Dierendonck in 2015 developed another multifactorial pain scale, the Equine Utrecht University Scale for Facial Assessment of Pain (EQUUS-FAP) using facial expression for assessing horses with acute colic (Table 18), reaching from 0 (no pain) to 18 (maximum pain) scores in total. Head movement, eyelids, focus on environment, tension of the nostrils, corner of the mouth and lips, ear position, muscle tonus, yawning and teeth gridding was evaluated for two minutes and scored respectively.

The EQUUS-FAP (Table 18) has been developed for evaluation of acute abdominal pain (van Loon and van Dierendonck, 2015; van Dierendonck and van Loon, 2016).

Table 18 - EQUUS-FAP: Type of pain: Acute colic, Van Loon and van Dierendonck (2015).

Facial Assessment of Pain (EQUUS-FAP)	Score sheet for the Equine Utrecht University	Categorie Scores (scored for 2 min)
Head	Normal head movement, Interested in environment; Less movement; No movement;	0 1 2
Eyelids	Opened, sclera can be seen in case of eye/head movement; More opened eyes or tightening of eyelids. An edge of the sclera can be seen for 50% of the time; Obviously more opened eyes or obvious tightening of eyelids. Sclera can be seen more than 50% of the time;	0 1 2
Focus	Focussed on environment; Less focussed on environment; Not focussed on environment;	0 1 2
Nostrils	Relaxed; A bit more opened; Obviously more opened, nostril flaring and possibly audible breathing;	0 1 2
Corners mouth/Lips	Relaxed Lifted a bit Obviously lifted	0 1 2
Muscle tone head	No fasciculation's Mild fasciculation's Obvious fasciculation's	0 1 2
Flehming and/or Yawn	Not seen Seen	0 2
Teeth grinding and/or moaning	Not heard Heard	0 2

Facial Assessment of Pain (EQUUS-FAP)	Score sheet for the Equine Utrecht University	Categorie Scores (scored for 2 min)
Ears	Position: Orientation towards sound/clear response with both ears or ear closest to source. Delayed/reduced response to sounds 1 Position: backwards/no response to sounds	0 1 2
Total		……../18

An other facial expression based pain scale was developed by Gleerup *et al.* in 2015. Their "Equine Pain Face" (Figure 14) evaluates six facial expression parameters which were verified by inducing experimental pain via topical Capsaicin and a tourniquet on the front leg of six healthy animals.

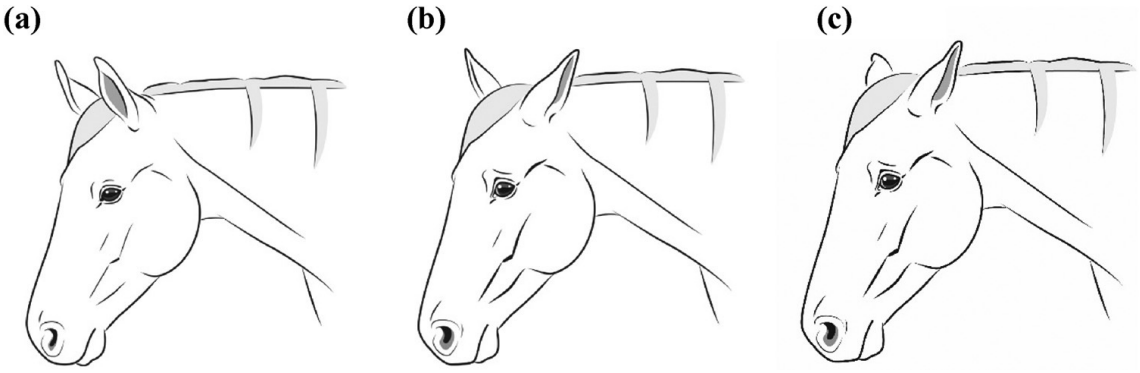

Figure 14 - Equine Pain Face; Type of Paine: Experimental (Gleerup *et al.*, 2015). (a) Facial expression of a pain free, relaxed and attentive horse. (b) Facial expression of a horse in pain, comprising all features of the pain face including asymmetrical ears. (c) Facial expression of a horse in pain, comprising all features of the pain face including low ears (drawings by Andrea Klintbjer).

Facial expressions of ridden horses

Weak horse performance can be caused by riders issues, training abnormalities or behavior. Riders also struggle to recognize symptoms of discomfort. The recently created facial expression scale of mounted horses can help diagnose lameness and musculoskeletal disorders at the earliest possible stage (Dyson *et al.*, 2017; Mullard *et al.,* 2017). The authors describe various characteristics at the eyes, ear, lip, tongue, nose and other facial features. The positioning of the head while been ridden, in relation to the vertical is also considered (Figure 15 and 16). The best signs of discomfort were the turning of the jaw, the asymmetric posture of the

bridle, the ear location (both the ears backward, one ear backward and one ear ahead) and the eye characteristics (sclera exposure, partial or complete closure of the eye, muscle stiffness to the eyes, deep stare)(Dyson *et al.,* 2017). Dyson *et al*., (2017) and Mullard *et al.,* (2017) claim that the goal was to increase awareness that certain alterations in face expressions may be a sign of pain. The following photographs in Figures 15 and 16 show clear signs of discomfort in mounted horses.

Figure 15 - Facial pain expressions in ridden horses (FEReq) by Mullard *et al. (* 2017).

