EQUINE VETERINARY EDUCATION/AMERICAN EDITION

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OCTOBER 2021

AAEP®

EQUINE VETERINARY EDUCATION

American Edition | October 2021

BEVA

The official journal of the American Association of Equine Practitioners, produced in partnership with BEVA.

IN THIS ISSUE:

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References:
[1] Brendemuehl JP, Kopp K, Altman J. Uterine Inflammatory Response to Frozen Semen is attenuated by Oral Supplementation of a Blend of Omega-3 Fatty Acids (Algal DHA and Flax Seed) in Susceptible and Resistant Mares. Submitted to Theriogenology. [2] Brendemuehl JP, Altman J, Kopp K. Influence of dietary algal N-3 fatty acids on breeding induced inflammation and endometrial cytokine expression in mares bred with frozen semen. J Equine Vet Sci. 2014; 34(1): 123-124. [3] A.M. Adkin, A.V. Muniz, C.J. Mortensen, L.K. Warren. Maternal fatty acid supplementation influences memory and learning ability in yearling and 2-year-old horses. J Equine Vet Sci. 2015; 35: 418-436. [4] A.M. Adkin, L.K. Warren, C.J. Mortensen, J. Kivipelto. Maternal supplementation of docosahexaenoic acid and its effect on fatty acid transfer to the foal (longitudinal study). Equine Vet Sci. 2013; 33: 321-329. t[5] A.M. Adkin, L.K. Warren, and C.A. McCall. Effect of maternal docosahexaenoic acid supplementation on behavior and cognitive development in nursing foals. J Equine Vet Sci. 2013; 33: 321-399.

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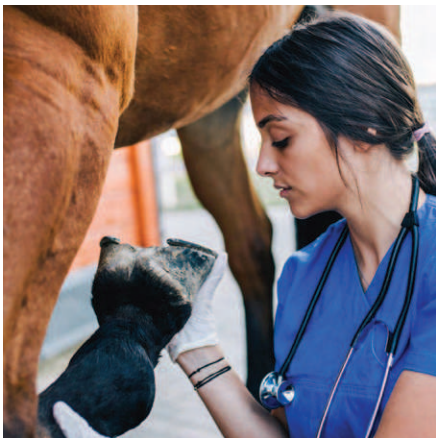

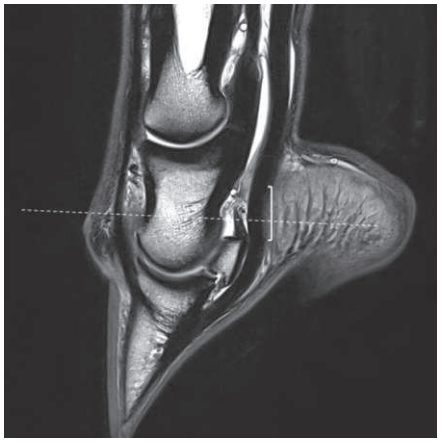

AAEP NEWS In this issue

Cover photo by Dr. Steven Berkowitz

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AAEP Mission Statement: To improve the health and welfare of the horse, to further the professional development of its members, and to provide resources and leadership for the benefit of the equine industry.

Equine Veterinary Education is a refereed educational journal designed to keep the practicing veterinarian up to date with developments in equine medicine and surgery. Submitted case reports are accompanied by invited reviews of the subject (satellite articles) and clinical quizzes. Tutorial articles, both invited and submitted, provide in-depth coverage of issues in equine practice.

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How to improve practice efficiency, revenue and job satisfaction by hiring a licensed veterinary technician

By Cara Wright, DVM, and Kelly Zeytoonian, DVM

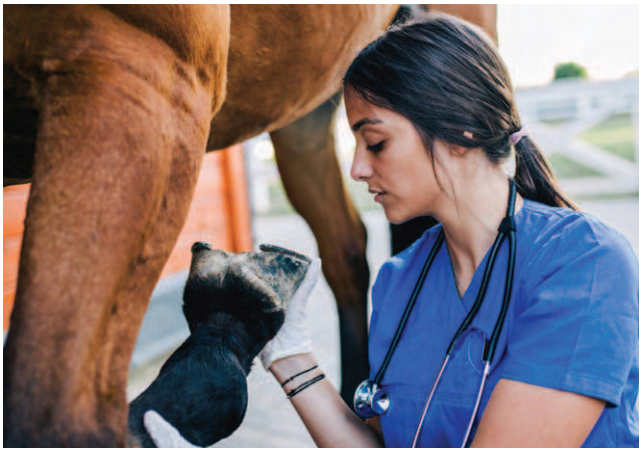
Improving efficiency and increasing revenue is a goal of many equine practitioners—who does not want to work less and earn more? One of the most underutilized ways to increase efficiency in equine practice is to hire a registered or certified veterinary technician. Not only can an RVT perform specific tasks that an unlicensed assistant cannot, but they can also be trained to perform many of the daily management tasks that take veterinarians' time away from revenue-producing appointments. The duties of an RVT are state-specific, so please check with your state practice act for more information.

First and foremost, having an assistant/technician with you can save time between and at farm calls. Doctors can work on callbacks, billing and medical records while the technician drives. If you get car sick, train them to do those things for you. Driving time is wasted time unless it is pulling double duty. Another benefit of an assistant is added safety at appointments with an experienced holder. A licensed technician can even be performing exams and sedating as well as setting up or putting away equipment while the doctor is talking or performing other exams.

Did you know that in many states, an RVT can do bandage changes, give IV and IM medications, perform laser/shockwave therapy and operate radiograph equipment while under the indirect supervision of a veterinarian? Imagine having a staff member who could go see certain appointments independently, giving the veterinarian an afternoon away from work or a chance to perform other, doctor-specific appointments. This can lead to an increase in job satisfaction for the veterinarian, leading to better work-life integration and less burnout over time.

If the physical and mental benefits don't have you convinced, consider the financial effects on your practice. Practices with multiple employees showed a trend in increasing veterinarian salaries as additional team members were hired. A solo practitioner adding an assistant earned just $120 less[1] in salary for the year—a small price to pay for a myriad of benefits.

Inventory is the second-highest cost as a percentage of practice expenses behind payroll. Many solo practitioners and small practices find themselves overstocking items to avoid regular ordering during a busy week, forgetting to bill for medications dispensed from the truck or simply turning inventory sales over to online pharmacies due to a lack of time to manage supply. Surplus items on the truck, expired goods and those we never remember to bill lead to added cost (i.e., lost profit) to the practice. An employee can be readily trained to provide inventory management and reduce inefficiencies in the ordering, storing and billing process.



AAEVT

A solo practitioner adding an assistant earned just $120 less in salary for the year—a small price to pay for a myriad of benefits.

How do you know if you can afford a technician? Some simple numbers can get you started. According to the Bureau of Labor Statistics, the nationwide average salary for a registered technician in 2020 was $17.43/hour, with a range from $12/hour to $25/hour[2]. A 2019 report from the Veterinary Hospital Managers Association reports a range of $16.85–$21.93 for credentialed technicians[3]. This report is also broken down by state and time in industry for easier comparison of wages. Since registered technicians are licensed individuals, continuing education and licensing fees are something to consider. Additional benefits are clinic- and location-dependent, but a practice can expect to invest an additional $6,000–$11,000 in employee benefits, payroll taxes and worker's compensation. See figure 1 for general assumptions.

Figure 1:

Considerations for Hiring

- National Median Salary - $36,260
- Health Insurance - $3,000–$6,000
- Dental/Vision - $600
- CE - $500-1000
- Worker's Comp (state and policy variability) - $500–$2,000
- PTO, Sick Days - $500
- Uniform - $300

Now that you have decided to invest in yourself and your practice by hiring a skilled technician, what is next? Check your finances; an RVT will often pay for themself as they mitigate inventory challenges, improve daily efficiency and see their own appointments so you can concentrate on veterinarian-specific cases. Be sure to

continued on next page

5 things to know about AAEP this month

1. New practitioners: Advance your training in a wet labs event designed specifically for you. Register for the AAEP New Practitioners Symposium at aaep.org/meetings.
2. Learn how to be a veterinary medical first responder by attending "Veterinarians' Role in Emergency Management," a free workshop on Saturday, Dec. 4 from 1:30-5:00 p.m. at the annual convention.
3. The Foundation for the Horse has provided hay, supplies and financial resources in support of equine disaster relief due to Hurricane Ida in Louisiana.
4. Provide up to $600 worth of free veterinary services to at-risk animals by signing up for The Foundation's Vet Direct Safety Net program at aaep.org/vet-direct-safety-net.
5. Receive a complimentary resumé evaluation from our partners at TopResume. Log into the AAEP Career Center at jobs.aaep.org and click the "Overview" tab.

New *EVE* podcast looks at equine renal disease

In the latest episode of the *Equine Veterinary Education* podcast, Dr. Zoe Gratwick discusses her review article, "An updated review: Laboratory investigation of equine renal disease." Download or listen to the 15-minute episode at equineveterinaryeducation.podbean.com.

New Practice Life podcast explores the benefits of using a vet tech

Having an extra set of hands in the form of a technician can add value and ease stress by increasing veterinarian efficiency, productivity and safety, especially for those in ambulatory practice.

During the September episode of the AAEP Practice Life podcast, entitled "Veterinary Technicians Add Value to Your Practice," Dr. Mike Pownall discusses strategies and experiences with integrating vet techs into practice with Dr. Lisa Kivett, owner of Foundation Equine Clinic in Southern Pines, N.C.; Dr. Shane Baird, owner of Mobile Veterinary Services, LLC in Golden, Colo.; and Dr. Kelly Zeytoonian, owner of Starwood Equine Veterinary Services and Starwood Veterinary Consulting in Woodside, Calif.

According to Dr. Baird, "Without technicians is where burnout starts because you've got all the process and all the projects but no relief at any point in the day and it carries over into the evening hours writing records, and all of those things just keep going and going."

Among the topics explored during the 36-minute episode are justifying the additional cost of a tech, desired skills and qualifications when hiring, the impact on veterinarian quality of life outside of work, the changing role of techs over the years, client reception to tech appointments and whether techs might be used to help bridge the gap between the shortage of equine practitioners and maintaining or enhancing service to clients.

Download or listen to the episode at podcast.aaep.org or on iTunes.

The AAEP Practice Life podcast is sponsored by Boehringer Ingelheim.

How to improve practice, continued

reconsider your personal veterinary duties and responsibilities so that when hiring you have a clear picture of expectations and job requirements. Start looking—the AAEVT career center is a good place to start, and local colleges often have technician certification programs.

Congratulations on taking this step to increase your practice revenue and efficiency, as well as your personal job satisfaction! For further discussion, Dr. Kelly Zeytoonian will tackle conversations surrounding technician utilization and business management to support sustainable equine practices at the upcoming AAEP/AAEVT Annual Convention in Nashville.

Footnotes:

1. American Association of Equine Practitioners. 2016 AVMA AAEP Equine Economic Survey. Available from: https://aaep.org/sites/default/files/Documents/2019%20FINAL_AMVA_AAEP_Equine_Report.pdf. Accessed January 24, 2021.

2. "29-2056 Veterinary Technologists and Technicians." U.S. Bureau of Labor Statistics, U.S. Bureau of Labor Statistics, 31 Mar. 2021, www.bls.gov/oes/current/oes292056.htm.

3. "2019 Report on Compensation and Benefits for Non-DVM Staff." Veterinary Hospital Managers Association and Veterinary Emergency and Critical Care Society report, published 2019.

Dr. Wright is a veterinarian in the East San Francisco Bay Region of California and a member of the AAEP-AAEVT Task Force. Dr. Zeytoonian is a practice owner and veterinary business consultant in Woodside, Calif.

Virtual Round Tables conclude October 27; to return in 2022

The first season of Virtual Wednesday Round Tables wraps up October 27 with the session "Opening my own practice: Should I do it?"

As a reminder, Round Tables are recorded and archived for viewing on-demand. Visit aaepanywhere.org, the AAEP's free-to-members online learning platform, to register for the upcoming session and to view the list of available on-demand sessions and resources such as PowerPoint slides, images and more.

Virtual Wednesday Round Tables will resume in spring 2022. If you are interested in serving as a Round Table moderator next year, simply check the appropriate box when completing or updating the Volunteer Interest Form accessible through the My Member Profile/Benefits button at the top of aaep.org. Round Table moderators are compensated for their work.

The AAEP thanks its Virtual Wednesday Round Table sponsors:

CONTINUING EDUCATION

Resort Symposium returns to Hawai'i with sports medicine, theriogenology focus

Registration open for midwinter tropical CE event

Relax and recharge for the year ahead by joining colleagues and thought-leaders for the AAEP's 23rd Annual Resort Symposium on the Kohala Coast of the Big Island of Hawai'i, Jan. 19–21, 2022.

This destination 15-hour CE event will be held at the Mauna Lani Resort, a private oceanfront sanctuary on the dramatic Kohala Coast. The meeting will feature half-day educational sessions that leave plenty of leisure time for relaxation and exploration of the island's natural riches.

On Days 1 and 2, you'll learn to manage and resolve the common and uncommon afflictions of pregnant and postpartum mares with Dr. Patrick McCue, and of newborn foals with Drs. Sarah Reuss and Phoebe Smith. On Day 3, you'll acquire diagnostic and management strategies for orthopedic issues in sport horses with Drs. Myra Barrett, David Frisbie and Omar Maher.

Following educational sessions, discover the natural wonders of Hawai'i or simply enjoy the sand between your toes while basking in the warm sunshine and turquoise waters.

View the educational program, register for the meeting and book your hotel room at aaep.org/meetings/resort-symposium.

Thanks to Zoetis for their sponsorship of the 23rd Annual Resort Symposium.

Come together with horse doctors from far and wide to celebrate equine practice at the AAEP's 67th Annual Convention. You'll reestablish important relationships across the industry and reconnect to your passion for equine practice by acquiring solutions that promote patient health and practice success.

Hear from the headliners

Dr. Jean-Marie Denoix

Learn to interpret clues and assemble the pieces of lameness puzzles when equine locomotion expert **Dr. Jean-Marie Denoix** delivers the Dec. 6 Milne Lecture "A Look at Lameness Through the Eyes of Functional Anatomy (and Biomechanics)." Dr. Denoix will elucidate the biomechanical and anatomic link as the central component of interpreting significance of imaging findings, making the final diagnosis and establishing an effective rehabilitation program. *Sponsored by Platinum Performance.*

Meagan Johnson

Discover how to make the unique perspectives of your staff from multiple generations work together in collaboration instead of conflict when generational humorist and expert **Meagan Johnson** presents the Dec. 5 keynote "Zap the Gap: Generational Differences Examined." Acquire tips and strategies for building multi-generational effective relationships that will help achieve the goals of patient health, practice success and professional fulfillment. *Sponsored by Merck Animal Health.*

Redefine injury recovery

Explore new horizons in rehabilitation when two prominent physical therapists from human athletics share unique insight and perspective on improving patient outcomes and the potential for crossover application in equine athletes during the Dec. 7 session, **"In-Depth: Frontiers in Athletic Rehabilitation: What is Translatable to the Horse?"** Joining equine rehabilitation authorities Drs. Sherry Johnson and Lauren Schnabel will be Dr. Brian Noehren, director of the Human Performance and Biomotion Laboratories at the University of Kentucky; and ESPN senior writer and injury analyst Stephania Bell, who is a licensed physical therapist, board-certified orthopedic clinical specialist, and certified strength and conditioning specialist. *Sponsored by Platinum Performance.*

Prepare to respond

Hurricane Ida's trail of destruction from the Gulf Coast through New England in late August and early September served as a stark reminder of the critical importance of being prepared to assist in equine disaster response. Join veteran disaster responders from California and Texas on the afternoon of Dec. 4 for **"Veterinarians' Role in Emergency Management"** and find out how to prepare and participate, the most common injuries and illnesses encountered, strategies to deal with the mental challenges of being a veterinary medical first responder, and more. This is a free session open to all convention attendees with no advance registration necessary. CE credit will be given. *Sponsored by The Foundation for the Horse.*

Join the discussion

With the popularity of the Virtual Wednesday Round Tables introduced this year, a slate of in-person **Member Roundtables** will be held on the afternoon of Saturday, Dec. 4. These 90-minute discussions are designed to help you navigate the following timely industry topics:

- Transitioning to a Pay at Time-of-Service Business Model for Equine Practice
- Veterinary Support Programs for Working Equids
- Euthanasia: Alternatives to Pentobarbital
- Retirement and Estate Planning

Each will be facilitated by one or more individuals experienced with the subject matter. No advance sign-up is necessary; just show up, listen, learn and ask questions. *Sponsored by Boehringer Ingelheim and CareCredit.*

Connect with employers virtually

Looking for a new opportunity? Let AAEP help get your resume in front of practices attending the convention and seeking to fill open positions. Simply (1) create or log into your AAEP Career Center account at jobs.aaep.org, (2) upload your resume, and (3) indicate on your account page that you'll be attending the Virtual **Career Fair** at the convention, which will flag your resume for participating employers to review and contact you (confidentially if you wish). Contact Megan Gray at mgray@aaep.org if you have Career Fair questions.

Celebrate in song

Join in the fun as several of the best hit-writers in country music share the stage with ultra-talented veterinarian storytellers from 8:00–10:30 p.m. on Sunday, Dec. 5 for **Storytelling Nashville Style.** This unforgettable night will feature performances by Grammy Award winner Rory Feek and a couple of his hit-writing friends, Wynn Varble and Brice Long. Reserve your seat for $75, which includes a complimentary beverage and gift to The Foundation for the Horse. *Sponsored by Merck Animal Health, Boehringer Ingelheim, National Veterinary Associates and Zoetis.*

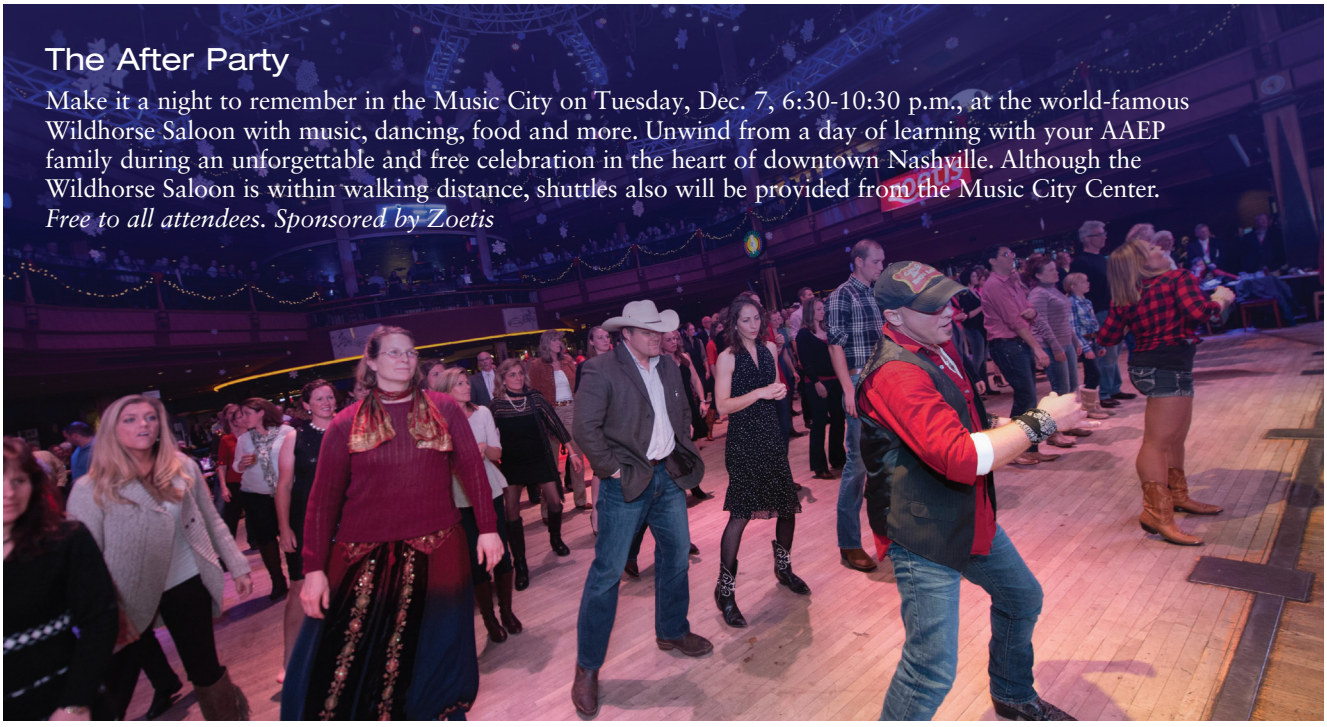
Your health and safety are top priorities!

The AAEP is committed to implementing all necessary protocols to provide a safe convention experience. Proof of vaccination for COVID-19 or a negative COVID-19 test 72 hours before the event will be required of all attendees. For added peace of mind, your registration is 100% refundable at any time should your plans change.

If you can't join us in Nashville, a virtual registration option is available that will provide on-demand access to all scientific sessions and live access to 12 Table Topics. On-site attendees will receive the virtual option at no additional cost.

The After Party

Make it a night to remember in the Music City on Tuesday, Dec. 7, 6:30-10:30 p.m., at the world-famous Wildhorse Saloon with music, dancing, food and more. Unwind from a day of learning with your AAEP family during an unforgettable and free celebration in the heart of downtown Nashville. Although the Wildhorse Saloon is within walking distance, shuttles also will be provided from the Music City Center. *Free to all attendees. Sponsored by Zoetis*



Register in advance for best rate: **convention.aaep.org**

AAEP launches labs-focused CE event for early-career practitioners

If you graduated in the past five years and are seeking new skills to grow your career, accelerate your learning by practicing essential techniques with which you may lack experience during the AAEP New Practitioners Symposium on the weekend of Feb. 19–20, 2022, at the University of Florida.

This comprehensive program combines two days of highly focused wet labs and virtual education to provide up to 60 early-career veterinarians with an engaging, meaningful and affordable hands-on learning opportunity. You'll return home with new knowledge and skills that can be put to immediate use.

The symposium will use a "flipped classroom" model in which attendees refresh their foundational knowledge by completing relevant instructional material at home prior to the event, so that in-person time is devoted to experiential learning through skills application and analysis.

Here's how it will work: At least one month prior to the in-person meeting, registrants will be provided digital resources through an online Learning Management System in the form of PowerPoints, scientific papers and instructional videos on the subject matter of the wet labs. Registrants will complete pre-meeting quizzes to ensure understanding and to qualify for CE credits.

When on-site in Gainesville, Fla., attendees will rotate in groups of 20 through three 90-minute wet labs each afternoon. Each lab, listed below, will have up to five instructors along with an adequate supply of equipment and horses to ensure plenty of hands-on training, instruction and skills development.

Saturday Wet Labs

- Flash Colic Ultrasound
- Ultrasound of the Metacarpus/Metatarsus
- Radiology of the Skull (Sinus & Teeth)

Sunday Wet Labs

- Podiatry: Films and Common Conditions
- Ophthalmology (Exams, Diagnostics)
- Ultrasound of the Stifle

Supplementing afternoon wet labs will be a series of 15-minute discussions on pertinent medical situations (in a "how-to" format) and important non-medical aspects of successful practice on Saturday morning; and business round table sessions on Sunday morning in which attendees can move between tables and discuss topics such as starting a practice, navigating parenthood in practice, managing student debt and more with subject matter experts.

In addition, evening social events on Friday and Saturday will enable attendees to enjoy the collegiality of colleagues and instructors, strike up friendships and expand their professional networks.

The AAEP New Practitioners Symposium offers 10 CE credits and is open to all AAEP members who graduated between 2017–2021. The registration rate is $400. Those who maintained an AAEP membership for all four years as a student will receive a 50% discount.

Registration will open in early November at aaep.org/meetings. Early registration is encouraged.

Thanks to CareCredit for their sponsorship of the New Practitioners Symposium.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Save money on many of the products and services used in everyday practice by enrolling in the AAEP's group purchasing program known as The Veterinary Club.

A complimentary benefit of your AAEP membership, The Veterinary Club offers pre-negotiated discounts on a robust catalog of more than 450 contracted suppliers in Diagnostic Imaging, Facilities Management, Office Solutions, Pharmacy, Surgical and Medical Supplies, Laboratory, Computers and IT Solutions, etc.

More than 800 AAEP members/practices are spending a combined $4 million annually through The Veterinary Club, accruing $750,000 in annual savings. This works out to average savings of $937 per participant, far exceeding the cost of their AAEP membership.

"I was pleasantly surprised to find out we were eligible for a savings of 54% on radiation badges from Radiation Detection Company," said Valley Equine Hospital's Dr. Lori Kayashima. "We look forward to exploring other cost saving contracts on The Veterinary Club's website."

Start saving today by registering at TheVeterinaryClub.com. If you have questions about this or other membership benefits, contact Megan Gray, member concierge, at mgray@aaep.org or (859) 233-0147. If you plan to attend the upcoming annual convention in Nashville, stop by The Veterinary Club booth within AAEP Connect inside the trade show to learn more.

Members in the News

Dr. Rocky Bigbie

Dr. Rocky Bigbie named distinguished alumnus

Dr. Rocky Bigbie, who retired as academic liaison for Zoetis in 2020, has been named a 2021 Distinguished Alumnus Award recipient by Oklahoma State University College of Veterinary Medicine.

Dr. Bigbie received his veterinary degree from the university in 1981 and spent 26 years in the U.S. Army Veterinary Corps (active duty and reserves) before transitioning to the pharmaceutical industry, where he was instrumental in establishing the academic liaison role serving all western veterinary colleges. Dr. Bigbie has been a strong advocate for his alma mater and has served the AAEP on a number of committees and councils, including Biologic and Therapeutic Agents, Equine Welfare, Foundation Advisory and Member Engagement.

Dr. Randi Borri

Dr. Randi Borri recognized for half-century of service

The Kenosha County Fair in Wisconsin recognized Honor Roll member Dr. Randi Borri for 50 years of service at the onset of the livestock auction on Aug. 21.

Dr. Borri received his veterinary degree from the University of Illinois in 1970, the year he first served as fair veterinarian. He co-founded Bristol Veterinary Service in Salem, Wisc., in 1972. Dr. Borri has also served as veterinarian for the Wisconsin State Fair for 35 years and is the veterinarian for the Professional Bull Riders during shows in the region.

Dr. Gregory Ferraro

Dr. Gregory Ferraro named Laffit Pincay Award winner

Honor Roll member Dr. Gregory Ferraro, chair of the California Horse Racing Board who for over half a century has made an enduring impact on California racing as a practicing veterinarian, equine surgeon and medical executive, received the Laffit Pincay Award on Aug. 21 at Del Mar. The award recognizes those who have served the sport "with integrity, extraordinary dedication, determination and distinction."

Dr. Ferraro, who earned his DVM from UC Davis and spent over 25 years in racetrack veterinary practice, served as director of the UC Davis Center for Equine Health from 1997-2011 and associate director of the UC Davis Veterinary Medical Teaching Hospital from 2011-2014. Among his many accomplishments and innovations are design and development of the horse ambulances used on North American tracks and development, in partnership, of a splint that can be applied to stabilize lower leg injuries.

Vet Direct funds enable resolution of mare's costly eye issue for COVID-strapped owner

By Sarah E. Coleman

A landlord in rural Kentucky when the COVID-19 pandemic emerged in early 2020, horse owner Kelly Seacrest soon began feeling the effects of tenants who were unable to pay their rent. The devastating loss of income and uncertainty of a return to normalcy prompted Seacrest to return home to Massachusetts with her son and her horses—Trixie and Dreamer.

While struggling to get back on her feet financially, Seacrest established herself as a client of Dr. Sara Cook, co-owner of Black Brook Veterinary Services in Hamilton, Mass. In December, during a follow-up visit after removal of a suspected squamous cell carcinoma from Trixie, Seacrest mentioned the mare had been squinting her left eye on and off for about two weeks. Upon examination, Dr. Cook suspected a corneal stromal abscess, subsequently confirmed via email consult with ophthalmologist Dr. Alison Clode.

The prescribed treatment regimen involved topical application of Terramycin three times a day. Although Seacrest diligently treated the mare, it wasn't long before Trixie expressed her displeasure and Seacrest struggled to get the medication in her eye. Dr. Cook recommended an eye lavage catheter so Ofloxacin and Voriconazole could be administered for two weeks, but the financial ramifications intimidated Seacrest. So the duo began searching for a way to ease some of the financial burden so that Trixie could get the help she needed.

> As a vet, it is a relief to me to be able to offer the support of a program like Vet Direct in certain cases, knowing the horse can get the care it needs in a timely manner.

Dr. Cook had learned of the Vet Direct Safety Net program from her office manager, Kim Maguy, who had seen the program in an AAEP email and suggested the clinic sign up. Designed to reduce the number of horses relinquished or sent to auction, the program reimburses practices for up to $600 worth of free veterinary services per horse to assist owners in need with emergency stabilization procedures, euthanasia or disposal.

Following a speedy onboarding process—just a 20-minute Zoom call—Dr. Cook and her team recognized Trixie as a prime case for funding and knew exactly which issues would and would not be covered by the program, which is administered by The Foundation for the Horse and the ASPCA.

Trixie with Kelly Seacrest's son, Seamus.

"Kelly consistently showed her commitment in terms of diligence in medicating the horse, keeping her inside when necessary, and following through with recommendations to ensure her recovery," Dr. Cook said as to why she felt Seacrest was an ideal candidate for the program.

Dr. Cook placed the catheter and then contacted The Foundation for the Horse with the invoice and an explanation of medical treatment. She soon received the $600 reimbursement and established a payment plan for Seacrest. Trixie has since made a full recovery, and Seacrest recently paid off the remainder of her bill.

"Although we live in a relatively wealthy area, not all horse owners have a large financial cushion to fall back on when things get difficult," said Dr. Cook. "This can result in deferred care, worsening medical problems or even the decision to give up the horse. As a vet, it is a relief to me to be able to offer the support of a program like Vet Direct in certain cases, knowing the horse can get the care it needs in a timely manner."

If you are an AAEP-member veterinarian in the U.S. with clients who potentially could struggle to pay for veterinary care, put yourself in a position to help by enrolling in Vet Direct Safety Net. Sign up or learn more by visiting aaep.org/vet-direct-safety-net or contacting Sue Stivers at sstivers@aaep.org.

AAEP Educational Partner Profile: Zoetis

Zoetis has been committed to providing horse care you can count on for more than 65 years. Our team includes numerous equine veterinarians and other experts who are inspired daily by the opportunity and profound responsibility to support horses, the owners who love them, and the equine veterinarians and other care team members who safeguard their wellbeing every day.

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Highlights of recent clinically relevant papers

Desmotomy of the AL-DDFT

This multicentre retrospective study by Emilie Wismann and co-workers in Denmark compared the long-term performance of 74 sports horses that underwent desmotomy of the accessory ligament of the deep digital flexor tendon (AL-DDFT) to that of 196 matched controls.

