EQUINE VETERINARY EDUCATION/AMERICAN EDITION

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FEBRUARY 2023

EQUINE VETERINARY EDUCATION

American Edition | February 2023

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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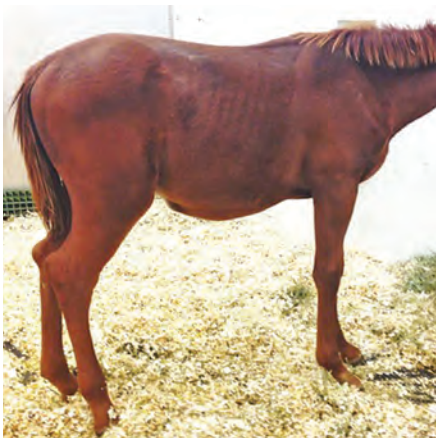

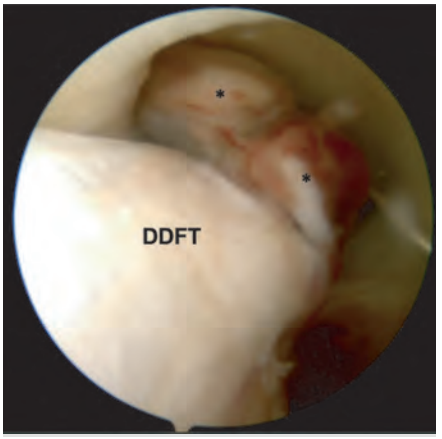

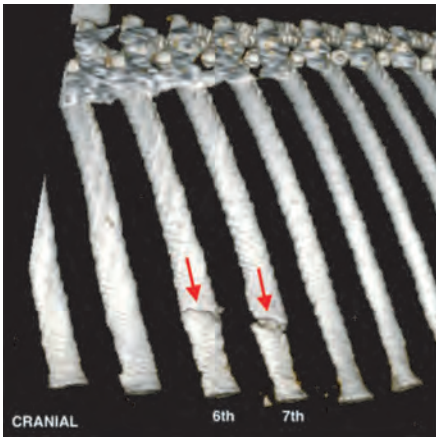

AAEP NEWS In this issue

Cover photo by Dr. Ruth Sobeck.

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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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Intentional mentoring of ethical standards in equine practice

By Duane E. Chappell, DVM

Ethical standards have been shaped in many of us through positive and negative experiences. Reflecting on where I am today and thinking back over my career in equine practice, I think of the folks who invested in my future. Their time and intentional efforts greatly impacted my professional trajectory. Can I name one or two mentors who had the greatest influence? No. Rather, it was the collective effort of many along my career journey that continues to humble and guide me to this very day.

At the 2022 AAEP Convention, I presented "Intentional Mentoring of Ethical Standards in Equine Practice." Here are the high points that were shared along with a few tips for implementing a "Mentoring Matters" program in your practice.

Mentoring starts with you

Let's begin with a few questions to consider. Is mentoring ethical standards required or optional in your practice? Is mentoring intentionally providing tools of discernment and judgment for future career shaping or is it more organic and filled with dos and don'ts? Is there an expected outcome?

> "...transferring and guiding a high bar of ethical standards is paramount for the individual and the equine profession."

For a mentoring program to be effective and have a sustaining outcome, there are many questions to answer. It starts by making an intentional decision to invest in a mentoring relationship that will provide a high yield of return. The finance world speaks of ROI—return on investment—and in the mentoring world we speak of ROIP—return on investment in people—a phrase coined by best-selling author and positivity coach Jon Gordon. "We must invest in our people and our relationships at work. When we do, teamwork improves, connections are strengthened, commitment levels go up and performance soars," says Gordon.

With this level of investment, we move to making our mentoring program one which is intentional and non-negotiable—even contagious. With an intentional program comes an expectation of a high degree of integrity. As noted by NFL Hall of Fame coach Tony Dungy, "Your reputation is the public perception of your integrity. Because your reputation is someone's opinion of you, it may or may not be accurate. Others determine your reputation, but only you determine your integrity."

Dr. Duane Chappell

Mentorship can take on many styles: classic mentoring, in which the more experienced guides the less experienced; co-mentoring, where peers walk alongside one another with the goal of raising certain skill levels, leadership qualities or navigating new challenges; and a more recent reverse mentoring scenario in which new ways of working are transferred from less experienced or younger generations to more experienced or older generations.

Independent of the type of mentoring relationship, transferring and guiding a high bar of ethical standards is paramount for the individual and the equine profession.

Mentoring Matters: Critical success factors

Following are five essential elements for successful establishment of a Mentoring Matters program in your practice:

1. **Role model evaluation and awareness:** Recognition that each role model placed in a mentoring relationship must carry the practice's same high standards to serve with excellence and integrity. Mentors placed in role model positions must recognize that what we say and do are both highly impactful to the outcome. We must walk the talk.
2. **Professional identity formation:** The human medical field describes this as a vital component to the long-term development of professionalism and high ethical standards. Intentional mentorship helps build self-esteem and the strength to stand on our own two feet during challenging times.
3. **A supportive, ethical practice culture** is a safe and inviting space for all employees. The mission and vision of the practice and ethical principles are embodied by the front office staff, technicians, associates and owners.

continued on next page

Dr. Chappell is associate director, equine pharmacovigilance and veterinary professional services for Merck Animal Health. He previously practiced at mixed animal clinics in the Midwest. Dr. Chappell serves as chair of the AAEP's Professional Conduct and Ethics Committee.

Lawsonia intracellularis (Equine Proliferative Enteropathy) Guidelines published

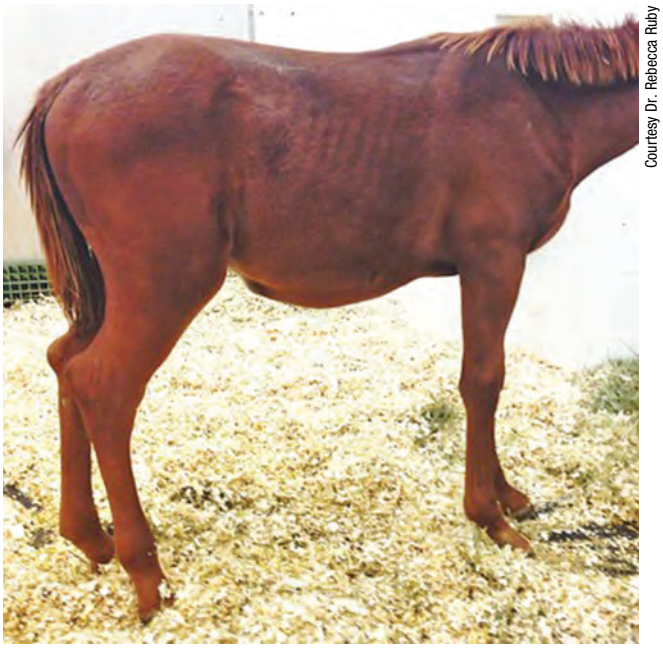
The AAEP has published on its website comprehensive guidelines to assist veterinarians with clinical signs, risk factors, treatment and other considerations associated with *Lawsonia intracellularis* (equine proliferative enteropathy), an enteric disease typically seen in weanling and yearling horses during the fall and early winter in North America.

EPE is caused by the obligate, intracellular bacterium *Lawsonia intracellularis*, which thrives in environments with low oxygen concentrations such as feces. Among the clinical signs of EPE are anorexia, rapid weight loss, dependent edema, depression, rough hair coat, fever, colic and diarrhea. Approximately 5% of exposed horses will develop clinical disease and an additional 5% will develop subclinical disease, manifest as sub-normal weight gain.

Uncomplicated cases of EPE have a high survival rate. Treatment consists of antimicrobial therapy and supportive care such as intravenous fluids. A standard time course of treatment, based on the antimicrobial selected, is typically sufficient. Affected horses should be isolated for seven days following the start of treatment to ensure the complete cessation of shedding.

The guidelines were co-authored by Dr. Allen Page, scientist/veterinarian at the University of Kentucky's Maxwell H. Gluck Equine Research Center, and Dr. Rebecca Ruby, assistant professor at the University of Kentucky's Veterinary Diagnostic Laboratory. The guidelines were reviewed by the AAEP's Infectious Disease Committee and board of directors.

"Equine proliferative enteropathy continues to be an issue for the horse industry," said Dr. Page. "With these new AAEP guidelines, Dr. Ruby and I hope the information will help veterinarians appropriately diagnose and treat this unusual disease."



Courtesy Dr. Rebecca Ruby

A weanling foal with decreased body condition, ventral and limb edema secondary to Lawsonia intracellular *infection.*

View the *Lawsonia intracellularis* (EPE) Guidelines or save them to your mobile device at aaep.org/document/equine-proliferative-enteropathy-guidelines. Guidelines for 24 other equine infectious diseases are available at aaep.org/guidelines/infectious-disease-control/using-guidelines.

Ethics: Intentional mentoring, continued

4. **Personal and practice life boundaries** are clearly defined and established.
5. **Effective communication systems** that support open and continuous feedback help turn the challenging confrontations we experience in practice into lessons we can grow from.

From a presentation by Brad Johnson, PhD, psychology professor in the Department of Leadership, Ethics and Law at the U.S. Naval Academy, the following building blocks can provide a strong foundation to a Mentoring Matters initiative:

- Autonomy
- Beneficence
- Mutual respect
- Fidelity
- Justice
- Transparency
- Boundaries
- Privacy
- Competency
- Reasonable expectations

As we look over our shoulders at our career experiences, we see gaps or holes where some things were done well and other areas that could have been improved. Let's gather these experiences and then mold and shape them to be more positive, influential and beneficial to our new equine colleagues so they can look in the mirror one day and be thankful for the mentoring relationships they had.

In closing, a quote from late author and motivational speaker Zig Ziglar: "Leaders often worry and ask, 'what if we spend all this money training people and they leave?' But the bigger question is what if we don't train them and they stay." Mentoring ethical standards is vital to equine practice.

5 things to know about AAEP this month

1. Learn the clinical signs, risk factors and other considerations for Equine Proliferative Enteropathy with AAEP's new guidelines at aaep.org/document/equine-proliferative-enteropathy-guidelines.
2. Navigate infectious disease outbreaks and report confirmed cases using the redesigned Equine Disease Communication Center website at equinediseasecc.org.
3. Access free and confidential support for personal or work-related stressors through the AAEP Member Assistance Program. Seek assistance simply by calling (800) 633-3353.
4. AAEP Virtual Convention participants are reminded that CE from on-demand viewing of educational sessions must be claimed by March 31.
5. The Foundation for the Horse's three-year comprehensive campaign wrapped up Dec. 31 with total gifts and commitments of more than $12 million. Thanks to all who contributed!

New *EVE* podcast sheds light on NSAID drug and dose selection

In the latest episode of the *Equine Veterinary Education* podcast, Dr. Callie Fogle discusses her original article, "Ex vivo COX-1 and COX-2 inhibition in equine blood by phenylbutazone, flunixin meglumine, meloxicam and firocoxib: Informing clinical NSAID selection." Dr. Fogle is a clinical professor of equine surgery at North Carolina State University College of Veterinary Medicine. Download or listen to the 30-minute episode at equineveterinaryeducation.podbean.com.

Stay current with industry trends on new Practice Life podcast

From macroeconomic fluctuations and continued corporate consolidation to heightened focus on retention and sustainability efforts, 2022 presented its share of challenges and opportunities for equine practitioners.

During the December episode of the AAEP Practice Life podcast, the panelists from the 2022 AAEP Annual Convention Business News Hour session—Drs. Catlin Daly, Jean-Yin Tan and Kelly Zeytoonian—joined host Dr. Mike Pownall for a discussion of the trends influencing equine practice and how practitioners can adapt.

During a discussion of inflation and the potential for a recession in 2023, Dr. Jean-Yin Tan offered several management strategies for practice owners to weather the economic storm:

- Raise fees more regularly—even if only by a small amount.
- Improve charge capture.
- Review charge codes and, if necessary, reduce the variety so there is less temptation to select the least expensive code to charge clients.
- Cluster-schedule clients in the same geographic location on the same day to maximize efficiency.

Among the other topics discussed are innovations and acquisitions within the equine industry, including new generic medications; updates on salaries, work schedules and benefit packages; the value of promoting DEI; the benefits of technician and support staff utilization; and measures to avoid burnout.

Download or listen to the 46-minute episode at podcast.aaep.org or on iTunes.