In the two photographs below (Figure 16), both horses show considerable tension, with backward ear positions, wrinkled upper eye muscles, and partially closed eyes. Nostril are contracted and the masseter muscle clenched. These are all indications of pain (Dyson *et al.,* 2017). In the accompanying drawing of a pain face (Gleerup *et al.*, 2015) the same characteristics can be seen.

It is not acceptable that horses are ridden although they show obvious signs of pain. However, behavior-based pain assessment criteria were created for clinical research. Using them in ridden horses will lead to big discussions and must be undertaken with caution (Gleerup *et al.,* 2017) because stress can also alter the animals facial expressions. Anyhow, it could help to improve horse welfare in future.

Facial movements are diverse and often nuanced signals that can shift dynamically in response to a variety of external factors (rein pulling, unsuitable tack, unbalanced rider), internal affective conditions (Hintze *et al.* 2016) and potential discomfort. Facial gestures and expressions can only be specifically differentiated from scenes, thus filming is essential for pain assessment (Wathan *et al.*, 2015; Gleerup *et al.*, 2017).

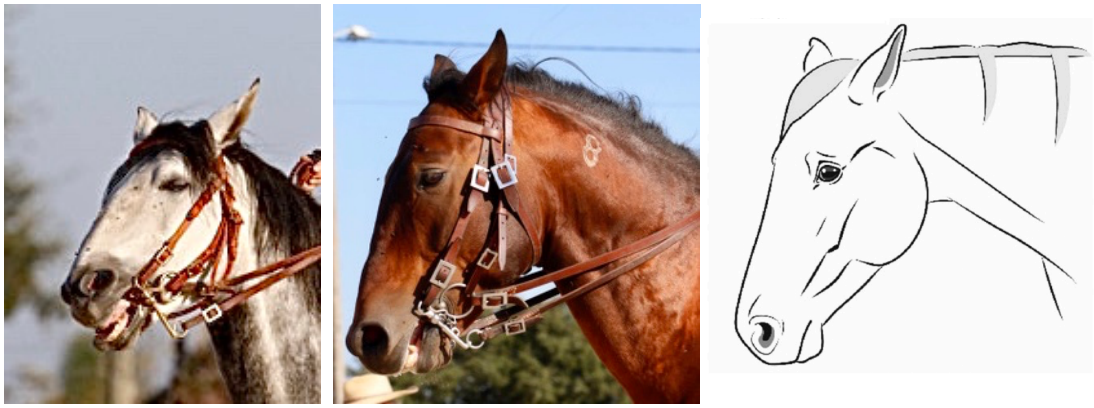

Figure 16 - Facial pain expression in ridden horse; drawing of a pain face of Gleerup *et al.* *(*2015): orbital tightening, stress around the eye region, tension in chewing muscles, rigid back ears, mouth strained, chin pronounced and strained nose.

Conclusion

The British Equine Veterinary Association (BEVA) concluded in January 2020 that the best proof of pain recovery will be focused on composite pain scales defining direct pain measures (e.g. lameness, rolling etc.) as well as generalized indicators of pain-like behavior, facial grimaces and posture (Bowen et al., 2020). The use of behavioral pain scales can enable a comparisons and evaluation of analgesic effect of different drugs, detection of adequate dose, and necessary time for effective analgesic therapy. At present, there are no existing guidelines for the quantification of suffering dependent directly on equine behavior.

The British Equine Veterinary Association (BEVA) in January 2020 concluded that the strongest evidence for improvement in pain would be one based on composite pain scores identifying direct measures of pain (e.g. lameness, rolling etc.) as well as generalized signs of pain-like behavior, facial grimaces and posture (Bowen *et al.*, 2020). Application of behavior-based pain scales can enable comparisons of the efficacy of different types of analgesics, determination of their dose rates, and the appropriate durations of analgesic therapy.

At the moment there exist no guidelines to quantify pain in horses based on behavior (Bowen *et al.*, 2020).

3.7. Therapeutic approaches

The etiological causes, mechanisms, and time properties of the pain are heterogeneous. Therefore, the emphasis should be on the neurobiologic pathways causing the overall symptom pain or its temporal characteristics, both acute and chronic (Scholz and Woolf, 2002). Pain management should concentrate on treatment as well as on prevention, as much as possible and provide a multimodal approach with pharmacological and non-pharmacological methods (Guedes, 2017; Taylor and Senior, 2018).

Additionally to the use of opioids, medications targeting at other different pain receptors can result in additive and synergistic impact. This involves alpha-2-agonists, NMDA receptor

antagonists, gabapentinoids, corticosteroids, NSAIDs, and acetaminophen (Helander et al., 2017). Pain modulation and treatment can be achieved by pharmacological (Table 11), manual and interventional therapeutic options. This text would only rely on pharmacological alternatives.

3.7.1 Pharmacologic options

Multimodal, preventive and systemic analgesia

In the past, utilization of analgesic drugs was driven by fears about the risk of adverse effects (Muir and Woolf, 2001, Price *et al.,* 2014). There has been a steady progression of new veterinary views towards animal suffering over the past two to three decades, and the use of analgesics has become more common (Taylor *et al.*, 2002). Analgesic techniques currently being promoted by pain specialists in both human and veterinary medicine are primarily focused on preventive pain control and/or multimodal treatment as soon as possible (Driessen, 2007; Taylor and Senior, 2018; Bowen *et al.,* 2020). Novel analgesic treatments include a range of nonsteroidal anti-inflammatory medications for reducing inflammation, drugs like alpha-2-agonists that modify excitatory and inhibitory neuronal conduction, local anesthetics to inhibit impulse transmission and opioids as a multimodal strategy (Muir and Woolf, 2001). Multimodal analgesia is a technique that seeks to integrate various analgesics (Table 19) that work on different levels within the pain pathway (Figure 17). This will lead to synergy between medications, resulting in increased analgesia and dose restriction, thereby reducing the frequency and intensity of possible adverse effects associated with each drug.