Twenty-one horses (28%) from the desmotomy group competed following surgery, whilst 74 (38%) from the control group entered competition. Of horses that entered into competition, there were 67% cases and 78% controls performing dressage, 19% cases and 12% controls showjumping and no cases and 1% controls eventing. Career longevity differed significantly between cases and control horses; the controls had significantly longer career durations (15.6 competitions over a median of 570 days) than horses that underwent desmotomy (9.7 competitions over a median of 219 days for unilateral desmotomy and 6.1 competitions over a median of 446 days for bilateral desmotomy). Age at surgery and whether the condition was unilateral or bilateral did not affect the chance of competing.

Desmotomy of the AL-DDFT, including the underlying reasons for performing the surgery, is associated with reduced long-term athletic performance in sports horses compared with a matched control group.

Laparoscopic vaginal ring closure

This retrospective case series by Belgium-based Hans Wilderjans and Michael Meulyzer described a novel, minimally invasive laparoscopic tacked intra-peritoneal slitted mesh (TISM) technique in the standing horse to close the vaginal rings and evaluated its efficacy in preventing recurrence of indirect inguinal herniation (IIH) in 17 stallions.

In total, 32 laparoscopic vaginal ring closures were successfully performed in 17 horses, aged 3–10 years. The IIH was reduced by manual reduction in 14 horses and at laparotomy in 3 horses. No intestinal resection was performed in any of the cases. The vaginal ring closure was performed between 5 and 37 days (median 14 days) after reduction in horses that did not undergo laparotomy, and between 28 and 67 days (median 42 days) after reduction in horses that underwent laparotomy.

No major intra- or postoperative complications occurred. Inguinal herniation did not occur in any of the horses following the procedure. Nine of the 13 active stallions returned to breeding, with similar semen quality as before treatment. The remainder were scheduled to resume breeding during the next season. None of the horses were castrated and none of the owners reported abnormal size or shape of the testicles following the procedure. In three stallions, postoperative pain and activity limitations were noted but gradually resolved after 6 months.

The use of slitted mesh appears to be a safe and effective technique to prevent recurrence of indirect inguinal herniation in stallions.

Perioperative prophylaxis regimens

Short-term perioperative antibiotic prophylaxis (PAP) is recommended for surgical interventions classified as clean or clean-contaminated, including laparotomy; however, in equine colic surgery PAP commonly exceeds 24 h. This study by Sabita Stöckle and co-workers in Germany compared a single-shot to a 5-day lasting PAP considering surgical site infections (SSI) and other adverse effects associated with the antimicrobial regimen.

All horses ($n = 67$) received the standard physical examination before and after surgery. Colic surgery was performed according to the current standard of the clinic. Horses were randomly assigned to two groups, receiving either the 'single-shot' or the '5-day lasting' antibiotic prophylaxis. The 'single-shot' group ($n = 30$) received penicillin and gentamicin only once before and, if needed, during surgery, whereas the '5-day lasting' group ($n = 37$) received antibiotics for 5 days. In addition to the standard laboratory examinations, serum amyloid A and fibrinogen were determined preoperatively and for 5 days after surgery. SSI, postoperative colitis and haemolytic anaemia were classified as postoperative complications potentially related to antibiotic use.

The occurrence of postoperative adverse events (i.e., SSI, postoperative colitis and haemolytic anaemia) lacked significant differences between the study groups. Single-shot PAP seems to be an alternative approach to the 5-day lasting protocol commonly used in equine abdominal surgery. However, proper hygiene management together with close clinical and laboratory monitoring of the equine patient is essential.

Influences on the faecal microbiome

In this study Carolyn Arnold and co-workers in the US assessed the effects of age, breed, sex, geographic location, season, diet, and colitis caused by antibiotic use (antimicrobial-associated diarrhoea [AAD]) and Salmonella *infection on faecal microbiota.*

Eighty healthy horses were sampled from nonhospital environments across multiple geographical locations in the US. Horses with AAD ($n = 14$) were defined as those that developed diarrhoea secondary to antimicrobial use. Horses with *Salmonella* infection ($n = 12$) were presented with spontaneous onset of colitis and subsequently tested positive on *Salmonella* quantitative PCR. All horses were >1 year of age and stratified by a dietary scale that included forages (pasture and hay) and concentrates grouped by percentage of fibre and amount. Illumina sequencing of 16S rRNA genes was performed on faecal DNA.

Healthy horses fed higher amounts of grain clustered separately from those fed lower amounts of grain. Horses with AAD and *Salmonella* had decreased richness and evenness compared to healthy horses. Univariable analysis of the three groups identified increases in Bacteroidetes and Protebacteria and decreases in Verrucomicrobia in AAD horses whereas *Salmonella* horses had less Firmicutes when

compared to healthy horses. Although the amount of grain in the diet had some impact on the faecal microbiome, colitis had a significantly larger influence. Horses with ADD have a more severe dysbiosis than do horses with *Salmonella*.

Antimicrobial-associated diarrhoea

This matched, case-controlled study by Carolyn Arnold and co-workers in the US compared the faecal microbiome and metabolome of horses on antibiotics that developed diarrhoea (AAD, n = 17) to those that did not develop diarrhoea (ABX, n = 15) and to a control population not exposed to antibiotics (CON, n = 31).

Faecal samples were collected from horses that were matched for diet and antimicrobial agent (including dose, route, and duration of therapy). Illumina sequencing of 16S rRNA genes was performed, and QIIME 2.0 was used to generate alpha and beta diversity metrics. Untargeted metabolomics using GC-MS platforms was performed and analysed using Metaboanalyst 5.0.

Microbiome composition was significantly different in AAD compared to CON but not to ABX. AAD and ABX horses had significantly decreased richness and evenness compared to CON horses. Horses on antimicrobials (AAD and ABX) had significant changes in 14 phyla compared to CON horses. Only Verrucomicrobia distinguished AAD from ABX and CON horses. Metabolite profiles of horses with AAD clustered separately from ABX and CON horses. Seven metabolites were found to be significantly different between groups: L-tyrosine, kynurenic acid, xanthurenic acid, 5-hydroxyindole-3-acetic acid, docosahexaenoic acid ethyl ester, daidzein, and N-acetyltyramine. Metabolite profiles of horses on antimicrobials, especially those with AAD, are altered compared to CON horses.

Tyzzer disease

This retrospective study and literature review by Juan García and co-workers in Argentina, Chile and USA analysed Clostridium piliforme *infection (Tyzzer disease) in horses.*

Tyzzer disease (TD) is caused by *Clostridium piliforme*, a gram-negative and obligate intracellular bacterium. The disease occurs in multiple species. A triad of lesions, namely colitis, hepatitis, and myocarditis, is described in cases of TD in some species, such as rats and mice. A retrospective analysis was performed of 25 equine cases with a diagnosis of TD; 24 of 25 cases occurred in foals <45 days old; the remaining foal was 90 days old. There were 12 males and 12 females; no sex information was available for one foal. The affected breeds were Quarter Horse, Thoroughbred, Arabian, Paint, and Hanoverian. Most of the cases (19/25) occurred in the spring. There were 9 cases of sudden death; the remaining animals had diarrhoea, fever, distended abdomen, depression, weakness, non-responsiveness, and/or recumbency. Gross findings included icterus, hepatomegaly with acinar pattern, serosal haemorrhages, pulmonary oedema, and/or fluid content in the small and large intestine. Microscopically, all foals had severe, multifocal, necrotizing hepatitis. Necrotizing lymphohistiocytic colitis was observed in 10/25 foals, and multifocal necrotizing myocarditis was found in 8/25. Gram-negative, Steiner-positive, intracytoplasmic filamentous bacteria were observed in hepatocytes, enterocytes, and myocardiocytes, respectively. PCR detected *C. piliforme* DNA in the liver (24/24), colon (20/24), and heart (5/25).

These results indicate that necrotic hepatitis is the hallmark of TD in horses; the so-called triad of lesions is not a consistent characteristic of the disease in this species.

Imaging horses with foot pain

This prospective study by Laurence Evrard and co-workers in Belgium and France compared the ultrasonographic and standing magnetic resonance imaging (sMRI) findings in deep digital flexor tendon (DDFT), navicular bone, and navicular bursa in horses with foot pain, positive digital analgesia, and without definitive radiographic diagnosis.

Ultrasonography detected more DDFT abnormalities (32/34 feet vs. 27/34 with sMRI) but identified less palmar navicular abnormalities (23/34 feet vs. 30/34 with sMRI). In suprasesamoidean DDFT lesions, which were mainly dorsally located, changes in echogenicity did not correspond to a particular pattern of sMRI signal change. Transcuneal ultrasonography did not allow assessment of morphology and extent of distal DDFT lesions, and sporadically discriminated the affected lobe compared to sMRI. Defects of the palmar compact bone were identified with both modalities except a parasagittal defect, which was only seen at sMRI.

S. WRIGHT
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Case Report

Oxytetracycline associated acute kidney injury in a neonatal foal

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Keywords: horse; nephropathy; flexural deformity; renal; tendon contracture

Summary

A 3-day-old Australian Stock Horse filly presented with fulminant acute kidney injury after receiving 4 g of intravenous (i.v.) oxytetracycline at 24 and 48 h of age, for medical management of congenital metacarpophalangeal joint (MCPJ) flexural deformities. The filly had appeared healthy prior to oxytetracycline administration. The observed parturition, immunoglobin G concentration and serum biochemical analysis at 24 h of age were normal. Nursing activity was reportedly sufficient prior to being found recumbent the following morning. At presentation, the filly was obtunded, with delayed capillary refill time and reduced suckle reflex. A 1 L bolus of lactated Ringer's solution with 20 mL of 50% dextrose was administered over 20 min, i.v. The i.v. fluid rate was continued at 250 mL/h. Laboratory results were available subsequent to the fluid bolus. Severe azotaemia, with a serum creatinine (Cr) of 667 μmol/L, severe hyperkalaemia and moderate hyponatraemia were noted. Abdominal ultrasonography revealed bilateral renomegaly and increased corticomedullary distinction, with an intact bladder (**Fig 1**).

Electrolyte imbalances showed improvement after 2 h of i.v. fluid therapy; consequently, the plan was continued. An indwelling nasogastric tube was placed, and 500 mL of mares' milk was fed every 2 h. Ceftiofur sodium (10 mg/kg i.v. q. 6 h) was administered prophylactically due to risk of sepsis. Sepsis was later considered unlikely due to negative blood culture and low modified sepsis score. At 10 h post-admission, serum Cr had increased (766 μmol/L); however, electrolyte imbalances had improved.

At 22 h post-admission (Day 2), the filly improved clinically, regaining the suckle reflex. Electrolyte imbalances had resolved, with improvement in serum hypercreatinaemia (567 μmol/L). The filly was assisted to nurse from the mare every 2 h, with proportional decreases in the enteral milk volume fed through the nasogastric tube. Urination occurred at least every 4 h, with urine-specific gravity measuring 1.008–1.011. There were no further ultrasonographic changes to renal architecture. Thoracic ultrasonography showed mild bilateral lung ring-down artefacts on the pleural surface, consistent with mild pulmonary oedema. The owners declined recommended monitoring with an indwelling urinary catheter and measurement of central venous pressure.

At 46 h post-admission (Day 3), serum Cr had increased (762 μmol/L), the filly became too weak to stand, and the suckle reflex was lost. Between 34 and 50 h, there was no evidence of urination. Mild subcutaneous oedema over the thoracic region started to become apparent at 46 h. Respiratory rate and effort, as well as bodyweight, did not increase at any point during hospitalisation. The i.v. fluid rate was maintained; however, the volume of mare's milk provided via the nasogastric tube was decreased to 300 mL every 2 h. Two doses of furosemide (1 mg/kg i.v. q. 4 h) were administered at 50 and 54 h post-admission, due to oliguria and developing peripheral oedema. A small volume of urine collected at 50 h remained isosthenuric (1.011). The filly did not urinate between 50 and 55 h.

The owner elected euthanasia at 55 h due to the declining response to treatment and guarded prognosis. Necropsy revealed bilaterally enlarged and asymmetrical kidneys, with cortical pallor and mild haemorrhage. The right hindlimb MCPJ had moderate flexural deformities, primarily involving the superficial digital flexor tendon. The thorax contained a mild serous effusion with mild pulmonary congestion. Proximal tubular epithelial cells showed eosinophilia, karyolysis, cellular fragmentation and lysis. In other tubules, there was elongation and pleomorphism of proximal epithelial cells, indicating proliferation and regeneration. A histologic diagnosis of acute, severe proximal tubular necrosis was made. No abnormalities were detected in the brain sections examined. The lungs were not examined histologically.

Key points

- The use of oxytetracycline in neonatal foals with flexural deformities is not innocuous; therefore, its nephrotoxic potential should be considered even in apparently healthy patients.
- Careful patient selection, with assessment of nursing, hydration status, urinalysis, serum biochemistry and other individual risk factors, should occur prior to administration of each dose of oxytetracycline.
- Alternative therapies or smaller doses of oxytetracycline (44 mg/kg) diluted into 500 mL of saline may be appropriate to mitigate risk of nephrotoxicity in future instances.

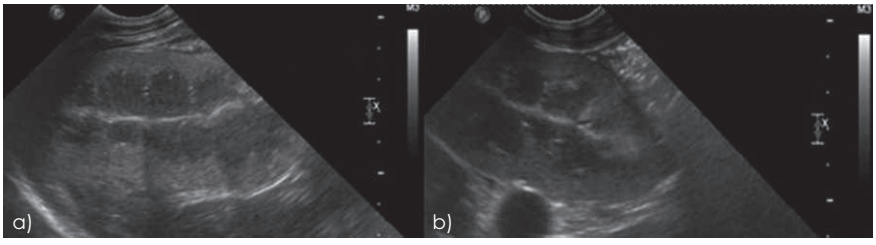

Fig 1: Sonographic images of the right (a) and left (b) kidney, showing asymmetrical enlargement, increased cortical echogenicity and increased corticomedullary distinction (R: 12 x 7 x 3 cm, L: 9 x 6 x 4 cm).

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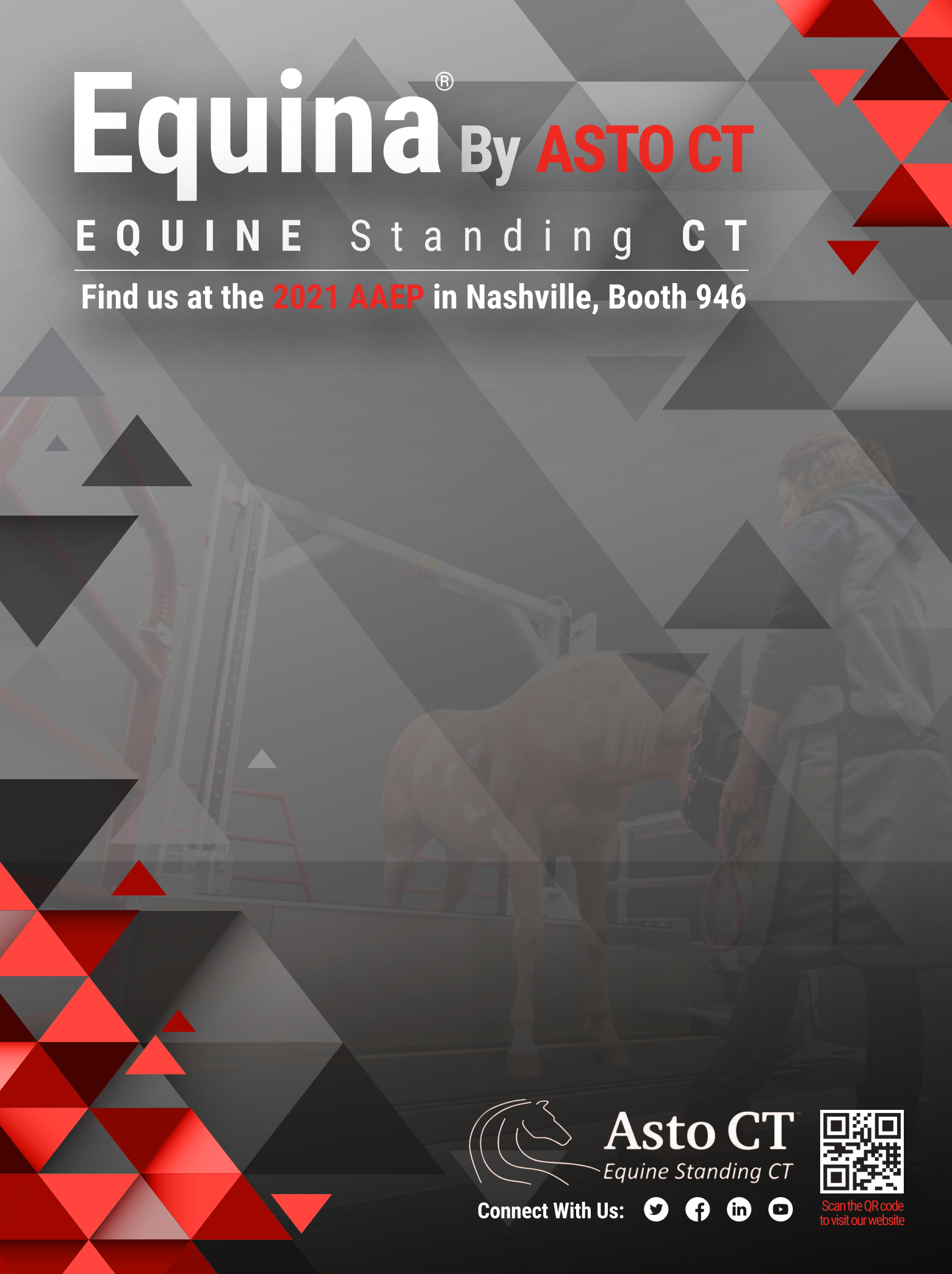

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Case Report

A tumour of vascular origin in a horse

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Keywords: horse; tumour; vascular tumour; haemangioma; subcutaneous tumour

Summary

An 18-month-old Quarter Horse colt was referred to the Charles Sturt University, Veterinary Clinical Centre for assessment of a large, firm mass, approximately 15–20 cm in diameter. The mass was easily palpated beneath the skin and was immobile. Resection of the 2.7 kg mass (**Fig 1a**), under general anaesthesia, involved extensive subcutaneous dissection. The tumour extended as far as, and was attached to, the tuber coxae and had infiltrated parts of the external and internal abdominal oblique muscles. There was a dense fibrous capsule, and minimal haemorrhage was encountered as the tumour was removed by a combination of sharp and blunt dissection. The surgical resection created a large subcutaneous tissue defect that could not be sutured closed and was packed with a povidone-iodine saline solution-soaked gauze bandage and the skin incision was closed in a vertical mattress pattern. On histopathological examination, the resected tumour consisted of mesenchymal tissue containing numerous variably sized cavernous spaces with multiple arteriolar profiles and focally extensive areas of lymphoid infiltration and proliferation. The vascular spaces were lined with a single layer of attenuated endothelial cells overlying a thin layer of collagen and contained variable amounts of high protein fluid and variable numbers of erythrocytes. Masson's trichrome stain confirmed the presence of abundant mature collagen throughout the tissue. Arteriolar profiles showed normal organisation of the intimal, medial and adventitial layers. Verhoeff-van Gieson stain demonstrated abundant mature fibrous tissue throughout (**Fig 1b**). Arteriolar profiles had an internal elastic lamina and a moderately thick smooth muscle wall. Cavernous vascular spaces were not associated with an internal elastic lamina. Endothelial cells lining small to cavernous vascular channels, all of which, showed strong positive staining for vWF, and mesenchymal cells directly adjacent to these endothelial cells showed strong positive staining for SMA. This histopathological appearance was most consistent with a diagnosis of haemangioma.

Although haemangioma is uncommon in the horse, the biological behaviour is expected to be similar to that of haemangiomas in other species. At the time of writing, there was no evidence of regrowth and surgical excision of the mass was deemed successful.

Key points

- Tumours of vascular origin occur infrequently in horses, and they are difficult to characterise requiring immunohistochemical staining techniques.
- Consistent with reports of haemangiomas in other species, complete surgical excision of the haemangioma described in this case was curative.

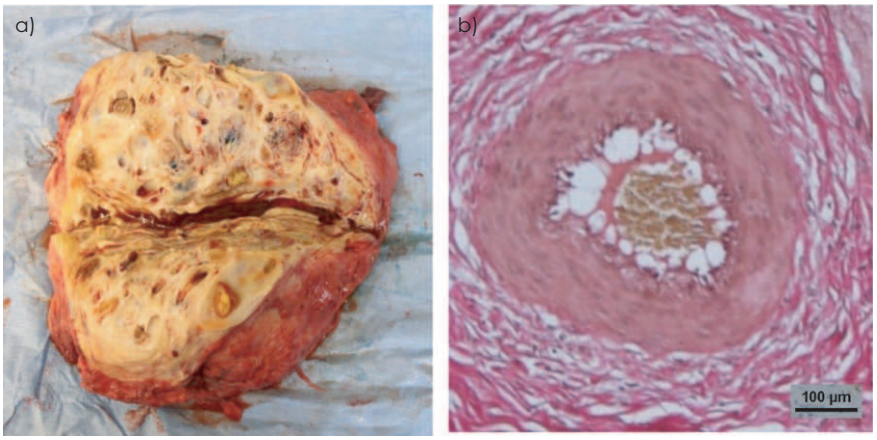

***Fig 1:** Appearance of the cut section of the tumour after surgical resection (a). Arteriolar profiles are lined with bland endothelial cells that show strong positive staining for von Willebrand's factor (not shown). They have a single layer of elastin (b, Verhoeff van Gieson), are surrounded by a muscular wall that stains strongly positive for smooth muscle actin (not shown) and are separated from surrounding vascular structures by abundant mature collagen.*

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Case Report

Gastric squamous cell carcinoma in the horse: Seven cases (2009–2019)

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Keywords: horse; gastroscopy; gastric neoplasia; squamous cell carcinoma; biopsy

Summary

This report describes seven cases of gastric squamous cell carcinoma (GSCC) and documents the clinical signs, treatment and outcomes. The duration of clinical signs before presentation ranged from 2 days to 6 months, with a median duration of 2 months. Main clinical signs were mostly nonspecific and included weight loss (6/7), tachypnoea (6/7), tachycardia (5/7), anorexia (5/7) and fever (4/7). Some more suggestive clinical signs were observed such as hypersalivation (5/7), recurrent choke (4/7) and halitosis (4/7). Blood analyses suggested that chronic anaemia (5/7) and hypoalbuminaemia (7/7) were the most common abnormalities. A combination of different complementary examinations is the key to diagnose gastric neoplasia. Gastroscopy remains the examination of choice, but has several limitations, including the incapacity of reaching the stomach when GSCC invades the distal oesophagus. A mass could be visualised in the nonglandular part of the stomach in 4/7 horses (**Fig 1**), and for three of them, the oesophageal neoplastic infiltration in the oesophagus impeded the stomach visualisation. Abdominal ultrasonography was useful to evidence stomach wall thickening in 4/7 horses (**Fig 2**). Neoplastic cells were detected by cytologic examination of the peritoneal fluid in only 2/7 horses. Based on histopathological examination, a definitive ante-mortem diagnosis was achieved in 3/7 horses, either by a trans-endoscopic biopsy (2 horses) or an ultrasound-guided biopsy of the thickened stomach wall (one horse). GSCC is associated with a poor short-term prognosis because of the high metastatic rate. In our cases, spleen and/or liver metastasis were detected in 100% of post-mortem examinations. Palliative treatment can be attempted but the mortality rate is high, and the short-term survival is poor (71% of the cases were subjected to euthanasia within one week).

Fig. 1: Endoscopic view of a multilobulated SCC in the nonglandular part of the stomach of a horse presented for weight loss, lethargy and fever. The definitive diagnosis was performed with biopsies using endoscope forceps.

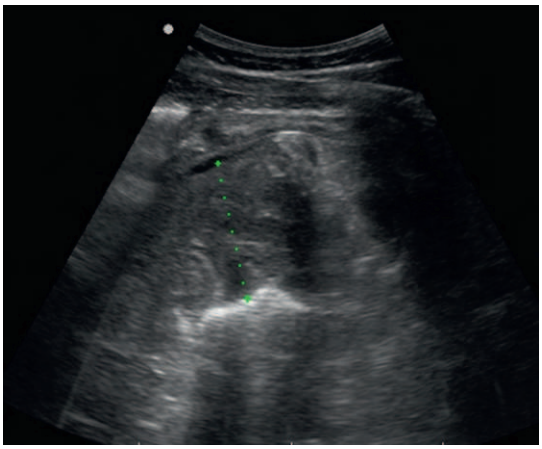

Fig. 2: Abdominal ultrasonography showing a severe thickening of the stomach wall (4.7 cm) in a pony. A gastroscopy was attempted, and the stomach could not be reached due to an oesophageal stenosis. An ultrasound-guided biopsy confirmed a GSCC.

Key points

- The combination of weight loss, fever, hypersalivation, halitosis and recurrent choke associated with anaemia and hypoalbuminaemia is suggestive of gastric neoplasia.
- GSCC diagnosis relies on histopathological examination of the stomach and/or distal oesophagus wall.
- To achieve diagnosis, several examinations should be combined, including gastroscopy, abdominal ultrasonography and cytology of peritoneal fluid and endoscopic or ultrasound-guided biopsies.
- Metastatic rate is high, and short-term survival is poor.

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Case Report

Abdominal aortic thromboembolism and subsequent pelvic limb myositis secondary to colitis and septicaemia in a 5-day-old Oldenburg colt

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Keywords: horse; aorta; thromboembolism; *Clostridium*; myositis

Summary

A 5-day-old Oldenburg colt presented for acute severe right hindlimb lameness. The foal had diarrhoea at presentation, and over the next 24 h became tachycardic and febrile with cold extremities in the hindlimbs and began to bear weight on the dorsum of both hind fetlocks (**Fig 1**). Diagnostic work-up included physical examination, radiography, ultrasonography and clinicopathological testing. Treatment consisted of antibiotics, anti-inflammatories, gastroprotectants, oral di-tri-octahedral smectite, hyperimmune plasma and isotonic crystalloid fluids for the diarrhoea. Bandages and splints were applied to the hindlimbs to assist ambulation and prevent weightbearing on the dorsum of the fetlocks. The foal developed oedema of both hindlimbs, and ultrasonographic evaluation revealed gas pockets within the subcutaneous tissues. Ultrasound-guided aspirate of the right hindlimb oedema was submitted for cytology, which revealed presumed *Clostridial* spores, and culture, which yielded heavy growth of *Escherichia coli*. Surgical fenestration of the hindlimbs was performed due to suspected *Clostridial* myositis. The foal continued to decline clinically and was humanely subjected to euthanasia. Post-mortem examination revealed evidence of septicaemia and thromboembolism of the terminal abdominal aorta (**Fig 2**) resulting in partial obstruction of blood flow to the pelvic limbs with resultant bacterial myositis (*Clostridium* (suspected) and *Escherichia coli* (confirmed)).

Fig 1: Physical appearance of foal. When assisted to stand 24 h following presentation to the hospital, the foal demonstrated progression from acute right hindlimb lameness to bilateral hindlimb weakness, weight-bearing on the dorsum of both hind fetlocks.

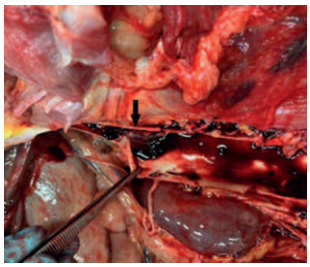

Fig 2: Post-mortem findings. Incised caudal abdominal aorta demonstrating a thrombus partially obstructing the lumen (arrow).

Thrombosis is a potential sequela to coagulopathy seen in septicaemia and should be considered a differential diagnosis in neonatal foals presenting for lameness. Septicaemic equine neonates frequently have altered coagulation profiles and haemostatic deficits. While other case reports of arterial thrombosis of the digital, brachial and aorto-iliac arteries in septicaemic foals have been published, this case report highlights a unique presentation of aortic thromboembolism, representing the first report of *Clostridial* myositis secondary to vascular stasis of the hindlimbs. *Clostridial* colitis was suspected on cytology and thought to have spread haematogenously to the limbs where myositis resulted following decreased peripheral perfusion and compression exerted by oedema on venous return. Transabdominal Doppler ultrasound and/or vascular nuclear scintigraphy angiography may have been useful to confirm clinical suspicion and accelerate ante-mortem diagnosis of arterial thromboembolism in this case. Prognosis in cases of arterial thromboembolism may be affected by the degree and chronicity of arterial occlusion and severity of concurrent disease.

Key points

- Arterial thrombosis is a potential sequela to coagulopathy seen in septicaemia and should be considered as a differential diagnosis for neonatal foals presenting for lameness.
- Clinical suspicion of arterial thrombosis based on history and physical examination may be confirmed ante-mortem in some cases using diagnostic imaging including Doppler ultrasonography and vascular nuclear scintigraphy angiography.
- Prognosis in cases of arterial thromboembolism may be affected by the degree and chronicity of arterial occlusion and severity of concurrent disease.

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Case Report

Presumed generalised seizure following caudal epidural administration of morphine and detomidine in a pony

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Keywords: horse; epidural; morphine; seizure; analgesia

Summary

A 9-year-old, 250 kg show pony mare was presented for further investigation and treatment of mild colic signs. Serum biochemistry at admission identified moderate hypoalbuminaemia (23 g/L, rr: 28–36 g/L) and abdominal ultrasonography identified thickening of the right dorsal colon wall, consistent with right dorsal colitis. In addition, severe multifocal, depressed, haemorrhagic lesions at the pylorus were noted during gastroscopy. Both findings were thought to be secondary to ongoing administration of nonsteroidal anti-inflammatory drugs (NSAIDs) for suspected laminitis. An acute right thoracic limb lameness was noted during hospitalisation and radiographs of the foot identified a bone sequestrum in the distal phalanx, which was debrided under general anaesthesia. Peri- and post-operative analgesia consisted of transdermal fentanyl, acetaminophen and morphine sulphate. Twenty-four hours post-operatively, a marked deterioration in the pony's comfort level was observed. Due to the right dorsal colitis, administration of further NSAIDs was not desirable. It was therefore planned to use caudal epidural analgesia, with a combination of morphine and detomidine administered in a larger volume (0.2 mL/kg bwt) to facilitate cranial diffusion and provide analgesia to the thoracic limbs. The sacrococcygeal space was identified by raising and lowering the tail while palpating the intervertebral space, and the overlying skin was clipped and aseptically prepared. Following desensitisation of the skin, an 18 gauge 1.5-inch hypodermic needle was inserted through the skin at approximately 60° to the horizontal plane until it was felt to penetrate the interarcuate ligament. Placement in the epidural space was confirmed by the hanging-drop technique and a lack of resistance to injection, and 60 mg morphine sulphate and 1 mg detomidine hydrochloride diluted in 0.9% sterile saline to a total volume of 50 mL were injected over approximately 90 s. Five seconds following completion of the injection, the pony became increasingly sedated with rigid extension of the limbs and collapsed into lateral recumbency. Extensor rigidity of all limbs was observed, and the pony appeared unresponsive to external stimuli. After 12 s, rapid paddling of all four limbs began and persisted for 35 s. The pony regained consciousness after approximately 45 s and remained in sternal recumbency for several minutes. She was responsive but appeared mildly sedated. No cranial nerve deficits were identified but recurrent chewing and lip smacking were noted. The pony stood up without difficulty. Abbreviated gait assessment within the stable three hours after the episode did not identify any evidence of ataxia or paresis. The epidural injection resulted in a marked improvement in comfort levels. Normal mentation and behaviour were observed throughout the remainder of hospitalisation. Epidural analgesia was not repeated. The pony was discharged from the hospital 8 days later. No further seizures or abnormal neurological behaviour has been reported.