Time running out to submit papers for 2023 convention in San Diego

Papers due March 15 at 3:00 p.m. ET

No matter if you're an experienced presenter or looking to develop your voice and reputation within the profession, contribute to the education of colleagues by submitting a paper to be considered for presentation at the AAEP's 69th Annual Convention in San Diego, Calif., Nov. 29–Dec. 3. The presenting author of selected papers will receive complimentary registration and an honorarium.

Eligible for consideration are scientific papers, "how-to" papers, review papers, abstracts, and business and lifestyle papers. All paper presentations are limited to 15 minutes with an additional 5 minutes for Q&A.

Submit papers by 3:00 p.m. ET on March 15 at https://s3.goeshow.com/aaep/annual/2023/aaep.cfm. Authors should visit the site in advance to set up a profile and provide paper and author information before uploading the paper when it is finished. Complete considerations and ethical guidelines are available in the General Instructions area of the site.

Contact Carey Ross, scientific publications coordinator, at cross@aaep.org with questions concerning educational paper submission.

Practical solutions to clinical challenges: 2023 AAEP CE opportunities

June 22–24, 2023

Focus on Podiatry

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Nov. 29–Dec. 3, 2023

69TH ANNUAL CONVENTION

San Diego Convention Center
San Diego, Calif.

Registration opens summer 2023

Oct. 6–8, 2023

Foundational Skills in Equine Practice*

Spy Coast Farm • Lexington, Ky.

Sponsored by CareCredit, Contura Vet, Dechra Veterinary Products and Merck Animal Health

Registration opens summer 2023

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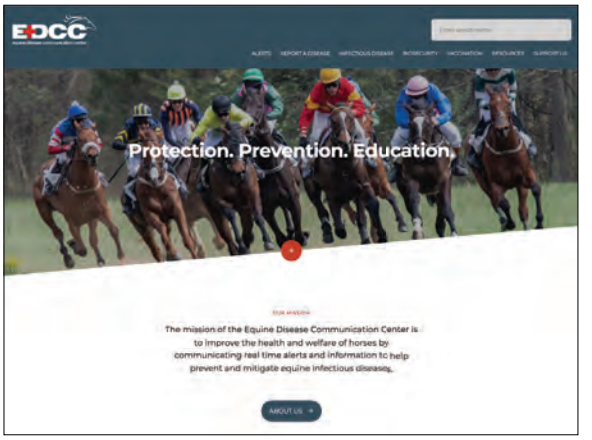
* Previously known as the New Practitioners Symposium

Acquire the latest disease information on redesigned EDCC website

The Equine Disease Communication Center (EDCC) has redesigned its website—equinediseasecc.org—which contains the information necessary to successfully navigate a disease outbreak, with resources for both owners and veterinarians.



EDCC Director Dr. Nat White said the redesign will help horse owners, veterinarians, event managers and state health officials stay current with disease outbreaks.

"Just as dealing with COVID-19 highlighted the need for disease education and streamlined communication, our new website offers a one-stop shop for disease information," he said. "We have created individual disease pages which link to factsheets and the latest information about diagnosis, treatment and vaccination guidelines for owners and veterinarians."

Veterinarians are encouraged to report confirmed cases through the Report a Disease link on the site. Timely reporting enables users to know when a disease is prevalent in their area to help make informed decisions about travel.

Foundation's 'Taking the Lead' campaign raises more than $12 million

The Foundation for the Horse's "Taking the Lead – The Campaign for the Horse," concluded Dec. 31 after three years and $12,034,260 in support. This marks a record three-year giving cycle for The Foundation and a successful first-ever campaign for the 28-year-old charitable arm of the AAEP.

Chaired by Dr. Monty McInturff, founding partner and president of Tennessee Equine Hospital in Thompson's Station, Tenn., the campaign launched quietly in January 2020 and announced its $10 million aspirations publicly in December 2021 with $6.8 million committed at that time.

"This is our way of giving back to the horse," said Dr. McInturff. "It's horse doctors, horse owners and industry organizations going above and beyond for the welfare of horses. I am exceptionally gratified by what we have achieved together, and I am especially proud of the 1,051 first-time donors to The Foundation who rallied to the cause with a campaign gift."

The ambitious three-year timeline reflected the urgency of its priorities to increase grant and scholarship support for equine medical research; veterinary students; and programs for horses at risk of abandonment, neglect, infectious disease, or in need of urgent medical care.

"This is what we're all about—providing resources so that students become first-rate equine veterinarians, researchers

Success of the campaign will boost support of projects and programs benefiting the welfare of horses, including sponsorship of disaster preparedness and emergency rescue training workshops.

improve the practice of equine medicine, and programs help horses in times of urgent need," said Foundation Chair Dr. Rick Mitchell, co-founder and partner-owner of Fairfield Equine Associates in Newtown, Conn. "It is our duty to serve the medical needs of the horse, and no other organization does what we do."

To learn more about The Foundation's impact on the welfare of horses around the world or to make a gift to The Foundation, visit foundationforthehorse.org.

Members in the News


Dr. Shannon Reed

Dr. Shannon Reed elected to Retired Racehorse Project board

Dr. Shannon Reed, a clinical associate professor of large animal surgery at Texas A&M University, has been elected to the board of directors of the Retired Racehorse Project, a charitable organization working to increase demand for off-track Thoroughbreds in the equestrian world.

Dr. Reed is a 2003 veterinary graduate of the University of Missouri whose commitment to the charity has progressed from Thoroughbred Makeover competitor to serving as consulting veterinarian and a driving force behind implementation of the Thoroughbred Makeover arrival exam. In addition, she served the AAEP on the Educational Programs and Professional Conduct and Ethics committees.


Dr. Michelle Tucker

Dr. Michelle Tucker awarded for research into 'roaring'

Dr. Michelle Tucker, assistant professor of large animal surgery at Purdue University, received the $10,000 grand prize for best platform presentation at the University of Calgary Faculty of Veterinary Medicine International Equine Symposium in fall 2022.

Dr. Tucker, who received her veterinary degree in 2014 from Texas A&M University, completed her residency and PhD at the University of Saskatchewan in 2020 and 2021, respectively. She presented a portion of her PhD work entitled, "Computational Fluid Dynamic Analysis of Upper Airway Procedures in Equine Laryngeses."

Drs. Lynn Hovda, Stephen Schumacher appointed to HISA committee

The Horseracing Integrity and Safety Authority board of directors has appointed Drs. Lynn Hovda and Stephen Schumacher as new members of its Anti-Doping and Medication Control Standing Committee, which advises on the implementation of HISA's ADMC Program nationwide in 2023.


Dr. Lynn Hovda

Dr. Hovda, appointed as an industry member representing state racing commissions, is chief commission veterinarian for the Minnesota Racing Commission and practices at Flying J Veterinary Clinic in Loretto, Minn. Dr. Hovda received her veterinary degree in 1985 from the University of Minnesota and served on the AAEP's Racing Committee from 2018–2020. She currently sits on committees with the American Quarter Horse Association, Association of Racing Commissioners International, and Racing Medication and Testing Consortium.


Dr. Stephen Schumacher

Dr. Schumacher, appointed as an independent member, is chief administrator of the United States Equestrian Federation's Equine Drugs and Medications Program, an advisory panel member at the University of Kentucky Equine Analytical Chemistry Laboratory and a list group member of the Fédération Equestre Internationale.

A 2003 veterinary graduate of The Ohio State University, Dr. Schumacher has served on the AAEP's Performance Horse Committee since 2015 and additionally serves on committees of the American Horse Council, Equine Disease Communication Center, and Racing Medication and Testing Consortium.

Kentucky VMA honors Drs. Katie Flynn and Stuart Brown

The Kentucky Veterinary Medical Association bestowed honors upon a pair of AAEP members during its annual meeting in late September. Dr. Katie Flynn, Kentucky state veterinarian since 2021, was named KVMA Veterinarian of the Year; and Dr. Stuart Brown, vice president of equine safety at Keeneland Association in Lexington, Ky., received the KVMA Distinguished Service Award.


Dr. Katie Flynn

Dr. Flynn, who received her veterinary degree from the University of Glasgow, Scotland, previously chaired the AAEP's Infectious Disease Committee and served on the Welfare and Public Policy Advisory Council. She received the AAEP President's Award in 2019. Dr. Flynn is stepping down as state veterinarian in late February to join the U.S. Equestrian Federation as staff veterinarian.


Dr. Stuart Brown

Dr. Brown, a veterinary graduate of Tuskegee University and member of the AVMA House Advisory Committee, has served as a commissioner for the Kentucky Horse Racing Commission, is a past president of the Kentucky VMA and Kentucky VMA Foundation, and is a past chair of the Gluck Equine Research Foundation.

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Welcome to new AAEP members!

We are delighted to welcome the following practitioners who joined the AAEP between Oct. 1–Dec. 31, 2022:

Natalie Barrett, DVM, Moorpark, CA
Theresa Beachler, DVM, Collins, IA
Steven Robert Bond, DVM, Whitesboro, TX
Paula Bradley, DVM, Saint-Jean-Baptiste, QC, Canada
McKenzie Ashtin Brewer, DVM, Gainesville, TX
Pricilla M. Brown, DVM, Lexington, KY
Eric Bruns, DVM, Beaver, PA
Rayna Campos, DVM, Terrytown, LA
Candelaria Chunco Azcoitia, DVM, Wellington, FL
Erin Clarke, DVM, Rocky View County, AB, Canada
Gerardo Coldivar Pena, DVM, Tlajomulco de Zuniga, Jalisco, Mexico
Kenyon Jeannette Conklin, VMD, Reisterstown, MD
Sabrina Bellaver Cousseau, DVM, Baton Rouge, LA
David Kenneth Cox, MRCVS, BVMS, Athens, GA
Alexandra Crowley, DVM, Dayville, CT
Courtney Culbertson DVM, New Hill, NC
Megan R. Darragh, DVM, Washington, PA
Leon Franklin Davis, DVM, Clinton, TN
Oscar De La Peña Garcia, MVZ, Zapopan, Jalisco, Mexico
Emma Deane, DVM, DACVECC, Rocklin, CA
Lana Dedecker, DVM, Auburn, AL
Gianhisy Diaz, DVM, San Antonio, TX
Linden Drake, DVM, Ivor, VA
Marie-Michelle Drouin, DVM, Saint-Georges, QC, Canada
Kelsey Duarte, DVM, Fredericksburg, TX
Julia Duarte S. Frati, DVM, Purcell, OK
Kathryn Duncan, DVM, Oklahoma City, OK
Cristina Duran, DVM, Quito, Pichincha, Ecuador
Mohamed Ahmed Elsherif, BVSc, PhD, Geiza, Egypt
Alberto Filho, DVM, Ribeirao Preto, Brazil
Chelsea Fishenfeld, DVM, Gilroy, CA
Alexandra Fitton, DVM, Fultonville, NY
Gary F. Fouts, DVM, Bristol, IN
Thomas Bennett Fraker, DVM, Lexington, KY
Bethany Frank, DVM, Roanoke, TX
Stephanie Frank, DVM, Lake Forest, CA
Fernando Garcia Lacy, DVM, Miguel Hidalgo, DIF, Mexico
Stephanie Gartner, DVM, Lloydminster, AB, Canada
Hermen Peter Geertsema, DVM, Langley, BC, Canada
Jessica Gilbertie, MS, DVM, PhD, Blacksburg, VA
Laurie Goodrich, DVM, PhD, Fort Collins, CO
Sarah Graboys, VMD, Manchester, MA
Bart Halsberghe, DVM, DECVSMR, Gilroy, CA
Marcy Hammerle, DVM, Troy, MO
Patrick Hatch, DVM, Pell City, AL
Jessica Hazel, DVM, Crosby, TX
Donna J. Henderson, DVM, Phillipsburg, MO
Ollie Hensley, DVM, Ashland, AL
Preston Hickman, DVM, Leon, KS
Rebecca Hicks, DVM, DACVS(LA), Oakdale, CA
Collin Rush Howard, DVM, Helotes, TX
Jessica Huntington, DVM, Stephenville, TX
Kathleen Kalbian, VMD, Alvarado, TX
Kathleen Kelly, DVM, Frankfort, IL
Candace Kendrick, DVM, Colorado City, TX
Yeonjong Kim, DVM, Gwacheon-Si, Gyeonggi-Do, Korea, Republic of
Annie King, DVM, Rocky View County, AB, Canada
Camille Christine Laird, DVM, Show Low, AZ
Larissa Lee, DVM, Poulsbo, WA
Ricardo Lopez, MVZ, San Luis Potosi, Mexico
Natalie Rosalia Lord, DVM, Granite Shoals, TX
Daniel R. Luehrs, DVM, West Plains, MO
Rohit Malhotra, DVM, Stoneham, MA
Homero Marin Lara, MVZ, Soledad de Doblado, Mexico
Gabrielle Martin, DVM, Mineral Wells, TX
Tyler Martin, DVM, Mineral Wells, TX
Dana Neelis, DVM, Emmett, ID
Luisa Nitzschke, DVM, Leesburg, VA
Cesar Noronha, DVM, Fort Collins, CO
Padraig O'Reilly, DVM, Westmeath, Ireland
Richard Osterloh, DVM, Stephenville, TX
Sarah Jane Owens, DVM, Issaquah, WA
Allyssa J. Parker, DVM, Nashotah, WI
Ashley M. Phelps-Dunn, DVM, Westfield, IN
Jesse Ray Poovey, DVM, Maiden, NC
Deanna Rae Post, DVM, Belen, NM
Carolina Silva Ramos, DVM, Baton Rouge, LA
Martha Lucia Rangel Smith, MVZ, Mexico City, Mexico
Alex R. Rendon, DVM, Fort Lauderdale, FL
Ansgar Reyering, DVM, Mettingen, Germany
Meredith A. Rhodes, DVM, Andover, NJ
Brooke Richards, DVM, New Smyrna Beach, FL
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Morgan Wood, DVM, Dixon, WY
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Dr. John Peterson, co-founder of Peterson Smith Equine Hospital, passes


Dr. John Peterson

Dr. John Peterson, co-founder of Peterson Smith Equine Hospital + Complete Care in Ocala, Fla., and 46-year AAEP member until his retirement in 2017, died Dec. 25. He was 81.