Table 19 - Classes of analgesic drugs used in horses (Knottenbelt and Malalana, 2015, Daglish and Mama, 2016; Guedes 2017; Helander *et al.*, 2017; Taylor and Senior, 2018).

Drug		Mechanism of Action
Local anesthetics	Lidocaine 2% Mepivacaine 1-2% Bupivacain 0,5- 0,75 %)	blockade of sodium ion channel, which prevents the conduction of electrical activity in nerves
Systemic NSAID	Phenylbutazone, Flunixin meglumin, Firocoxib, Ketoprofen, Aspirin	Inhibition of cyclooxyrgenase and reduction of prostaglandins PGE2, PGI2, TXA2
Corticosteroids	Methylprednisolon, Triamcinolone	Inhibition of phospholipase A2
Opioids	Buprenorphine Morphine Methadone Fentanyl Butorphanol	Primarily mu opioid agonists; kappa Opioid agonistic activity in Burophanol

Drug		Mechanism of Action
Alpha-2-agonists	Xylazine, Detomidine Romifidine Medetomidine Dexmedetomidin	Alpha -2 -receptor agonists, possible imidazolin receptor agonist
NMDA receptor antagonist	Ketamine	N-methyl-D aspartate antagonist
Other	N-Butylscopolamine Biphasphonates Interleukin-1-Receptor Antagonist Protein	Parasympatholytic , spasmolytic effect

Therapeutic strategies should take in consideration several factors, e.g etiology of pain, desired analgesic effect, duration and side effects. The procedure should be focused on the potential source of pain (e.g. inflammation), the type of trauma, the intended analgesic effect (strong, weak), the anti-inflammatory effect or sedation, the duration of medication (short-term, long-term treatment), and the maximal dose and toxicity, including likely side effects (Muir and Woolf, 2001). Pharmacotherapy can be applied to peripheral nociceptors, primary and secondary spinal nerves, and to CNS pain-processing and retrograde modulation regions (Guedes, 2017; Muir and Woolf, 2001). Drugs can modulate either the transduction of pain, the transmission, modulation, and perception (Figure 17). Pain transduction (electro-physiological signaling) is the transformation of a chemical, mechanical or thermal pain impulse into a neuroelectrical signal. Mainly free nerve ends, specific nociceptors with C- and A-δ-fibers, then transmit the message to the spinal cord.

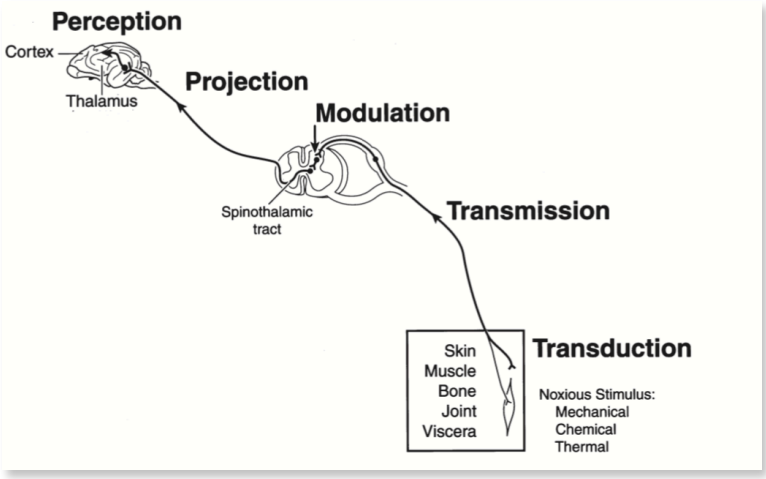

Figure 17 — Schematic diagram form Muir and Woolf (2001): Pathways and physiologic processes involved in pain sensation, including stimulus transduction, transmission, modulation, projection, and perception.

The local site of the injury develops a postraumatic inflammatory response with edema, structural response and neuromodulator release (Ronchetti *et al.,* 2017). By the means of local anesthesia, NSAI and Corticosteroides the transduction can be reduced or inhibited. Transmission can be blocked for example by peri-neural infiltration of local anesthetics. This is routinely used in equine practice for analgesic testing to localize lameness.

Alfa-2-agonists and opioids influence the modulation by having direct analgesic effect on alfa-2 and opioid receptors avoiding the development of hyperalgesia. Perception is the subjective sensation and awareness of pain produced by the message of nociceptors and requires the convergence of several sensory signals into a cohesive and significant whole (Muir and Woolf, 2001). Perception is a dynamic process of a variety of mechanisms, involving expectation, experiences, and awareness. Damage to different tissue types, including visceral, muscle, and neural tissue, can stimulate a variety of pathways that contribute to a pain impulse.