To the authors' knowledge, this is the first report detailing this complication secondary to caudal epidural injection of morphine and detomidine in a horse. A change in intracranial pressure resulting from rapid injection or diffusion of morphine into the CSF is thought to be the most likely cause for the seizure activity. Further work is needed to determine the optimum volume and speed of intra-thecal injection in horses but in the meantime, it appears prudent to administer large volumes over a period of several minutes, using a flexible extension set or an epidural catheter to maintain correct positioning in the epidural space.

Key points

- The speed of injection is thought to have caused a change in epidural and intracranial pressures resulting in a generalised seizure.
- Large volume intra-thecal injections should be administered slowly, over several minutes.
- Generalised seizures in an adult horse may pose a serious risk to people, and safety should be taken into consideration, particularly if the epidural is performed in a confined area.

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Clinical Commentary

Use of caudal epidural analgesia for management of orthopaedic limb pain in horses

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The case report by Tallon *et al*. (2021) in the current issue describes the development of a presumed generalised seizure in a pony following administration of morphine (0.2 mg/kg bwt) and detomidine (0.004 mg/kg bwt) diluted with saline to a relatively large total volume of 50 mL (0.2 mL/kg) into the caudal epidural space over approximately 90 s. The reason for performing the epidural injection was to treat severe pain of a thoracic limb, for which it proved to be successful. Despite the patient's swift recovery after the generalised seizure, the reporting and discussion of the use of large volumes of solution for caudal epidural analgesia are of great interest to all clinicians dealing with pain management in horses.

Severe orthopaedic pain in horses can be very challenging to manage with systemically administered drugs, although a plethora of suggestions and prescriptions exists (Matthews and Carroll 2007; Bardell 2017; Mama and Hector 2019). When severe orthopaedic pain is related to the pelvic limb, the most obvious and reliable pain management solution is, in the authors' opinion, caudal epidural administration of opioids alone or in combination with alpha$_2$ agonists. For example, the use of epidural morphine (0.1–0.2 mg/kg bwt) alone or in combination with detomidine (30 μg/kg) has been reported to provide effective pain relief for various painful pelvic limb conditions (Valverde *et al*. 1990; Sysel *et al*. 1996; Goodrich *et al*. 2002; Van Loon *et al*. 2012). However, when it comes to severe pain of the thoracic limb, the situation is somewhat different, as epidural analgesia is probably not the first pain management option to appear in most clinicians' minds despite its proven effectiveness (Freitas *et al*. 2011; Hopster and van Eps 2019; Tallon *et al*. 2021). Furthermore, the perceived complexity of the epidural technique and risk of side effects may deter many practitioners from using caudal epidural analgesia for pain management in horses. However, due to its role as a valuable analgesic option for both thoracic and pelvic limb pain, the practitioner should be acquainted with the technique and follow a few simple steps in order to maximise the chance of treatment success and minimise the risk of unwanted side effects. The main technical challenges associated with performing epidural injections in horses is to identify the correct injection site at the sacro-coccygeal or the first coccygeal intervertebral space and to place the needle/catheter exactly in the midline in order to ensure a symmetrical spread of the analgesic drugs in the epidural space and thus produce successful bilateral analgesia. For correct needle placement, it is important that the horse is properly restrained and is standing squarely with even weight

Fig 1: Preparation of a horse for caudal epidural injection: The horse should be slightly sedated and restrained in stocks (if possible). The area should be clipped and aseptically prepared. The site for injection can be identified by palpating for the first moveable coccygeal articulation while having an assistant lifting and lowering the tail.

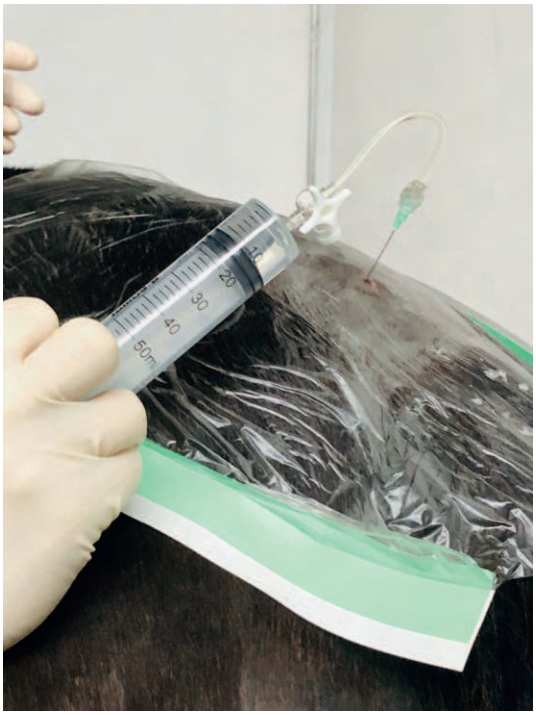

Fig 2: Caudal epidural injection using a hypodermic needle. A flexible extension set is used to decrease the risk of inadvertent movement of the needle if the horse moves during the slow injection. Note, the use of a sterile adhesive plastic drape to ensure asepsis during the procedure. If available, an extension set up to 50 cm could be used. It is important to prime the extension set with the solution to be injected and to pay attention to the residual volume left in the extension at the end of injection.

bearing on all four limbs and a symmetrical croup (**Fig 1**). Other important considerations when performing an epidural injection include choosing an appropriate drug, dose, volume and administration rate. Adverse effects can be caused by the administered drugs per se, but since the epidural route offers the opportunity for a more targeted analgesic effect, it is generally associated with fewer systemic side effects than systemic routes of administration. The most common side effects of epidural opioids include pruritus, sweating and decreased gastrointestinal motility (Haitjema and Gibson 2001; Boscan *et al*. 2006; Kalchofner *et al*. 2007; Sano *et al*. 2011; Kjærulff *et al*. 2021), whereas the epidural administration of alpha-2 adrenoceptor agonists can produce more serious side effects, such as sedation, cardiopulmonary depression, and motor blockade resulting in ataxia or recumbency (LeBlanc *et al*. 1988; LeBlanc and Eberhart 1990; Skarda and Muir 1994; Chopin and Wright 1995; Skarda and Muir 1996; Wittern *et al*. 1998; Dória *et al*. 2008; Bird *et al*. 2019). Adverse effects may also occur from the use of large volumes of solution and/or high rates of injection irrespective of the drug used. For example, it is well-described that the epidural injection of large volumes can cause compression of the spinal nerves in the epidural space which may cause significant discomfort, ataxia or even recumbency of the horse (Natalini and Robinson 2000; Olbrich and Mosing 2003). As hypothesised in the case report by Tallon *et al*. (2021), a rapid epidural injection (1.8 s/mL) of large volumes of solution (0.2 mL/kg) may also cause a change in the epidural and intracranial pressure resulting in generalised seizure. On an interesting note, we have had a very similar experience, in which a 500 kg Warmblood mare with severe thoracic trauma developed the exact same type of generalised seizure after caudal epidural injection of morphine (0.1 mg/kg bwt) and xylazine (0.17 mg/kg bwt) diluted with saline to a total volume of 0.1 mL/kg at a rate of 6 s/mL. The epidural analgesia was sufficient for a 4-h pain relief as assessed by using the Equine Pain Scale (Gleerup and Lindegaard 2016). Contrarily, we did not experience any side effects when administering the same drugs (at the same doses diluted to the same total volume) into the caudal epidural space at a rate of 22.2 s/mL to a 270 kg pony with severe laminitis of all four limbs. The epidural analgesia effectively relieved the pain of the pelvic limbs, whereas the decreased weight bearing of the thoracic limbs remained unchanged. For effective analgesia at the thoracic limbs, it has been recommended to use a large total volume of 0.2 mL/kg to facilitate more cranial migration of the drugs (Hopster and van Eps 2019). However, in the study by Freitas *et al*. (2011), it was shown that experimentally induced joint pain in the thoracic limbs was effectively controlled by epidural morphine diluted to a total volume of 0.15 mL/kg injected at a rate of 10 s/mL and that no side effects occurred. Combining these personal experiences with the clinical findings of the case report by Tallon *et al*. (2021) and the study by Freitas *et al*. (2011), it seems reasonable to conclude that successful provision of analgesia for thoracic limb pain after caudal epidural injection probably requires a total volume of 0.15–0.2 mL/kg and that it should not be injected at a rate faster than 10 s/mL. Slow injection of large volumes can, however, be particularly challenging if the horse is continuously weight shifting or in other ways difficult to keep standing still and if the syringe is attached directly to the epidurally placed hypodermic needle (Tallon *et al*. 2021). In these situations, the simplest solution for a single injection is to attach a flexible extension set between the needle and syringe since this will prevent movement of the needle when the horse moves (**Fig 2**). Alternatively, the injection could be performed through an epidural catheter, which is a more expensive option that will, however, allow for repeated administrations if needed. Regardless of the preferred method, strict adherence to aseptic technique during administration is of the utmost importance to avoid contamination of the epidural space and potentially resultant meningitis, although this is actually a rarely described complication.

In conclusion, high volume epidural analgesia can be useful to control pain in both thoracic and pelvic limbs in horses, and all practitioners are therefore encouraged to always consider the epidural route for management of severe orthopaedic pain in horses. By planning the injection ahead and adhering to the few steps outlined above, the risk of side effects is reduced and the chance of success is increased.

Author's declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Not applicable.

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None.

Authorship

Both authors contributed equally to the manuscript preparation.

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Case Report

Endoscopic sealing of a chronic bronchopleural fistula using acrylate co-monomer glue

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Keywords: horse; bronchopleural fistula; Acrylate co-monomer glue; methylene blue; thoracotomy; pleuropneumonia

Summary

A 13-year-old Oldenburg gelding was admitted with a necrotising pleuropneumonia. Despite extensive treatment with broad-spectrum antibiotics and bilateral thoracic drainage, clinical signs of pleuropneumonia remained. A right-sided thoracotomy with partial resection of the 7th rib was performed 25 days following admission, to assist in removing remaining pleural debris. The right hemithorax was flushed daily, but the gelding would cough and excrete fluid from the nostrils, consistent with a bronchopleural fistula (BPF). The horse was discharged from the hospital on day 110 following admission, to await spontaneous closure of the BPF. After 7 months, the horse was re-admitted to the hospital. The external thoracotomy incision had not completely healed, and the horse was still coughing, with a putrid nasal discharge. External thoracic lavage resulted in drainage of fluid from the nostrils. Taking into account the patient's history and clinical signs, it was assumed that the BPF was the underlying cause of the impaired wound healing.

An attempt was made to locate and close the BPF endoscopically. The BPF was identified by following a mucous track within the bronchi, until it reached a location where the mucosa of the peripheral bronchus appeared thickened and hyperaemic. Following retrograde instillation of methylene blue through the thoracotomy site, the location of the BPF was confirmed by the presence of methylene blue in the suspected bronchus (**Fig 1**). The size of the BPF was estimated to be 5–10 mm. The BPF was sealed with endoscopic application of 1–2 mL of acrylate co-monomer glue into the affected bronchus. The procedure was repeated four times, until a total of 6 mL acrylate co-monomer glue provided a complete seal over the BPF. Subsequently, the thoracotomy site healed and clinical signs disappeared within 4 weeks of the final glue application. A repeat endoscopy revealed the formation of granulation tissue in the affected bronchus 8 weeks post-treatment (**Fig 2**). The horse competed successfully at elite-level showjumping 4 months following closure of the BPF.

Fig 1: Methylene blue appearing at the affected bronchus a), confirming the presence of a bronchopleural fistula. With this technique, the BPF could be precisely located and the size carefully estimated.

Fig 2: The bronchopleural fistula with granulation tissue (arrow) 1 month following the last application of acrylate co-monomer glue.

Key points

- The presence of a BPF can delay and even prevent healing of a thoracotomy site, with clinical signs of coughing and putrid purulent nasal discharge often seen.
- Localisation of a BPF in a horse can be achieved endoscopically, by retrograde instillation of methylene blue through the thoracotomy site.
- The bronchoscopic application of acrylate co-monomer glue can result in successful closure of a chronic BPF and should be considered a viable minimally invasive treatment option in selected cases.

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Clinical Commentary

Bronchopleural fistula in the horse: A conduit of chronicity

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Summary

Bronchopleural fistulas occur secondary to severe, chronic, bacterial pleuropneumonia in horses. Primary closure is rarely reported, and most bronchopleural fistulas resolve with time and prolonged antimicrobial administration. The case report in this issue describes primary closure with acrylate co-monomer glue. When faced with severe pleuropneumonia, clinicians can anticipate a good clinical outcome when infection can be eradicated which requires patience, persistence and the client's financial fortitude.

Descriptions of bronchopleural fistula development and management in equids are sparse in the veterinary literature. Most commonly, a bronchopleural fistula is preceded by severe, chronic, necrotising bacterial pleuropneumonia that ultimately results in communication between a peripheral portion of the conducting airway (segmental bronchus, bronchioles or terminal bronchioles) in the region of the affected lung and the pleural space (Reuss and Giguère 2015) (**Fig 1**). This certainly was the situation described in the companion article from Madsen *et al*. (2021) in this issue as pulmonary infection and the horse's immune system response led to parenchymal necrosis, formation of an abscess and eventual development of the fistula. It is important to note, however, that bronchopleural fistulas are not the most common complication of pleuropneumonia in horses. In one report, they occurred in approximately 6.5% of cases (Byars and Becht 1991). It is possible that they occur more often and simply are not recognised or remain undiagnosed, since clinical signs of a bronchopleural fistula are indistinct from clinical signs commonplace in horses with pleuropneumonia (nasal discharge and cough). The development of a bronchopleural fistula was associated with a poorer prognosis for return to racing in Thoroughbred horses (Seltzer and Byars 1996), and they are perceived to delay healing and prolong the duration of treatment (Dechant 1997).

The diagnostic approach to identifying bronchopleural fistulas in horses has been summarised in a small number of case reports, while closure of the fistula has been described in only a few, including the companion article in this issue. In many instances, surgical intervention to drain an abscess or remove necrotic lung tissue is undertaken via a thoracotomy with or without rib resection, only to later discover the presence of a bronchopleural fistula. In these cases, the thoracotomy provides the access needed for lavage and decontamination of the affected pleural cavity. However, when a bronchopleural fistula is present, as the pleural space is being lavaged, fluid may be seen trickling from the nostrils or the horse may begin to cough.

It is important to recognise that discovery of a bronchopleural fistula should not lead to immediate dread and despair that complete healing will never be achieved. If, however, a fistula results in the acute onset of bilateral pneumothorax, as occurred in a horse in one report (Sanchez *et al*. 2002), steps should be taken quickly to stabilise the patient before crafting a plan to close the fistula. If the fistula is not associated with pneumothorax, most likely it will close given time, prolonged antimicrobial treatment and diligent lavage and debridement. Once a fistula is suspected or identified, high-volume lavage should be avoided to prevent spread of infected debris into the airway or associated pulmonary tissue (Chaffin *et al*. 1994). The primary goal in the management of these horses is to provide a hospitable, infection- and debris-free environment to promote granulation tissue to replace the damaged tissue, seal the fistula and to eventually 'fill' the abscess cavity. In time, contraction of these tissues will lead to closure of the space and healing of the surgical site from the inside out.

A critical part of the treatment plan is to eliminate infection. The authors of the companion article in this issue suggest that the fistula was responsible for the return of the horse's cough and putrid nasal discharge, and that may well have been the case; however, typically bronchopleural fistulas themselves are unlikely sources of infection. It is probably more accurate to think of a fistula as a natural conduit for infected material to escape the pleural cavity and enter the airway. In this author's experience, the cavitations that develop after thoracotomy with rib resection can contain numerous 'nooks and crannies' in which infected material can persist. Consequently, it is possible that infected material was not completely vacated from the space, resulting in chronic abscessation. A mature abscess may have ruptured into the airway or communicated with the bronchopleural fistula, and this was the cause for the horse's cough and putrid nasal discharge. In those instances in which the infection cannot be resolved or a bronchopleural fistula is determined to be the reason for a nonhealing thoracotomy site, primary closure is reasonable to consider.

The companion article in this issue sheds light on another important aspect of this disease process – time. In fact, the timeline for this particular case might be even more surprising to some readers than the concept of sealing a bronchus with medical grade glue. For example, it appears that the horse had been affected for at least one week before being examined at the veterinary clinic, was hospitalised for nearly 4 months before being discharged for continued lavage at home, and returned 7 months later with a persistent cough and putrid nasal discharge after the thoracotomy site had spontaneously closed. The horse was hospitalised for an additional month, during which time the bronchopleural fistula was sealed. Four months later, the horse returned to

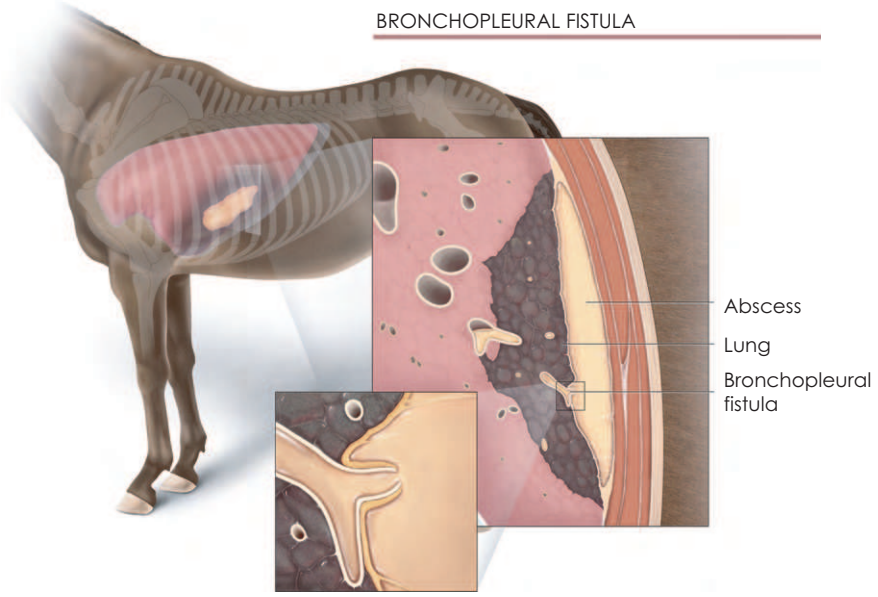

Fig. 1: Pleural abscess with bronchopleural fistula in the horse. A longitudinal section through the abscess is magnified, depicting the communication between the peripheral bronchial tree and the pleural abscess. Note that this is a chronic stage in disease; therefore, most of the lung in this image is normal (indicated by pink coloured lung tissue) opposed to the red-brown discoloured abnormal lung axial to the abscess and in the location of the bronchopleural fistula. (Illustration by Ali Ennis, Courtesy of the Educational Resource Center, University of Georgia, Athens, GA).

work as a performance animal. Consequently, the horse was under treatment and out of training, for approximately one year. This is not out of the ordinary for severe pleuropneumonia cases. Clients should be forewarned that the road ahead is long with most horses requiring treatment for many months beyond the initial hospitalisation period before the disease is resolved. It also is important to note that a mature pleural or pleuropulmonary abscess had to develop before surgical intervention via thoracoscopy or thoracotomy could occur. Otherwise, the risk of pneumothorax and spread rather than containment of infection would have been too great.

A final point to glean from the companion article is that the most important aspect of successfully managing a horse with pleuropneumonia might very well be client education. On Day 1 of the diagnosis of severe pleuropneumonia, it is prudent to discuss the financial commitment, convalescent period, the likelihood of both short- and long-term complications, and the nearly inevitable fact that the horse will need a thoracotomy at some point. As exemplified by the companion article, the prognosis for pleuropneumonia in horses with prepared, dedicated and financially committed owners is good.

Author's declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Not applicable to this clinical commentary.

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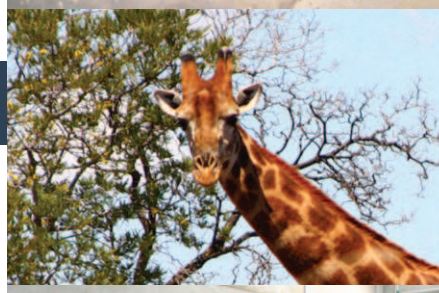

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Case Report

Fibromatous epulis in a Campolina horse

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Keywords: horse; oral cavity; odontogenic tumour; immunohistochemistry

Summary

An 11-year-old Campolina horse was referred due to the presence of an exophytic mass located in the rostral region of the mandible for approximately 3 years. The vital parameters were within the normal range and upon inspection of the oral cavity, an exophytic mass of approximately 5.0 × 5.0 cm was found, situated in the rostral region of the mandible, between the mandibular central (401) and intermediate incisor (402), extending from the labial vestibule to the sublingual floor (**Fig 1**). The radiographic examination showed an area with soft tissue radiopacity and well-defined margins between teeth 401 and 402, causing labial/mesial and labial/distal displacement of the teeth, respectively; tumour infiltration in the mandibular bone was not evident. Macroscopically, the biopsies exhibited firm consistency, compact regular appearance and whitish colouring. Histopathological evaluation showed a benign neoplastic proliferation with two distinct components, the first composed of islets of epithelial cells and the second composed of densely arranged connective tissue, slightly atypical and abundant in collagen (**Fig 2**). The immunohistochemical evaluation demonstrated positive labelling for pancytokeratin (AE1 + AE3 cocktail) in the epithelial islands, and smooth muscle actin (1A4) and vimentin (VIM384) in vessels. Histopathological and immunohistochemical findings were compatible with a fibromatous epulis. Surgical excision was performed under general anaesthesia by means of removing the oral mucosa 3 cm adjacent to the mass, except in the region of contact with the incisor teeth, followed by dissection until total detachment from the underlying tissue. Extensive bone curettage of the rostral portion of the mandible was performed and mucosal closure was not performed due to the impossibility of apposition of the wound edges. The follow-up showed satisfactory results over a year; however, recurrence occurred between 1 and 3 years after surgery. Unfortunately, the owner did not want to continue with the treatment. This report describes a rare case of fibromatous epulis in horse, highlighting the histopathological and immunohistochemical diagnosis as well as the recurrence of the mass after surgical resection.

Fig 1: Exophytic mass of approximately 5 × 5 cm, located in the rostral region of the mandible, between the mandibular central (401) and intermediate incisor (402).

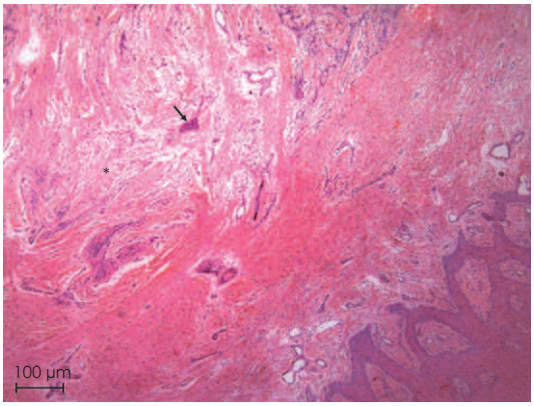

Fig 2: Histopathological examination. Benign neoplastic proliferation consisting cells organised in multiple bundles arranged in several directions interspersed with abundant fibrovascular and collagenous stroma (asterisk). Rounded polygonal cells organised into multiple islands interconnected and delimited by fibrovascular tissue (arrow) (haematoxylin and eosin, 40×).z

Key points

- Fibromatous epulis is a rare neoplasm of the oral cavity in horses.
- The histopathological and immunohistochemical evaluations are essential in determining the diagnosis and exclude differential of malignant neoplasms, such as fibrosarcoma.
- The recurrent characteristic of the mass even without evidence of tumour infiltration in radiographic examination suggests that more invasive surgical approaches should be considered to ensure safe surgical margins.

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Clinical Commentary

Fibromatous epulis and peripheral odontogenic fibroma in horses

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Keywords: horse; cancer; tumour; neoplasia

Summary

Fibromatous epulis is a rare tumour in horses which is analogous to the same condition in dogs and peripheral odontogenic fibromas in man. The nomenclature is varied throughout the veterinary literature, but these tumours are most correctly known as peripheral odontogenic fibromas. Although these lesions are benign, they have a high recurrence rate in other species, so wide local excision is important to give the best possible prognosis.

Clinical commentary

The oral mucosa is constantly exposed to a variety of stimuli and can develop a complete spectrum of disease, from developmental, reactive and inflammatory to neoplastic. Chronic trauma can induce inflammatory changes, leading to the development of granulation tissue that then proliferates into a tumour-like lesion known as reactive hyperplasia. All pedunculated and sessile gingival lesions have been designated as 'epulis', with an epulis being a nonspecific, descriptive term for a benign, locally exophytic growth of the oral mucosa (Gardner and Baker 1991). The terminology can become confusing, with ossifying epulis, fibromatous epulis, fibroosseous epulis and peripheral odontogenic fibroma being used interchangeably throughout the veterinary literature. Masses in the oral cavity that are derived from the periodontal ligament are most accurately called a peripheral odontogenic fibroma, partly to avoid confusion with the human condition known as fibrous epulis, which is reactive, localised inflammatory hyperplasia rather than a truly neoplastic lesion (Manabe *et al*. 2019), and partly because more recent small animal veterinary literature has recognised that the peripheral odontogenic fibroma described in the human literature is directly analogous to the veterinary condition, and therefore preferentially use this terminology (Gardner and Baker 1991; Fonseca *et al*. 2014; Khot *et al*. 2017; Wingo 2018). Fibromatous epulis will therefore be referred to as peripheral odontogenic fibroma (POF) for the rest of this discussion.

Peripheral odontogenic fibroma is extremely common in dogs and are occasionally seen in cats, but is very rare in horses. POF appears to originate from the periodontal ligament, arising in the soft tissue adjacent to a tooth, and is covered by epithelium. They are generally nonpainful but may cause discomfort if the overlying epithelium becomes inflamed and ulcerated. They often become large and may interfere with mastication due to their space-occupying nature, which may be the first clinical sign observed by owners. They are microscopically characterised by a well-vascularised, dense stroma that is populated by cells with abundant collagen fibrils that resemble the periodontal ligament. The main differential diagnoses for POF are ameloblastoma (and other odontogenic neoplasms) and non-neoplastic growths such as gingival fibrous hyperplasia.

In human subjects, although reactive hyperplasia and gingival growths are common, peripheral odontogenic tumours are rare (Khot *et al*. 2017). The most commonly diagnosed peripheral odontogenic tumour in people is the peripheral odontogenic fibroma (Khot *et al*. 2017). These lesions have a strong predisposition towards the incisor region (Ritwik and Brannon 2010), similar to that described in the Campolina horse in the case report by Schade *et al*. (2021). It is thought that breakdown of the dental lamina is more likely to leave odontogenic epithelial remnants in this region, leading to the increased incidence of POF in this region in people (Ritwik and Brannon 2010). However, lesions have been described in the premolar and molar regions in human subjects, albeit less commonly than in the incisor region, so these lesions may occur in any location and are seen in the mandible and maxilla with equal frequency (Ritwik and Brannon 2010). The small number of cases described in horses makes it impossible to draw any definite conclusions about any possible predilection sites, although it is interesting to note that these lesions have been described in both the incisor region and in front of the premolars in the mandible of horses (Hablolvarid *et al*. 2012; Schade *et al*. 2021).

Peripheral odontogenic fibromas are most commonly diagnosed in middle-aged to older people and are benign, slow-growing, exophytic lesions with the potential for recurrence following excision (Gardner and Baker 1991; Khot *et al*. 2017). In general, gingival lesions have a tendency to recur which may be due to incomplete excision or due to ongoing local irritation (Kashyap *et al*. 2012; Khot *et al*. 2017). Only a small number of cases have been reported in the human literature; of those, the recurrence rate was 50% (Ritwik and Brannon 2010). There are histological variables that appear to be associated with the risk of recurrence of peripheral odontogenic fibromas. Budding of the basal cells appears to be associated with an increased risk of recurrence, and the presence of calcification in opposition to odontogenic epithelial rests appears to be associated with a reduced risk of recurrence (Ritwik and Brannon 2010). Due to the small number of cases reported in the equine literature, it is not possible to make any inference as to the likelihood of histological variables being associated with recurrence of the lesions, and the description of the histological findings in the reported cases is minimal. However, it would be interesting to note the presence or absence of these specific features in any future cases. In cats, a small case series has noted that radiotherapy gave long-term control of POF, in contrast to surgery alone where recurrence is common (Moore *et al*. 2000). It may therefore be useful to consider radiotherapy

of these lesions in horses as an adjunct to surgical excision. To the author's knowledge, there are no reports of radiotherapy for the treatment of POF in a horse, but it has been described for treatment of other oral and sinonasal lesions such as juvenile ossifying fibroma (Robbins *et al*. 1996; Orsini *et al*. 2004; Witte 2014).

Where POF is diagnosed in a horse, similar to in other species, complete excision is required to give the best prognosis. Advanced imaging techniques such as computed tomography could be considered to more thoroughly evaluate the underlying bone, as more radical resection may be required to reduce the risk of recurrence. The case described by Schade *et al*. (2021) described recurrence of the lesion between 1 and 3 years post-resection; other equine cases have only had short-term follow-up. In human patients with POF, it is recognised that long-term follow-up is required due to the relatively high risk of recurrence which may occur many years after the initial surgical resection (Khot *et al*. 2017). It is therefore prudent to warn owners of the possibility of late recurrence and to perform wide local excision, possibly with the addition of adjunctive radiotherapy.

Author's declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Ethical approval not required for this clinical commentary.

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Original Article

Difficult horses – prevalence, approaches to management of and understanding of how they develop by equine veterinarians

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Keywords: horse; veterinarian; injury; learning theory; behaviour

Summary

Despite the considerable risk of veterinary occupational injury due to adverse horse behaviour, limited information is available about the prevalence of unwanted equine behaviours or common approaches to managing them. An understanding of learning theory may affect veterinarians' approaches to dealing with unwanted equine behaviours; however, learning theory is not widely taught. The aim of this study was to document the challenges equine veterinarians face when working with difficult horses and define their approaches to managing them, including their understanding of the processes through which horses learn. A link to an online survey was distributed via email amongst UK equine veterinarians. Descriptive and Kruskal–Wallis statistical analyses were performed. We found that 95% of equine veterinarians reported working with difficult horses on at least a monthly basis, resulting in 81% of them sustaining at least one injury in the last 5 years. The most popular methods of dealing with unwanted behaviours were physical and chemical restraint. 46% of those surveyed had never received any tuition on the processes through which horses learn. Despite 79% believing they had at least a moderate understanding of equine learning theory, they performed poorly when tested, with only 10% able to get at least five out of six questions correct. Further education on the subject of learning theory may be beneficial.