After receiving his veterinary degree from Iowa State University in 1966, Dr. Peterson worked in private practice until founding Peterson Smith in 1981 with Dr. Johnny Mac Smith. He retired from the partnership and became an ambulatory associate in 2007, continuing to see patients until the end of 2017.

Dr. Peterson's specialties included racing and sports medicine, lameness, reproduction and pediatrics. In addition, he served on the AAEP's Political Liaison and Reproduction committees in the mid-1990s.

Longtime Colorado veterinarian Dr. Mark Fitch dies at 72


Dr. Mark Fitch

AAEP Honor Roll member Dr. Mark Fitch, who practiced for 45 years in the Boulder, Colo., region and served on the AAEP's Equine Welfare Committee from 2008–2010, died Nov. 9. He was 72.

Dr. Fitch received his veterinary degree from Colorado State University in 1976. Following an internship at the Littleton Large Animal Clinic, Dr. Fitch established his own practice in Boulder in 1977. He brought on his first associate in 2001. Nine years later, Dr. Fitch sold the practice, which became Quality Equine Veterinary Services, Inc., and remained on as an associate until his passing.

His professional interests included dentistry, lameness and behavioral counseling. Dr. Fitch also enjoyed mentoring aspiring veterinarians and horse-lovers alike.

AAEP Past President Dr. John T. Vaughan dies at 90


Dr. John T. Vaughan

AAEP Past President Dr. John Thomas "J.T." Vaughan, dean emeritus of veterinary medicine at Auburn University, died Jan. 13 at the age of 90.

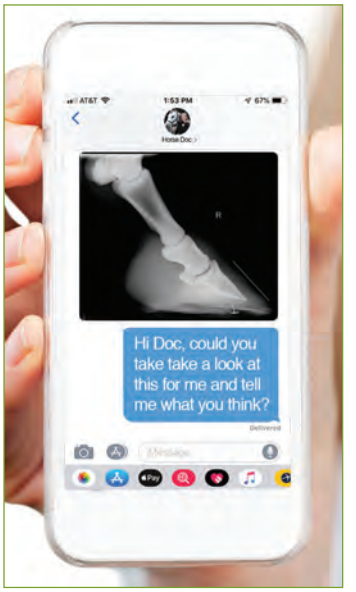
Dr. Vaughan received his veterinary degree from Auburn in 1955. He practiced briefly in Tuskegee, Ala., before returning to Auburn as an instructor in the large animal clinic. He went on to study equine surgery at the University of Pennsylvania and, in 1968, passed the inaugural board exam of the American College of Veterinary Surgeons. Following several years as a professor of surgery and director of the large animal teaching hospital at Cornell University, Dr. Vaughan retuned to Auburn in 1974 as department head in large animal medicine.

He soon moved into leadership roles in academia and organized veterinary medicine. He became dean at Auburn in 1977 and served as president of the ACVS and the AAEP in 1980 and 1981, respectively. During his tenure as dean, the college expanded its research program and graduate training, clinics and clinical faculty. He provided leadership during the growth of veterinary colleges in the South and the increase in female veterinary students across the country.

After his retirement in 1995, Dr. Vaughan served as a trustee of the AVMA PLIT from 1996–2009, including a term as chair from 2001–2003. His extensive volunteer service within the AAEP included terms as chair of six different committees.

Dr. Vaughan's many accolades include the AAEP awarding him Distinguished Life Member status in 1999 and Auburn renaming its large animal hospital in his honor in 2003.

FDA to resume enforcement of all federal VCPR requirements for veterinary telemedicine



Beginning Feb. 21, the Food and Drug Administration (FDA) will resume holding veterinarians to the federal requirements for the veterinarian-client-patient relationship, according to the AVMA. The federal VCPR definition "requires animal examination and/or medically appropriate and timely visits to the premises where the animal(s) are kept" and "cannot be met solely through telemedicine."

In March 2020 during the early days of the COVID-19 pandemic, the FDA temporarily suspended federal enforcement for an in-person animal examination or premise visit to establish a VCPR for activities covered by the federal VCPR definition, including extralabel drug use and issuing veterinary feed directives.

The FDA now says the conditions that created the need for the enforcement policy have evolved such that the policy is no longer needed. As a result, as of Feb. 21, veterinarians will need to meet all the requirements of the federally defined VCPR, including an in-person examination or premise visit, to establish the relationship prior to engaging in covered activities. A VCPR that meets the federal definition cannot be established through telemedicine. Once established, the VCPR may be maintained via telemedicine between medically appropriate examinations and premise visits.

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Equine Veterinary Education

RESEARCH HIGHLIGHTS

Highlights of recent clinically relevant papers

SEPTIC ARTHRITIS IN FOALS

This retrospective cohort study by Katrijn Whisenant and co-workers in the United States aimed to determine the racing prognosis for Thoroughbred foals, 6 months of age or less with a single septic joint of presumed haematogenous origin without recognised systemic sepsis or other serious comorbidity compared with a group of maternal sibling controls.

Data were collected from in-patient records from 2009 to 2016. Parameters evaluated included diagnostic tests, therapeutic regimens, final diagnosis and outcome. Racing records were obtained from a public archive for cases and two maternal siblings. Racing performance data were collected for the number of starts, age at first race, number of wins/places/shows and total winnings per career. Univariable analyses of categorical variables were conducted.

Ninety-five cases were included in this study, of which 93% survived to discharge. The last measured synovial nucleated cell count (SNCC) prior to hospital discharge or euthanasia (OR 0.5, 95% CI: 0.3–0.8) was an indicator of poor prognosis for survival to discharge. In cases nonresponsive to treatment, the last SNCC measured prior to euthanasia was higher (median 86.8×10^9/L; IQR 30.6–113.2×10^9/L) than the final measured SNCC in cases discharged alive from the hospital (median 7.2×10^9/L; IQR 0.8–91.6×10^9/L). Total winnings per career were the only statistically significant racing performance variable between cases and paired controls (IRR 0.7, 95% CI: 0.5–0.99).

The prognosis for survival was high (93%) and the prognosis to race was similar to healthy maternal siblings, but the total earnings were lower.

HEMIEPIPHYSIODESIS OF THE DISTAL METACARPUS

The objective of this retrospective study by US-based Sophie Boorman and Dwayne Rodgerson was to report the outcome of foals treated for metacarpophalangeal varus deformity with a single-incision drilling technique for hemiepiphysiodesis of the distal lateral metacarpal physis.

Medical records of 207 Thoroughbred foals were reviewed for signalment, limb(s) treated, location of the surgery and any reported complications. Follow-up radiographs obtained for the yearling sale were assessed for abnormalities. Horses were matched to 171 maternal siblings using an online database. Sales and racing performance data were compared between cohorts.

The average age at the time of surgery was 97 days. The treated limbs were the left front (n = 52), right front (n = 31), both fronts (n = 119), unknown (n = 5). Three horses developed calcinosis circumscripta lesions adjacent to the physis, which were removed successfully. No radiographic abnormalities associated with the surgery site were detected on yearling prepurchase radiographs. There were no differences in sales and racing performance data between treated horses and maternal controls.

The authors concluded that hemiepiphysiodesis is a safe and effective treatment for metacarpophalangeal varus deformities in foals. No negative effect on sales or racing performance was identified. This technique avoids risks, costs and the need for second surgery associated with an orthopaedic implant. The surgeon should be aware of the potential for the development of a calcinosis circumscripta lesion with this technique.

PULMONARY BLEEDING IN RACEHORSES

In this study, Guido Rocchiagiani and co-workers in the UK, Italy and USA performed a gross, histological, and ultrastructural comparison of exercise-induced pulmonary haemorrhage and exercise-associated fatal pulmonary haemorrhage in racehorses.

Exercise-induced pulmonary haemorrhage (EIPH) is common in Thoroughbred racehorses and usually causes reduced performance, while exercise-associated fatal pulmonary haemorrhage (EAFPH) is characterised by severe pulmonary bleeding of unknown pathogenesis resulting in sudden death during strenuous exercise. The aim of this study was to characterise and compare anamnestic data together with pulmonary gross, histological and ultrastructural findings in racehorses with EIPH (n = 10), EAFPH (n = 10), and control horses (n = 5).

No differences in anamnesis were identified between the three groups. Grossly cranial lobe reddening and oedema scores were more prevalent and severe in the EAFPH group compared with the EIPH and control groups. Histologically, haemorrhage scores were higher in the EAFPH group, while haemosiderophages, iron encrustations of collagen and elastin fibres, and vascular remodelling scores were higher in the EIPH group compared with the EAFPH and control groups. In all groups, caudal lung locations exhibited a higher score for vascular remodelling, haemosiderophage accumulation, iron encrustation and type II pneumocyte hyperplasia when compared to cranial, dorsal and ventral locations. Ultrastructural analysis of perivascular collagen showed fibrils with larger diameters in the

EAFPH group compared with the EIPH group but not compared with the control group. This study demonstrates that lungs of horses that experienced EAFPH show significantly less vascular remodelling and other long-term pulmonary abnormalities that characterise horses with EIPH.

PROTEIN CONCENTRATIONS AFTER PPG INJECTION

The aim of this prospective longitudinal study by Danielle Gordon and co-workers in the United States was to evaluate the effects of intramuscular (IM) procaine penicillin G (PPG) injections on acute phase protein (APP) concentrations in horses.

Procaine penicillin G was administered intramuscularly to six healthy horses, twice daily, for 5 days. Plasma fibrinogen (FIB), serum amyloid A (SAA), haptoglobin (HAP), creatine kinase (CK) and aspartate aminotransferase (AST) were quantified daily for 5 days before the first injection, during the 5 days of injections and for 4 days after the final dose.

Creatine kinase was increased over baseline on Days 1–6 and AST was increased above baseline on Days 2–7 and 10. Increased FIB was noted over baseline on Days 6–8 and 10. Clinically significant increases in SAA were noted in half the horses over several days, but due to the wide individual variability, SAA was only statistically significantly increased above baseline on Day 6. There was no change in HAP.

Serial IM PPG injections may result in increased concentrations of some acute phase proteins in horses, and this must be considered when these test results are interpreted.

ANTIMICROBIAL RESISTANCE

In this study Jennifer Lord and co-workers in the United States aimed to describe antimicrobial resistance patterns and identify predictors of antimicrobial resistance (AMR) and multidrug resistance (MDR) (resistance to three or more antimicrobial classes) among equine Streptococcus zooepidemicus and Rhodococcus equi isolates.

Antimicrobial susceptibility data from equine specimens submitted to a diagnostic laboratory over a 6-year period were used in the study. Temporal trends in AMR and MDR were assessed using the Cochran-Armitage test. Logistic regression was used to identify associations between patient characteristics and the following outcomes: (a) MDR among *S. zooepidemicus* isolates and (b) resistance to macrolides and ansamycins (rifampin) among *R. equi* isolates. Logistic regression was also used to investigate whether resistance of *S. zooepidemicus* and *R. equi* isolates to an antimicrobial class could be predicted by resistance to other drug classes.