3.7.1.1. Local anesthetics

Local anesthetics (i.e. Lidocaine 2%, Mepivacaine 1-2% , Bupivacain 0,5- 0,75 %) influence the transduction of a mechanical, thermal or chemical stimulus into a neuro-electrical message and its transmission from the trauma site to o the CNS. The analgesic effects is due to a total block of sodium channels, which inhibits depolarization and the development of actions potentials to transmit the signal in thinner type A fibers. Higher dose can even inhibit transmission in large A-Betas for example in the epidural anesthesia or perineurial mixed nerves and can become an issue in an animal as huge as the horse as it leads paresis to paralysis due to loss of motor functions (Hector and Mama, 2018).

Lidocaine, Mepivacaine, Bupivacaine have a long tradition in equine medicine (Taylor and Senior, 2018). They facilitate surgical procedures as well as lameness evaluation and can be administered by many routes: subcutaneous infiltration, intraarticular, perineurial, epidural and systemic. Analgesic testing is routinely used in equine practice to localize lameness. Local anesthetic drugs have different onset, different duration of action and different concentrations (Knottenbelt and Malalana, 2015). Their dose must be adjusted to the animals weight, the operating field or the thickness of the nerve.

Mepivacain 1-2% is most popularly utilized for local anesthesia to suture traumatic wounds or for diagnostic blocks in lameness evaluations. Its onset is fast and it has an intermediate duration of action (90- 240 minutes).

Lidocaine is a local anesthetic of the acid amide type whose onset of action is very rapid due to its high diffusivity. At the same time it has a lasting effect with very deep anesthesia which lasts for about 60 - 90 minutes. Lidocaine is locally and generally well tolerated due to its low toxicity and it is commonly used for subcutaneous and perineurial infiltrations as well as intraarticular.

Bupivacain has an intermediate onset of action and can be used for subcutaneous and perineural infiltrations and intraarticular as well. It has a longer effect up to 360 minutes (Knottenbelt and Malalana, 2015).

Transdermal administration of local anesthetic can have a superficial anesthetic effect on the skin directly over the injury (Söbbeler and Kästner, 2018).

3.7.1.2. Systemic NSAIDs: Phenylbutazone, Flunixin meglumin, Firocoxib, Ketoprofen, Meloxicam

For management of moderate, acute and chronic pain, NSAISs such as Phenylbutazone, Flunixin Meglumin, Firocoxib, Meloxican or Ketoprofen are recommended. Sometimes they are the first-line alternative of lameness-related pain control and the most commonly-used treatment in riding horses (Taylor and Senior, 2018). Systemic NSAIS have different efficacy to inhibit cyclo-oxygenase (COX), the enzyme that produces prostaglandins PGE2, PGI2 and TXA2 form arachidonic acid, and modulate cytokine production which explains their differences in their analgesic versus antiinflammatory effect profile. Most NSAIDs approved for horses work by inhibition of both COX 1 and COX 2. Drugs with selectivity to COX 2 are Meloxicam and Firocoxib. NSAIDs are commonly used oral or via intravenous routes (Knottenbelt and Malalana, 2015). Visceral pain relief can also be provided, especially in particular afflictions which cause inflammation or endotoxemia. Flunixin meglumine and ketoprofen, in particular, give extended analgesia and reduce endotoxin effects (Clark and Clark,1999; Bowen, 2020). Side effects to be aware of are nephrotoxicity, ulceration of the gastrointestinal tract (particularly foals) as well as hepatotoxicity (Knottenbelt and Malalana, 2015).

3.7.1.3 Corticosteroids: Methylprednisolon, Triamcinolone

The analgesic effects of corticosteroids comes from their profound anti-inflammatory property. Methylprednisolon and Triamcinolone are used intraarticulary (Knottenbelt and Malalana, 2015) for their anti-inflammatory effects by inhibiting phospholipase A2 and reducing the chemical mediators which lower the pain receptors excitation threshold. Adverse effects are chondrocyte toxicity, immunosuppression and laminitis (systemic use of corticosteroids)

3.7.1.4. Opioids: Butorphanol, Buprenorphine, Morphine, Methadone, Fentanyl

The pillar of the human pain regulation for decades has been opioid analgesics. The horse had little benefit from an improved knowledge of opioid pharmacology compared to cats and dogs in small animals (Taylor *et al.,* 2002).

While several medications with μ and/or kappa opioids have been available, the use of systemic opioids in horses remains controversial. Specific advantages have not yet been clarified and adverse reactions (e.g. paralytic ileus, excitement) with increasing doses are worrisome (Daglish and Mama, 2016).

Preterm experiments did not study the analgesic effect of drugs but its possible adverse effects.It was concluded that the dose that has a good therapeutic effect is dangerously close to the dose where dangerous side effects appear(Robertson and Muir, 1983; Hellyer *et al.,* 2003; Price *et al.*, 2002; Taylor *et al.*, 2002; Robertson and Sanchez, 2010). The fear of side-effects such as CNS excitement and agitation, intestinal paralysis, was generated by studies which lack objective evaluation. This is because the studies were conducted on a small number of painless

horses, which were artificially subjected to nociceptor stimulation instead of surgical or traumatic and these horses did not receive a sufficient dose of analgesic drugs (Clutton, 2010).

As pain behavior and opioid side effects in horses are extremely similar if not identical, it is very challenging to differentiate adverse reactions from insufficient pain relieve (Clutton, 2010). Given the size and weight of horses, which makes handling much more difficult, the use of opioid in this domestic species therefore traditionally is rather restrictive in outdoor equine practice (Taylor *et al.*, 2002; Robertson and Sanchez, 2010).