Introduction

Working as an equine veterinarian has been shown to carry a high risk of occupational injury, with horse behaviour being a well-recognised risk factor (Reijula *et al*. 2003; Jäggen *et al*. 2005; Nienhaus *et al*. 2005; Fritschi *et al*. 2006; Houpt and Mills, 2006; MacLeay 2007; Parkin *et al*. 2018). To the authors' knowledge, there have been no previous studies investigating the prevalence of unwanted equine behaviours that veterinarians currently experience, or their approaches to managing these unwanted behaviours. It was hypothesised that equine veterinarians would frequently encounter horses aversive to various aspects of veterinary care and that many horses exhibit potentially dangerous behaviours such as kicking with a hind leg, barging, rearing or striking with a foreleg.

Formal training on the subject of equine behaviour and specifically the processes through which horses learn new behaviours (learning theory) remains limited. Current literature on undergraduate veterinary training suggests the emphasis remains on physical restraint when faced with a difficult horse (Austin *et al*. 2007; Cawdell-Smith *et al*. 2007; Chapman *et al*. 2007; Hanlon *et al*. 2007; Stafford and Erceg, 2007), and so it was hypothesised that veterinarians would be reliant on chemical and physical restraint to mitigate against the potential adverse effects of these equine behaviours. Developing a greater understanding of the most common types of unwanted behaviours seen, the popular methods of dealing with these and the current level of understanding of learning theory by equine veterinarians have the potential to highlight areas where further education or research may help reduce the risk of occupational injury.

Materials and methods

Questionnaire

A questionnaire was drafted using web-based proprietary software[1] and piloted amongst equine veterinarians at the authors' institution. Responses and comments about the questionnaire from 13 staff were used to make adjustments to the questionnaire. The final questionnaire (**Supplementary Item 1**) consisted of 26 questions, the majority with closed options (e.g. scale and multiple choice) and the others with open ended (free text comments). All data were anonymised.

The questionnaire was distributed via an electronic survey invitation included as a link in two editions of the British Equine Veterinary Association (BEVA) e-Newsletter and also included in an email sent to referring practices of the authors' institution. A second, reminder email, was sent out one month later. Approximately 1700 veterinarians received the BEVA eNews and/or direct email (Brown *et al*. 2014). Aside from question 12 (which related to the consequences of any injuries sustained, so did not apply to respondents who had not sustained an injury), all closed ending questions were compulsory. Only fully completed questionnaires were included in the results.

The questionnaire was divided into five sections:

1 Demographics of respondents (questions 1–7).
2 Prevalence of difficult horses and unwanted equine behaviours (questions 8–10).
3 Number of injuries sustained from horses within the last 5 years, the consequences of these injuries and how frequently they perceived they were in a dangerous situation when working with horses (questions 11–13).

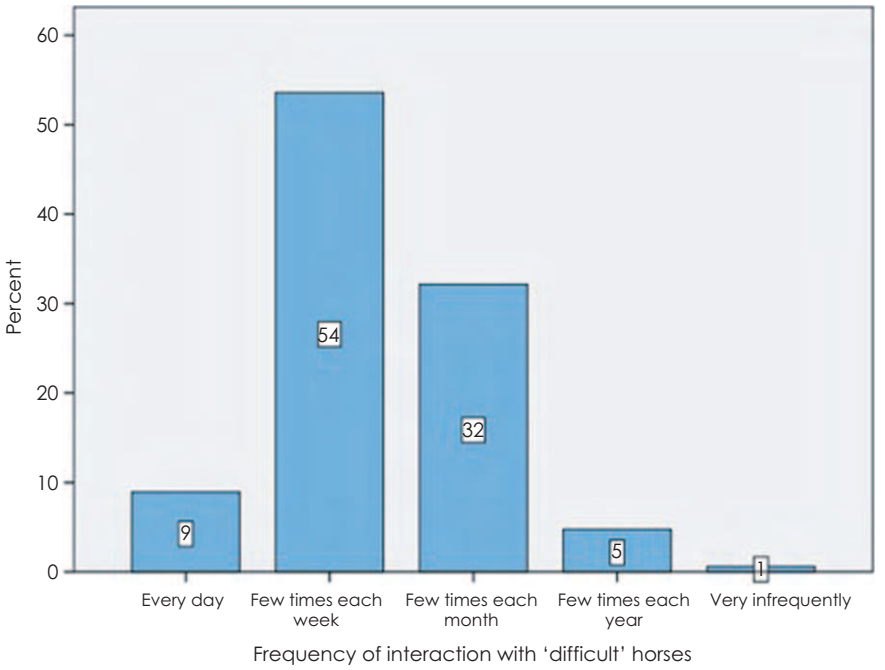
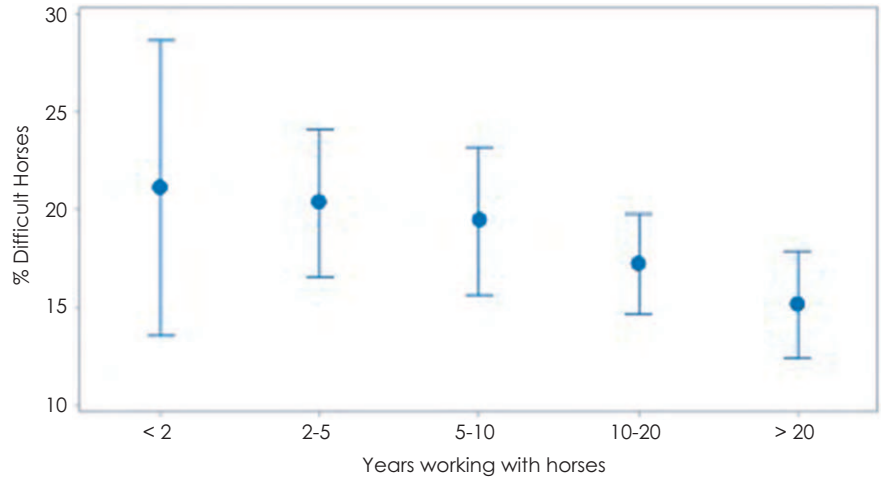


Fig 1: Box plots showing the frequency of interaction with horses that the veterinarian perceived as difficult (percentage shown in box).



Individual standard deviations were used to calculate the intervals.

Fig 2: Interval plot showing the percentage of horses treated that were considered 'difficult' subdivided by number of years spent working as an equine veterinarian. The dots represent the mean, and error bars represent 95% lower and upper confidence intervals of the mean.

4 Value placed on different specified methods of controlling difficult horses (questions 14–15).
5 Knowledge of learning theory:

   a How much teaching they had received, how well they understood how horses learn and how effectively they could apply this knowledge (questions 16–18).
   b Understanding of specific terms relating to learning theory: Respondent's perceived understanding of specific terms, for example negative reinforcement (yes, no) and respondent's actual understanding tested by their ability to select the correct description of specific terms.

Statistical analyses

To investigate whether the number of years working as an equine veterinarian was related to the number of difficult horses/number of specific unwanted behaviours (such as needle shy horses), veterinarians encountered, the frequency

of these scenarios were defined. The number of horses seen per month was converted from an ordered category (from the survey) into a single numerical value (*a*), estimated as the middle of the group, see **Supplementary Item 2**. The frequency of experiencing an unwanted behaviour was also converted from an ordered category into a single numerical value (*b*) as shown in **Supplementary Item 2**, attempting to take into account how frequently these scenarios were encountered per month, based on 20 working days per month. A percentage value was then calculated as the number of times an unwanted behaviour was encountered divided by the number of horses veterinarians treated each month multiplied by 100 ($b/a \times 100$). Frequencies of encountering unwanted behaviours were tested for normality using Ryan Joiner tests and were not significantly different to normal and so were compared between 'years working with horses' groups using Kruskal–Wallis tests (Minitab[2]), and $P < 0.05$ was considered significant.

Descriptive statistical analyses of the remaining data were undertaken using IBM SPSS[3].

Results

Demographics

Of 220 completed questionnaires, 28 (12%) were excluded as the veterinarians reported they were based outside of the UK. A further 27 questionnaires (12%) were excluded as they reported routinely treating 20 or fewer horses each month, which made comparisons of frequency data for these respondents unreliable. This left 168 respondents that were included in the final analyses.

The majority of respondents (73%, n = 123) reported spending 100% of their time working with horses, with 79% (n = 132) seeing more than 50 horses each month.

Frequency of difficult horses and unwanted behaviours

Ninety-five per cent of veterinarians reported interacting with horses that they perceived to be difficult at least a few times each month (**Fig 1**). Although there appeared to be a relationship between increasing veterinary experience and decreasing frequency of dealing with 'difficult horses' as well as decreased variance (**Fig 2**), this was not statistically significant (P = 0.11).

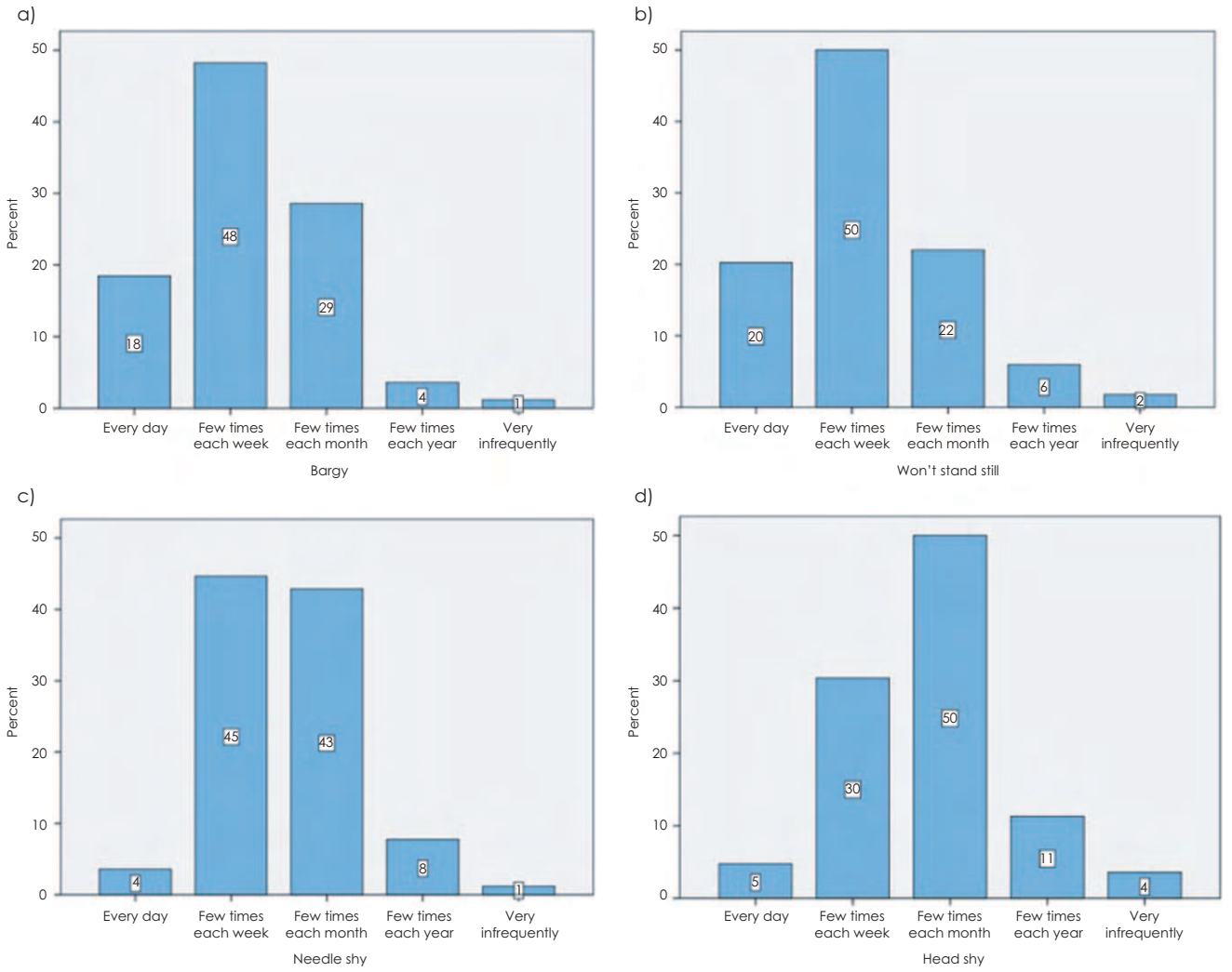


Fig 3: Box plots showing the most common unwanted behaviours equine veterinarians encountered (percentage shown in box).

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TABLE 1: The frequency of unwanted behaviours encountered and association between reduced prevalence with experience

Unwanted behaviour	Percentage (%) of veterinarians encountering the behaviour on at least a monthly basis	Association between decreased frequency of unwanted behaviour and increased years working in equine practice
Bargy/Pushy	95	**P = 0.002**
Won't stand still	92	**P = 0.002**
Needle shy	92	**P = 0.005**
Head shy	85	**P = 0.009**
Clipper shy	84	P = 0.138
Kick with a hind foot	67	**P = 0.019**
Pull away	58	P = 0.051
Refusing to load	55	P = 0.335
Strike with a fore foot	50	**P < 0.001**
Rearing	49	**P = 0.007**
Refuse to enter stocks	49	P = 0.407
Refuse to be caught (stable or field)	49	P = 0.279
Bite	41	**P < 0.001**
Refuse to enter examination room	41	P = 0.205

Values in bold indicate significant results.

The most common unwanted behaviours were horses that were bargy/pushy, would not stand still, were needle shy or head shy (**Fig 3**), all of which were encountered significantly less frequently with increasing years working in equine practice (**Table 1** and **Fig 4**). Other unwanted behaviours encountered included head butting/striking with head (8 respondents, 5%), crushing people against walls (7 respondents, 4%), refusing to lift feet (4 respondents, 2%,), resenting palpation/handling of feet/limbs (2 respondents, 1%) and refusing endoscopy (2 respondents, 1%).

Injury rates

Eighty-one per cent of respondents (n = 136) had sustained at least one injury, caused by a horse that they were treating or examining, in the previous 5 years. In total, 579 injuries were reported in the previous 5 years, with one further respondent reporting more than 30 injuries in the past 5 years. Of these injuries, 88 (15%) required a visit to hospital, 61 (11%) required a visit to their general practitioner, 92 (16%) required days off work and 215 injuries (37%) resulted in continued discomfort or loss of function.

Frequency of dangerous working situations

A cumulative frequency of 92% of respondents reported that they put themselves in a potentially dangerous situation when working with horses on at least a monthly basis (**Fig 5**).

Methods of restraint or control of difficult horses

The most popular method of restraint was chemical sedation with 99% of respondents considering it either very or fairly useful, for full results see **Table 2**. Further free text responses reported physical restraint with 20 respondents (12%) suggested an ear twitch and six suggested use of a lip chain/ stabiliser. Use of stocks or a crush was suggested by 13 respondents (8%) with a further 8 (5%) suggesting other methods of confining the horse such as in a stable or trailer. Blindfolding was suggested by 7 respondents (4%). Help by a competent person was suggested by 12 respondents (7%). Many other single responses are not described but are available in **Supplementary item 1**.

Perceived understanding of learning theory

Forty-six per cent of respondents (n = 65) reported that they had received no tuition on the subject of learning theory, and yet 78% of respondents (n = 131) reported that they understood how horses learn and were able to apply this knowledge either moderately, well or very well (**Fig 6**).

Perceived understanding of learning theory terminology

With regard to operant conditioning, a high percentage of respondents thought they understood the term positive reinforcement, 84% (n = 118), and negative reinforcement, 80% (n = 113). The respondents were less confident when asked about punishment with only 38% (n = 54) (positive punishment) and 47% (n = 66) (negative punishment) saying they understood the terms. The majority of respondents, 79% (n = 111), also reported understanding the term habituation, but were less confident about the term classical conditioning 57% (n = 81).

Actual understanding of learning theory terminology

When tested, of the 84% (n = 141) who stated that they did understand the term positive reinforcement, only 19% (n = 22) were able to correctly identify the scenario as incorrect. Of the 80% (n = 134) who had stated they correctly understood the term negative reinforcement, only 33% (n = 37) were correct. Whilst far fewer respondents had originally stated they understood the terms positive punishment (38%, n = 64) and negative punishment (47%, n = 79), those respondents still only correctly identified the scenarios in 43% (n = 23) and 67% (n = 44) cases, respectively. Better results were seen for the terms habituation (97% [n = 129] of the 79% [n = 132], who thought they understood the term) and classical conditioning (91% [n = 87] of the 57% [n = 96] who thought they understood the term), as shown in **Table 3**.

Discussion

The cause of the low response rate of 13% (of approximately 1700 members) is unknown, but is not dissimilar from another BEVA survey (Parkin *et al*. 2018) which received 318 responses to three emails in comparison with our 220 responses from two emails. Whilst equine veterinarians with differing levels of experience from across the UK were included, whether the 168 respondents are representative of the estimated 1900 equine vets (Mayes 2015) in the UK is unknown. It is likely that some selection bias occurred; the title of the link was 'difficult horse survey' so veterinarians that held opinions on horses

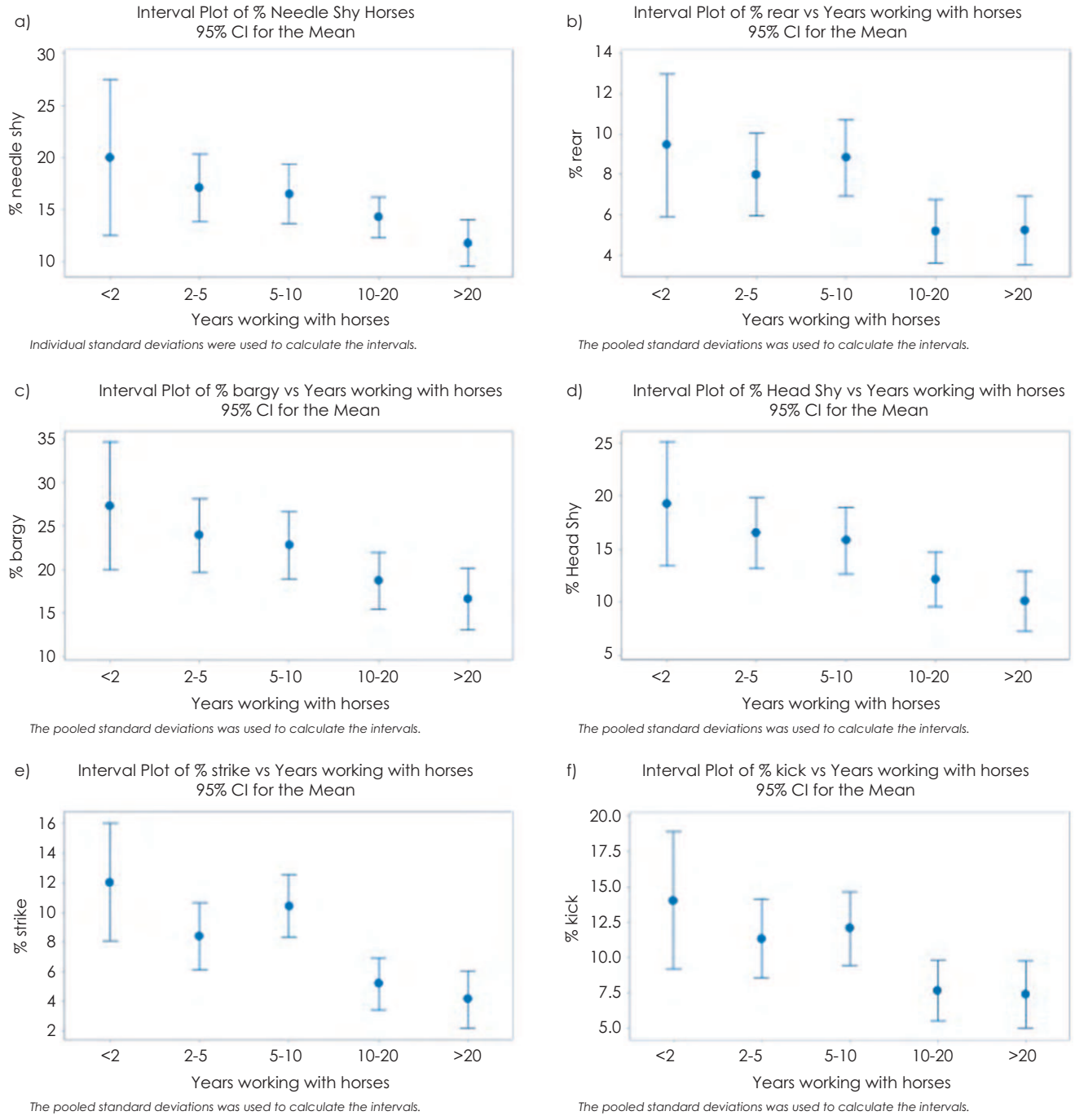

Fig 4: Interval plot graphs demonstrating the effect of years working as an equine veterinarian on the percentage of cases seen demonstrating various unwanted behaviours. The dots represent the mean, and error bars represent 95% lower and upper confidence intervals of the mean. All results were significant ($P < 0.05$).

they perceived as difficult and those that had sustained an injury may have been more likely to participate. Scotland was over-represented with 41 respondents (24%); this would be expected considering the majority of the authors' institution referral practices emailed were based in Scotland. The rest of the responses for UK distribution, gender, nature of practice and years working in equine practice were similar to those described in other studies (Parkin *et al*. 2018) The survey was distributed in winter 2014 and so may not fully reflect the current situation amongst UK veterinarians, although this time delay between collection of data and publication is similar to other publications such as Parkin *et al*. (2018)

'Difficult horses' were seen at least monthly by 95% of respondents. Whilst the definition of a 'difficult horse' likely varied slightly between respondents, this gives an overview of how commonly veterinarians experience challenging equine patients. The subsequent definitions provide more details of specific unwanted behaviours.

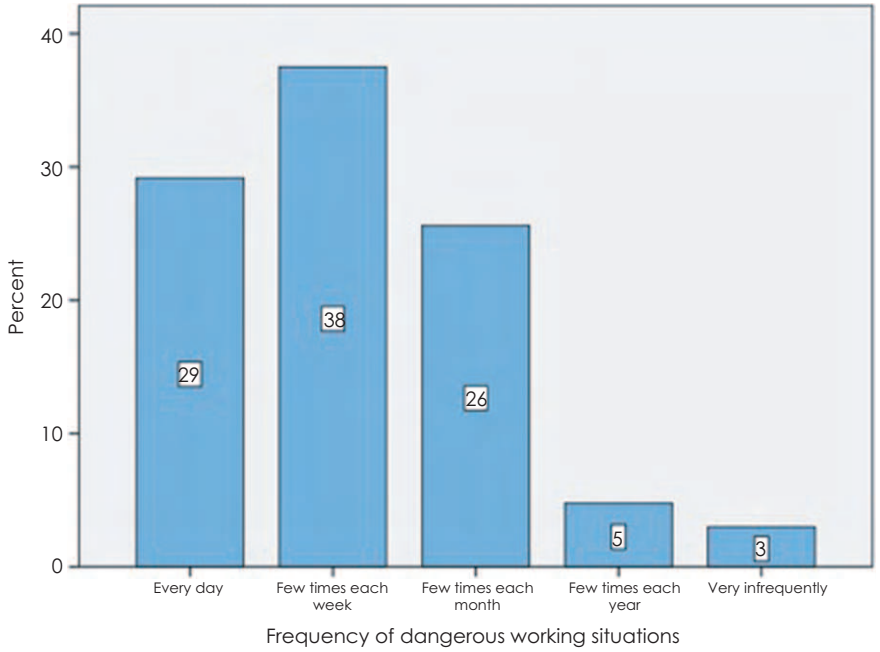

Fig 5: Box plot showing the prevalence of situations equine veterinarians perceived as potentially dangerous.

TABLE 2: Value placed on methods of restraint for control of difficult horses

Method of restraint	Percentage (%) of veterinarians considered the method			
	Very or fairly useful	Useful	Unhelpful, very unhelpful or useless	Don't understand or have not heard of technique
Sedation	99	1	0	0
Nose twitch	74	23	3	0
Neck twitch	69	24	7	0
Chifney bit	57	40	3	0
Bridle	49	46	5	0
Holding up a foreleg	47	42	11	0
Food distraction	39	46	15	0
Positive reinforcement	20	41	8	11
Remote injection	18	39	33	10
Lunge line	14	51	33	2
Overshadowing	8	9	16	67
Negative reinforcement	7	31	50	11

The two most commonly encountered unwanted behaviours (bargy/pushy and refusing to stand still) were indicative of poor stimulus control. A horse is described to be under stimulus control when they consistently respond to a cue or stimulus from the handler and are not influenced by the environment (McGreevy 2010). Further education and training of horse owners and handlers to be able to achieve stimulus control may be useful for reducing these most common unwanted behaviours.

Aversions to specific stimuli (injections, handling of their head and clippers) were the next most common unwanted behaviours. Many of these stimuli are veterinary context specific, suggesting that further training in methodology to treat horses with aversions safely and effectively might be beneficial for veterinarians.

The prevalence of behaviours that have the potential to cause human injury (kicking with a hind foot, striking with a front foot, rearing or biting) was high, providing further insight into the rate of occupational injuries in the profession. It is also consistent with findings in other studies (Lucas *et al*. 2009; Brown *et al*. 2014; Parkin *et al*. 2018) where the most common causes of injuries were a result of a kick from a hindlimb, strike with a forelimb and crush injuries.

The association between increasing veterinary experience and decreasing adverse behaviours may suggest that veterinarians have a direct influence on the horse's behaviour. It is also consistent with other work demonstrating that veterinarians sustained fewer injuries per year with increasing experience (Parkin *et al*. 2018). Despite more recent graduates making up the smallest groups (<2 years = 6%, 2–5 years = 16%) of veterinarians included; they had much wider variation in their responses to the prevalence of various unwanted behaviours, when compared to the most experienced graduates who made up the largest groups (10–20 years = 30%, >20 years = 25%). This might reflect greater variation in the handling skills of recent graduates and that veterinarians adapt their techniques over time. Alternatively, it is also possible that veterinarians encountering many unwanted and potentially dangerous behaviours leave the equine sector.

The unwanted behaviours that were not significantly influenced by the number of years' experience included

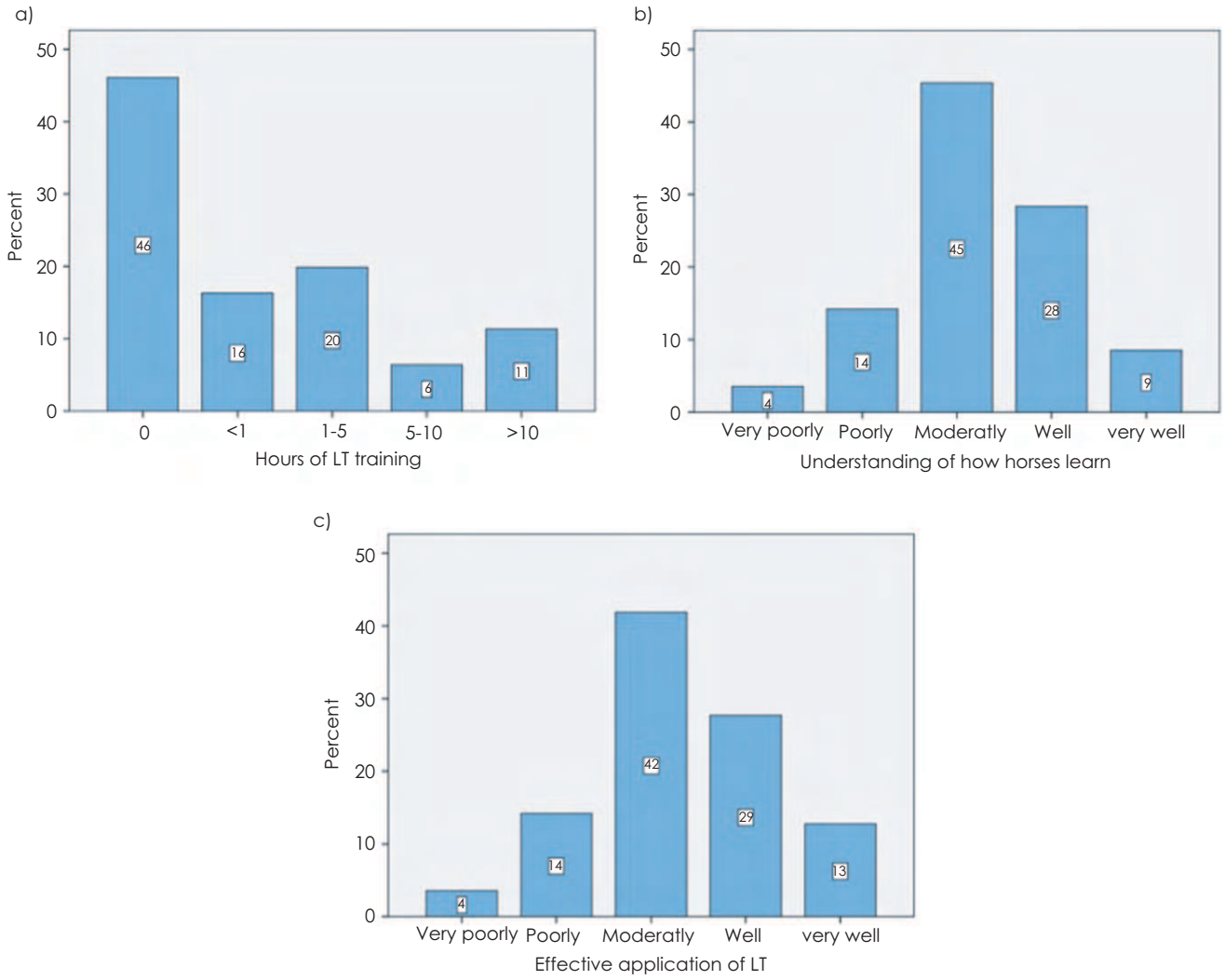

Fig 6: Box plots showing the reported hours of tuition respondents had received on the subject of learning theory, their perceived knowledge of understanding of how horses learn and ability to apply it.

TABLE 3: A summary of the responses given by participants who had previously stated they understood terminology related to learning theory

		Response to scenario by those who reported understanding the term		
Terminology	Number who reported understanding the term	Number who chose the correct answer	Number who chose the incorrect answer	Number who stated they did not know the answer
Positive reinforcement	118 (84%)	22 (19%)	90 (76%)	6 (5%)
Negative reinforcement	113 (80%)	37 (33%)	72 (64%)	4 (3%)
Positive punishment	54 (38%)	23 (43%)	25 (46%)	6 (11%)
Negative punishment	66 (47%)	44 (67%)	13 (20%)	9 (13%)
Habituation	111 (79%)	108 (97%)	0 (0%)	3 (3%)
Classical conditioning	81 (57%)	74 (91%)	2 (3%)	5 (7%)

those which had a reduced frequency generally, so may be related to lack of power of the study and those which might be expected to be more established in other situations outside of the veterinary environment; for example refusing to load into trailers.