The majority of *S. zooepidemicus* (99.6%) and *R. equi* isolates (83%) were resistant to at least one antimicrobial agent, but no significant temporal trends in AMR were observed. Approximately half (53.3%) of the *S. zooepidemicus* isolates were multidrug-resistant, and there was a significant increasing temporal trend of MDR among *S. zooepidemicus* isolates. Resistance to penicillin, which is typically recommended for the treatment of suspected *S. zooepidemicus* infections, also increased during the study period from 3.3% to 9.5%. Among *R. equi* isolates, 19.2% were resistant to one or more macrolide antibiotic, 24% were resistant to rifampin, and 15.6% were resistant to both macrolide(s) and rifampin. For both organisms, resistance to an antimicrobial class could be predicted based on resistance profiles to other drug classes. For instance, significant predictors of β-lactam resistance among *S. zooepidemicus* isolates included resistance to macrolides (OR 14.7) and ansamycins (OR 9.3). Resistance to phenicols (OR 3.7) and ansamycins (OR 19.9) were associated with higher odds of macrolide resistance among *R. equi* isolates.

The increase in MDR among *S. zooepidemicus* isolates is concerning. The observed levels of resistance to macrolides and rifampin among *R. equi* are also of concern given the limited number of antimicrobials available for treatment of this organism. The findings of this study highlight the importance of ongoing surveillance of AMR to guide treatment decisions and directions for future research.

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Equine Veterinary Education

EDITORIAL

Time for change in the equine veterinary industry

Across the globe, equine practice is becoming a veterinary career that is uncommonly chosen. Although close to a third of applicants to veterinary school in the United States say that their career aspiration is to be a horse doctor (L. Greenhill, personal communication, 2022), by the time the students are accepted and finish 4 years of their veterinary medical education, in the last decade the percentage entering equine practice directly after graduation has dwindled to less than 1.5% (AVMA AAEP, 2017). In 2020, 1.4% of graduates took positions in private practice for horses directly after graduation (Bain, 2021). Another 100 or so generally enter equine internships, bringing the total number entering equine practice to about 150 annually in the United States. AAEP membership figures show that just over 50% of these new veterinarians drop their membership within 5 years of graduation, a trend that has been growing for the last decade.

These data support the frequent anecdotal reports of difficulty in attracting and retaining doctors in equine practice. AVMA census figures showed a national gain of 59 equine exclusive veterinarians in 2021 over 2020, but 44% of AAEP members are more than 50 years of age, with 17.4% of members 51–60 years of age and 26.6% of members >60 years of age (N. Altwies, AAEP, personal communication, 2022). This is likely to mean a significant number of retirements in the next decade. Meanwhile, the AVMA predicts a rise in the number of horses in the United States to just over 7 million in 2030 from their current estimate of 6.97 million present in 2020, with a concomitant rise in demand for equine veterinarians (AVMA Veterinary Workforce Dashboard, 2022).

A survey conducted in November 2021 showed that equine practices were much busier in 2021 than in 2020, and in 2020 than in 2019 (Grice, 2022). That busyness included an increase in appointments, emergencies, new clients, revenue and hours worked. Perhaps as a result, equine practitioner respondents cited high levels of exhaustion and low levels of self-care.

AVMA data show that new graduates who enter equine practice directly after veterinary school are offered salaries almost half of those who enter companion animal practice (Bain, 2021). However, unpublished data collected from 388 equine associates in early 2022 show that most associates earn an average of $110,000 after 5 years in practice, but this figure is still substantially less than the compensation of comparable doctors in the small animal sector. AVMA data reveal that, in 2020, 83% of new graduates reported educational debt, with an average obligation of $188,883 for those with loans. Of these, 34% reported more than $200,000 in educational debt, 12.5% more than $300,000 and 1.4% more than $400,000 (AVMA, 2021). The debt-to-income ratio for equine graduates was 3.7 in 2021 (C. Hansen, personal communication, 2022), with 1.6 being considered reasonable for a professional such as a physician, engineer and attorney. The need to pay loan obligations increases new graduates' concern about salaries.

Within this perfect storm, there are strong competitive forces pulling actual and potential equine practitioners into companion animal practice. Higher salaries, more flexible work weeks, shorter work hours and no emergency duty draw overwhelmed equine doctors like bears to honey. AVMA data show that in 2021, there were 18.6 jobs for every veterinarian jobseeker across the country (M. Salois, AVMA). Small animal practices, especially those that are corporately owned, are competing for veterinarians as demand has risen, with large signing bonuses, six-figure starting salaries and robust benefit packages (M. Larkin, AVMA). The result of these forces is a looming shortage of doctors to care for the nation's horses.

Fortunately, with changes to our industry, we can meet this challenge and create sustainable careers for the many young people who dream of being a horse doctor. It is within our power to renew the pipeline of veterinarians into the field and sustain those already working in this amazing profession.

Change is not easy for anyone. Change most readily happens when the pain of not changing exceeds the pain of change. As an industry, we have reached that point. All must now embrace the discomfort of doing things differently, adopting new business models, supporting a new demographic of veterinarians and leading with intention. People need to feel belonging. Acceptance and belonging are in the second tier of Maslow's hierarchy of needs after food, water and shelter. This new generation of equine doctors needs to be able to see themselves as fitting into the workplace, while being respected, listened to, and receiving acceptance and pride in them from the practice leaders. Leaders must model the way.

One of the most important changes will be to pay higher salaries to equine doctors more comparable with companion animal positions, which will require increased service fees, higher efficiency, broader use of technical staff and embrace of technology in order to promote higher revenue production. With most of the new equine veterinarians being female and in their prime childbearing years, building positions that allow for a hard stop to the day, shorter work weeks and minimal emergency shift obligations will allow more horse doctors to stay with the career. Other adjustments will require reducing clients' unfettered access to doctors, creating collaborative emergency duty arrangements and transforming top-down autocratic management styles. Business models will need to pivot to these new realities. Practice cultures will need to embrace diversity, collaboration and the value of every team member to the effort.

Continued on page 72

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Equine Veterinary Education

CASE REPORT

Chronic tuberculosis caused by *Mycobacterium bovis* in a domestic donkey in Central Europe

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SUMMARY

A 30-year-old female donkey was examined for lesions under the skin, which appeared as swellings at the base of her neck. The clinical examination revealed BCS 3/5, normal behaviour and vital signs. The only detected abnormality was the presence of enlarged lymph nodes – submandibular, superficial-cervical and supramammary. The enlarged lymph nodes were firm with a lobular surface, movable, painless and not abnormally warm. An ultrasound biopsy of the lymph nodes was not possible. Two and a half years later, the owners noticed a deterioration in the body condition and dullness. The donkey died naturally on the farm after unsuccessful symptomatic treatment. On gross post-mortem examination, the BCS of the donkey was 1.5/5. The examination revealed enlargement and concretion of numerous lymph nodes (submandibular, prescapular, popliteal, inguinal, mesenteric and mediastinal) (Figure 1). The previously examined lymph nodes had become larger and unmovable. Small numerous, whitish-grey, firm nodules were observed within the liver, spleen, stomach, jejunum, colon wall, pulmonary parenchyma and tongue. The normal lymph node structure was completely obliterated, additionally by intense and generalised calcification. Multi-organ failure leading to cachexia was suspected as the cause of death. The pulmonary tissue had infiltrations of mixed-cell populations, indicating chronic interstitial lung disease. The appearance of the lesions suggested tuberculosis. Specially prepared homogenates from lymph nodes were used for direct microscopic examination, culture and PCR. In the prepared Ziehl-Neelsen smears, single acid-fast bacilli were visible and their growth was observed in the culture test after 5 weeks. PCR results indicated the *Mycobacterium bovis* species. The GenoType CM test also gave a positive result, and species of Mycobacteria were identified as the *Mycobacterium bovis ssp. bovis*.

KEYWORDS
equidae, horse, latent tuberculosis, lymphadenopathy, *Mycobacterium bovis*, *mycobacterial infection*

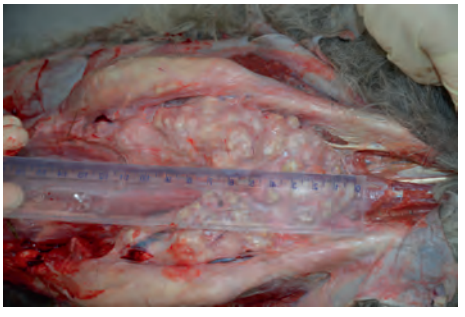

FIGURE 1 Size and appearance of the submandibular lymph nodes during the post-mortem examination.

Key points

- Tuberculosis is a rare disease in equids.
- Chronic tuberculosis may be silent for long periods of time, and clinical manifestations of the disease can be non-specific and easily mistaken with more common diseases.
- Intravital definitive diagnosis is difficult, acid-fast bacilli staining may yield false results, the results of the culture may only be available after several weeks, so molecular tests like PCR are one of the most reliable and fastest methods of detecting *Mycobacterium*.

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Equine Veterinary Education BEVA AAEP

CASE REPORT

Incarceration of the caecum through a rent in the gastrosplenic ligament

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SUMMARY

A 3-year-old Thoroughbred gelding presented for evaluation of colic. The horse began displaying signs of discomfort 12 h prior to admission and had been treated with flunixin meglumine, metamizole and intravenous fluids. The horse was referred to the hospital as the clinical signs of colic became more severe and did not respond to medical treatment.

On admission, the horse was sweating and restless with a heart rate of 60 beats/min. Intestinal motility was decreased on auscultation in all four quadrants of the abdomen. Transcutaneous ultrasonographic examination of the abdomen revealed a viscus with a mural thickness of up to 1.6 cm in the cranioventral aspect of both sides of the abdomen. A nasogastric tube was passed, and no reflux was obtained. Peripheral blood analysis revealed a packed cell volume of 40%, total plasma protein concentration of 50 g/L, plasma lactate concentration 4.6 mmol/L and total nucleated cell count of 8.6×10^6/L. An exploratory laparotomy under general anaesthesia was performed. Abdominal exploration revealed incarceration of the caecum through a rent in the gastrosplenic ligament with the spleen displaced to the right, across the midline and the caecum positioned on the left side of the abdomen. The caecum had an oedematous, purple, thickened wall and was orientated with the apex caudal to the gastrosplenic ligament. The ventral aspect of the rent was ligated and transected (Figure 1) as the manual reduction of the caecum was not possible due to mural thickness. The caecum was freed, and normal orientation was confirmed. The serosal colour quickly improved, and therefore, the caecum was not resected or bypassed. Complete abdominal exploration was performed but no other abnormalities were present. The horse recovered uneventfully from surgery. Post-operative treatment included antimicrobials, anti-inflammatory drugs and prokinetics. Abdominal ultrasound was performed daily post-operatively. Caecal mural thickness returned to normal 24 h post-operatively. Caecal content was predominantly fluid initially but returned to normal by Day 5. The horse was discharged from the hospital 11 days post-operatively. Five months later, the horse returned to race training.

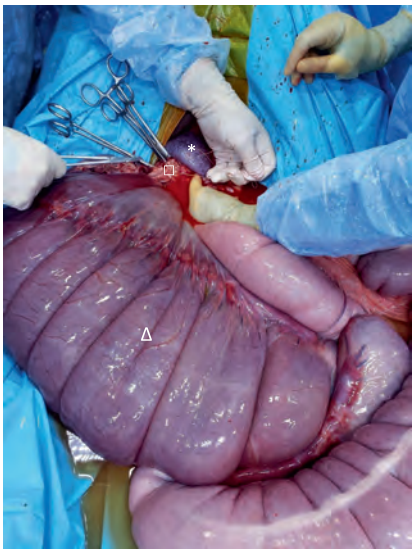

FIGURE 1 Ligation of the ventral aspect of the rent in the gastrosplenic ligament prior to transection. * denotes the spleen, Δ the caecum and □ the gastrosplenic ligament.

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KEYWORDS

horse, caecum, colic, gastrosplenic ligament, surgery

Key points

- Pre-operative ultrasonography showed that the caecum had an increased mural thickness and was visible in the left, mid and right cranioventral abdomen.
- The abnormal location and mural thickness of the caecum was due to incarceration by a rent in the gastrosplenic ligament; this could only be determined intra-operatively.
- Resection of the ventral aspect of the rent in the gastrosplenic ligament allowed the caecum to be returned to its normal orientation.

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Equine Veterinary Education BEVA AAEP

CASE REPORT

Otitis media secondary to trigeminal schwannoma in a Quarter Horse

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SUMMARY

An 18-month-old Quarter Horse colt was presented with a deep corneal ulcer of the right eye and mastication difficulties lasting for 2 weeks.