Some studies have shown that opioids are more important for the treatment of pain in horses, and radioligand studies discovered possible explanations for the equine reaction pattern based on the opioid analgesics (Clutton, 2010). In 2020, the BEVA panel concluded, that Buprenorphine in combination with alpha-2 agonist can be indicated for horses in pain, depending on the situation, but horses in severe pain should get pure mu-agonist opioids. (Bowen *et al.*, 2020).

Opiates exert analgesic properties and pain tolerance by interrupting and suppressing the transmission of nociceptive impulses by activating μ and κ and delta opioid receptors. Receptors for these μ and κ and delta opioids are located in various regions of the brain, in the spinal cord with particularly high density in the dorsal horn, in peripheral nerve endings, but also within a short time in acutely inflammatory joints (van Loon *et al.,* 2014).

Available opioids include μ-agonists like morphine, fentanyl and methadone, partial μ-agonist like buprenorphine and κ- agonist/ μ-antagonists like Butorphanol and Nalbuphine. In humans μ-agonists are considered to provide the most potent analgesic effect. The different effect on equines may be explained partly by different binding affinity of opioid receptors, different density and location in the brain and spinal cord compared to humans. It also might be related to inadequate dose (subanesthesic or overdose) or a side effect in clinical trials where it only was used on horses without pain stimuli.

Opioid administration has led to frequent side effects, particularly agitation, in pain-free horses, while horses which were definitively suffering had significant benefit from opioid use (Robertson and Sanchez, 2010). Opioids are valuable components when the practitioner has to perform surgical or diagnostic procedures with the horse remaining standing. They are helpful preemptively when strong surgical pain is expected, but also serve to achieve all desired levels of analgesia in combination with sedative drugs (LeBlanc, 1991).

Morphine represents the prototype of opioids and is therefore given as a reference value with a potency of "1". Although morphine has no approval for use in horses, it can be used in horses on the basis of EU Regulation 122/2013 (list of substances essential for the treatment of equidae). Methadone is a synthetic opioid with predominantly agonistic activity at the μ receptor. (Kristensen *et al.,* 1995) It also has an antagonistic effect at the N-methyl-D-aspartate (NMDA) receptor (Gorman *et al.*, 1997) which plays an important role in central pain processing.

In contrast to Morphine and Methadone, Butorphanol is a κ-agonist/ μ-antagonist with weak analgesic effect. It is frequently used in veterinary practice to amplify sedative effect of the alpha-2-adrenoreceptor agonist through the concept of neuroleptanalgesia. One IV dose of Butorphanol has an analgesic effect between 60-90 minutes and a lower potential for side

effects (Clutton, 2010). Although Butorphanol has a potency of three to five compared to Morphine, its analgesic effectiveness is limited due to a ceiling effect (Gaynor and Muir, 2008). At the dose used in clinical practice Butorphanol has poor analgesic effect and if there is indication for opiate analgesia, analgesics with more potency should be used. According to Taylor *et al.* (2016), Butorphanol has less analgesic effect than buprenorphine in the therapy of surgical pain.

Generally, all existing opioids reduce gastrointestinal motility, shown in a variety of experimental research. The risk of postoperative ileus and post-operative colic should not preclude the use of opiate analgesia in horses with strong pain, as pain itself may even enhance profound gastrointestinal paralysis (Bowen *et al.*, 2020).

Stimulation of the vegetative sympathetic pathways as part of a stress response to pain reduces gastrointestinal peristaltic in humans (Steinbrook, 1998; Clutton, 2010) and may have the same effects in equines (Little *et al.,* 2001).

Suggested horse doses of opioids differ extensively in literature as there are many factors influencing the desired effect. The higher the pain level, the greater the dosage, the lower the probability to have adverse effects (Clutton, 2010). While opioids are defined in terms of action time (i.e. short acting, long acting), they should be administered according to the observed effect: i.e. when the required analgesia has dwindled below appropriate thresholds, and not by the time (Clutton, 2010). According to Muir (1991), symptoms of underdosage can resemble those of overdose.

3.7.1.5. Alpha-2- Agonists: Xylazine, Detomidine, Medetomidine

Sedation, analgesia and muscle relaxation are induced by activation of central and peripheral alpha-2-receptor-agonists, such as Xylazine, clonidine, romifidine, detomidine, medetomidine and Dexmedetomidine. They differ individually by their selectivity to alpha receptors, the chemical structures, metabolism and elimination (Jochle *et al*, 1989; Hector and Mama, 2018).

In the CNS stimulation of alpha-2-receptors decreases the release of excitatory neurotransmitters producing analgesic effect by modulation of transmission and perception.

Alpha-2 agonists reduce gastrointestinal peristaltic and may lead to paralytic subileus. In some cases, according to Hector and Mama (2018), adverse effects as reflex bradycardia due to peripheral vasoconstriction with second degree atrioventricular block, profound sedation with ataxia may limit their use as analgesics (Hector and Mama, 2018). Paradoxic excitement or aggression, upper airway obstruction can be seen occasionally (Knottenbelt and Malalana, 2015). A combination with opioids for standing sedation is common: it has less side effects and better analgo-sedative effects using a lower dose in total due to synergism (Hector and Mama, 2018).