Overall, 81% of respondents reported 579 injuries sustained due to the horse they were working with and 37% of these resulting in continued discomfort or loss of function, demonstrating repeatability as Parkin *et al*. (2018) found 80% of 620 UK veterinarians were injured by a horse. These figures continue to be concerning and do not suggest any reduction in the risk of occupational injury, despite previous studies highlighting the problem and suggesting action taken to improve these figures should be prioritised. Whilst variation in survey design prevents direct comparison, Landercasper *et al*. (1988) found 65% of 995 American veterinarians had sustained a major animal-related injury, with 17% or respondents being hospitalised in the previous year in 1988 and in 2006 (Fritschi *et al*. 2006) found 65% of large animal veterinarians had sustained an injury during their career that required hosptial admission or significantly affected their work. Whilst these studies did not specifically look at injuries induced by horses, 71% of all accidents to veterinarians were associated with horses in the Netherlands in 2003 (Stembert *et al*. 2003).

Heath (2004) reported that equine veterinarians acknowledge the risk of occupational injury. This is supported by this survey where 29% of respondents stated that they put themselves in a potentially dangerous situation every day and a concerning 92% of respondents who acknowledge that they put themselves in a potentially dangerous situation, when working with a horse, on at least a monthly basis.

Currently equine veterinarians rely on chemical and physical restraint to allow them to complete their work when dealing with difficult horses; given the high prevalence of injuries, it is possible that these methods are not the most effective. As flight animals, horses prefer to withdraw from a situation they find aversive. If restraint prevents retreat, however, they are more likely to act aggressively instead with these behaviours being shaped into more dangerous responses surprisingly quickly (Lucas *et al*. 2009; Brown *et al*. 2014). Education of equine veterinarians, particularly with regard to management of difficult horses, may help to reduce these dangerous scenarios, as has been previously suggested (Doherty *et al*. 2017). Considering this, it is therefore disappointing that respondents reported having received limited training on the processes through which horses learn.

Despite many respondents reporting that they had a reasonable knowledge of how horses learn and with the ability to apply this knowledge, the respondents demonstrated a poor understanding of learning theory terminology. A similar lack of understanding in larger studies of horse trainers based in Australia and Canada (Warren-Smith and McGreevy, 2008; Wentworth-Stanley 2013) has been reported, suggesting a possible gap of knowledge across the equine industry. It is possible that equine veterinarians understand the processes through which horses learn without understanding the terminology. Although when asked how highly they rated various methods of dealing with unwanted behaviours, the respondents rated methods based on learning theory very poorly. Whilst this may simply represent a lack of understanding of the terminology, the preference for physical restraint was emphasised in the free comments section, where there were no descriptions of techniques based on learning theory; this suggests there is a genuine lack of understanding. It is possible that increased training of equine veterinarians in the field of equine learning theory may reduce the high prevalence of occupational injuries caused by a horse's behaviour. Indeed, a 45-minute lecture on learning theory, and its application in the veterinary environment, was found to increase undergraduate students perceived confidence when confronted with a difficult horse. Even more encouragingly several students reported being able to successfully apply this new knowledge to difficult horses they encountered whilst on rotations, with many reporting they felt safer and less likely to become injured (Pearson 2017). Incorporation of education of learning theory into the undergraduate curriculum and as postgraduate training is indicated.

Authors' declaration of interests

No conflicts of interest are declared.

Ethical animal research

This study was approved by the Human Ethical Review Committee (HERC), The Royal (Dick) School of Veterinary Studies, HERC_509_20.

Source of funding

None.

Antimicrobial stewardship policy

This study did not involve or discuss any antimicrobials.

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Authorship

G. Pearson designed and executed the study, analysed and interpreted the data and prepared the manuscript. R. Reardon assisted with study design as well as analysis and interpretation of the data. J. Keen and N. Waran assisted with study design. All authors gave their final approval of the manuscript.

Manufacturers' addresses

[1]Bristol Online Survey, Bristol, UK.
[2]Minitab 17 Statistical Software, Pennsylvania, USA.
[3]IBM SPSS Statistics 21, IBM, Online

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Supplementary Item 1. The questionnaire distributed amongst equine veterinarians within the UK, including results from those included in the final analysis.

Supplementary Item 2. The methodology used to determine the prevalence of unwanted behaviours.

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For additional information, see brief summary of prescribing information on the following page.

References: 1. Zimeta® (dipyrone injection) [package insert], Rev. 12/2020. **2.** Morresey PR, et al. Randomized blinded controlled trial of dipyrone as a treatment for pyrexia in horses. *Am J Vet Res.* 2019;80(3):294-299.

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Original Article

Magnetic resonance imaging changes of the navicular bursa following navicular bursoscopy in seven horses

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Keywords: horse; bursitis; proliferative; deep digital flexor tendon; adhesions

Summary

Navicular syndrome is a multifactorial disease process in horses with multiple structures in the foot contributing to lameness. Surgical debridement is a treatment option for lesions of the navicular bursa and deep digital flexor tendon. This retrospective case series describes the magnetic resonance imaging (MRI) appearance of the navicular bursa following bursoscopy. Seven horses (three being bilaterally affected) with forelimb lameness isolated to the foot, and pre- and post-operative MRI were included. All limbs had concurrent lesions associated with the deep digital flexor tendon, navicular bone, impar ligament, collateral sesamoidean ligament and/or distal interphalangeal joint. All bursae developed or had progression of proliferative bursal tissue following surgery. At recheck MRI, following rehabilitation protocols, almost all horses had improved to resolved lameness with relatively unchanged concurrent lesions despite the navicular bursa appearance worsening. Outcomes for return to work were poor with only two horses going back to the previous level of work.

Introduction

Chronic forelimb lameness associated with pain arising from the navicular bone and associated structures is defined as navicular syndrome/disease (Ackerman *et al*. 1977; Dyson *et al*. 2003; Murray *et al*. 2006; Dyson and Murray, 2007; Smith and Wright, 2012). Damage to multiple structures in the foot can be concurrent, often involving the navicular bursa, a synovial structure that allows the deep digital flexor tendon (DDFT) to glide smoothly along the flexor surface of the navicular bone. Treatment of the navicular bursa may involve medical and, in some cases, surgical approaches. While not always considered the primary cause of lameness (Sampson *et al*. 2009) nor the sole pathological change in the foot (Dyson and Murray, 2007; Dyson *et al*. 2005), the navicular bursa is an important component of the injuries that affect the navicular apparatus.

Navicular bursoscopy can be used for both diagnostic and therapeutic purposes for DDFT lesions in the suprasesamoidean region or for navicular bone flexor cortical erosions (Smith *et al*. 2007). Reasons to elect for bursoscopy can include dorsal border tearing of the DDFT, proliferative navicular bursitis and accessible lesions of the navicular bone. Previous data have demonstrated a positive outcome for soundness (11/15; 73%) and return to previous level of work (9/15; 60%) following bursoscopy for nonseptic changes associated with the DDFT and/or navicular bone flexor cortex (Smith *et al*. 2007).

Navicular bursitis can be effusive or proliferative. Effusive bursitis is accumulation of bursal fluid without changes to the bursal wall, while proliferative bursitis is characterised by thickening of the bursal wall and intrathecal synovial proliferation with or without adhesion formation (Barrett *et al*. 2017). It is thought that purely effusive bursitis tends to be more acute and responsive to medications such as intrathecal steroid administration (Bell *et al*. 2009; Marsh *et al*. 2012), while the proliferative form is more chronic and more often to be found in conjunction with other pathology and lameness (Murray *et al*. 2006; Blunden *et al*. 2006; Bell *et al*. 2009; Marsh *et al*. 2012; Holowinski *et al*. 2012).

The aim of this descriptive case series is to describe the MRI appearance of the navicular bursa before and after bursoscopy, and report the degree of lameness at the time of each MRI, as well as outcomes for return to work.

Materials and methods

Subject selection

The study was a retrospective, descriptive case series; institutional approval for the data collection was established via a signed client consent form for use of patient data at hospital admission. A computerised medical record search was conducted from 2012 to 2019 for horses undergoing navicular bursoscopy with referral or in-house MRI both prior to, and after, bursoscopy. Cases were included in which bursoscopy was performed on a single limb or multiple limbs in the same patient.

Data recorded

For each included horse, the following clinical findings as reported in the medical record were recorded: signalment, use and pertinent historical data including history of trauma, prior relevant treatments, and onset and duration of lameness in days. Examination parameters recorded included degree of lameness based on the American Association of Equine Practitioners (AAEP) grading scale (grade 0–5) and response to diagnostic analgesia in per cent change. All musculoskeletal and lameness examinations had been performed by experienced lameness practitioners board certified in surgery or equine sport medicine and rehabilitation or by referral veterinarians.

MRI examinations were either performed at Colorado State University or a private referral practice. Sequence selection

[Correction added on 14 August 2020, after first online publication: The corresponding author has been amended in this version.]

varied somewhat between the different MRI systems; however, all studies included transverse proton density (PD), transverse and sagittal short tau inversion recovery (STIR), and sagittal or dorsal plane T1-weighted gradient-echo sequences. University MRI findings from Colorado State University were recorded from the veterinary radiologist report, written at the time of image acquisition and reviewed by a board-certified veterinary equine radiologist. Referral private practice MRI findings were acquired from reports generated by board-certified veterinary radiologists who regularly consult for this practice. Images were reviewed in conjunction with reports at the time of data collection. Structures evaluated included the navicular bursa, navicular bone, DDFT, collateral ligament of the navicular bone, impar ligament, distal interphalangeal joint, collateral ligament of the distal interphalangeal joint and subchondral bone. Findings were graded subjectively as mild, moderate, or severe by the reporting radiologist and reviewed and corroborated at time of data collection by the authors. In only one case did the original report differ from the findings when the images were reviewed by the authors. In that case, the authors included a lesion of the DDFT that was not described in the original report. Data were collected for all available subsequent recheck MRI examinations in the same fashion, and time between recheck examinations was recorded as days elapsed.

Intraoperative findings, treatments and rehabilitation protocols, when available, were recorded. Outcome data were obtained a minimum of 6 months from initial diagnosis from the medical records or via telephone interview. Overall outcome for surviving horses was categorised as returning to the same or higher level of work, returning to lower level of work or lack of return to work.

Data analyses

Simple descriptive statistics were performed (Microsoft Excel 2010, USA). Data were tested for normality using the Shapiro–Wilk test (GraphPad Prism 7, USA) and were not normally distributed. Therefore, medians and ranges were reported.

Results

Signalment, history and clinical findings

Fifty-two horses in the time period underwent navicular bursoscopy. Ten limbs in 7 horses (or 13% of the navicular bursoscopy population) had pre- and post-operative MRI examinations and were included in the study (**Table 1**). Two were mares, five were geldings, and ages ranged from 6 to 13 years old (median 8 years). There were three Warmbloods, three Quarter Horses and one Arabian mix representing Western Performance (n = 3), eventing/jumping (n = 2), trail/pleasure riding (n = 1) and dressage (n = 1) disciplines. All limbs affected were forelimbs (6 right, 4 left), with three horses being bilaterally affected. Duration of lameness was chronic in all cases, ranging from one month to 2.5 years (median 150 days). None of the horses had a history of trauma. Four of the seven horses (57%) had a history of previous intrathecal treatment with both steroids and hyaluronic acid (n = 3) or stem cells (n = 1). One horse received systemic bisphosphonates.

Median degree of lameness at presentation was 3/5 (range 2/5–4/5). Lameness resolved or substantially improved following palmar digital nerve analgesia in 9 of the 10 limbs (range 75–100%, median 100%). In all bilaterally affected cases, performing bilateral palmar digital nerve blocks resulted in complete resolution of the lameness.

MRI protocols

Seven horses met inclusion criteria and underwent a total of 24 MRI examinations, 10 before surgery and 14 after surgery. Two horses had two bilateral forelimb post-operative MRI examinations at different time points. Most MRI examinations were performed with a 1.0 Tesla magnet in lateral recumbency (20/24; 84%). Two examinations were performed with a 3.0 Tesla magnet in lateral recumbency, both post-operative scans in two different patients (Case 1, Case 6). Two examinations were performed in a standing low-field magnet (0.3 Tesla) at a private practice referral

TABLE 1: Case signalment, presentation, history, examination and blocking pattern in limbs that underwent navicular bursoscopy

Case	Signalment	Forelimb	Duration	Lameness grade (AAEP 0–5)	Block performed	Block results
1	6-year-old WB gelding, hunter/jumper	Right	4 months	3	Palmar digital	100% (switched to left)
2	13-year-old WB mare, eventing/jumping	Right	6 months	3	Palmar digital	100% (switched to left)
3	8-year-old QH gelding, reining	Bilateral	2.5 years	L: 3 R: 1	Palmar digital	L: 100% (switched to right) R: not performed
4	6-year-old Arab mix gelding, trail/pleasure riding	Left	1 month	4	Palmar digital	'Blocked'
5	12-year-old WB gelding, dressage	Right	1 year	3	Simultaneous palmar digital/digital tendon sheath	75%
6	8-year-old QH gelding, cutting	Bilateral	4 months	L: 2 R: 2	Palmar digital	L: 100% (switched to right) R: not reported
7	6-year-old QH mare, reining	Bilateral	2 months	L: 4 R: 3	Palmar digital	L: 'blocked' R: 'blocked'

L, left; R, right.

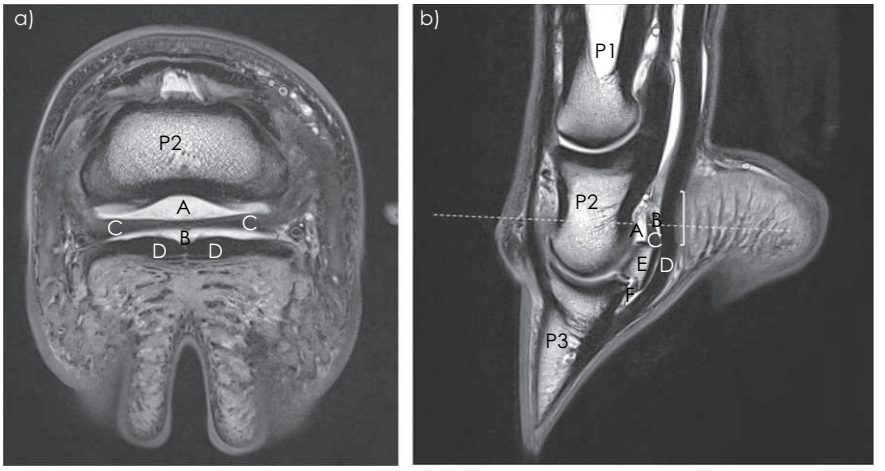

Fig 1: PD weighted transverse (a) (lateral is to the right and dorsal to the top of the image) and DIXON in-phase sagittal (b) images from a 3 Tesla magnet in a normal horse; a white dashed line on the sagittal (b) image indicates the level of the transverse image. The navicular bursa (B) is located between the bilobed DDFT (D) and collateral sesamoidean ligament (C). Note the thin wall of the bursa and slight amount of fluid in the normal bursa, as well as a mild amount of effusion in the more dorsal distal interphalangeal joint (A), separated from the bursa by the collateral sesamoidean ligament. (P1: proximal phalanx, P2: middle phalanx, P3: distal phalanx, E: navicular bone, F: distal sesamoidean impar ligament). The white bracket indicates the suprasesamoidean region of the DDFT.

hospital, both preoperative scans in two different patients (Case 5, Case 6).

Preoperative MRI findings

The navicular bursa was normal in 4/10 limbs on initial MRI (**Fig 1**). In 3/10 limbs, the bursa was considered effusive (moderate in 2, severe in 1) (**Fig 2a**). In the remaining three limbs, the navicular bursa was moderately proliferative with little to no effusion (**Fig 2b**). Bursal distention with saline was performed in one case with proliferative bursitis (Case 6), in which adhesion formation was diagnosed between the DDFT and navicular bursa, as well as between the DDFT and adjacent flexor cortical erosion.

Diffuse, mild thickening of the collateral sesamoidean ligament was observed in 5 of 10 limbs. In three limbs, the distal sesamoidean impar ligament was mildly diffusely thickened and there was mild irregularity or sclerosis of the distal phalanx at the impar ligament insertion.

All limbs had DDF tendinopathy of varying severity on initial MRI (**Table 2**). All had pathology in the navicular bursa in the suprasesamoidean region and most had multifocal lesions distal (n = 8; 80%) to this area as well. There was no specific predisposition for medial lobe, lateral lobe or both, and a variety of lesion types were present (**Table 2**). Moderate to severe DDFT and navicular bone degenerative changes were also observed in all three limbs with proliferative bursitis.

One horse (Case 5) had moderate distal interphalangeal joint effusion and synovial proliferation; Case 1 had a focal cartilage defect of the mid-lateral aspect of the distal phalanx in addition to mild distal interphalangeal joint synovial proliferation.

Operative findings

Navicular bursoscopy was performed using the previously described indirect approach via the digital tendon sheath

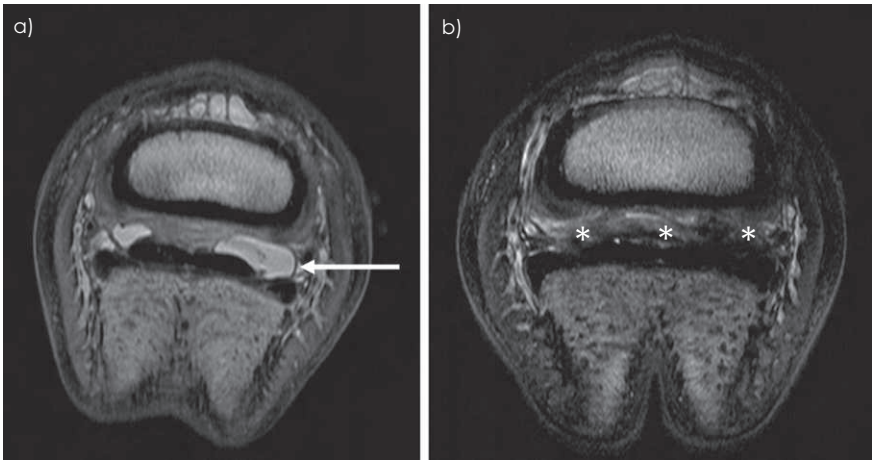

Fig 2: Severe effusive (a) and severe proliferative (b) navicular bursitis. Both are transverse PD images using a 1.0 Tesla magnet, lateral is to the right, dorsal to the top. Note the thin wall (arrow) of the effusive bursa (a). There is marked proliferative tissue in the bursa (*) with little to no fluid (b).

(Wright *et al*. 1999; Haupt and Caron, 2010), by experienced diplomate surgeons with 10 to over 25 years of experience. A single surgeon with over 20 years of experience performed surgery on 5 of the 7 horses. Surgery was performed on average 25 days following the initial MRI (range 2–56 days, median 23 days) and identified adhesions within the bursa in 5/10 limbs, 3 of which were suspected on MRI or diagnosed following bursal distention. Adhesions were diagnosed on MRI in one horse that were not identified intraoperatively. Inflamed synovium and fraying/tearing of the DDFT was observed and debrided with a synovial resector in the majority of bursae (n = 8/10 limbs). Adhesions were transected with a synovial resector and/or radiofrequency probe. Navicular bone fibrocartilage erosions were debrided with a curette or synovial resector (n = 3). Intraoperative hyaluronan (HA) with (n = 2 limbs) or without tissue plasminogen activator (TPA) (n = 4 limbs) was injected into the digital tendon sheath prior to closing the surgical portals.

Treatment

All horses were engaged in a rehabilitation programme (2 cases at home with oversight from the referring veterinarian, 5 at the institution's rehabilitation centre) for 2–7 months (median 2 months) post-surgery. One horse (Case 6) underwent two separate rounds of rehabilitation following each post-operative MRI examination (first 7 months, second 2 months).

A variety of medical treatments were applied at the clinician's discretion to each horse: daily systemic nonsteroidal anti-inflammatories (n = 3), mesenchymal stem cells (n = 6) (intrathecal [n = 3], intra-arterial regional perfusion [n = 2], intra-venous regional perfusion [n = 2] and undescribed [n = 2]), interleukin-1 receptor antagonist protein (IRAP) (n = 2), systemic bisphosphonates (n = 1), intrathecal tissue plasminogen activator/amikacin/hyaluronan (n = 2) and autologous conditioned serum (n = 1). Horses that were bilaterally affected had the same treatments applied to both forelimbs.

Post-operative lameness and MRI findings

Post-operative MRI was performed several months following surgery (average 386 days, range 201–926 days, median 273 days). An additional post-operative MRI was performed at 93 days (Case 3) and 817 days (Case 6) following the first post-operative MRI. Post-operative MRI findings are reported in **Table 2**.

Lameness scores at time of recheck MRI were improved in seven limbs (70%) and remained the same in three limbs (30%). Improvement ranged from 1 to 3 grades.

Post-operative MRI findings of the navicular bursa, DDFT and navicular bone are reported in **Table 2**.

In two cases, intermediate signal tissue was observed between the distal sesamoidean impar ligament and DDFT, associated with the distal aspect of the navicular bursa (Case 7, right front foot; Case 6 both feet) (**Fig 3**), which was not observed preoperatively. This tissue was identified in the sagittal plane with both PD and STIR sequences. Both cases had associated moderate to severe proliferative bursitis and changes associated with the DDFT and navicular bone.

Outcomes

One horse (Case 4) that underwent surgery for a grade 4/5 lameness remained 4/5 lame 2 years post-operatively and was eventually subjected to euthanasia in spite of medical management and extensive rehabilitation. One case (Case 2) had been back to trotting under saddle one month after recheck MRI, but was subjected to euthanasia for an unrelated traumatic humeral fracture 2 months later. Case 1 went back to a similar level of work 4 months after recheck MRI. One horse went back to a lower level of work (Case 7) one month following recheck MRI. This horse has remained intermittently lame since surgery (4 years at time of publication), although dealing with concurrent upward fixation of the patellae bilaterally at time of data collection. Two horses initially improved to the same level of work, but following severe reinjury in the foot (Case 6) or development of another site of lameness (Case 5), have not been able to maintain their former level of work. One horse (Case 3) was able to go back to the same level of work for 2 years, but has since been decreased to a lower level of work for reasons unrelated to the feet.

Discussion

In this case series, the MRI appearance of the navicular bursa worsened in all horses following bursoscopy, becoming more proliferative with reduced fluid. These changes did not appear to correlate with the degree of lameness at recheck MRI. These imaging features are most consistent with chronic, proliferative bursitis, although this was not confirmed histopathologically due to the retrospective nature of this study. The authors speculate that the proliferative bursitis in these cases may be due to iatrogenic trauma/inflammation secondary to surgery, natural disease progression of the concurrent pathology of the navicular apparatus or a combination of both.

On MRI, the normal navicular bursa should have clearly defined margins and contain homogeneous fluid without evidence of abnormal distention, proliferative tissue or bursal wall thickening. Navicular bursitis can be effusive or proliferative. In previous studies, the two forms of bursitis are often not separately distinguished (Blunden *et al*. 2006; Dyson and Murray, 2007; Bell *et al*. 2009). Although the same terminology was not used, effusive and proliferative type bursitis has been previously reported: navicular bursitis with increased fluid only (effusive bursitis) was reported in 15 horses, while navicular bursitis with scar tissue with or without fluid (proliferative bursitis) was reported in four horses of 101 horses undergoing MRI for palmar foot pain (Marsh *et al*. 2012). In that study, 65% of horses had injury to the DDFT in the portion of the tendon at the level of the navicular bursa. Nearly all (14/15; 93%) of the horses with only bursa effusion went back to work 2 days after intrathecal therapy, whereas only one of the four (25%) with proliferative bursitis went back to work. Mean duration of soundness following intrathecal bursa injection with corticosteroid and hyaluronan was 7 months for horses with effusive bursitis alone compared to 1.5 months in horses with proliferative bursitis (Marsh *et al*. 2012). The findings from our population are similar to those with described proliferative bursitis.

Not surprisingly, all horses had concurrent pathology of the DDFT in the suprasesamoidean region of the navicular bursa, which was accessible by bursoscopy. As has been reported previously (Holowinski *et al*. 2012), MRI and surgical assessments did not always agree with regards to adhesion formation in the navicular bursa. Without the use of bursa

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TABLE 2: MRI and clinical findings of the navicular bursa, DDFT, and navicular bone (NB) pre- and post-operative forelimb bursoscopy

Case	Bursa preoperative	Bursa grade preoperative	Bursa post-operative	Bursa grade post-operative	DDFT preoperative	DDFT change post-operative	NB preoperative	NB change post-operative	Change in lameness	Outcome
1	Normal	Normal	Proliferative	Moderate	Medial lobe tear†, mild lateral lobe fraying	Improved	No degenerative changes	None (normal)	improved 1 grade	Same level of work
2	Normal	Normal	Predominantly effusive with mild proliferation	Moderate effusion, mild proliferation	Moderate dorsal border tearing†, both lobes; core lesion in medial lobe	Improved lateral lobe, progressive medial lobe	No degenerative changes		Stayed the same	Subjected to euthanasia (humeral fracture)
3	Both normal	Both normal	Both proliferative	Both moderate	L: Moderate (lateral) and mild (medial) fraying† R: Core lesion lateral lobe†, mild medial dorsal border fraying	L: Improved R: Improved	L: Mild fibrocartilage damage, mild synovial invagination dilation R: Mild fibrocartilage damage	L: Unchanged R: Mildly progressive	L: Improved 3 grades R: Improved 1 grade	Same level of work
4	Effusive	Moderate	Proliferative	Severe	Mild tear of the medial lobe, dorsal border	Worsened	Multiple full-thickness erosions, endosteal sclerosis and moderate to severe fluid signal, moderately enlarged synovial invaginations		Stayed the same	Subjected to euthanasia
5	Effusive	Moderate	Proliferative	Moderate	Moderate chronic tearing, lateral lobe†	Stable	No degenerative changes	None (normal)	Improved 1 grade	Initially same level of work, then lower due to unrelated lameness
6	L: Effusive, R: Proliferative	L: Severe, R: Moderate	Both proliferative	L: Moderate R: Severe	L: Moderate medial lobe sagittal tear†, moderate dorsal margin fraying both lobes R: Moderate lateral lobe sagittal tear and dorsal margin fraying†	L: Stable to improved R: Stable to improved	L: Irregular endosteum, increased fluid signal, mildly dilated invaginations (mild to moderate degenerative changes and mild fluid signal) R: Flexor cortical erosion, moderate fluid signal (moderate to severe degenerative changes, erosion, and moderate oedema like syndrome)	Stable (degenerative changes) to improved (oedema syndromes)	Improved 2 grades	Initially same level of work, then retired due to progression of foot pathology
7	Both proliferative	Both moderate	Both proliferative	Both severe	L: Moderate, extensive tearing, most severe in the lateral lobe† R: Moderate tearing both lobes†, dorsal margin fraying and thickening	L: Improved R: Worsened	L: Flexor cortical erosion, moderate endosteal sclerosis, dilated synovial invaginations (marked degenerative changes) R: Mild synovial invagination dilation (mild degenerative changes)	L: Mildly progressive R: Mildly progressive	L: Improved 3 grades R: Improved 1 grade	Returned to lower level of work

L, left; R, right.
† Indicates injury in the suprasesamoidean region.

distention, which is not always clinically practical, proliferative bursal tissue can be difficult to differentiate from adhesion formation (Maher *et al*. 2011). In at least one case that did not undergo bursa distention, adhesions were diagnosed on MRI that were not present in surgery, indicating that MRI can have false-positive diagnosis of adhesion formation.

In all cases in which lameness improved (n = 7) between pre- and post-operative MRIs, the lesions of the DDFT had also improved and the navicular bone changes remained static, despite the bursa becoming more proliferative. This seems to suggest that the degree of lameness may be more correlated to the DDFT lesions rather than to the appearance of the navicular bursa. In one horse (Case 4), in which the unilateral lameness was unchanged (grade 4/5), the appearance of the bursa progressed from moderate, effusive to severe, proliferative bursitis. In this horse, a small tear in the medial lobe of the DDFT also significantly progressed to severe, extensive, multifocal tendinopathy with medial and lateral lobe enlargement. It is possible that both lesions could be contributing to the lack of improvement of lameness in this case; however, the progression of the DDFT lesions was likely more clinically significant.

The navicular bursa can show extensive pathology, but may not be the primary cause of lameness, as illustrated by the cases with two post-operative MRI examinations (**Fig 4**). In Case 3 and Case 6, both horses were sound at the first post-operative MRI. In both cases, lesions of the DDFT and navicular bone had been static to improved, while the bursa had become moderately to even severely (Case 6, right front foot) proliferative. Following second post-operative MRI, one horse (Case 3) remained sound with static to mildly progressive proliferative bursitis, and static DDFT and navicular bone lesions. In comparison, Case 6 was bilaterally 3/5 lame at the time of the second post-operative MRI, which revealed progressive severe proliferative bursitis of the left front, and persistent severe proliferative bursitis of the right front. In this case, the DDFT lesions were severely progressive in the left front foot, and a new partial thickness flexor cortical lesion was diagnosed in the left front navicular bone. Similarly, the right front DDFT lesions and navicular bone degenerative changes were also progressive. In both of these cases, the appearance of the navicular bursa did not improve over time, rather remained moderate to severely proliferative.

An MRI finding seen in some horses with moderate to severe proliferative bursitis (**Fig 3**) is that the proliferative tissue is not confined to the suprasesamoidean region but also extends into the distal recess of the navicular bursa with tissue extending between the distal sesamoidean impar ligament and DDFT. The increased tissue in the distal recess of the bursa may result in pressure resorption and secondary sclerosis of the flexor surface of the distal phalanx over time. This change should be critically evaluated in cases with navicular bursitis and warrants further investigation both clinically and histopathologically, as it may be an irreversible contributory factor to foot pain in horses and may be related to poorer outcomes.

Horses with more severe bursal changes on MRI preoperatively tended to have more severe pathology in other structures, including the DDFT and navicular bone (**Table 2**), while horses with normal or effusive bursae on preoperative MRI examination tended to have less severe pathology of the DDFT and navicular bone. Despite aggressive medical management and rehabilitation protocols, the patients with more severe changes did not return to full work or were subjected to euthanasia Although the navicular bursa pathology was moderate to severe and progressive, the concurrent DDFT and navicular bone changes were often also progressive and likely contributed more to the poor outcomes in these cases. MRI can be of benefit in these cases to determine severity of the related lesions when making clinical decisions.

Despite rehabilitation and additional medical therapies, outcomes of this study were poor with only two of the seven horses returning to their previous level of work following bursoscopy. Two horses initially went back to work for a period of time prior to reinjury or other lameness resulting in layoff. Three horses did not go back to work, one of which was subjected to euthanasia due to the severe foot pathology. The poor prognosis for our study population contrasts with another study in which 11 of 15 horses with follow-up were sound by 6 months post navicular bursoscopy and nine of these went back to their previous level of work (Smith *et al*. 2007). Interestingly, all horses in this study had DDFT lesions identified at the level of the bursa. The differences in outcome may be related to level of pre-existing injury, surgical approach and case management. While the ability to return to work is likely more heavily weighted towards the concurrent DDFT or navicular bone changes, a component of pain or comorbidity from the navicular bursa could be a contributing factor to lameness.