Examination of the right eye revealed a deep corneal ulcer, keratomalacia and secondary uveitis. On neurological examination, significant muscle atrophy of the right temporal and masseter muscles, and loss of sensation on the right side of the face were noted. These findings were consistent with right trigeminal nerve (CN-V) paralysis. Deviation of the head to the left was also noted during mastication.

Dental examination, upper airway endoscopy and radiography of the skull were unremarkable. Despite medical treatment consisting of systemic nonsteroidal anti-inflammatory drugs, systemic antimicrobials (procaine penicillin) and adaptation of the diet, the horse showed minimal improvement.

Contrast CT scan of the skull revealed hyperattenuating material completely filling the right tympanic bulla suggesting otitis media, and marked contrast enhancement after iopamidol administration at the level of the right trigeminal nucleus in the pons/hindbrain, compatible with a mass.

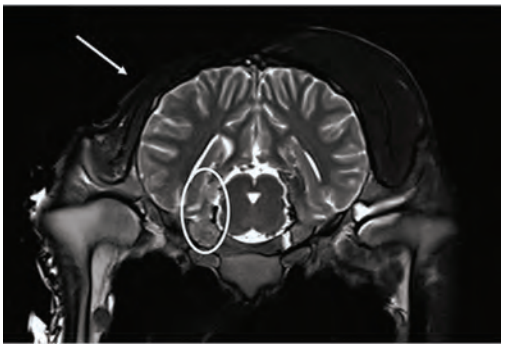

FIGURE 1 MRI without contrast (T2W). Enlargement of the right trigeminal nerve at its intracranial emergence (circle). Temporal muscle atrophy (arrow)

Cerebrospinal fluid analysis revealed severe inflammation (lymphocytic pleocytosis, neutrophilia and rare eosinophils, mild hyperproteinorachia and increased creatine kinase concentration) and negative bacterial culture. Despite adaptation of the medical treatment (tetracyclines, ivermectin and corticosteroid treatment at tapering doses), the colt continued worsening and was euthanised 65 days after referral.

Post-mortem MRI showed severe muscle atrophy of the right temporal, pterygoid, masseter and hyoid muscles and of the right *tensor veli palatini* (TVP) and *levator veli palatini* muscles, and enlargement of the right CN-V at the level of its intracranial emergence, supportive of a mass (Figure 1).

Histopathology of the mass revealed fusiform tumoral cells, positive in vimentin and S100 immunohistochemistry, consistent with a schwannoma. Otitis media was presumed secondary to CN-V paralysis and denervation of the right *tensor veli palatini* muscle involved in the opening of the Eustachian tube.

KEYWORDS
horse, Schwann cell tumour, nerve paralysis, tumour, tensor veli palatini, otitis

Key points

- Trigeminal schwannoma is a rare neoplasm of horses, which should be considered in the presence of trigeminal paralysis nonresponsive to treatment.
- CT scan can be valuable for visualisation of the neurological lesion, can be performed under standing sedation and should be considered as an alternative to MRI.
- Otitis media is uncommon in horses and presumably developed as a consequence of CN-V paralysis involving the *tensor veli palatini*. This mechanism warrants further investigation of the auditory system in cases of trigeminal paralysis.

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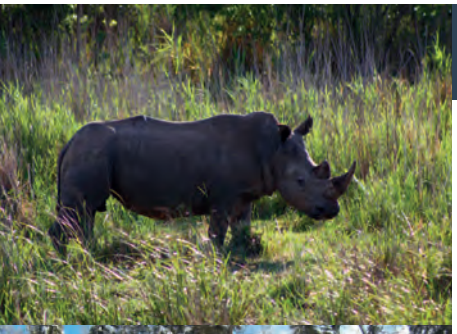

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Equine Veterinary Education

CASE REPORT

Successful cardiopulmonary cerebral resuscitation incorporating defibrillation in a filly with neonatal maladjustment syndrome following a routine anaesthetic procedure

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SUMMARY

A 10-h-old 56-kg Thoroughbred filly was presented for treatment of partial failure of passive transfer of immunity and presumed neonatal maladjustment syndrome (NMS). The filly was hospitalized, and supportive care initiated. On day 5 of hospitalization, seizures were observed and controlled with IV diazepam. Due to the progression of clinical signs of NMS, magnetic resonance imaging (MRI) of the filly's brain was performed.

During the MRI, the filly experienced bradycardia and hypotension and was treated with four IV doses of hyoscine, a 6% Hydroxyethyl bolus, a dobutamine constant rate infusion, and three IV doses of ephedrine throughout the 120-min MRI. Prior to the end of the MRI, the MAP started declining and measured 40 mmHg while discontinuing isoflurane.

Following the MRI, the filly was moved into a recovery stall and CPA was detected via ECG. CPCR was immediately initiated with external cardiac compressions along with the provision of 8–12 breaths/min supplemented with 100% oxygen via endotracheal tube. Contra-abdominal compressions were also applied. Epinephrine and atropine were administered IV. After 12, 2-min cycles of compressions with advanced life support, pulseless ventricular tachycardia was identified on the ECG.

A defibrillator was not immediately available; therefore, IV lidocaine was administered followed by IV epinephrine. Alternating chest and abdominal compressions continued without ROSC; therefore, another dose of IV epinephrine was administered. Five minutes later, the ECG displayed ventricular fibrillation (VF). External defibrillation was performed administering 4 J/kg with a monophasic defibrillator without resolution of VF. Another defibrillation attempt was administered, and VF was controlled for a few seconds but reappeared. A third attempt at defibrillation was performed following a cycle of cardiac compressions, after which normal sinus rhythm was confirmed. ROSC and spontaneous respiration occurred for approximately 6 min after which CPA was detected again and CPCR was restarted. The patient received another dose of IV epinephrine. Shortly thereafter, ROSC was observed approximately 45 min after the initial CPA detection and a total of approximately 20, 2-min cycles of CPCR (48 min).

Post-ROSC care was initiated and included intranasal oxygen insufflation, glucose supplementation, fluid therapy, temperature and antioxidant support, as well as continuation of antimicrobial and supportive therapies previously initiated. By day 8, the filly began reliably nursing. Serum cardiac troponin I levels decreased from 22.00 ng/mL (137 min post-CPA) to 1.53 ng/mL (rr: 0.047 ± 0.085 ng/mL) five days following CPA. The filly was discharged on day 12 and was reported healthy 12-month post-discharge.

KEYWORDS
horse, cardiac troponin, CPR, defibrillation, foal, NMS

Key points

- Prolonged CPCR incorporating monophasic electrical defibrillation (4 J/kg) in a foal can be a successful treatment for VF.
- Additional research is needed to evaluate the extent to which NMS may impact the cardiovascular system as well as to establish acceptable arterial blood pressure ranges especially in anaesthetized foals and to determine the degree that hypothermia may contribute to the success of defibrillation.
- Although the majority of CPCR events are discontinued following 10 minutes of activity, this case report elucidates the need for further research to confirm if prolonged CPCR efforts should be extended beyond the currently acceptable 10-minute period.

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Equine Veterinary Education BEVA AAEP

CASE REPORT

Transient hypogammaglobulinaemia of the young in a Thoroughbred yearling

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SUMMARY

A 12-month-old Thoroughbred colt was presented for chronic recurrent respiratory disease characterised by persistent mucopurulent nasal discharge, intermittent pyrexia (38.9-39.7°C [102–103.4°F]) and productive coughing of several months' duration. These episodes were responsive to empirical antimicrobial therapy but returned once therapy was discontinued. Physical examination and thoracic auscultation revealed intermittent wheezing over the left lung fields and a scant amount of mucopurulent nasal discharge bilaterally. Routine bloodwork revealed hypoproteinaemia (53 g/L; RR: 61–84 g/L) characterised by hyperglobulinaemia (21 g/L; RR: 24–49 g/L). Thoracic ultrasound revealed pleural surface roughening and small (<1 cm diameter) multifocal lesions of consolidated lung bilaterally. Transtracheal wash fluid culture yielded moderate growth of a mixed bacterial flora, which included *Enterobacter cloacae*, a-haemolytic *streptococci* and gram-positive cocci. Additional diagnostics were performed and found to be normal included upper airway endoscopy, bronchoalveolar lavage, thoracic radiographs and nasal swab PCR (*Streptococcus equi*, equine arteritis virus, equine influenza virus, equine herpes virus type 1 and 4, and equine rhinitis virus A and B). The recurrent nature of the patient's clinical signs and mixed population bacterial growth on transtracheal wash sample coupled with hypoglobulinaemia prompted further evaluation for a potential underlying immunodeficiency.

Serum immunoglobulin concentrations and peripheral blood lymphocyte phenotyping revealed low serum IgG and IgM concentrations. These values were considered particularly low in the face of chronic antigenic stimulation from recurrent respiratory infection and were suggestive of inadequate humoral immunity. Peripheral blood lymphocyte immunophenotyping revealed lymphocyte subpopulation distributions appropriate for a yearling. A presumptive diagnosis of transient hypogammaglobulinaemia of the young was made based on the colt's age, history of recurrent respiratory infections, and low serum IgG and IgM concentrations. The colt was started on broad-spectrum antimicrobials (ceftiofur crystalline free acid), and the owner was advised that additional courses of antimicrobials would likely be necessary to address recurrent opportunistic infections until serum immunoglobulins reached protective levels. Repeat immunologic testing at 4 and 7 months postdischarge revealed gradual improvement and eventual normalisation of serum IgG and IgM concentrations. No additional episodes of fever or respiratory signs were observed, and the colt successfully transitioned into a race training programme at 21 months of age.

Transient hypogammaglobulinaemia of the young is a primary humoral immunodeficiency characterised by delayed production of endogenous immunoglobulins and increased susceptibility to opportunistic pathogens. Recurrent fevers and opportunistic infections, particularly of the respiratory tract, are the hallmarks of impaired immune function in horses, and the presence of either should prompt veterinarians to evaluate for an underlying immunodeficiency via serum immunoglobulin concentrations and peripheral blood lymphocyte phenotyping. Transient hypogammaglobulinaemia of the young, as the name implies, is transient in nature and resolves in months to years. Thus, serial monitoring of serum immunoglobulin concentrations is recommended in affected horses until all values are within normal range.

KEYWORDS
diagnostic, equine immunology, horse, immunodeficiency

Key points

- Transient hypogammaglobulinaemia of the young is a primary humoral immunodeficiency characterised by delayed production of endogenous immunoglobulins and increased susceptibility to opportunistic pathogens.
- Recurrent fevers and opportunistic infections, particularly of the respiratory tract, are the hallmarks of impaired immune function in horses, and the presence of either should prompt veterinarians to evaluate for an underlying immunodeficiency.
- The diagnosis of humoral immunodeficiencies in horses includes confirmation of recurrent infection, elimination of other potential aetiologies and assessment of immune status via serum immunoglobulin concentrations and peripheral blood lymphocyte phenotyping.

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Equine Veterinary Education

CLINICAL COMMENTARY

Pathological approach to respiratory infections: Should underlying immunodeficiencies be widely considered?

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In this issue, the article by Cock et al. (2023) describes a 12-month-old Thoroughbred colt with recurring and persistent nasal discharge, pyrexia and cough for months' duration, which recurred despite antimicrobial therapy. As part of the diagnostic workup, cultures isolated a mixed bacterial pneumonia composed of opportunistic agents. This finding combined with a low serum globulin level raised concern for transient hypogammaglobulinaemia. Serum immunoglobulin isotype testing and lymphocyte phenotyping identified low serum IgG and IgM levels, which are consistent with the diagnosis of transient hypogammaglobulinaemia of the young and indicated delayed humoral immunity. As mentioned by the authors in the discussion of this case presentation, hypogammaglobulinaemia is an important topic, which is underrepresented in the literature and likely underdiagnosed in the equine community.

Overall, there are a handful of manuscripts highlighting primary immunodeficiencies in horses and many questions yet to be answered about the underlying genetic, physiological and environmental factors, which contribute to these conditions. What is understood is that immune responses of neonatal and young foals differ widely from the adult horse, affording a unique environment for susceptibility to specific pathogens (Crisman & Scarratt, 2008; Perkins & Wagner, 2015). As such, Cock et al. (2023) provides a thorough and comprehensive discussion on what is known about transient hypogammaglobulinaemia of young horses. Therefore, this commentary aims to focus on the pathological approach to respiratory infections in young horses, highlighting the important infectious agents in this age group, aiming to emphasise when underlying immunodeficiency should be considered.