3.7.1.6. N-methyl-D-aspartate (NMDA) receptor antagonist: Ketamin

Ketamine is frequently used for general anesthesia as an induction and maintenance drug. It antagonizes NMDA receptors in the CNS and by activation of descending inhibitory pathways, analgesia and pain modulation is achieved (Hirota and Lambert, 1996). The analgesic effect of Ketamin is transmitted by ketamine-stimulated release of neurotransmitters (dopamine,

norepinephrine, serotonin) (Mion and Villevieille, 2013) and its interaction with μ/ κ and delta - opioid receptors which potentiate opioid effects. A background sedation with alpha-2-agonists is necessary (Hirota and Lambert, 1996) as single use of ketamin can lead to psychosensory adverse effects. In humans ketamine produces hallucinations (Mion and Villevieille, 2013). On the other hand, ketamine in low dose can be useful for opioid induced analgesia as sub-anesthetic doses of ketamine potentiate opioid-analgesia via NMDA receptor block (Mion and Villevieille, 2013). Apart from the already mentioned properties ketamine also has an anti-inflammatory effect by reduction of inflammatory cytokines (Hirota and Lambert, 1996), reduction of tumor necrosis factor alpha as well as reduction of interleukins (Kawasaki *et al.,* 1999). Due to this action, ketamine might be used in the clinical syndrome laminitis and systemic inflammation in equines (Fielding *et al.*, 2006).

3.7.1.7. Non-classical analgesic drugs: Gabapentin, Tramadol, N-Methyl-Scopolammonium bromide

Medications from a range of pharmacology groups with non-pain primary indicators can be used as a complementary analgesic. The safety of conventional analgesics such as NSAID and Opioids can be increased when reducing their dosage. This co-administration provides a multimodal analgesia at lower dose und might reduce de incident of side effects of increasing the dose of NSAID and opioids. Gabapentin is used in humans for the treatment of neuropathic pain and as anticonvulsant. In horses it may be supportive for recovery in laminitis and chronic lameness (Young *et al.*, 2020). Tramadol, a weak mu-receptor agonist and its metabolite O-desmethyltramadol act centrally. It is modulating as well the inhibitory pathways within the CNS. Prevention of serotonin and noradrenalin uptake lead to analgesia. In horses there are substantial individual variation of the effect with short half-life. In combination with ketamine it enhances its analgesic effect in horses with laminitis (Guedes *et al.,* 2012). Other modalities like physiotherapy, massage, cryotherapy, therapeutic exercise, cold or low-level lasers, extracorporeal shock wave therapy, acupuncture and chiropractic manipulation can have a synergic positive analgesic effect but were considered outside the scope of this report.

3.8. Example for pain therapy performed in the externship for routine castration

Castrations are the most frequently performed operations on horses and it is an undisputedly painful procedure. Unfortunately the use of painkillers is by no means routine. According to a British survey of veterinarians, non steroidal anti-inflammatory drugs (NSAIDs) and intratesticular injection of local anesthetics are only performed in 55% percent of castrations, (Bowens *et al.*, 2020). In fact, there are hardly any legal obligations to administer painkillers worldwide, nor are there any concrete recommendations as to how post-operative pain therapy should look like. In the externship in an ambulatory equine practice, a multimodal approach was used for pain management in routine elective castration in stallions. All ochiectomies were performed in a combination of local anesthesia, sedation and additional systemic analgesia with the horse standing. As the horses were castrated in their stable, no excitation or nervousness was observed before the operation. The following analgesic protocols was used in a 10 year old stallion undergoing standing castration: Before performing sedation and local anesthesia the

vital parameters were checked. As the stallion was in his normal routine environment he was calm and not agitated. His heart frequency was 30 bpm, respiratory rate 12 per minute, normothermia, humid mucosas with capillary refill time below two seconds. His face expression was relaxed. The dose for standing sedation was 1,5 ml of detomidine (Hypnoton® 0,03mg/kg bwt IV) and 1,25 ml of butophanol (Butomidor® 0,01 mg/kg bwt IV), adjusted to his body weight of 500 kg administered via a catheter in the left jugular vein. The onset of sedative effect was within 5 minutes. Detomidine in this concept reduces pain perception in the brain by providing sedation and central analgesia, butorphanol provides additional systemic opioid analgesia and has a synergistic effect, reducing the dose of detomidine and possible side effects.

Physiologic parameter like heart rate and heart frequency are no longer reliable after application of detomidine and butorphanol as both provoke a marked bradycardia and first- and second degree AV-block, as well as sweating and promoting diuresis (Knottenbelt and Malalana, 2015). Flunixin meglumine (Flunixin® 50 mg/mL) was then administered at 1,0 mg/kg IV and ceftiofur at 2,2 mg/kg IM, providing peri- and postoperative analgesia and antibiotic protection. Prior to local anesthesia, the region was washed with alternatively, iodopovidone 4% foam solution and 70% ethyl alcohol in extrinsic circles to get aseptic conditions. Local anesthesia of the skin and the spermatic cord was performed with Lidocaine 2% (Anestesin®) using a 18-G needle. Eight milliliters were deposited subcutaneous under the scrotal skin on each side of the median raphe along the planed incision line and 15 ml each side intratesticular as well as parafunicular. This guaranteed a reduced or total block of transduction and transmission of somatic pain impulses via nociceptors in the skin and the visceral nociceptors in the testicles and the spermatic cord. During the castration the vital signs were checked constantly. Heart frequency stayed normofrequent within a range of 28 to 36 bpm, respiratory frequency was between 8 and 18 per minute. No physiological parameter gave a hint of insufficient analgesia.