Limitations of this retrospective study are inherent. There is a selection bias both for horses undergoing bursoscopy, which had pathology amenable to surgical intervention, and for horses receiving follow-up MRI. It is likely that the cases selected for surgery had more severe pathology compared to those that received only medical management and these horses often had a poorer prognosis prior to surgery. This also eliminated cases with solitary navicular bursitis as well as those that responded to medical management and did not need surgery. Additionally, included cases required follow-up MRI, often performed following a rehabilitation protocol. Follow-up MRI may be less likely to be elected in horses that respond quickly and return to full work without lameness. This is a small descriptive case series, thus statistical calculations were not considered appropriate. Another limitation is that there were different MRI systems utilised. While most of the MRI examinations were performed using the same MRI, comparison between different systems, especially low and high field magnets, can be challenging and may limit detection of subtle lesions due to field strength resolution limits (Murray *et al*. 2009; Barrett *et al*. 2017).

Future goals include comparing the appearance of the navicular bursa over time on MRI in horses that do not have surgery to those that do, to see whether the changes in the bursa may be related to surgical trauma, natural disease progression or both. A larger or multi-institutional study could be performed to see whether the trends noted in this case series are consistent in a larger and/or different population of post-bursoscopy cases. More horses with subsequent MRI examinations could also be evaluated to see whether the changes in the bursa remain or whether they can improve. In this small sample, the length of time between some of the MRI examinations following surgery (upwards of 30 months) may indicate that these navicular bursa changes are unlikely to improve over time.

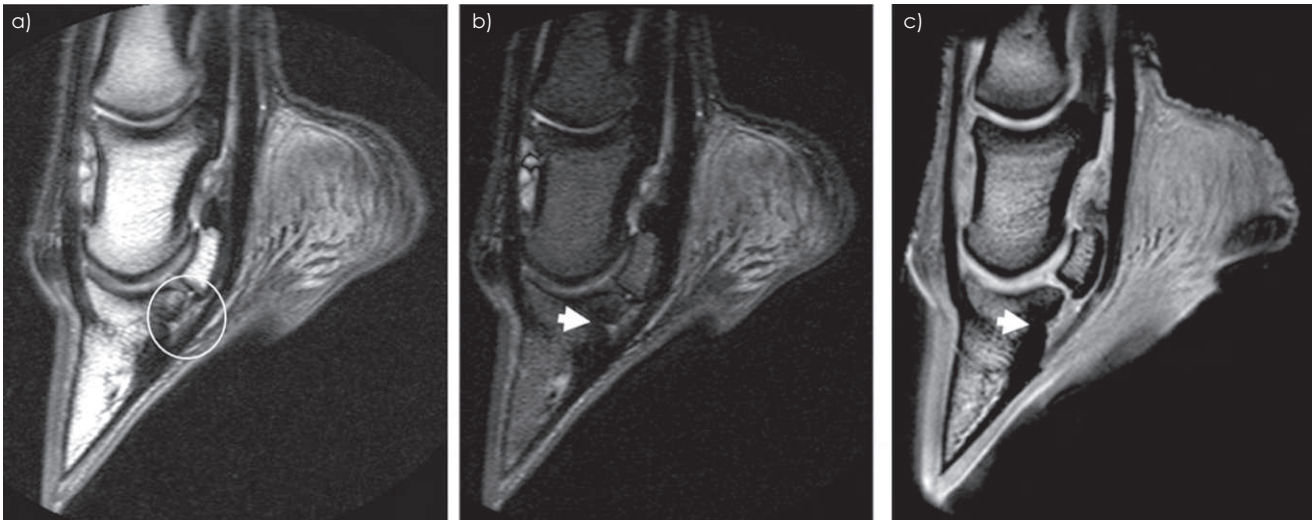

Fig 3: Sagittal PD (a), STIR (b) and T1 gradient-echo (3DGE) (c) sequences of Case 6 (right front) at second recheck MRI (1.0 Tesla). Note the intermediate signal tissue between the distal sesamoidean impar ligament and DDFT (circle), which can be compared to Figure 1, where no intermediate signal tissue is present. Also, note the sclerosis and focal osseous resorption of the distal phalanx at the level of and distal to the impar insertion (arrows).

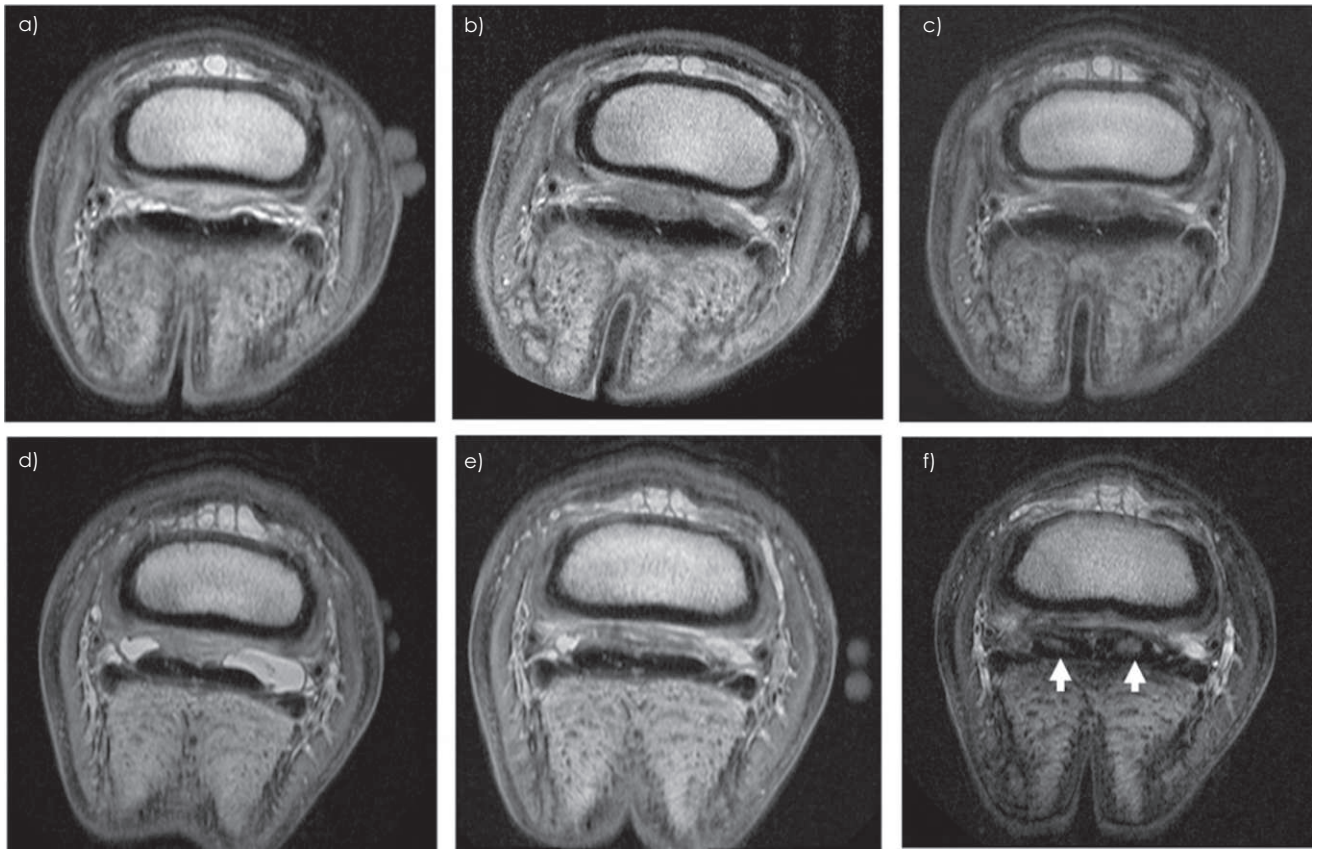

Fig 4: Transverse images using a 1.0 Tesla magnet (lateral is to the right, dorsal to the top of all images). Panes a–c are Case 3, panes d–f are Case 6. On the initial MRI (a and d), the navicular bursa was classified as being mildly proliferative (a) and effusive (d). Following bursoscopy, the bursae worsened to moderately proliferative (b and e). On the third MRI examination, Case 3 remained sound, with similar appearance to the navicular bursa (c), and the DDFT remains relatively similar between examinations. In comparison, Case 6 became much more lame (grade 3/5) between the second and third MRI. In (f), the DDFT is markedly enlarged with core lesions (arrows), while the bursa remained proliferative and was mildly progressive.

While the appearance of the navicular bursa often worsens on MRI following bursoscopy by becoming more proliferative, these changes did not correlate with degree of lameness at the time of repeat MRI, in this case series. Despite this, outcome for return to work in this small group of horses was poor. Findings associated with the navicular bursa should not drive clinical decision making, particularly in horses with other pathologic changes, such as DDF tendinopathy or navicular bone erosions, as these are more likely to be contributory to clinically relevant lameness.

Author's declaration of interest

No competing interests have been declared.

Ethical animal research

No approval required for this retrospective study.

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Authorship

Both authors contributed to study design and execution. Data analysis and interpretation and preparation of the manuscript were performed by Elizabeth Hoaglund. Both authors approved the final version of the manuscript.

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Review Article

Outpacing the resistance *tsunami*: Antimicrobial stewardship in equine medicine, an overview

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Keywords: horse; antimicrobial stewardship; antimicrobial resistance; equine medicine; major elements; editorial

Summary

Antimicrobial stewardship (AMS) is the term increasingly used to describe the multiple approaches needed to sustain the efficacy of antimicrobial drugs in the face of the increasing development and spread of antimicrobial resistance in bacterial pathogens, and the global crisis in medicine that it is engendering. The concept and the practices associated with AMS continue to evolve but the general approach is a dynamic and multifaceted one of continuous improvement based on reducing, improving, monitoring and evaluating the use of antimicrobials so as to preserve their future efficacy and to protect human and animal health. Using many equine examples, this basic overview discusses the multiple and interacting elements of AMS: Practice guidelines, infection control and prevention, clinical microbiology, resistance and use surveillance, dosage, pharmacokinetics and pharmacodynamics, regulation, education and owner compliance, leadership, coordination and measurement. There have been impressive advances in recent years in reporting and analysis of AMR in horses, in the scrutiny and assessment of how antimicrobial drugs are used in horses and in identification of areas for improvement including dosing, surgical prophylaxis, infection control, development of practice standards and the use of clinical microbiology. Antimicrobial stewardship is taking shape as we start to see the emergence of evidence-based recommendations but far more is required. Containing and even rolling back AMR will need the continued engagement of practitioners, equine national and international practitioner organisations, researchers and educators in the academic community, horse owners, regulators and others.

Introduction

It is hard to get a clear assessment of the overall state of antimicrobial resistance (AMR) in equine bacterial pathogens, in part because there is so little reporting by diagnostic laboratories. As a generalisation, it is perceived as generally stable or slowly increasing over time, but definitely not the *tsunami* it is becoming in human medicine. However, resistance in bacterial pathogens is so different. For example, *Streptococcus equi* subsp. *equi* and *zooepidemicus* remain exquisitely sensitive to penicillin G, despite the provocation of nearly 70 years of use, while MRSA (methicillin-resistant *Staphylococcus aureus*) has emerged in the last two decades as a significant problem in equine medicine. There are virtually no national level surveys (Bourély *et al*. 2020), since diagnostic samples are not collected systematically, since methodologies and breakpoints may be slightly different, and since antimicrobial use (AMU), the driver of resistance, can be dynamic (Prescott *et al*. 2002). In general, AMR in *E. coli* isolated from infections in horses is increasing, notably to ceftiofur, gentamicin and enrofloxacin (Theelen *et al*. 2014; Johns and Adams 2015). Extended-spectrum β-lactamase producing (ESBL) *E. coli* have been isolated from clinical infections in horses in a number of countries. Resistance problems are significantly more common in hospitalised horses where multi-drug resistant (MDR) opportunists including those sometimes called the ESKAPE pathogens (*Enterococcus faecium*, MRSA, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.) can be highly problematic. Successful MDR clones of *E. coli* and *K. pneumoniae* can also be a problem; the carriage of CTX-M-15 group extended-spectrum β-lactamase (ESBL) *E. coli* by hospitalised horses was shown to have increased in one equine hospital from 30% in 2008 to 50% in 2017 (Isgren *et al*. 2019). Resistance is associated with bad outcomes. For example, MDR bacteria were associated with highly significant poor survival rates in horses with septic synovial structures (Gilbertie *et al*. 2018) and foals with MDR *Enterococcus* spp. infection were more likely to die than foals not infected with MDR isolates (Willis *et al*. 2019). In some cases, the poor prognosis from MDR infections may reflect delays in proper diagnosis (and drug selection) when culture is not a routine practice. Since 'history is written by the winners, not by the losers', failure to address AMR in equine medicine now will inevitably make infections increasingly difficult to treat in the future. Equine practitioners are facing increasing AMR challenges in horses.

Antimicrobial stewardship (AMS) is the term increasingly used to describe the multiple approaches needed to sustain the efficacy of antimicrobial drugs in the face of the increasing development and spread of AMR in bacterial pathogens, and the global crisis in medicine that it is engendering (WHO 2015). The concept and the practices associated with AMS continue to evolve but the general approach is a dynamic and multifaceted one of continuous improvement based on reducing, improving, monitoring and evaluating the use of antimicrobials so as to preserve their future efficacy and to protect human and animal health. Antimicrobial use in veterinary practice can be evaluated and assessed against the concept of Good Stewardship Practice (GSP) (Weese *et al*. 2013) and an underlying '5R' approach of responsibility, reduction, refinement, replacement and review. Inherent in the GSP and 5R approach is the importance of coordination, evaluation and measurement. There are no magic bullets in AMS; complex

problems such as AMR require multiple solutions. Success in defeating or containing AMR will depend on the cumulative effects of multiple approaches and interventions combined with a mindset of continuous improvement based on measurement. AMS is a global movement to address AMR, with some excellent recent discussions relating to equine medicine (Bowen 2013; Slater 2015; Weese 2015; Raidal 2019).

The basic elements underlying the GSP include those identified in **Fig 1** (modified from Weese *et al*. 2013). The figure is not comprehensive; for example, 'benchmarking' is not included but is increasingly recognised as a valuable feedback tool to improve AMS.

Practice guidelines

The Protect ME approach to development of individual equine practice guidelines pioneered by the British Equine Veterinary Association (BEVA) (Bowen and Slater 2012) is an outstanding and globally exemplary model for practice level involvement in AMS in veterinary medicine. Supported by step-by-step downloadable instructions and wall chart materials, including non-antibiotic prescription forms, this toolkit is deservedly prize winning. Important elements include development of practice policies on a hierarchy of antimicrobial choice (first choice, alternate, 'protected', 'avoided' antimicrobials), on surgical prophylaxis, and on dosages and routes. The Protect ME approach uniquely puts the onus on the practice to engage with developing its own policies rather than being prescriptive. The critical element is thus engagement, for example through designation of roles as resistance leaders, resistance monitors and resistance reporters, thus addressing the behavioural, 'mindset' and educational changes required as we start to both reduce as well as to improve the way we use antimicrobials. Despite the excellence of Protect ME, including its use of a downloadable BEVA Antibiotic Champion Award certificate if certain criteria are met, it is not clear how many equine practices have adopted this voluntary approach. A survey published in 2013 reported that only 1% of equine practices in the UK had written practice AMU guidelines (Hughes *et al*. 2013) although the BEVA Protect ME website reports that two-thirds of equine practices had self-imposed policies for responsible AMU (see Protect ME website, Bowen and Slater 2012).

A study of antimicrobial selection in wound treatment found that 8.5% of horses were treated with 'protected' antimicrobials that were unlikely to be justified (Ross *et al*. 2016). In choosing antimicrobials, it is useful to remember that important or serious infections do not necessarily need 'important' (second or third line) antimicrobials.

Surgical prophylaxis is an area for considerable improvement in equine practice. The Protect ME suggested prophylaxis guidelines are traditional since they include routine antimicrobial prophylaxis for clean surgeries. For example, peri-operative benzyl penicillin t.i.d. i.v. for 24 h in horses undergoing clean surgery is suggested as a policy, with post-operative penicillin and gentamicin for 5 days suggested in contaminated surgery. It is, however, well established in human surgery that infection complication

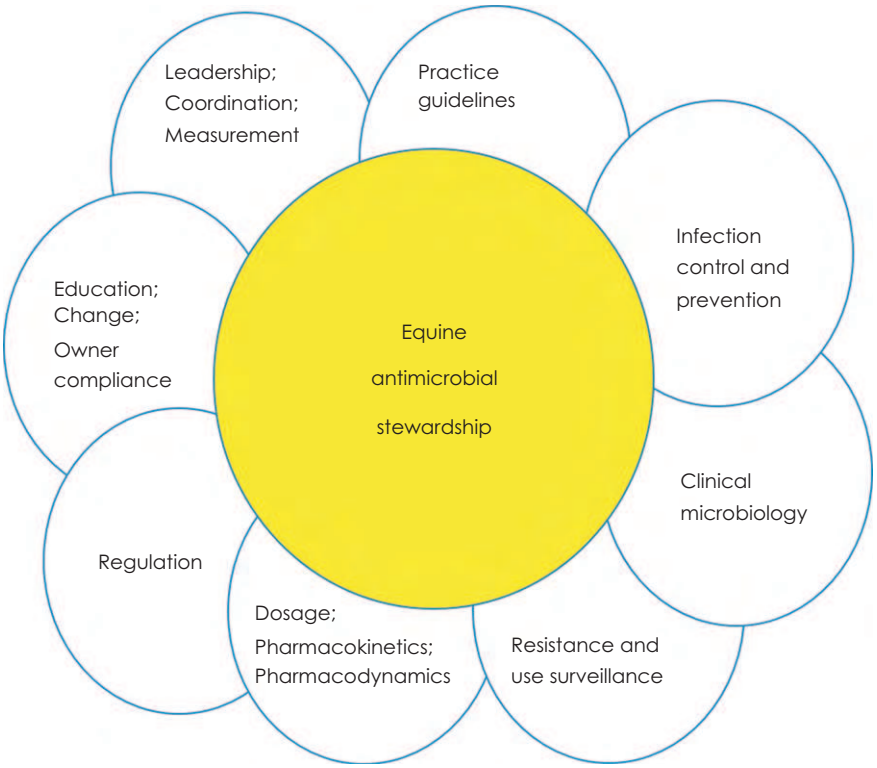

Fig 1: The basic multifactorial elements of equine antimicrobial stewardship supporting the Good Stewardship Practice (GSP) continuous improvement approach to addressing antimicrobial resistance and sustaining antimicrobial use. Modified from Weese et al. (2013).

rates for clean surgeries of short duration without antimicrobial prophylaxis are similar to those with prophylaxis (Southwood, 2014). If surgical prophylaxis is required, since the infection rate exceeds 5% in the absence of prophylaxis, then antimicrobials must be administered peri-operatively, not post-operatively, timed so that peak tissue concentrations occur during surgery. This is usually within 60 min of, but before, incision. Re-dosing is required if surgery times exceed two half-lives of the drug administered (Southwood 2014). There is no evidence supporting the use of prophylaxis for more than the 24-h peri-operative period in clean, clean-contaminated or contaminated procedures (Southwood 2014), but we need this evidence for equine medicine.

A retrospective study of surgical prophylaxis in horses undergoing colic surgery found that only 33% of horses received the appropriate antimicrobial dose, that the pre-operative dose was received a median of 70 min before incision, and that 64% should have been re-dosed during surgery. Only 2% were re-dosed correctly (Dallap Schaer *et al*. 2012). Horses remained on peri-operative antimicrobials for a median of 3 days. A survey of AMU at veterinary teaching hospitals in the United States found that 88% were not aware of any guidelines or standard protocols for AMU in equine colic surgery patients in their institutions (Traub-Dargatz *et al*. 2002). A study of pre-operative prophylaxis in elective arthroscopy found that only 6.3% of horses received antimicrobials within 60 min of incision (Weese and Cruz 2009).

In a survey of prophylaxis practices of five common surgical procedures by Australian equine practitioners against the Protect ME guidelines, Hardefeldt *et al*. (2018a) found that suboptimal compliance (correct drug but dose, duration or timing inappropriate) was moderate for all scenarios (48–68%). Appropriate timing was reported by fewer than 20% of respondents and appropriate dosing by fewer than 30% of respondents (except for one scenario). Duration was too long (5 days) in ~50–80% procedures apart from castration in which inappropriate duration (>24 h) was reported by about 40% of respondents. It was evident from the survey that the use of antimicrobials in surgical practice in Australia was common even for clean surgeries and that respondents did not seem to consider the need for antimicrobials in the scenarios presented. New veterinary graduates, who might be anticipated to be more aware of evidence-based recommendations for surgical prophylaxis, were no more likely to be optimally compliant than more experienced veterinarians.

An interesting aspect of post-colic surgery is that many horses develop short-lasting (6–36 h) slight to mild pyrexia (38.3–39.4°C) following surgery that is not associated with infection but may be a trigger for antimicrobial treatment. Careful documentation of peak rectal temperatures (>39.2°C), time to peak (>48 h) and duration of pyrexia (>48 h) when combined and equally weighted predicted genuine infection 72% of the time (Freeman *et al*. 2012).

In summary, there is considerable scope to reduce the use, including duration of use, of prophylactic antimicrobials in equine surgery, and to improve the timing of dosing, to bring criteria for use in line with evidence-based practices from human medicine. There is, however, a far broader and urgent need for development of improved equine practice AMU guidelines at both the national, and preferably at the global level, involving contributions from experts with different perspectives, which move guidelines from the 'voluntary engagement' approach of Protect ME to those of internationally agreed best practices, including selection, dose and dosage practices. This would be of enormous value in improving AMS in equine medicine. Who will take this on?

There is also clear need to establish the evidence supporting or refuting current practices in equine medicine through randomised case-controlled studies, something which is relatively easy to do. The persistence of overuse of antimicrobials in equine surgery may be because of the high value of horses undergoing surgery and fear of blame for surgical infections, but more likely represents simply an unexamined practice. Antimicrobial use is, however, never without risk of unintended consequences in horses, for example by promoting and selecting AMR bacteria such as MRSA and by promoting *Clostridiodes difficile* or *Salmonella* infections.

Infection prevention and control

The emergence of methicillin-resistant *S. aureus* (MRSA) infections in horses is a useful illustration not only of factors driving the development of AMR pathogens but more critically of the importance of continuous attention to infection control and prevention measures within the broad concept of AMS (**Fig 1**). MRSA infections were virtually unknown until the late 1990s but since then have become common and serious infections (Anderson *et al*. 2009), in North America particularly associated with the spread of a rare human epidemic clone CMRSA-5. Other clones, predominantly the livestock-associated MRSA strain ST398, are common in horses in Europe (Guérin *et al*. 2017). Equine MRSA can cause infection in humans (Weese *et al*. 2006). The genetic basis of adaptation of isolates of ST398 to become a host-generalist and possibly even further adapted to horses has been analysed (Walther *et al*. 2018) but any host-adaptive features have not been identified in equine CMRSA-5 isolates. Risk factors for equine MRSA community and hospital-acquired infection have been well documented (Anderson *et al*. 2009). Of all the different veterinary sub-groups, equine veterinarians are the most likely to be colonised by MRSA. The numbers are dramatic: 10% of equine-associated veterinary staff in one study (Anderson *et al*. 2008) and 21% of equine veterinarians in Australia (Jordan *et al*. 2011). While these high carriage rates may be the result of the unique character of these equine-adapted isolates, as well as antimicrobial selection over time, it likely also reflects poor equine infection control practices. There was a marked correlation between nasal MRSA colonisation and failure of equine veterinarians to wash their hands between infected cases or between visits to different farms (Anderson *et al*. 2008). Experience in the UK of the control of human MRSA blood-stream infections (BSI) by >80% illustrates the effectiveness in hospitals of improvement and implementation of hand hygiene standards, combined with changes in other infection control procedures, in AMU drug choices, in documentation and reporting of MRSA rates, and of MRSA screening in reducing BSI (Duerden *et al*. 2015). This remarkable success is an important example of the multifactorial nature of AMS (**Fig 1**) which includes not only infection prevention and control but a combination of approaches, including predisposing factors and of measurement to guide improvement.

The story of MRSA in equine veterinary medicine is likely just the 'canary in the coal mine' in documenting the impact of poor equine infection control practices, including basic hand hygiene. It is equally likely that focus on reduction of MRSA would have collateral benefits of control of other resistant bacterial pathogens. Good infection control and prevention is an important but often neglected part of GSP.

Immunisation against infectious diseases, where available, is a part of AMS.

Clinical microbiology

The use of clinical microbiology for diagnosis of pathogens and for susceptibility and resistance testing is a critical but underused resource in AMS. Its cost, in some cases lack of access, and its delayed nature (usually in practice a minimum of 48 h for conventional culture and susceptibility, C&S) are factors that prevent routine use (De Briyne *et al*. 2013; Bourély *et al*. 2018). European equine practitioners were found to be slightly more likely to perform C&S testing than food or companion animal practitioners, but the frequency of testing varied with the country of origin of the practitioner (De Briyne *et al*. 2013). Protect ME suggests susceptibility testing before using of Category 1 antimicrobial (critically important antimicrobials, the third- and fourth-generation cephalosporins and fluoroquinolones) drugs. In France, a regulation in 2016 requiring both clinical examination and susceptibility testing before use of these drugs (except for emergencies), including the demonstration that lower category antimicrobials are ineffective, reduced their use in horses by 94–95% between 2013 and 2017 (ANSES-ANMV, 2018). The 2016 decree has both increased the use of C&S and reduced the use of these drugs by veterinarians who previously used them regularly (Bourély *et al*. 2018). For foals, some veterinarians continue to use critically important antimicrobials with or without C&S (Bourély *et al*. 2018), perhaps because some cases were regarded as emergencies (which are exempt from the decree) or because of the perceived greater efficacy of these drugs. The decree has been embraced by veterinary practitioners, who regard it as having public and animal health benefits and educational value, as well as causing a paradigm shift in habits including harmonising practices between veterinarians (Bourély *et al*. 2018).

Diagnostic bacteriology laboratories have an important role in AMS but have not yet fully addressed how they can improve their role, perhaps because they are often insufficiently knowledgeable about clinical practice or uncertain about their potential real value. The availability and quality of the service, and the relationship of the veterinarian with the laboratory, are important factors in determining use of clinical microbiology (Bourély *et al*. 2018). There is considerable scope for diagnostic laboratories to improve their reporting, for example by not reporting non-pathogens and selectively reporting susceptibility. For example, it is not GSP for diagnostic laboratories to report susceptibility of *Streptococcus equi* subspecies to third-generation cephalosporins since these will be susceptible to penicillin G. The Clinical Laboratory Standards Institute (CLSI), a world leader in this area, recently issued an excellent guide to understanding susceptibility test data in veterinary settings (CLSI 2019). These guidelines include a chapter on equine-specific and other breakpoints, the applicability of CLSI-approved equine-specific breakpoints to specific infection sites based on different drug dosage regimens, and the factors affecting antimicrobial susceptibility testing for horses. Given the small size of the equine antimicrobial drug market globally, further work on development of equine-specific breakpoints for different body sites, drugs and dosage regimens is, however, likely to be pitifully slow. The development of rapid, real time, diagnostic and susceptibility testing was identified as a global priority in tackling AMR (O'Neill 2016) but it is unlikely that any such tests will be developed specifically for horses. A survey of Australian veterinarians reinforced the important barriers of cost of C&S and lack of availability of rapid diagnostic tests (Norris *et al*. 2019). We need to address this.

One approach to the problem of the current 48 h delay between taking samples for microbiology and obtaining the C&S results is to use it retrospectively to confirm the choice of first-line antimicrobials (Robinson *et al*. 2016) or to 'de-escalate' from a 'protected' to a first-line antimicrobial should the pathogens be susceptible to the latter.

Resistance and use surveillance

Documenting AMR and AMU is fundamental to AMS, part of the concept that 'if you can't measure it, you can't manage it'.

Research around the use of antimicrobials in controlling *Rhodococcus equi* pneumonia in foals is an excellent example of evidence-based GSP in equine medicine that has led to improved AMS. *R. equi* pneumonia in foals is an endemic problem on some horse-breeding farms globally, with a cumulative incidence of 5–20% and mortality that can reach 30% of affected foals. There is a limited range of effective antimicrobial drugs (macrolides and rifampin) so that acquired resistance to these drugs is a serious problem and was shown to be slowly creeping up in the USA by the mid-2000s. More recently, resistant *R. equi* were isolated from the soil of horse-breeding farms in Kentucky at 'alarming rates', reflecting both macrolide use and horse density (Huber *et al*. 2019). Ultrasound screening of foals showed that 40–85% had small lung abscesses so it was a logical *prima facie* conclusion that infection could be controlled by prophylactic administration of macrolide antimicrobials to foals in the first 6 weeks of life, the period of greatest risk. It became clear, however, that resistance was becoming common on those farms taking this approach (Burton *et al*. 2013). The basis of resistance was eventually documented to be a novel macrolide resistance gene, *erm*46, present on a mobile genetic element (Anastasi *et al*. 2015), which had spread between breeding farms. In a series of brilliant controlled, randomised, double-blinded clinical studies, Venner and Giguère and their colleagues showed that mass antimicrobial therapy of foals with small 1-10 cm subclinical pulmonary abscesses was not only unnecessary, since almost 90% did not develop clinical disease, but also did not speed recovery (Venner *et al*. 2012, 2013). There is a need for the establishment of better criteria to determine the necessity of treatment of subclinically affected foals (Giguère *et al*. 2011) since most will not develop clinical disease. These studies illustrate the importance of understanding how antimicrobials are being used in horses for specific purposes, of documenting associated problems with AMR, and then critically of assessing the value of the usage.

Culture and susceptibility testing have critical value in identifying pathogens, in infection control (Maddox *et al*. 2015) and in treatment of individual infections. It is important to report trends in cumulative data (Davis *et al*. 2013; Johns and Adams 2015; Theelen *et al*. 2014), and to document the emergence and spread of resistance, since these reports often reinforce the urgency of change. However, we need also to acknowledge that reports from diagnostic laboratories will inevitably have a resistance bias since many submissions are made from animals with serious infections failing to respond to therapy (Weese *et al*. 2013). Cumulative data reports from diagnostic laboratories, however, do have special value in documenting changes in targeted resistance phenotypes (e.g. MRSA) or genes (e.g. ESBLs). This will increasingly be assisted as whole-genome sequencing becomes a routine and inexpensive diagnostic laboratory service and the public health importance of targeting resistance becomes an important, publicly funded, function of veterinary diagnostic laboratories.

Use surveillance and understanding the reasons for choice of antimicrobials is also important in improving AMS (Hughes *et al*. 2013; Ross *et al*. 2016; Hardefeldt *et al*. 2018a), including in identifying infection circumstances where AMU may be inappropriate. Such studies need to continue and their results used to make change.

Dosage, pharmacokinetic and pharmacodynamic issues

Recent studies based on survey scenarios or actual practice have shown that horses are being incorrectly dosed with antimicrobial drugs. In some cases, this is because weights of horses are underestimated and not measured (e.g. by tape-measure) (Hughes *et al*. 2013; Ross *et al*. 2016). However, even if weights are known, inappropriate dosing may also occur (Hughes *et al*. 2013). One study found under-dosing (by <90% of the recommended dose) in over half of horses admitted to a referral hospital (Ross *et al*. 2016). Heavier horses were found far more likely to be under-dosed (Ross *et al*. 2016), perhaps because of the volumes of potentially painful injectable drugs required. Hardefeldt *et al.* (2018a) and Hardefeldt *et al.* (2018b) also found extensive under-dosing. Dosage based on use of pharmacokinetic supported recommended doses (Hardefeldt *et al*. 2019) and on accurate weight determination will be an important advance in equine AMS.