CLINICAL AND PATHOLOGICAL APPROACH TO RESPIRATORY INFECTIONS

Respiratory infections can be broadly divided into upper and lower airway disease. Upper airway disease commonly refers to diseases affecting the nasal cavity, sinuses, guttural pouches and nasopharynx, while lower airway disease refers to diseases affecting the trachea, bronchi and lungs. Localisation of airway disease can be challenging, but clues within the signalment, physical examination and exercise history in addition to diagnostic assays such as endoscopy, radiography, ultrasonography and computed tomography can help distinguish between upper and lower airway infections (Sellon et al., 2018). In general, a horse with airway disease will have a combination of clinical signs including persistent or intermittent nasal discharge, fever, lethargy, lymphadenomegaly, cough and an increase in respiratory effort (Sellon et al., 2018). The type of nasal discharge, whether it be mucoid, mucopurulent, purulent, or haemorrhagic and distribution of discharge (unilateral versus bilateral), can often provide clues as to the type of infection and location of the lesion. Many upper airway diseases such as mycotic infections, ethmoid haematomas, paranasal cysts/polyps, tooth root infections and neoplasia may present with unilateral discharge or more severely affect one side over the other (Maxie, 2016). Therefore, the presence of bilateral nasal discharge with concurrent cough and an increase in respiratory effort raises concern for lower airway disease.

Lower airway disease is pathologically classified based on lesion distribution, as the pattern of pulmonary disease will provide clues as to the underlying causative agent(s). These patterns may overlap with radiographic or CT patterns. There are four morphologic patterns of pulmonary disease, which include (1) airway (tracheitis/bronchitis), (2) bronchopneumonia, (3) interstitial pneumonia and (4) bronchointerstitial pneumonia (Maxie, 2016). In airway disease, the main target of injury is the airway epithelium lining the trachea/bronchi, which results in necrosis and inflammation. In bronchopneumonias, the initial target and site of injury is the tertiary bronchiole often causing inhibition of appropriate mucociliary clearance, which results in inflammatory cells accumulating and obstructing the bronchioles and alveoli. Conversely, in interstitial pneumonias, the target and site of injury is the alveolar and interlobular septa. Finally, in bronchointerstitial pneumonias, the target is a combination of airway and interstitial disease. Inhaled bacterial agents will most commonly cause a pattern consistent with a bronchopneumonia, while

haematogenous bacterial agents may present with an interstitial pattern. Viral, mycotic, toxic and parasitic agents associated with respiratory infections either target the airway or the interstitium. Common causes of pneumonias will differ for foals and yearlings than adult horses with some overlap to differentials (Table 1).

INCIDENCE AND CAUSES OF PNEUMONIAS IN FOALS AND YEARLINGS

Since 2010, the University of Kentucky Veterinary Diagnostic Laboratory (UKVDL) has had 1121 equine autopsy cases with the diagnosis of pneumonia, amounting to an 8.3% incidence. Of these cases neonate, foal and yearling pneumonias represent a total of 751 cases, or 66.9% of the population. Five hundred and five (67.2%) of these cases are attributed to an underlying bacterial agent, while aspiration (15%), viral (1.3%) and mycotic pneumonias (1.6%) represent less frequent causes (Figure 1).

Bacterial pneumonias are generally not associated with spontaneous disease in horses. However, foals represent an age group which are particularly susceptible to the bacterial infections due to their unique immune system, including reduced antibodies, altered T cell responses and modified cytokine profiles (Perkins & Wagner, 2015). Arguably, these adaptions to immunity early in life are better defined as an immature but capable immune system and not true deficiency (Perkins & Wagner, 2015). In foals, bacterial pneumonias are overwhelmingly attributed to septicaemia likely from partial or complete failure of passive transfer (Liepman et al., 2015). At the UKVDL, 443 out of 505 or 87.7% of the identified bacterial pneumonias occurred prior to 6 months of age. Twenty-eight percent, or 142 cases, classified as bacterial pneumonias did not identify an underlying causative agent likely due to antimicrobial administration prior to autopsy. Overwhelmingly, the most common bacterial agents isolated from lung cultures from the UKVDL cases are as follows: *Rhodococcus equi*, *Streptococcus equi ssp. zooepidemicus*, *Klebsiella pneumoniae*, *Escherichia coli* and *Actinobacillus equuli*, which directly mirror what is represented in the literature. These agents either exist in the environment, are commonly present in faecal matter or are normal commensals of equine skin.

S. zooepidemicus, *K. pneumoniae*, *E. coli and A. equuli* are frequently associated with in-utero or umbilical infections, gaining entry into the circulation resulting in systemic signs of septicaemia. In the lungs, these bacterial agents most frequently cause an embolic or diffuse interstitial pneumonia (Figure 2a). In these instances, the lungs are frequently noncollapsing and mottled red to dark red in coloration with dark red haemorrhages scattered throughout the parenchyma. Rib impressions may be present on the pleural surfaces. Gross lesions coincide with histological lesions, which often include bacterial emboli or thromboemboli within small pulmonary vessels and capillaries associated with areas of haemorrhage, interwoven

TABLE 1 Common causes of pneumonia in horses based on age

Common causes of pneumonia in horses		
Foals (0–1 year)	**Juvenile (1–5 year)**	**Adult (5+ years)**
Bacterial • *Rhodococcus equi* • *Streptococcus equi ssp.* zooepidemicus • *Actinobacillus equuli* • *Klebsiella pneumoniae* • *E. coli* • *Staphylococcus sp.* • *Bordatella bronchiseptica*	Bacterial • *Streptococcus equi ssp.* zooepidemicus • *Streptococcus equisimilis* • *Streptococcus sp.* • *Pasteurella sp.* • *Actinobacillus sp.* • *Bordatella bronchiseptica* • *E. coli* • *Mycoplasma felis*	Bacterial • *Streptococcus equi ssp.* zooepidemicus • *Streptococcus equisimilis* • *Streptococcus sp.* • *Pasteurella sp.* • *Actinobacillus sp.* • *Bordatella bronchiseptica* • *E. coli* • *Mycoplasma felis*
Viral • Equine Herpes Virus-1, 4 • Equine influenza • Equine adenovirus	Viral • Equine Herpes Virus-1, 4 • Equine influenza	Viral • Equine Herpes Virus-5
Fungal • *Aspergillus sp.* • *Pneumocystosis*	Fungal • *Aspergillus sp.* • *Coccidomycosis* • *Cryptococcosis* • *Pneumocystosis*	Fungal • *Aspergillus sp.* • *Coccidomycosis* • *Cryptococcosis*
Parasitic • *Parascaris equorum* migration • *Dictyocaulus arnfieldi*	Parasitic • *Dictyocaulus arnfieldi*	Parasitic • *Dictyocaulus arnfieldi*
Neoplastic	Neoplastic	Neoplastic • Granular cell tumour • Adenocarcinoma • Lymphoma

fibrin accumulation and variable numbers of neutrophils and macrophages (Figure 2b).

Rhodococcus equi is a unique Gram-positive bacterium, which commonly causes pneumonia in 1- to 6-month-old foals (Giguère et al., 2011). *Rhodococcus* is a pathogen found in the environment, which is endemic to some farms. At the UKVDL, *Rhodococcus equi* infections were diagnosed in 165 out of 505 cases (32.6%) of bacterial pneumonia in foals and yearlings. Overwhelmingly, *Rhodococcus* is the most common cause of pneumonia in foals. The primary route of rhodococcal infection is through inhalation of the pathogen into the lower airways. Once inhaled, the bacteria are phagocytosed by macrophages and depending on the strain of *Rhodococcus*, and presence of virulence factors including virulence associated plasmid A, will persist, survive and replicate within macrophages resulting in pyogranulomas, which may progress to clinical disease (Giguère et al., 2011). Immunity to Rhodococcal infections is complex and is continuously being studied. Treatment of foals with hyperimmune plasma prior to the development of lesions is effective at reducing the incidence of development of clinical disease (Sanz et al., 2016). Foals with Rhodococcal infections most commonly present with a pyogranulomatous bronchopneumonia consistently present within the cranioventral lung fields. Grossly, the lungs are collapsed with cranioventral consolidation with one to frequently multiple variably circumscribed and encapsulated pale tan to yellow semi-firm to firm pyogranulomas, which may exude inspissated yellow tan material on cut section (Figure 3a). Histologically, these pyogranulomas are composed of varying numbers of neutrophils, macrophages, epithelioid macrophages and multinucleated giant cells, which may be surrounded by organising fibrous connective tissue and variable numbers of lymphocytes and plasma cells. Frequently, macrophages will have intracytoplasmic rhodococcal bacteria (Figure 3b).

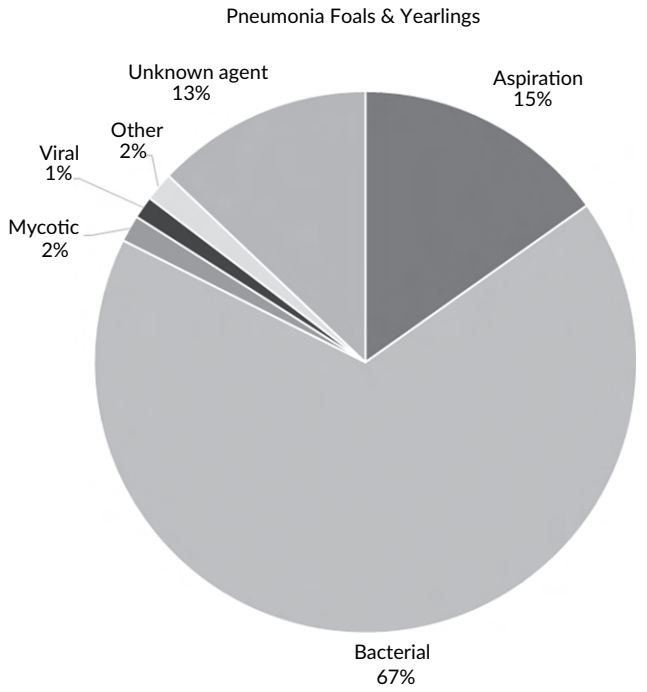

FIGURE 1 Graph demonstrating the most common causes of pneumonia in foals and yearlings diagnosed from autopsy at the University of Kentucky veterinary diagnostic laboratory. A total of 751 cases of pneumonia are represented

A subset of pneumonia cases diagnosed at the UKVDL (15%) have an unknown cause. In this instance, diagnostic testing via bacterial cultures, virus isolation, immunofluorescent antibody testing and real-time polymerase chain reaction assays do not identify or isolate an agent associated with these processes. These pneumonias are most often attributed to atypical interstitial pneumonia caused by acute respiratory distress syndrome (ARDS) or toxic lung injury. Acute respiratory distress syndrome occurs in young foals

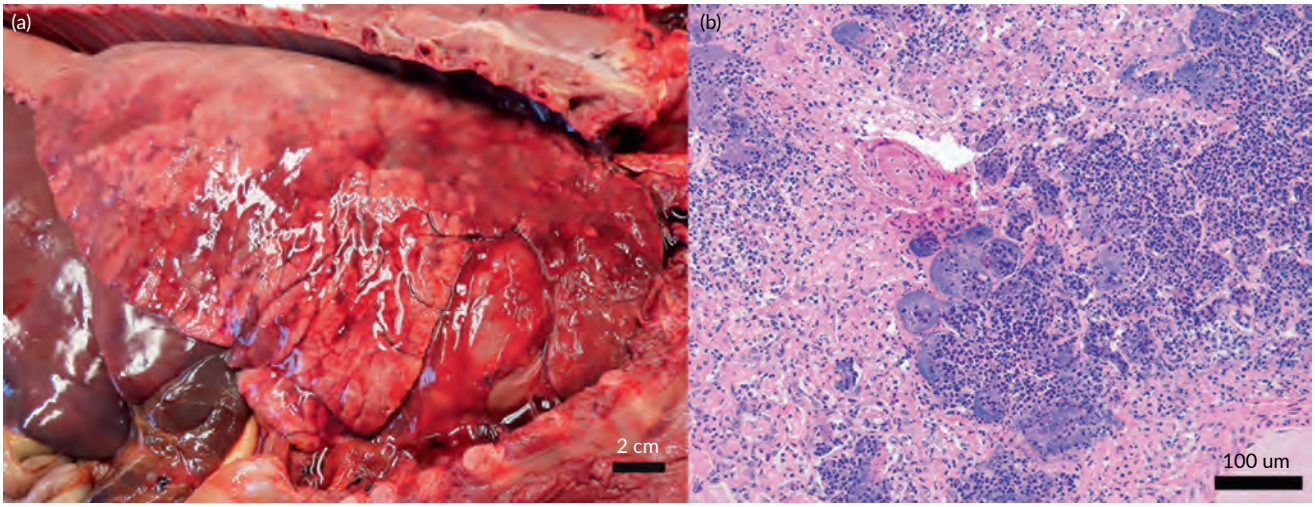

FIGURE 2 Image (a) Photograph of the chest cavity showing a noncollapsing left lung with a diffuse interstitial pneumonia due to haematogenous dissemination of *Streptococcus equi subsp. zooepidemicus* and *Actinobacillus equuli* from omphalophlebitis. Bar = 2 cm. Image (b) Photomicrograph of a lung from image (a) exhibiting an embolic pneumonia. In the image, the alveolar septa are necrotic and the alveoli are flooded with a mixture of interwoven fibrin, neutrophils and macrophages amongst large colonies of mixed bacteria. Small pulmonary vessels are occluded by fibrin thrombi with global fibrinoid necrosis of the vascular wall. H&E stain; bar = 100 μm