His facial expression showed some signs of pain with asymmetrical ears. Nostrils and nose were relaxed in contrast to the drawing by Gleerup *et al.* (2015) (Figure 18).

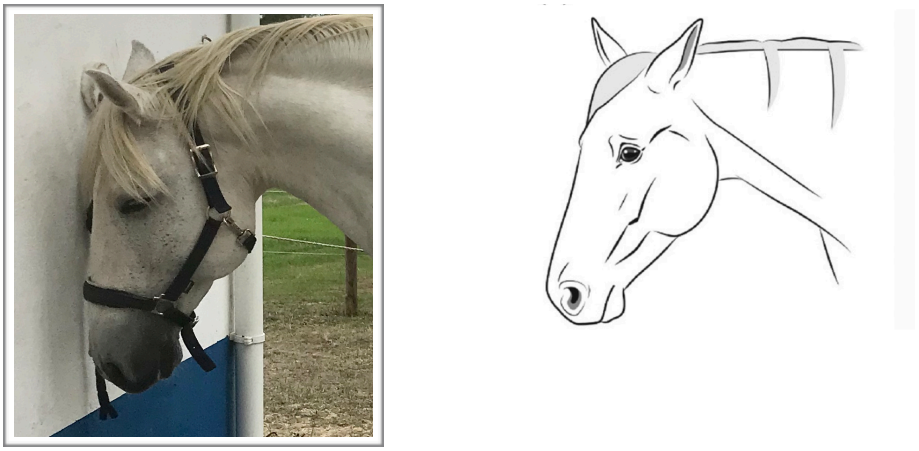

Figure 18 - Pain face: Stallion during castration in externship: only asymmetrical ear position evident; drawing from Gleerup *et al.* (2005), is showing additional: orbital tightening, tension

above the eye area, prominent strained chewing muscles, mouth strained and pronounced chin, strained nostrils and flattening of the profile.

After the castration the animal was put back into his box and monitored for another hour for signs of pain. When he awoke from sedation he was immediately interested in his environment and in hay, moving around in his box with no open signs of scrotal/inguinal or abdominal pain in his behavior or posture.

His face expression, using the Horse Grimace Scale from Dalla Costa *et al.*, (2014), was relax with obviously no great distress or pain. This applied composite descriptive pain scale based on six different facial parameters showed no hint for actual pain. His ears were turned to the front, no tension present around the eye, no mouth straining or eye closing, no clenched chewing muscles, no tense nostrils and profile flattening (figure 19).

In the post-surgical period antibiotic coverage with ceftiofur (Ceffect® 25 mg/mL) was maintained at 1,0 mg/kg IM BID for two days and analgesia with flunixin meglumine at 1,1 mg/kg IV every 24 hours for three days (Knottenbelt and Malalana, 2015). Twenty-four hours after the procedure, the horse started working by hand to stimulate the drainage and keep the incisions clean and open and received cold water showers three times a day, to minimize the

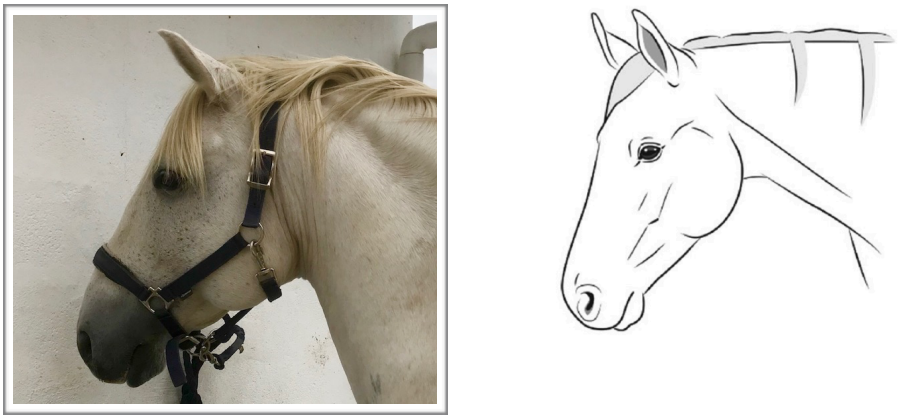

Figure 19 - No obvious pain after castration. Foto of the stallion in the externship and drawing from Gleerup *et al.* (2015).

formation of edema of the preputio and scrotum. The horse returned to work 10 day after the operation with good performance, no signs of abdominal or inguinal pain or lameness, with good appetite and normal behavior and interaction with his box neighbors. There was no knowledge of post-surgical complication in the accompanied cases.

3.8.1. Review of actual recommendations for pain treatment in castrations

Since January 2020, BEVA has started to develop guidelines for clinical equine practice in ambulatory settings. These guidelines synthesize current evidence and combine this to provide recommendations on the use of analgesics in clinical practice with expert opinions on results

and adverse effects (Bowen et coll., 2020):

Local intra-testicular anaesthesia in routine castrated horses whether standing or under general anesthesia is recommended (Table 20). It does not make any difference if local anesthesia if performed intra-testicular or mesorchial as they have equal quality in loss of sensation (Bowen *et al.,* 2020).

Additionally to the local anesthesia, a pre-operative systemic analgesia should be administered, keeping in mind that butorphanol alone is insufficient. Additional guidelines surrounding the use of buprenorphine on standing castration horses cannot be made before better evaluation of spontaneous locomotive agitation. For a minimum of 3 days, analgesics should be given. In this clinical setting, there was no proof that any NSAID is superior to others (Table 20).