Regional antimicrobial administration has been used in horses and found effective as an alternative or adjunct to systemic AMU in horses since it has the pharmacokinetic advantage of providing high and persistent concentrations of antimicrobials within target tissues such as limb joints while reducing the potential for development of AMR. Local infusion of and irrigation with antimicrobials, for example in septic synovial structures, also produce high local drug concentrations. Local or regional AMU would benefit from the use of concentration (e.g. aminoglycosides and fluoroquinolones) rather than time-dependent antimicrobials (e.g. beta-lactams) since in the former case there is the pharmacodynamics advantage that bacterial killing is directly proportional to the amount of the drug over the minimum inhibitory concentration.

Regulations

The remarkable reduction in use of critically important antimicrobials in horses after the introduction in 2016 of French regulations (ANSES-ANMV, 2018) has been noted earlier. One reason suggested for their widespread acceptance of the requirement for C&S before using critically important antimicrobials was that far more restrictive practices were originally considered, including no longer allowing veterinarians to dispense antimicrobial drugs (Bourély *et al.* 2018). The Netherlands has similar regulations and has banned the use of carbapenems in animals. Clearly, although most veterinarians likely prefer voluntary restriction to regulation, examples of the effectiveness of regulation in some countries will likely influence similar changes elsewhere. Equine veterinarians will not be exempt from regulatory change which will likely become more draconian if the AMR *tsunami* continues. Most professional regulatory bodies globally have failed to grasp the nettle of including AMS as a standard of practice despite rhetoric of concern about AMR and of the veterinary 'One Health' contribution to addressing the problem.

Education, change and owner compliance

Education is the multifactorial process by which individuals gain knowledge and understanding of specific topics or problems, resulting in new skills as well as in ingrained patterns of thoughts and behaviour. The AMR crisis has led to extensive evaluation of the knowledge, attitudinal and behavioural factors influencing AMU and of what educational interventions are required to improve such usage (Belongia *et al*. 2005). A review of the evidence has produced rather pessimistic conclusions about the long-term sustainability of changes produced by public education plans (Fletcher-Miles *et al*. 2019).

Education is about change, which people find difficult. Change has many aspects, including the need to understand the need for and the urgency of change, to understand the barriers to change, to communicate the desired change and 'vision' to those involved, to develop the leadership needed, to plan and support this by training and measurement, to embed change into systems, processes and the culture, to empower broad support for action, to generate, celebrate and reward short-term 'wins', to never give up, and to measure and report outcomes that promote continuous improvement. Much of this process is captured in the philosophy of Protect ME. Change has to engage the emotions not just the intellect. Apocalyptic visions such as those of O'Neill (2016) may provide the sense of urgency needed but may backfire if they are not balanced by evidence and critical thinking. Panic is not helpful. Bacterial change to resistance is quite easy but people's resistance to change is profound. However, people, technologies and systems do change over time, a process helped considerably by identifying and addressing the barriers to change. Barriers to appropriate antimicrobial prescribing by veterinarians in Australia include lack of AMS governance structures, client expectations and competition between practices, the cost of C&S, and the lack of access to education, training and AMS resources (Hardefeldt *et al.* 2018a). Enablers of AMS included concern about the impact of AMR in animals on human

health, pride in the quality of veterinary service and preparedness to change.

Protect ME educational resources including posters are available to equine veterinarians for distribution to their clients to promote compliance with prescriptions and awareness of AMS.

Leadership, coordination, measurement

Leadership is an essential part of change, as is coordination of effort and measurement of progress against desired outcomes. The ideal form of leadership is probably a 'disseminated leadership', where everyone understands and takes responsibility (the first of the '5Rs') for their part in achieving desired outcomes. However, someone or some group has to coordinate the effort. Groups such as BEVA (Bowen and Slater 2012) have shown considerable leadership in this area, focused on the practice level, as have numerous mostly university-based individuals or consortia and journal editors. Although AMS is an evolving global movement, involving many disciplines, what would help in equine medicine is a global coordinating individual or group; it is not obvious how this might be funded.

The best metrics of success of AMS are reduction of the total and change in the type of antimicrobial use, a reduction in AMR, and uptake of GSP practices as identified in **Fig 1**. There are quite variable 'baseline' data on AMR and AMU in horses in different countries but the ability to measure these in a reliable way is important as a way of showing success, even if the starting date may have to be 'now'. Apart from measuring AMR and AMU, the other critical elements of equine AMS (**Fig 1**) can be measured qualitatively or quantitatively at a local, national or even international level.

Conclusion

There have been impressive advances in recent years in the reporting and analysis of AMR in horses, in the scrutiny and assessment of how antimicrobial drugs are used in horses, and identification of areas for improvement including dosing, surgical prophylaxis, infection control, development of practice standards and the use of C&S. Equine AMS is taking shape as we recognise its multiple dimensions (**Fig 1**) and start to see the emergence of evidence-based recommendations but much more is required. Containing and even rolling back equine AMR will need the continued engagement of practitioners, equine national and international practitioner organisations, researchers and educators in the academic community, horse owners, regulators and others. No one is exempt from the problem of AMR or playing a part in the solution (WHO 2015). We are off to a reasonable start but there is a very long way to go. The dimensions of the issues to be addressed have been outlined by the researchers cited in this review. Some of the findings reported have been frankly quite shocking while others have been more encouraging.

No one has done this yet but there is potential to assess GSP quantitatively at a practice level, either for the purposes of certification (e.g. 'Gold, Silver or Bronze Star GSP Practice') or of regulation by national veterinary regulatory bodies, or both.

Author's declaration of interests

No conflicts of interest have been declared.

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Review Article

An updated review: Laboratory investigation of equine renal disease

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Keywords: horse; renal; kidney; urinalysis; azotaemia

Summary

A variety of laboratory tests are available to assist the clinician in the assessment of kidney health and function. The majority of widely used tests are indicative of altered renal function, not becoming abnormal until function is significantly compromised. These include serum urea and creatinine concentrations, serum electrolyte concentrations, urine specific gravity (USG), fractional electrolyte excretion ratios and symmetric dimethylarginine (SDMA) concentrations. Some of these parameters may also be affected by nonrenal disease. The results of a further group of tests can indicate renal damage, but do not reflect renal function. These include urine tubular enzyme concentrations, urine protein concentrations, urine neutrophil gelatinase-associated lipocalin (NGAL) concentrations and cytological abnormalities.

Introduction

The kidney plays an essential role in the homoeostatic balance of body water percentage, electrolyte concentrations and acid–base status. It is also responsible for the removal of waste products and the synthesis of hormones such as erythropoietin (Guyton and Hall 2016a). Diseases leading to reduced renal function can therefore lead to a reduced ability to perform these tasks effectively. Kidney injury can develop as a result of any disease process leading to reduced renal blood flow, reduced glomerular filtration rate (GFR) or direct toxic insult to the glomeruli, tubules or interstitium. Symptoms of renal disease are variable but can include reduced athletic performance, lethargy, reduced appetite, changes in urine output and thirst, peripheral oedema or weight loss. In cases of acute renal failure (ARF), the predominant signs may be those of an underlying disease process such as colitis or other severe systemic disease. Investigation may be prompted following perceived risk of renal disease, clinical concern or the observation of suspicious features upon serum biochemical analysis. Such inciting abnormalities could include azotaemia, hypoalbuminaemia or electrolyte derangements. If renal disease is identified, additional diagnostics can enable further characterisation of the disease. Clinical history and examination, complete blood count, renal ultrasonography and occasionally renal biopsy may provide useful information. Discussion of these modalities is beyond the scope of this article but information is available (Wilson 2007; Slovis 2014; Schott and Woodie 2018).

The aim of this review is to consider how available diagnostic tests may be used effectively to assess renal health and function.

Reagent strip analysis (dipstick analysis)

Reagent strip analysis should be performed according to the manufacturer's guidelines, as factors such as time to interpretation following urine contact or recommended technique may vary. Strips should not be used after their expiry date. Typically strips should be kept refrigerated but subsequently allowed to return to room temperature prior to use. The urine sample being tested should also be allowed to return to room temperature prior to testing (compared with cytological examination for which samples should remain refrigerated until examination). Clean gloves should be worn when performing dipstick analysis to prevent external interference from products on one's skin.

Urine reagent strip analysis offers a number of basic forms of urine test, some of which can provide useful information pertaining to renal health. Equine-specific reagent strips are not available. Strips designed for human urine are widely used, but demonstrate limitations. Strips designed for canine urine have not been evaluated for equine use. The tests to be included are variable, but typically include the following:

Leucocytes

Leucocyte reagent pads respond to leucocyte esterase enzymes present within granulocytic leucocytes. These are not present in lymphocytes, therefore reagent strips cannot be used to test for these cells. When used to test human urine, reagent strips demonstrate 80%–90% sensitivity and specificity for the detection of moderate levels of urinary leucocytes (Kouri *et al*. 2000). The reliability of reagent strips for detecting leucocytes in equine urine is unknown. Leucocytes in urine can indicate infection or noninfectious inflammation (e.g. secondary to trauma or neoplasia) anywhere within the urinary tract. Particularly in alkaline urine, leucocytes may lyse within hours of sample collection (Kierkegaard *et al*. 1980). This may lead to a lack of microscopic pyuria, but the relevant esterases would still be available to the test strip pad, potentially creating a discrepancy between the two test types.

Nitrites

Nitrites are not present in normal equine urine. Urinary nitrite testing is included on reagent strips to aid the detection of bacteriuria. Many Gram-negative bacteria synthesise nitrate reductase which leads to the production of nitrites (James *et al*. 1978). However, not all bacteria produce nitrites and bacterial culture is thought to be a more sensitive diagnostic test for bacteriuria (Nys *et al*. 2006). Pigmenturia may lead to false positive results (Kouri *et al*. 2000). The utility of reagent strip nitrite testing has not been evaluated in horses.

Protein
Reagent strip analysis is both poorly sensitive and poorly specific for the detection of equine proteinuria. Proteinuria is discussed below in further detail under the heading 'Urine protein levels'.

pH
Adult equine urinary pH is normally alkaline, whereas that of foals is acidic (Edwards *et al*. 1990; Wood *et al*. 1990). Metabolic acidosis, proximal renal tubular acidosis and paradoxically, hypochloraemic metabolic alkalosis can lead to aciduria (Arroyo and Stampfli 2007; Schott 2018). Two types of reagent strip were recently demonstrated to be unreliable for the measurement of equine urinary pH (Hekmatynia *et al*. 2019).

Blood/haemoglobin/myoglobin
Neither blood, haemoglobin nor myoglobin are present in normal equine urine. When present, reagent strip pads are reported to indicate the presence of blood versus haemoglobin or myoglobin; however, differentiation between the latter two molecules is not possible without additional testing. Subjective differentiation between haematuria and pigmenturia does not always provide a clear answer, therefore adjunctive cytological examination is recommended. Blood in the urine may indicate bleeding at any level of the urinary tract, this is discussed further under the heading 'Urine cytology'. Haemoglobinuria could indicate intravascular haemolysis or *in vitro* haemolysis (e.g. in older samples). Intravascular haemolysis can lead to pigment nephropathy (Norman *et al*. 2005). Myoglobinuria reflects rhabdomyolysis and can also lead to pigment nephropathy (Sprayberry *et al*. 1998). High urinary nitrite concentrations may lead to false positive results (Kouri *et al*. 2000).

Specific gravity
Two types of reagent strip have demonstrated unreliability for the assessment of equine USG (Hekmatynia *et al*. 2019). Use of a refractometer is recommended instead. This is discussed in further detail under the heading 'Urine specific gravity'.

Ketones
Ketones are not present in normal equine urine. Ketogenesis is not thought to be an important part of metabolic homoeostasis in the horse and ketonuria is rarely described (Rose and Sampson 1982).

Bilirubin
Bilirubin is not present in normal equine urine. Bilirubinuria may represent negative energy balance, haemolysis, hepatic disease or post hepatic obstruction. Bilirubinuria is not an indicator of reduced renal health or function.

Glucose
Glucose is not present in normal equine urine. Urine glucose is typically identified through the use of reagent strip analysis. Different methods of equine urinary glucose measurement have not been compared. Equine glycosuria is discussed in further detail under the heading 'Urine glucose levels'.

Serum creatinine levels

Creatinine is produced as a byproduct of muscle activity (Narayanan and Appleton 1980). Levels are predominantly affected by GFR, but are also influenced by other factors (Finco and Groves 1985). Creatinine is freely filtered at the glomerulus and was once thought to be neither secreted nor reabsorbed anywhere along the tubular length. However, it is now recognised that both tubular reabsorption and secretion of creatinine take place in people, the extent of which varies according to factors such as age and hydration status (Sjöström *et al*. 1988; Musso *et al*. 2009; Ciarimboli *et al*. 2012). Tubular secretion of creatinine has been identified in the horse but details of its variability have not been elucidated (Bickhardt *et al*. 1996). If renal blood flow becomes low enough, glomerular filtration rate will become reduced. Intrinsic protective mechanisms minimise the effect of a reduced circulating volume on renal blood flow, but in severe situations these are overwhelmed and GFR is subsequently compromised, leading to an associated increase in the serum creatinine level (Guyton and Hall 2016a). This has traditionally been known as 'prerenal azotaemia'. Despite the reversibility of azotaemia seen in this circumstance, it is thought that in many cases nephron injury occurs and for this reason the term 'acute kidney injury' (AKI) may be preferable and is now commonplace in human medicine. Acute renal failure describes more severe injury, with concurrent dysfunction in concentrating ability and abnormalities in other renal processes such as electrolyte balance. In acute renal failure conditions compromising the glomerular capillaries or glomerular epithelium can lead to reduced filtration of creatinine. Acute renal failure can progress to chronic kidney disease (CKD). Postrenal obstruction or loss of integrity of the urinary tract can also cause increases in creatinine concentration. Normally during glomerular filtration water and solutes move down a hydrostatic pressure gradient. However, when the tract is obstructed the postglomerular pressure is increased, reducing the gradient and therefore the rate of filtration. When loss of urinary tract integrity occurs, filtrated creatinine is reabsorbed into local capillaries, leading to increased circulating concentrations.

Serum creatinine levels are not a sensitive measure of renal disease as approximately 75% of nephrons may be nonfunctional before increases in serum levels are observed (Osbourne and Polzin 1983). It is acknowledged that people with AKI can have normal serum creatinine concentrations (Lopes and Jorge 2013). The IRIS classification system for canine and feline CKD recognises the fact that significant renal disease can be present in the absence of azotaemia (nonazotaemic kidney disease) (IRIS Kidney Guidelines - IRIS Staging of CKD 2019). There is no equine-specific classification system for CKD. When azotaemia is present, subtle changes in serum levels are considered sensitive indicators of further renal deterioration (loss of more nephrons). In cases with a low muscle mass, baseline creatinine concentrations are low. This means that significant increases in these patients can lead to creatinine levels that still fall within reference range and can go unnoticed. The converse may also be true for well-muscled animals, for example, Quarter Horses. In human medicine AKI is classified according to systems that observe for sequential increases in serum creatinine concentrations, rather than absolute creatinine concentrations alone (Bellomo *et al*. 2004; Mehta *et al*. 2007; Acute Kidney Injury (AKI) – KDIGO 2012). Alongside consideration of absolute values, this approach has also been incorporated into classification systems in canine and feline medicine (IRIS

Kidney Guidelines - IRIS Grading of AKI 2016). An equine-specific AKI classification system is not yet available.

Fasting, rhabdomyolysis and exercise can also lead to mild nonrenal increases in creatinine concentration. Placental dysfunction can lead to spurious hypercreatininaemia in neonatal foals, which typically resolves within 72 h of life (Chaney *et al*. 2010).

Serum urea levels

Urea is a nitrogenous waste product produced by the liver during the catabolism of amino acids (Guyton and Hall 2016b). Although excretion of urea also occurs via the gastrointestinal tract, this is minimal due to enterohepatic cycling. In people, approximately half of filtered urea is reabsorbed across the renal tubule and in horses this appears to be variable (Bickhardt *et al*. 1996; Guyton and Hall 2016a). This subsequently contributes to the maintenance of the hypertonic medullary interstitium required for ongoing urine concentrating ability. Increases in serum urea concentration offer low sensitivity for the detection of renal damage. As with creatinine, approximately 75% of nephrons may be nonfunctional before increases in serum levels are observed (Osbourne and Polzin 1983). Like creatinine concentrations, serum urea concentrations can be increased due to prerenal, renal or postrenal factors. Additionally, factors other than glomerular filtration rate can affect serum urea levels, including prolonged exercise, high protein diets, muscle catabolism and gastrointestinal haemorrhage (Mouton and Holder 2006).

Serum symmetric dimethylarginine levels

Symmetric dimethylarginine is produced in all nucleated cells and is released into the circulation during protein degradation. SDMA is excreted by the kidneys, making its concentration proportional to GFR. For this reason, its concentration will be affected by any prerenal, renal or postrenal factors which affect GFR. In some small animal species, SDMA has been demonstrated to be a sensitive indicator of kidney function, with levels becoming increased earlier than serum creatinine concentrations (Hall *et al*. 2014). An equine serum SDMA test is now commercially available in many countries and a recent study of 165 draught breed horses found their serum SDMA levels to be within the suggested range of 0–14 µg/dL (Schott *et al*. 2018). However, there is not yet published evidence that SDMA levels can be used to diagnose renal disease in the horse. Further research is required to confirm the clinical utility of this test and care should be taken in extrapolating expected performance from other species.

Serum or plasma electrolyte profiles

Electrolyte derangements are common in both horses with ARF and CKD. No specific disturbances are highly specific or sensitive for the diagnosis of ARF or CKD but a panel of sodium, chloride, potassium, calcium and phosphorous may support a diagnosis in conjunction with other tests. Hyponatraemia, hypochloraemia, hypocalcaemia, hypokalaemia, hyperkalaemia and hyperphosphataemia have been reported in association with ARF in equine patients (Schott *et al*. 1997; Bayly 2018). In a study of electrolyte profiles in horses with 'chronic renal failure' the following abnormalities were observed: hypercalcaemia (67%), hyponatraemia (65%), hyperkalaemia (56%), hypophosphataemia (47%) and hypochloraemia (46%) (Schott *et al*. 1997). In patients with kidney injury, tubular damage may directly account for the reduced absorption or secretion of electrolytes, or tubular damage may influence factors such as acid–base status which may affect electrolyte concentrations. However, abnormalities may also be secondary to a concurrent condition where losses may be occurring.

Hypercalcaemia in horses with CKD is not thought to be a result of increased parathyroid hormone action (Brobst *et al*. 1982). Horses absorb excessive amounts of dietary calcium across the intestinal tract and eliminate the excess as calcium carbonate (and to a lesser extent calcium oxalate) crystals in urine. In horses with CKD, urinary calcium excretion is reduced and the magnitude of hypercalcaemia varies with the amount of calcium in the diet (Tennant *et al*. 1978). Hypoalbuminaemia may also be a contributing factor, as reduced calcium binding by plasma albumin will increase serum ionised calcium levels.

Multiple complex mechanisms are involved in the regulation of circulating potassium concentrations in patients with reduced renal function. As both hyperkalaemia and hypokalaemia can be observed in patients with reduced function, it is likely that the degree of presence of each factor determines the overall circulating level. In people with CKD hypokalaemia is a common concern, whereas in horses hyperkalaemia appears to be the more frequent concern (Fielding 2015). The high potassium diet consumed by horses may be a significant factor in this difference, furthermore reduced dietary consumption in compromised patients may contribute to a lowered circulating level. In the healthy kidney, reduced circulating volume and therefore GFR leads to an increase in aldosterone production, with a subsequent decrease in proximal tubular potassium reabsorption and an increase in distal tubular potassium excretion, with the consequence of increased potassium excretion (Guyton and Hall 2016a). However, when GFR is reduced below a certain threshold, potassium excretion is reduced by an alternative mechanism and circulating potassium levels increase (Alcázar Arroyo 2008). Blood pH and the concentration of other electrolytes can also influence potassium concentration (Aronson and Giebisch 2011; Fielding 2015). In people, intestinal excretion of potassium is so significant that constipation can precipitate symptomatic hyperkalaemia (Loubieres and Chereau 2005). Although unknown, perhaps in horses with both a reduced GFR and a reduced intestinal transit rate this could contribute to increased circulating potassium levels.

Following complete filtration at the glomerulus, in the healthy kidney sodium and chloride are freely reabsorbed along the tubular length, the majority of which occurs at the level of the proximal tubule. Reabsorption is dependent upon functional renal tubules. When significant tubular damage occurs reabsorption is reduced and hyponatraemia and hypochloraemia ensue.

Renal phosphate excretion is affected by GFR (Moe 2006). In cases of AKI, hyperphosphataemia is thought to be a product of reduced GFR. In people with hyperphosphataemia parathyroid hormone levels subsequently increase, with normalisation of phosphate levels, provided no other overriding factors are present (Moe 2006). In human CKD patients

hypophosphataemia is uncommon. The reason for hypophosphataemia in horses with CKD is unknown, but it is not thought to be a result of increased parathyroid hormone levels (Brobst *et al*. 1982). Hypophosphataemia could perhaps be secondary to other factors, such as reduced feed intake or reduced intestinal absorption.

Urine specific gravity

Damage to the renal tubules or interstitium can lead to an inability to concentrate or dilute urine. Concentrating ability is not a sensitive test for renal damage, as a significant loss of nephrons can occur prior to loss of renal concentrating ability. In addition to adequate functional tubular mass, the kidney's ability to concentrate urine depends upon a hypertonic medullary interstitium. Additionally, antidiuretic hormone (ADH) must not only be produced, but the cells of the collecting duct must be responsive to it. Loss of any of the above can lead to an inability to concentrate urine. Central diabetes insipidus and nephrogenic diabetes insipidus describe the reduced production of ADH and reduced tubular response to ADH respectively. Both of these syndromes have been reported in horses (Schott *et al*. 1993; Brashier 2006; Durie and van Galen 2020). Urine specific gravity represents the total weight of molecules in suspension and can therefore be affected by both proteinuria and glycosuria. Urine specific gravity can be categorised as hyposthenuric (<1.008), isosthenuric (1.008–1.014) or hypersthenuric (>1.014). These terms correspond to urine which has been diluted, unaltered or concentrated by the kidney respectively. Horses with AKI yet normal renal function should have hypersthenuric urine. With mild nephron loss USG may remain between 1014 and 1025, reflecting the loss of some but not all concentrating ability. Horses in renal failure lose the ability to concentrate or dilute urine, leading to isosthenuric urine. Hyposthenuria is seen secondary to increased free water intake or diuresis. It is normal for foals to demonstrate hyposthenuria owing to the liquid nature of their diet and consequently increased free water intake (McKenzie 2018).

Other measures of urine concentrating ability have been described, including urine to serum creatinine ratios. Ratios exceeding 50:1 are considered consistent with concentrated urine (Grossman *et al*. 1982).

Urine protein levels

Protein in the urine may be prerenal, renal or postrenal in origin. Furthermore when using reagent strips, artefactual indication of low level proteinuria is common in alkaline urine (Carroll and Temte 2000). Equine urine is typically alkaline in nature therefore this may be commonly observed (Wood *et al*. 1990). Furthermore, sample contamination by chlorhexidine can also lead to false positive results (Rudensky 1981). Prerenal refers to the presence of abnormal amounts of protein in the plasma and can include molecules such as haemoglobin, myoglobin and Bence–Jones proteins (Lees *et al*. 2005). These are not indicative of renal disease but may, depending on the protein, be liable to cause renal injury. Renal proteinuria refers to increased protein in the urine due to abnormal renal handling of normal amounts of plasma protein. This can be due to structural or functional lesions. Renal proteinuria is most commonly associated with the increased filtration of plasma protein due to glomerular disease. Defects in this process can lead to increased amounts of low molecular weight protein (and small amounts of albumin) in the urine. Interstitial renal disease, that is, infection or inflammation of the interstitium can lead to increased urinary proteins as a consequence of increased protein secretion into the peri-tubular capillaries and subsequently the renal tubules. Postrenal proteinuria refers to the presence of protein secreted into the urine distal to the kidney. This is usually associated with inflammation or infection of the urinary tract or genitalia and can also be seen alongside haemorrhage in these regions (Lees *et al*. 2005). Prerenal proteinuria can be identified by increased levels of plasma proteins upon biochemical analysis. If increased, protein electrophoresis may be useful in identifying the types of proteins responsible. The determination of renal versus postrenal protein increases is not always simple. Nonlaboratory- based diagnostics such as cystoscopy and transabdominal ultrasonography may help to identify renal or postrenal protein sources. Urine may be collected from the ureters under cystoscopic guidance in order to differentiate between proteinuria originating from the kidney or ureter, versus the bladder, urethra or genitalia. Any ureteral sources of protein are technically postrenal, but differentiation of renal proteinuria and that of ureteral origin can only be made based on other diagnostic findings. Equine ureteral protein loss is thought to be rare.

Urine samples should be routinely centrifuged at 1500–2000 rpm for 5 min prior to the measurement of protein concentration in order to minimise the confounding effects of the largest mucoproteins and protein aggregates on the determined protein value (Wilson 2007; Sharkey 2018). Despite this, smaller mucoproteins will still remain in solution. The significance of this on urine protein measurements has not been evaluated.

Proteinuria may lead to an increase in urine protein concentration. However, proteinuria alongside hyposthenuria may lead to a normal urine protein concentration. For this reason, the diagnostic value of urinary protein concentration alone, either by specific quantification or urine reagent strip analysis is limited and may lead to proteinuria being overlooked. Therefore, if wishing to assess for proteinuria, a urine protein: creatinine ratio (UPC) is recommended. Urine protein: creatinine ratios are more useful than total urine protein measurements as the effect of urine concentration on the measured protein level is eliminated. Uberti *et al*. (2009) studied UPCs in normal horses and observed a range of 0.03–0.93. When proteinuria is detected during reagent strip analysis, further clarification as to whether this is true (versus artefactual) and to what degree should be clarified by a subsequent UPC. In human patients, assessment of urine albumin concentration has been determined to be more sensitive than a UPC for the early detection of increased glomerular permeability. It is also more closely correlated with the severity of glomerular damage and with subsequent development of renal failure (Danziger 2008). Studies in cats and dogs suggest that microalbuminuria is an early indicator of renal disease and that urine albumin: creatinine ratios may be useful in the determination of disease severity and the prediction of disease progression in these species too (Whittemore *et al*. 2006, 2007). An assay suitable for measuring microalbuminaemia in horses has not as yet been validated

for this purpose and a UPC remains the recommended test for the assessment of proteinuria in horses.

Urine glucose levels

Glycosuria can be prerenal or renal. In the healthy animal, glucose is freely filtered at the glomerulus and is subsequently completely reabsorbed by the cells of the proximal tubule. When the filtered load of glucose exceeds the reabsoptive capacity of the proximal tubule glucose will be excreted in the urine. The concurrent presence of hyperglycaemia is key to differentiating prerenal from renal glycosuria. Alpha-2 adrenergic agonist administration can lead to hyperglycaemia and in some cases, glycosuria (Gasthuys *et al*. 1987; Kritchevsky *et al*. 2020). Although stress does not typically cause glycosuria in horses, it is reported to be observed in some cases suffering from chronic or severe stress. Diabetes, neoplasia or the use of parenteral nutrition can also lead to hyperglycaemia, which could potentially lead to glycosuria (Lopes and White 2002; Johnson *et al*. 2005; Ruby *et al*. 2020).

Renal glycosuria often accompanies proximal tubular disease, as damage to the tubular epithelial cells prevents normal reuptake of glucose (Guyton and Hall 2016a). A rare, alternative cause of glycosuria is Fanconi's syndrome. This is a disorder of proximal renal tubular function which leads to poor tubular reabsorption of multiple molecules, causing increased renal losses of glucose, bicarbonate, amino acids and electrolytes (Roth *et al*. 1981). This syndrome can develop in the presence or absence of structural renal disease and can be an inherited adult-onset disorder or be acquired (Roth *et al*. 1981). The syndrome has been reported in two adult quarter horses (Ohmes *et al*. 2014). Both cases were suspected to have the acquired form of the condition, owing to the fact that the clinical and laboratory abnormalities resolved. The inciting factor was not identified in either case.

Urinary enzyme levels

The measurement of urinary levels of renal tubular enzymes is an established diagnostic approach in the assessment of tubular damage in human patients. Unfortunately, there is significantly less information available regarding the use of urinary enzymology in the assessment of the equine renal patient. During periods of inflammation or necrosis of the renal tubules, urine enzyme levels may be increased. This is more likely to be a consistent finding in AKI or ARF than in CKD (Stroo and Hook 1977; Price 1982). Gamma glutamyltransferase (GGT) is the most studied enzyme in equine nephrology and it is widely commercially available, although data is still limited. GGT is a proximal tubular brush border enzyme. It is produced by many other organs of the body, in particular the liver. Circulating levels of this enzyme should not affect urinary GGT levels as this enzyme is not filtered by the glomerulus. However, although secretion of GGT is specific to proximal tubular cells, urinary levels may also be increased in the presence of glomerular damage due to subsequent filtration of this molecule. In the presence of a proteinuria this should be considered. Increased urinary GGT: creatinine (Cr) ratios were observed in ponies receiving gentamicin compared with baseline values (Hinchcliff *et al*. 1987). Furthermore, these changes preceded the development of azotaemia, indicating that urinary GGT: Cr ratios may be useful as an early indicator of renal damage, potentially enabling the identification of patients with renal disease prior to the loss of 75% of nephrons. Normal GGT: Cr ratios of <25 IU/g were described. During gentamicin administration but prior to azotaemia, GGT: Cr ratios of 25–100 IU/g were observed and following onset of azotaemia levels greater than 100 IU/g Cr were observed. The clinical relevance of GGT: Cr ratios between 25 and 100 IU/g Cr remains debatable.

N-acetyl-beta-D-glucoaminidase (NAG) is a proximal tubular lysosomal enzyme and has received recent attention for diagnostic purposes in the equine patient, including validation of an assay for equine use (Bayless *et al*. 2019). Measurement of urinary NAG: Cr ratios may provide clinically useful information. Currently, a well-defined reference range is lacking and the above study demonstrated an overlap in ratios between azotaemic and nonazotaemic horses. Further work is required to enable appropriate interpretation of these ratios. Whether or not other pathologies can affect NAG levels in the horse remains unknown. NAG concentration has been reported to be affected by urinary pH, with alkaline urine leading to a drop in concentrations; this may be applicable in the interpretation of such ratios in equine patients, given the alkalinity of equine urine (Bayly 1990). However, further work is needed to ascertain the effect of this on different assays.

Other urinary enzymes, including alkaline phosphatase and lactate dehydrogenase have been measured in the horse, but have not gained widespread attention for clinical use (Schmitz and Green 1987).