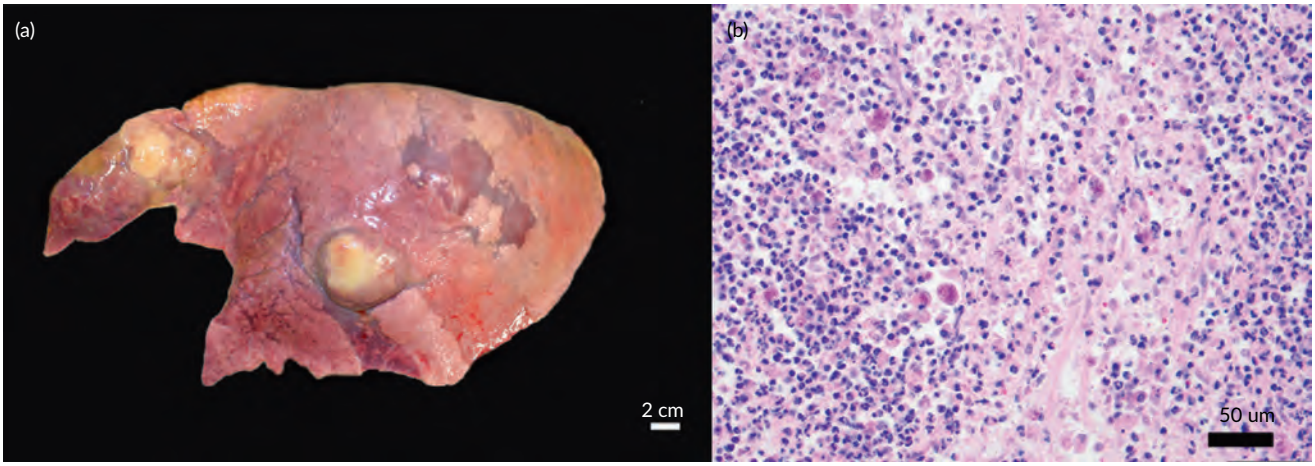

FIGURE 3 Image (a) Photograph of the right lung showing predominantly a cranioventral distribution of pyogranulomas, which isolated *Rhodococcus equi* on culture. Photograph provided courtesy of Dr Alan Loynachan. Bar = 2 cm. Image (b) Photomicrograph of a pulmonary pyogranuloma. Within the image there is a mixture of neutrophils and macrophages amongst interwoven fibrin and organising strands of collagen. Many of the macrophages within the section contain variable numbers of intracytoplasmic bacteria consistent with *Rhodococcus*. H&E stain; bar = 50 μm

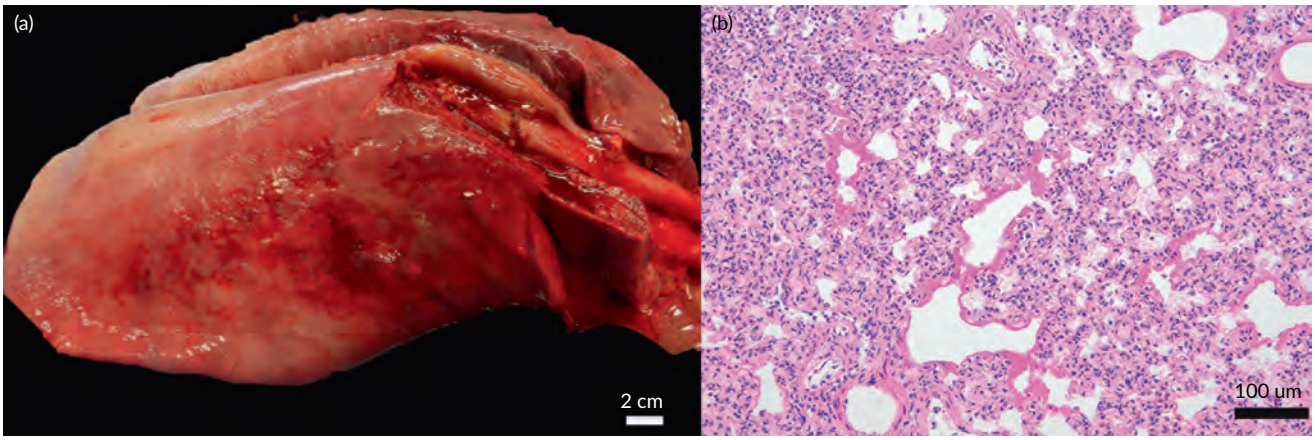

FIGURE 4 Image (a) Photograph of diffusely noncollapsing lungs, which are mottled pink to red to purple and rubbery in texture consistent with an interstitial pneumonia due to acute respiratory distress syndrome (ARDS). Bar = 2 cm. Image (b) Photomicrograph of alveoli with hyaline membranes associated with the septa. The alveolar lumen contains interwoven fibrin with small numbers of neutrophils and macrophages. H&E stain; bar = 100 μm

as a response to systemic inflammatory mediators presenting with an acute onset with dyspnoea, tachypnoea, tachycardia and radiographically a diffuse bronchointerstitial pattern with focal alveolar radiopacities (Dunkel et al., 2005). Grossly, the lungs are noncollapsing, mottled grey to red to dark red and rubbery in texture (Figure 4a). Rib impressions may be present on the pleural surfaces. Gross lesions coincide with alveoli that are flooded with interwoven fibrin, eosinophilic material and variable numbers of neutrophils and macrophages. Hyaline membranes are frequently adhered to the alveolar septa, and small vessels or capillaries frequently contain fibrin thrombi (Figure 4b).

Viral pneumonias represent a relatively uncommon diagnosis in this age group, representing only 1.3% of the total pneumonias diagnosed. At the UKVDL, the most common viral cause of pneumonia isolated from foals and yearling's is equine herpes virus-1 (EHV-1, 8 cases) with rare instances of equine herpes virus-5 (EHV-5, 1 case) infections and equine adenovirus (1 case). Equine adenovirus is frequently detected in healthy foals and mares but rarely causes clinical disease including upper respiratory infections, pneumonia or diarrhoea (Bell et al., 2006). Fatal adenoviral pneumonia has been reported in Arabian foals with severe combined immunodeficiency syndrome (Thompson et al., 1976). In severely immune deficient or suppressed animals, adenoviral infection may present as a bronchitis. Histologically, the mucosa lining the airways is attenuated and often aciliate with occasional 2–3 um irregularly round basophilic intranuclear inclusions (Figure 5). Therefore, diagnoses of adenoviral respiratory infections and pneumonia should not be made solely based on results of diagnostic testing alone and should be interpreted based

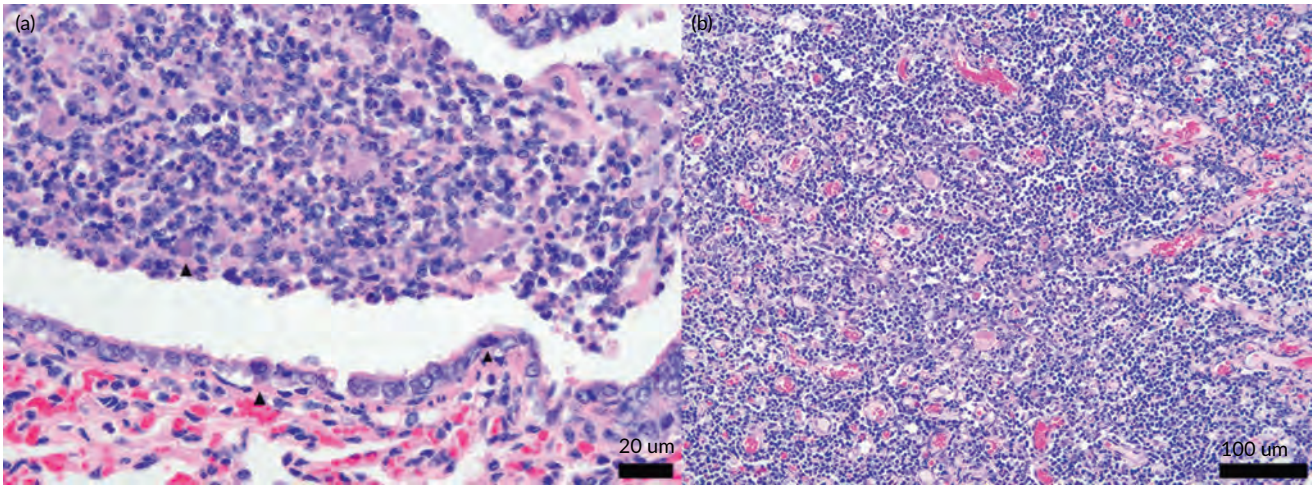

FIGURE 5 Image (a) Photomicrograph of a tertiary bronchiole exhibiting bronchitis. The bronchiole is lined by low cuboidal epithelium, which is aciliate and attenuated. The lumen of the bronchiole is occluded by neutrophils and sloughed epithelial cells. Occasional epithelial cells have 2–3 μm irregularly round amphiphilic inclusions (arrow). H&E stain, bar = 20 μm. Image (b) Photomicrograph of the thymus from the same foal with severe lymphoid atrophy. H&E stain, bar = 100 μm

on the clinical picture, demonstration of pathological lesions and presence of underlying immunodeficiency.

Mycotic infections, like viral infections, are a relatively uncommon cause of pneumonia, representing 1.6% of pneumonias. The most frequent agent isolated via fungal culture from lung is *Aspergillus sp*. Most of these infections are a likely result of in-utero exposure from fungal placentitis, which can result in aborted or weak live foals. The presence of fungal agents such as *Candida sp*. or *Pneumocystis sp*. out of a bronchoalveolar lavage culture or lung culture would be atypical and raise concern of underlying immunodeficiency or functional defect. Thirty-seven cases of pneumonia at UKVDL have been reported in foals older than 6 months of age and yearlings, which represents 4.9% of the total pneumonias in young horses. At this age, maternal immunity is no longer protective, and the foal is reliant on its own immunity. Therefore, the presence of a bacterial rhinitis or pneumonia is infrequent and raises concern for other underlying causes. It is within this age group that underlying immunodeficiencies beyond failure of passive transfer should be considered. Foals and yearlings which develop multiple or mixed bacterial infections that are refractory, persist or recur after appropriate antibiotic therapy are candidates for underlying immunodeficiency or may have functional or anatomic abnormalities predisposing them to infections.

PNEUMONIAS AND IMMUNODEFICIENCY

Respiratory infections are commonly diagnosed in the equine population and represent a major cause of death in foals and yearlings. There is an extensive list of agents which cause pneumonias in these foals and yearlings, of which only select agents with the utilisation of the clinical picture, past treatment history and supporting diagnostic assays should be considered for underlying immunodeficiency. Immunodeficiencies most commonly present with recurring or persistent respiratory infections and fevers (Crisman & Scarratt, 2008). The most common immunodeficiency in foals is failure of passive transfer (FPT), which should be considered as a potential underlying cause of pneumonia, especially opportunistic bacterial agents in foals less than 6 months of age (Liepman et al., 2015). Foals older than 6 months of age which present with mixed bacterial infections or multiple bacterial infections despite appropriate antibiotic therapy, true adenoviral infection, pneumocystis or candida infections should raise concern for underlying immune compromise. A definitive diagnosis of immunodeficiency requires demonstration of a decrease, absence or functional defect of immune cells, immunoglobulins and or cytokine profiles which on routine bloodwork may present as hypoglobulinaemia and or a decrease in circulating lymphocytes. These findings prompt further exploration by measuring serum immunoglobulin concentrations in addition to lymphocyte phenotyping.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

No conflicts of interest have been declared.