Table 20- Recommendation for castration, BEVA 2020 (Bowen *et al.*, 2020)

Routine castration:		Recommendation	Dose
Lokal anesthesia injected into testicle during routine castration (even using general anesthesia)	Lidocain	HIGH	Lidocain 2%: 8-20 ml in each testicle (adapted to size of animal)
Pre-operative NSAR administered prior to surgery	Phenylbutazone	HIGH	2,2-4,4 mg/kg bwt i.v/ per os Interval 12-24 h
Post-operative NSAR for 3 days	Phenylbutazone	MODERATE	
No Single use of **Butorphanol**		HIGH	——-
Butorphanol Post-operative analgesia but not as only analgesic agent	Butorphanol in combination	MODERATE	0,01- 0,05 mg/kg bwt i.v. Interval 3-4 h 0,04- 0,1 mg/kg bwt i.m. Interval 4-6 h

This BEVA concept for pain management in horses favors preventive as well as multimodal and mechanism-based pain treatment. The published guidelines contain suggestion for most common cases like routine castration, acute orthopedic pain, laminitis, acute visceral pain (Colic), and recommendations for opiate use (Bowen *et al.*, 2020)

Pain management should rely as much as practicable on mitigation and provide a multimodal approach to pharmacology and non-pharmacology techniques (Guedes, 2017).

3.9 Discussion

A basic goal of veterinary medicine is to identify and relieve suffering and pain associated with injury or illness. More than 50% of all interventions in ambulatory veterinary practice concern painful events like lameness and colic (Traub-Dargatz *et al.,* 2001; Drissen and

Zarucco, 2007). There is a great deal of debate about how suffering is and precisely the distinctions are between damage and pain. Multiple studies have concentrated on pain recognition in recent years (Bussières *et al.,* 2008; van LOON et al., 2014; Gleerup *et al.*, 2015; de Grauw and van Loon, 2016; Guedes, 2017; Mullard et al., 2017; Taylor and Senior, 2018). Vets typically rely on clinical measures such as cardiac and respiratory rates, as well as lameness assessment in case of musculoskeletal discomfort. Unfortunately there exists no clinical sign or blood biochemistry parameter which is pathognomonic for pain. More complex pain assessments are based not only on the recording of physiological parameters but also on behavior, description of posture, pain face, and the reaction/ interaction to environmental stimuli. In combination physiological and behavioral data, discomfort and reaction to care of an individual animal are more useful than vital signs alone (Driessen and Zarucco, 2007).

The problem with all different existing subjective pain assessment scales is that they are difficult to validate because there is no gold standard for objective comparison (Bowen *et al.,* 2020). Although there are many studies in equine medicine, pain therapy remains challenging and limited in this species (Mama and Hector, 2019).

An adequate pain evaluation in animals is important for optimal analgesic care (Dugdale, 2014). Negative effect on animal welfare certainly has the still existing lack of consensus on recognition and treatment of pain. Better methods for pain scoring could greatly expand existing standards for evaluating the therapeutic feasibility of novel analgesic medications and methods. Knowledge of the unspecific adverse effects of multiple systemic medications and local anesthesia is important (Waran *et al.,* 2010). In order for vets to properly differentiate uncommon from normal behavior, they should be familiar with the usual specific equine behavior (Hansen *et al.,* 1997).

At the moment, equine behavior and face expression are considered the best methods for pain assessment and prove of effective pain therapy (Guedes, 2007). However, a single evaluation technique cannot be suited to all pain forms (Wagner, 2010; de Grauw and van Loon, 2016). The elusive nature of pain ensures that its subjective evaluation is likely to be a dominant approach in healthcare settings (Barnett, 1997).

To test analgesia in future experiments, a validated composite pain scale in the horse is required. A standardized pain scoring system is also important to ensure accurate comparability between future studies (Bowen *et al.*, 2020). An up to date effective pain therapy should be performed as a multimodal concept, using the synergetic effect by combination of different drugs with distinct pharmacologic properties (Driessen and Zarucco, 2007; Bowen *et al.,* 2020). Given the evidence available to date, it appears reasonable to conclude that the evaluation of pain is equally relevant in physical examination as the vital parameters .

Veterinarians have no way of verbal communication with their patients. Thus, a comparison of veterinary versus medical approaches to disease and treatment may be educational for both sides.

4. Conclusion

The externship in an outpatient clinic for equines was an important experience and essential professional training for the extern. It helped to develop diagnostic abilities in horses, understanding examination-, and treatment procedures, decision making and to learn professional interaction with clients. It allowed the extern to compare her experience as Anesthesiologist in pain therapy in human medicine with equine pain management in veterinary medicine and enabled to consolidate the new acquired veterinary knowledge and its different application in practice. The veterinary followed in the outpatient clinic has a vast experience in the area of orthopedic medicine and emergency medicine trained in Ghent, Belgium. In this way, the trainee has especially deepened her knowledge in this important area of the equine clinic. The elaboration of the casuistry of this report allowed to consolidate the theoretical and practical knowledge obtained in the activities developed during the externship and helped to increase the awareness of differences to human medicine concerning diagnostic and medication doses and different side effects and economic restrictions.

The literature review allowed to understand the approach in pain assessment in horses, according to the latest scientific findings and publications. Unfortunately economic factors are often limiting the choice of treatment in equine practice.

The choice of the subject of pain management in horses resulted from the interest in Anesthesia and Emergency medicine.

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