Urine neutrophil gelatinase-associated lipocalin levels

Neutrophil gelatinase-associated lipocalin is a glycoprotein expressed and secreted by renal tubular cells, activated neutrophils and a number of other cell types during disease states (Flo *et al*. 2004). A porcine ELISA was validated for the measurement of equine serum NGAL concentrations and has been subsequently used to demonstrate increased urinary NGAL levels in horses with increased serum creatinine concentrations, as well as those with systemic inflammation (Jacobsen *et al*. 2018; van Galen *et al*. 2018). Further work is required to determine how inflammation affects NGAL concentrations in horses.

Urine cytology

Urine should be examined as soon as possible after collection in order to minimise the likelihood of cell lysis or cast dissolution. Examination within one hour of collection is considered ideal, although this is rarely practical in ambulatory practice. Sample refrigeration is recommended to help delay cytological changes, although despite this significant changes in leucocyte counts were observed in human urine within 4 h (Kierkegaard *et al*. 1980). Although this is an important consideration when interpreting urine cytology, leucocytes are frequently observed in older samples and cytological assessment will often still be worthwhile when analysis of refrigerated samples occurs within 24 h.

Normal equine urine is usually rich in calcium carbonate crystals (**Fig 1**), with calcium oxalate (**Fig 2**) being common

too (Sharkey 2018). Occasionally normal equine urine may contain other crystals such as calcium phosphate, struvite (**Fig 3**) or hydroxyapatite (Sharkey 2018).

In cases experiencing tubular damage renal casts may be observed upon microscopic urine sediment examination. Casts can be identified at x10 magnification. These structures are formed within the renal tubules and subsequently take on a cylindrical shape. Their primary constituent is Tamm–Horsfall glycoprotein, the tubular secretion of which is normal and contributes to normal renal physiology (Micanovic *et al*. 2020). Hyaline casts mostly consist of protein, whilst other casts are characterised by the cell type included within their protein framework (erythrocytes, leucocytes, renal tubular epithelial cells [RTE cells]). Pigment such as myoglobin may also be incorporated. Granular casts may be observed if cellular features have begun to degrade, whilst waxy casts may be seen when cellular components are no longer recognisable. The inclusion of erythrocytes or leucocytes indicates haemorrhage or inflammation within the nephron. The inclusion of RTE cells indicates disease leading to structural tubular damage.

In cases experiencing renal tubular damage free RTE cells may also be observed upon microscopic sediment examination (Bohn 2013). Although the sensitivity of RTE cell or cast observation may be lower than that of enzyme: Cr ratios, sediment examination may constitute a particularly useful component of assessment when access to urinary enzymology is not possible.

Normal urine contains less than eight leucocytes per high power field (×40 magnification) (Bohn 2013). Increased leucocyte numbers indicate the presence of inflammation, which could be in the kidney or anywhere else along the urinary tract. Renal inflammation could be due to any form of renal pathology.

Normal urine contains less than eight erythrocytes per high power field (×40 magnification) (Bohn 2013). Renal haemorrhage can be seen due to trauma, pyelonephritis, neoplasia, urolithiasis, verminous glomerulonephritis, vascular defects and idiopathic renal haematuria, as well as potentially other conditions (Behm and Berg, 1987; Laverty *et al*. 1992; Kisthardt *et al*. 1999; Majzoub *et al*. 2000; Larsdotter *et al*. 2009; Wise *et al*. 2009; Martin *et al*. 2019). Nonrenal sources of haematuria are reviewed elsewhere (Schumacher 2007).

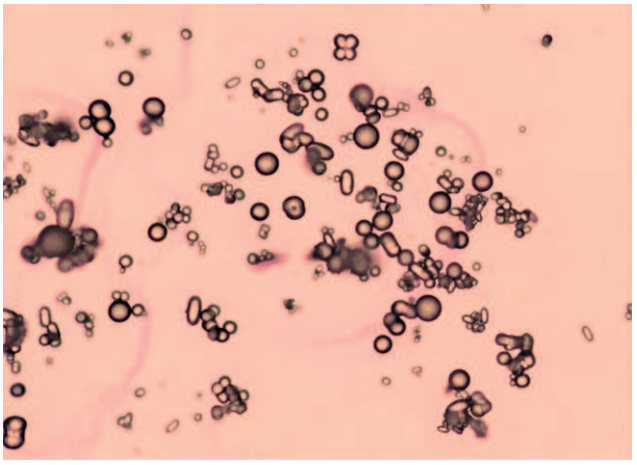

Fig. 1: Calcium carbonate crystals stained with Modified Wright Giemsa stain. Original magnification ×20.

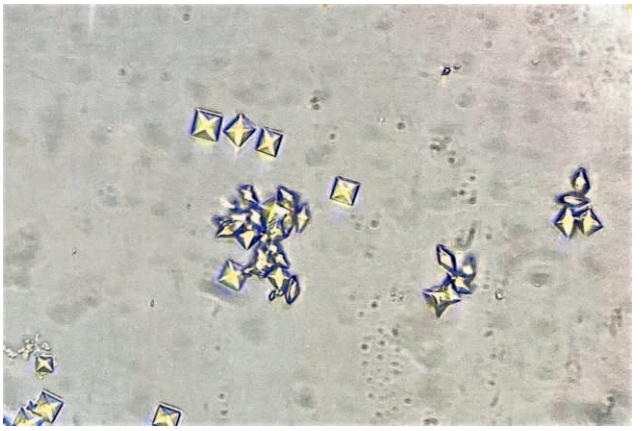

Fig. 2: Calcium oxalate crystals, unstained. Original magnification ×20.

Fig. 3: Struvite crystals, unstained. Original magnification ×20.

Occasionally cytological examination may provide more specific information pertaining to the cause of renal damage. Renal neoplasia is uncommonly reported in the horse. Diagnosis through urine cytology does not carry a high sensitivity in people. However, in some cases, it enables the identification of neoplastic disease (Raab *et al*. 2007). Primary tumours including adenocarcinoma, carcinoma, adenoma and nephroblastoma are also described, as are multicentric neoplastic processes affecting the kidneys, such as lymphosarcoma and metastatic melanoma (Knottenbelt *et al*. 2015a,b). The identification of equine renal neoplasia through observation of neoplastic cells during urine sediment exam has not yet been described. This is considered likely to be owing to a combination of the fact that not all neoplasms reliably exfoliate cells into the urine and a low frequency of sediment exam utilisation in cases where it could be helpful. The symptoms of renal neoplasia are highly variable and can include weight loss, reduced appetite, poor performance,

lethargy, recurrent colic and haematuria (Wise *et al*. 2009). Halicephalobus gingivalis can cause granulomatous nephritis and in such cases larvae may be present in the urine sediment (Kinde *et al*. 2000). Nephrolithiasis is thought to be an uncommon cause of renal disease in the horse and is considered to be less common than cystolithiasis, with 25% of 68 horses with urinary tract calculi having nephroliths or ureteroliths in one study (Laverty *et al*. 1992). Equine uroliths are usually composed primarily of calcium carbonate and the crystalline appearance of urine sediment in such cases is therefore not significantly different from that of normal equine urine (Laverty *et al*. 1992). For this reason, further diagnostics are typically required to diagnose urolithiasis.

Fractional electrolyte excretion ratios

A fractional excretion ratio describes the amount of a specific electrolyte in the urine compared with the plasma and is adjusted according to the relative creatinine levels in both fluids. This gives a value for the fraction of the electrolyte excreted in the urine which is adjusted for urine concentration. The principle underlying utilisation of fractional electrolyte excretion ratios is that disease leading to tubular dysfunction leads to altered electrolyte reabsorption or secretion.

It has been suggested that a fractional sodium excretion ratio of less than 0.50 is evidence of an absence of renal azotaemia in an azotaemic horse (normal <1 [Aleman *et al*. 2001]) (Grossman *et al*. 1982). In this study, all horses with 'prerenal azotaemia' had higher urine-specific gravity values (1.028–1.038) than those with 'renal azotaemia' (1.006–1.020). The superiority of the fractional excretion of sodium over urine-specific gravity for differentiating between such cases therefore remains questionable. The fractional excretion of electrolytes is a useful diagnostic tool in the identification of patients with Fanconi's syndrome. As the kidneys play an important role in electrolyte homoeostasis, electrolytes are absorbed (and some secreted) in order to achieve normal physiological levels, meaning that factors other than tubular disease can affect secretion. Horses given electrolyte supplements are likely to have increased sodium, chloride and potassium levels in the urine, as dietary excess is eliminated via the kidneys. Exercise has also been demonstrated to affect electrolyte excretion: a 320% increase in the fractional excretion of sodium and a 47% decrease in the fractional excretion of chloride were observed in horses that had been running for an hour at 55%–60% of maximal heart rate (McKeever *et al*. 1991; McKeever *et al*. 2002). Decreases of 50%–60% in the fractional excretion of sodium, potassium and chloride were noted in horses after 3 days of submaximal training (McKeever *et al*. 2002). Fractional electrolyte excretion may also be affected by medications: excretion of sodium (1190%), potassium (104%) and chloride (125%) were increased in ponies after xylazine administration (Trim and Hanson, 1986). Medetomidine, furosemide and cisplatin are reported to affect such values in other species; however, their effects on values in horses are unknown (Hardie *et al*. 1991; Burton *et al*. 1998). Administration of intravenous saline solution in horses caused variable changes in the fractional excretion of sodium (149%–880% increase), chloride (630%–2957% increase), potassium (1% decrease–311% increase) and phosphorous (1%–569% increase) (Roussel *et al*. 1993). Furthermore, the intravenous administration of 5% glucose solutions to horses also leads to significant alterations in the fractional excretion of sodium (750%–845% increase), chloride (493%–4922% increase), potassium (182%–435% increase) and phosphorous (65% decreases–2922% increase) (Roussel *et al*. 1993). Therefore, fluid therapy may interfere with the use of these indices for diagnostic purposes. Age and potentially lactation can also affect these tests: fractional excretion of potassium and phosphorous was higher in healthy neonatal foals than in adults, whereas the fractional excretion of sodium was unchanged and chloride was lower (Edwards *et al*. 1990; Brewer *et al*. 1991). In another study, the same changes were observed for sodium and phosphorous but the fractional excretion of potassium was lower in 1- to 2-week-old foals than in adults (Koterba *et al*. 1985). In cows both circadian and seasonal variations have been reported but this has not yet been documented in horses (Itoh 1989; Spieker 1989). As calcium carbonate and calcium oxalate crystals are common in equine urine, the calcium concentration in urine supernatant is not representative of the excreted urine concentration. For this reason, fractional excretion of calcium ratios cannot be interpreted in a useful manner without prior crystal dissolution.

Conclusion

No single test will provide adequate information to diagnose and evaluate renal disease in an equine patient. Combinations of methods based upon clinical findings and the results of sequential tests should enable comprehensive assessment of the horse with renal disease.

Key points

- Some diagnostic tests results can indicate renal damage, whilst others can indicate reduced renal function.
- In thin animals serum creatinine levels can remain within reference range despite significant kidney damage.
- Other nonrenal factors can influence certain test results.
- Although 'prerenal azotaemia' is reversible, it is thought that in many cases nephron injury occurs and for this reason the term 'acute kidney injury' (AKI) may be preferable.
- If azotaemia is observed subsequent urinalysis is likely to provide helpful information.
- Small increases in urea and creatinine levels, the absence of enzymuria and certain combined electrolyte derangements may be more indicative of CKD than ARF.
- Having identified ARF or CKD, additional diagnostics can help to further characterise the nature of disease. In addition to the tests described, clinical history and examination, complete blood count, renal ultrasonography and occasionally renal biopsy may provide helpful information.

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Author's declaration of interests

The author is employed by a veterinary laboratory, which offers some of the tests discussed in this review.

Ethical animal research

Not applicable to this review article.

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Hypothesis Article

A free ride: Is long-term omeprazole therapy safe and effective?

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Keywords: horse; omeprazole; safety; stomach; treatment; ulcer

Summary

Omeprazole has been widely used in the horse for nearly 20 years. Yet, to date, few studies have evaluated its safety with specific regards to the adverse effects reported in human medicine. Recent studies on omeprazole in the horse have highlighted the potential for rebound gastric hyperacidity at the time of discontinuation of therapy, for decreased calcium absorption during administration and for disruption to hindgut function when administered alongside non-steroidal anti-inflammatory drugs. Unlike human medicine, no clear evidence exists for a link between omeprazole administrations and an increased risk of fractures in the horse. However, evidence exists that the proposed pathophysiological pathways for increased fracture risk which are present in human medicine are also present in the horse. Limited evidence suggests that decreased efficacy may occur over time with long-term omeprazole administration.

Introduction

Omeprazole is a commonly used medication in equine practice, and it is widely believed that administration of omeprazole is safe in the horse, both in the short term and the long term. However, a recent study that demonstrated an increased risk of phenylbutazone-induced gastrointestinal disease associated with the concurrent administration of omeprazole has challenged the notion that it is universally safe (Ricord *et al*. 2021). Similarly, omeprazole is widely believed to be effective for long-term administration as a preventative for equine gastric ulcer syndrome (EGUS) and it is registered for this purpose. However, little systematic evaluation has been performed on the efficacy of long-term (>60–90 days) dosing. Omeprazole is known to upregulate its own metabolism via the cytostome p450 pathway in other species and a 50% decrease in bioavailability has been reported after 28 days of dosing in the horse (Di Salvo *et al*. 2017). Whether this decreased bioavailability affects long-term efficacy in the horse is poorly described.

The purpose of this article is to review the current literature with a focus on specific safety aspects of omeprazole in the horse including rebound gastric hyperacidity, changes in faecal microbiota richness and diversity, interactions with non-steroidal anti-inflammatory drugs and increased fracture risk. Evidence supporting the efficacy of long-term administration is also reviewed. The author hypothesises that the commonly held belief that long-term administration of omeprazole is universally safe and effective should be challenged, and that further investigations are required to document both the safety and efficacy of long-term administration in the horse.

Rebound gastric hyperacidity

Rebound gastric hyperacidity, which manifests as severe heartburn, is a well-recognised adverse effect of abrupt discontinuation of proton pump inhibitor (PPI) therapy in humans (Haastrup *et al*. 2018). Up to 44% of healthy human volunteers receiving a 4-week course of a PPI experienced symptoms consistent with rebound gastric hyperacidity in one study (Niklasson *et al*. 2010). In another study, approximately 22% of healthy human volunteers experienced symptoms consistent with rebound gastric hyperacidity after 8 weeks of PPI therapy (Reimer *et al*. 2009). The most commonly agreed hypothesis to explain rebound gastric hyperacidity is through increases in serum gastrin concentrations. Gastrin is produced by the epithelial G-cells of the pyloric antrum, pancreas and duodenum in response to a range of stimuli associated with feeding (**Fig 1**). Its production is inhibited in a negative feedback loop by decreased intragastric pH via somatostatin release from D-cells (Helgadottir and Bjornsson 2019). Gastrin stimulates intragastric acid secretion directly via the parietal cell, and indirectly via enterochromaffin-like (ECL) cell activation, which, in turn, causes release of histamine, another potent stimulator of the parietal cell (Waldum *et al*. 2019). The ECL-cell/histamine pathway is the dominant signalling mechanism for gastric acid production (Helgadottir and Bjornsson 2019). Acid suppression, when induced by drugs such as the PPIs, increases intragastric pH and results in loss of this negative feedback on gastrin production which subsequently causes hypergastrinemia (**Fig 2**). Gastrin also has trophic effects on a range of gastric mucosa cells with prolonged hypergastrinemia resulting in proliferation of the ECL-cell population (Waldum *et al*. 2004). When acid-suppressive therapy is discontinued, a rebound hyperacidity is observed because of both the hypergastrinemia and increased ECL-cell population (**Fig 3**).

- It has recently been demonstrated that oral omeprazole therapy induces an increase in serum gastrin in the horse over a 2-week treatment period. Serum gastrin levels doubled over a 14-day period when omeprazole was administered at approximately 4 mg/kg q. 24 h (Pagan *et al*. 2020).

The clinical implications of rebound gastric hyperacidity have not been systematically investigated in the horse to date. Pilot studies have demonstrated the rapid development of grade III/IV Equine Squamous Gastric Disease (ESGD) ≤76 h after the last dose of omeprazole (Sykes, unpublished data). Although the development of ESGD lesions within 72 h using a 24 h on/off fed/fasted model has previously been reported (Murray 1994), the severity of the lesions observed by the

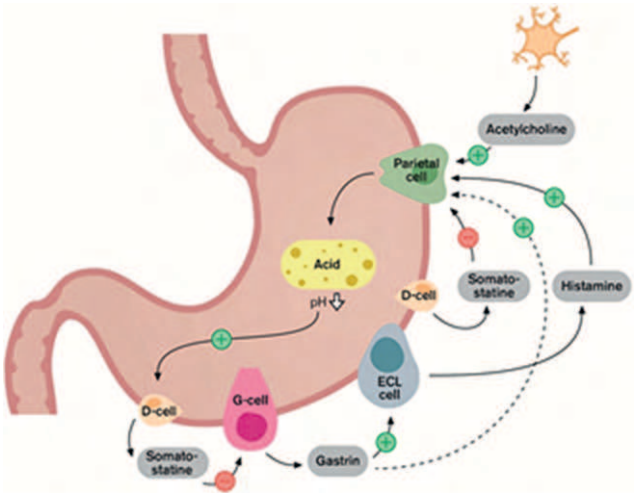

Fig 1: Feeding stimulates gastrin release from G-cells, which has direct stimulatory effects on the parietal cell as well as stimulating histamine release from ECL-cells, which, in turn, stimulates the parietal cell. The later, indirect pathway, via the ECL-cell and histamine, is the dominant signalling mechanism for HCl acid production. As a negative feedback mechanism, decreasing intragastric pH stimulates release of somatostatin from D-cells which, in turn, suppresses G-cell function and gastrin release. Figure reproduced from Helgadottir and Bjornsson (2019).

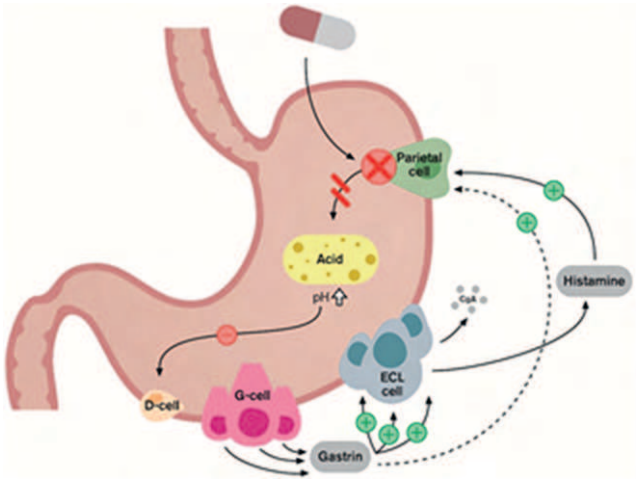

Fig 2: Proton pump inhibitors (PPIs) inhibit acid production at the common, terminal pathway of the parietal cell. The consequent rise in intragastric pH results in inhibition of the negative feedback loop, normally mediated via the D-cell, leading to hypergastrinemia which in turn causes hyperplasia of ECL-cell. Figure reproduced from Helgadottir and Bjornsson (2019).

author is more severe than previously described, especially in horses that were allowed ongoing access to feed during the omeprazole withdrawal period. This suggests that rebound gastric hyperacidity may play a role in the rapid recurrence of disease in some patients. Further, it suggests that moderate to severe ESGD can recur within the current racing withdrawal periods for omeprazole, a finding which warrants further investigation as it would have significant implications for the regulations surrounding the use of omeprazole in racehorses.

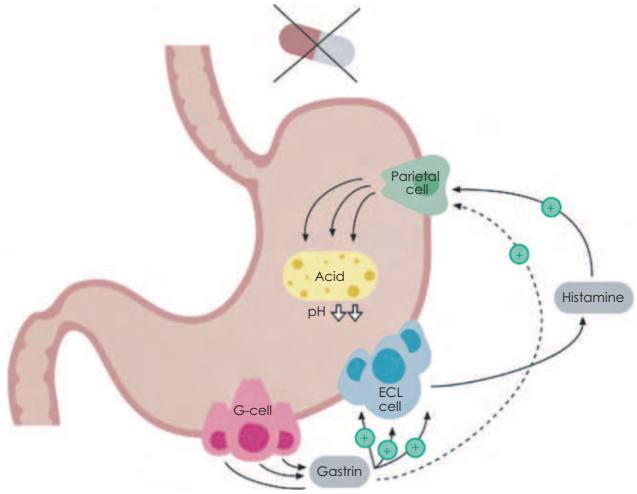

Fig 3: The recovery of acid production can be exaggerated following PPI discontinuation due to a direct effect of hypergastrinemia, and an indirect effect of ECL-cell hyperplasia causing exaggerated release of histamine, both of which stimulate the parietal cell. Figure reproduced from Helgadottir and Bjornsson (2019).

Impact on faecal microbiota richness and diversity

An increased risk of antimicrobial-associated diarrhoea is a well-recognised side effect of omeprazole in humans (Sheen and Triadafilopoulos 2011), and omeprazole has been shown to increase the risk of non-specific diarrhoea in neonatal foals (Furr *et al*. 2012). A rich and diverse microflora is believed to be associated with a decreased risk of gastrointestinal disease (Schoster *et al*. 2017). Established methods for the determination of faecal microbiota richness and diversity are relatively new, and to date, there has been limited research into the potential for omeprazole to induce dysbiosis. Two studies in the peer-reviewed literature found no effect of short-term (7 day [Cerri *et al*. 2020] and 28 day [Tyma *et al*. 2019]) omeprazole administration on the faecal microbiota, but to date, the effects of long-term administration have not been evaluated.

Concurrent administration with non-steroidal anti-inflammatory drugs

It has recently been demonstrated that concurrent administration of omeprazole increases the risk of phenylbutazone-induced gastrointestinal toxicity, over that of administration of phenylbutazone alone (Ricord *et al*. 2021). Reported complications in that study were impactions (small colon, n = 1; and large colon, n = 1) in 2/8 horses in the phenylbutazone only group and impactions (small colon, n = 1; and large colon, n = 1), non-specific colic (n = 1), and diarrhoea or colitis (n = 3) in 6/8 horses in the omeprazole/phenylbutazone group (Ricord *et al*. 2021). Complications included two fatalities from colitis in the omeprazole/phenylbutazone group (Ricord *et al*. 2021). The occurrence of inflammatory lesions is consistent with findings in dogs where concurrent omeprazole administration exacerbates intestinal inflammation associated with administration of

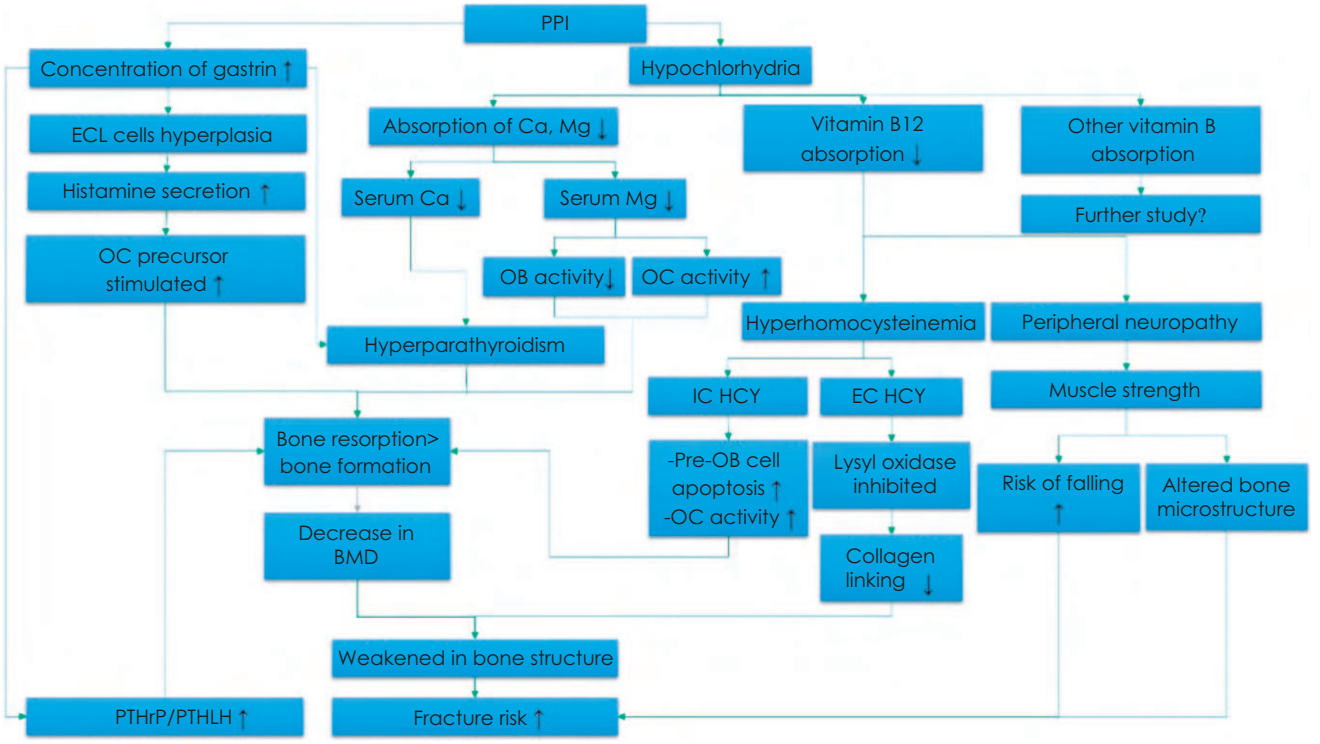

Fig 4: Summary of the systemic effects of proton pump inhibitors (PPIs) in increasing fracture risk. Abbreviations: IC HCY, intracellular homocysteine; EC HCY, extracellular homocysteine; ECL cells, enterochromaffin-like cells; Ca, calcium; Mg, magnesium; BMD, bone mineral density; PTHrP, parathyroid hormone-related peptide; PTHLH, parathyroid hormone-like hormone; OB, osteoblast; OC, osteoclast; ↑, increase; ↓, decrease. Figure reproduced from Thong* et al. *(2019).

carprofen (Jones *et al*. 2020). Collectively these findings suggest that, although omeprazole's site of action is the stomach, deleterious effects of administration may be observed elsewhere in the gastrointestinal tract. This is likely to be particularly important in the horse as a hindgut fermenter and warrants further investigation.

Fracture risk in racehorses

In human medicine, the use of omeprazole, and related proton pump inhibitors, is associated with an increased risk of fractures in geriatric patients (Sheen and Triadafilopoulos 2011), infants (<1-year-old) (Malchodi *et al*. 2019), children (4–18 years old) (Freedberg *et al*. 2015) and young adults (18–29 years old) (Freedberg *et al*. 2015). In human infants, an increase in fracture risk was observed after the administration of treatment courses as little as <30 days and the increased risk remained for at least 12 years after discontinuation of therapy (Malchodi *et al*. 2019).

The potential impact of omeprazole on fracture risk in the horse is especially relevant to the racing industry. Although uncommon (Parkin *et al*. 2004; Georgopoulos and Parkin 2017) fractures are a high-impact event that result in significant negative publicity, especially, when they occur during high-profile events (Matthey 2020). Increased awareness of the adverse effects of PPIs has resulted in concerns over their widespread use in humans being raised in both the scientific and lay press (Bakalar 2019). Similarly, concerns have been raised in equine industry publications as to a potential link between omeprazole administration and increased fracture risk (Pietrzak 2020). In the author's opinion, growing awareness of the existence of a potential link between omeprazole administration and increased fracture risk poses a significant threat to the social licence under which racing operates. It is important that the equine industry develop a deeper understanding of whether such a link exists, and if it does, what factors contribute to it.

The mechanism of increased fracture risk in humans remains poorly understood, but it is believed to be related to several factors including changes in mineral absorption and direct effects of the drugs on bone remodelling at the cellular level. **Figure 4** outlines the currently hypothesised mechanisms of action. The three key proposed mechanisms include the induction of hypergastrinemia, decreased absorption of calcium and magnesium, and decreased absorption of vitamin B12. It is considered unlikely that decreased absorption of vitamin B12 would be a significant factor in the horse as it primarily absorbs vitamin B12 via its large intestine as a hindgut fermenter, which is less expected to be impacted by omeprazole therapy. However, a recent study suggested that the first two mechanisms, namely hypergastrinemia and decreased absorption of calcium occur in the horse with omeprazole therapy (Pagan *et al*. 2020). This contrasts with an early study that found no effect on serum calcium, bone mineral content or bone mineral density (Caston *et al*. 2015), although the use of compounded omeprazole in that study raises concerns over the validity of the negative findings. The recent findings demonstrating omeprazole's capacity to impact upon serum gastrin and calcium absorption emphasise the need for further research to understand any potential relationship between omeprazole administration and increased fracture risk.

Upregulation of omeprazole metabolism and decreased efficacy over time

The efficacy of omeprazole for the prevention of ESGD at either 1 (McClure *et al*. 2005) or 2 (Andrews *et al*. 1999; Doucet *et al*. 2003) mg/kg q. 24 h following 27–28 days treatment at 4 mg/kg q. 24 h has been evaluated. In all three studies, 16–20% of horses experienced either the development of new lesions or worsening of ulcer severity between Days 27–28 and 54–59. In a fourth study (Kerbyson *et al*. 2016), omeprazole was continued at 4 mg/kg q. 24 h for 90 days. No difference was observed in the percentage of horses healing to ESGD grade ≤ I/IV between 30 and 60 days, but the percentage of responders halved between 60 and 90 days. When complete healing was assessed the percentage of responders dropped from 28.8% at 30 days, to 19% and 10.6% at 60 and 90 days, respectively (Kerbyson *et al*. 2016). To the author's knowledge, there are no peer-reviewed studies to support the use of long-term omeprazole therapy for the prevention of equine glandular gastric disease (EGGD).

Potential reasons for the drop in response over time include a reduction in dose in the first three studies, decreasing owner compliance with time or upregulation of omeprazole metabolism reducing systemic bioavailability over time. The plausibility of the later mechanism is supported by a recent study that demonstrated reductions of 50 and 62% in Area-Under-the-Curve (AUC) and Maximal Concentration (C_{max}), respectively, between Days 1 and 29 in horses administered oral omeprazole at 4 mg/kg once per day (Di Salvo *et al*. 2017). As AUC is the primary determinant of efficacy in other species (Lind *et al*. 1983), a decrease in AUC over time would be expected to be associated with decreased efficacy over time. Considering this, the author believes that the validity and efficacy of long-term (>60−90 days) prophylactic treatment warrants further investigation.

Conclusions

Omeprazole remains an important medication for the treatment of EGUS. To date, its use appears to be well tolerated overall based on the absence of overt adverse effects being recognised despite its widespread use over an extended period. However, a recent study demonstrating increased complications associated with its use alongside phenylbutazone (Ricord *et al*. 2021), a practice that has been assumed to be safe for years, highlights that lack of evidence for an adverse effect does not preclude the possibility of an adverse effect being present. Instead, specific studies should be performed to investigate any potential adverse effects. Likewise, in the absence of specific studies to document long-term (>60–90 days) efficacy for ESGD prevention, efficacy should not be assumed. Further studies documenting both the efficacy and specific safety of long-term omeprazole are warranted.

Author's declaration of interests

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Ethical animal research

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