ETHICAL STATEMENT

All photographs were acquired with the written consent of the client at the time of submission for autopsy per the University of Kentucky Veterinary Diagnostic Laboratory policy. The photographs utilised within this commentary provide examples of the pathology associated with respiratory infections and provide no personal identifiers.

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Continued from page 60

With the pipeline empty and the existing workforce exhausted and waiting for reinforcements that are not coming, the time of reckoning has arrived. Change is imperative.

Amy L. Grice

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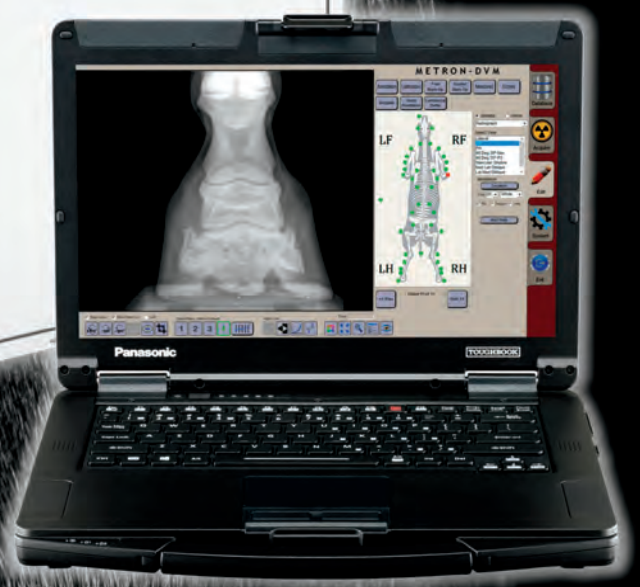

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[1] West Nile Virus Challenge Vaccine Efficacy, BI study number: V9 2009 WNV 12mo DOI
[2] Equine Influenza Challenge, BI study number: 01 V9 6mo DOI OH/03.
[3] Lack of Interference - Influenza Challenge, BI study number: 2012-001 Inf. Data on file at Boehringer Ingelheim.

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Equine Veterinary Education BEVA AAEP

CASE REPORT

Chronic eosinophilic granulomatous tenosynovitis in a Quarter Horse mare

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SUMMARY

A 5-year-old Quarter Horse mare was presented to the Michigan State University Equine Surgery Service for evaluation of a right hind metatarsophalangeal joint injury. On presentation, the horse was a grade of 4/5 lame. Radiographs and ultrasonography showed peritendinous ossification/mineralisation of soft-tissue structures and digital flexor tenosynovitis with profound intracapsular mineralisation (Figure 1). A digital flexor tendon sheath tenoscopy was performed with a plantar annular ligament desmotomy and a manica flexoria ligament tenotomy. During surgery, a significant amount of tan granular material was found within the digital tendon sheath (Figure 2). Approximately 80% of this material was removed, and a sample was sent for histopathology. The horse was diagnosed with eosinophilic granulomatous tenosynovitis. Long-term follow-up revealed the improvement with four treatments of intralesional triamcinolone given 2–4 weeks apart. The horse became serviceably sound (grade 1/5) and was beginning light work under the saddle approximately 5 months post-tenoscopy.

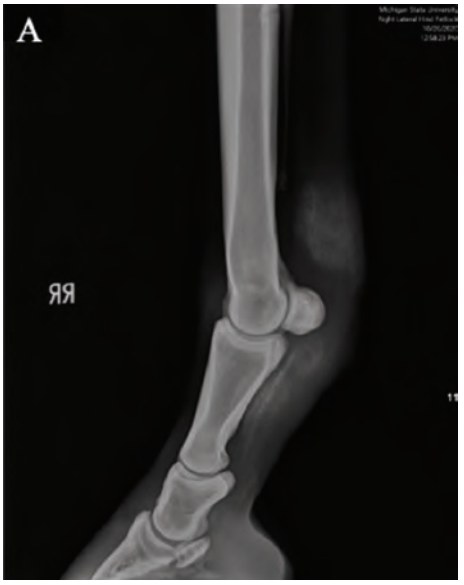

FIGURE 1 Lateral radiograph of the right hind distal limb showing soft-tissue thickening and mineralisation.

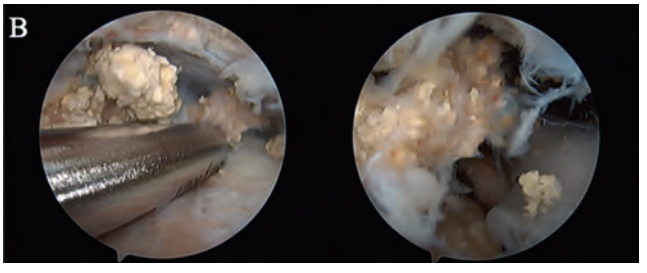

FIGURE 2 Tenoscopy images showing significant amounts of granular material adhered by fibrin to peritendinous structures in the digital tendon sheath.

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KEYWORDS
desmotomy, eosinophilic, granulomatous, horse, tenosynovitis

Key points

- Eosinophilic lesions can occur secondary to parasitic migration, bacterial antigens, tissue injury and neoplasia.
- The present chronic eosinophilic granulomatous tenosynovitis (EGT) was likely due to an initial soft tissue injury.
- EGT was successfully treated with surgical debridement and intralesional triamcinolone.

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Equine Veterinary Education

CLINICAL COMMENTARY

Tendon sheath masses – What are the differential diagnoses and what diagnostics are needed?

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Williams et al. (2023) describe the first reported case of eosinophilic granulomatous deep digital flexor tenosynovitis in a horse. The presence of eosinophils in the tendon sheaths and joints of horses affected with mastocytosis has been previously reported (Leadbeater et al., 2010; Uehlinger et al., 2010; Williams & van den Boom, 2020), but these mastocytosis cases appear to be a separate entity from both the current case and other reported cases of intra-articular eosinophilic synovitis (Climent et al., 2007; DiDomenico et al., 2021; Madison & Zimmer, 1993; Turner et al., 1990). Intra-synovial mast cell tumour cases are equally rare but have a distinct neoplastic pathological appearance are generally associated with mast cells in other locations in the body and can be associated with substantial self-trauma necessitating euthanasia (Leadbeater et al., 2010; Uehlinger et al., 2010; Williams & van den Boom, 2020). The current case report of an eosinophilic granuloma adds another differential diagnosis to our list for tendon sheath masses and underscores the importance of thorough clinical examination and diagnostic investigation.

Non-specific synovial or tendon masses within the deep digital flexor tendon sheath of the horse have been reported (Fortier et al., 1999; McIlwraith et al., 2014; Nixon, 2002, 2019), most commonly in association with tenosynovitis and annular ligament constriction, and are seen in our clinical practice. The pathogenesis of such masses, although often presumed to be trauma, remains unclear. In our experience, which is predominantly English sport horses, these masses tend to be associated with the deep digital flexor tendon at the level of the pastern and can present without mineralisation, especially when acute (Figures 1 and 2). If tenosynovitis and annular ligament constriction are present, surgery is generally recommended as it was for the case in Figure 1 and is associated with a fair to good prognosis for soundness and return to athletic performance in the literature (Fortier et al., 1999) and a fair prognosis in our experience dependent upon degree of tendon pathology present and other existing injuries. If lameness is mild and tendon sheath effusion is acute without evidence of annular ligament constriction, intra-synovial injection of the digital flexor tendon sheath with corticosteroids (generally triamcinolone acetonide [9 mg] and hyaluronic acid) may be performed prior to consideration of surgical intervention as was the case in Figure 2, which is still under treatment. Whilst our case numbers on this specific subset of tendon mass cases are too low to draw any conclusions, we have had reasonable success in this regard. Direct injection of corticosteroids as was performed on the granuloma in this current case report has also anecdotally been reported to be performed on these non-specific tendon masses and should be considered.

An important point in this current case report by Williams et al. (2023) is the potentially critical information that could be obtained from analysis of the digital flexor tendon sheath fluid. Whilst sampling is easy to perform in effusive digital flexor tendon sheaths (Horne et al., 2019; Jordana et al., 2012; Rocconi & Sampson, 2013), and fluid is often drained prior to injection of the sheath for treatment, rarely is this fluid submitted for analysis. Admittedly, none of our clinical cases with tendon masses had digital flexor tendon sheath fluid submitted for analyses, nor were the masses that were resected at surgery always submitted for histopathology. The presence of eosinophils is never normal in a synovial structure and large numbers/percentages of eosinophils have been reported in all four cases of intra-articular eosinophilic synovitis to date (Climent et al., 2007; DiDomenico et al., 2021; Madison & Zimmer, 1993; Turner et al., 1990), including the one from our group, suggesting the possible utility of such analyses in these digital flexor tendon sheath cases.

Perhaps the biggest question in our minds is whether or not some of the tendon masses in our case population could have been early

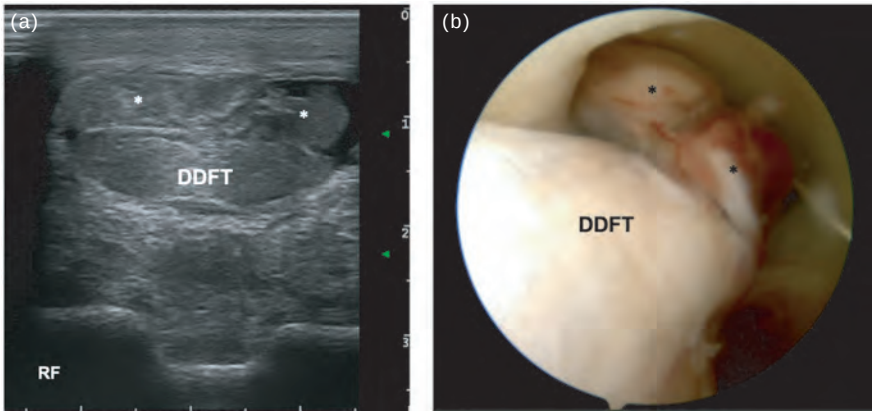

FIGURE 1 (a) Ultrasonographic image at the level of the middle scutum (proximal aspect of P2) of a horse that presented with severe lameness, marked tenosynovitis and annular ligament constriction with a large tendon mass (*) associated with the deep digital flexor tendon (DDFT). (b) Tenoscopic image from surgery in which the large tendon mass and the dorsal aspect of the DDFT was debrided and a palmar annular ligament desmotomy was performed

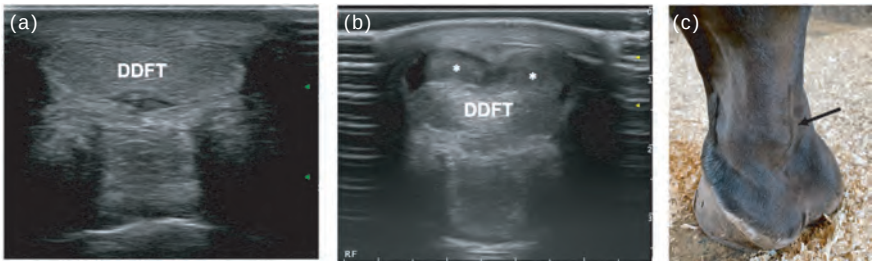

FIGURE 2 (a) Normal ultrasonographic image of the pastern region at the level of distal P1. (b) Ultrasonographic image of the pastern region of a horse currently under treatment for a tendon mass (*) associated with the deep digital flexor tendon (DDFT) and with moderate acute digital flexor tendon sheath effusion and mild lameness. (c) Gross appearance of this horse's pastern region with black arrow pointing to the evident bulge at the location of the tendon mass

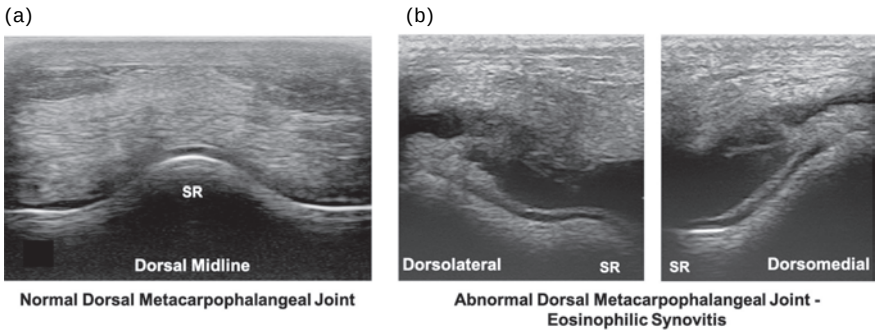

FIGURE 3 (a) Normal ultrasonographic appearance of the dorsal aspect of the metacarpophalangeal joint. (b) Abnormal ultrasonographic appearance of the dorsolateral and dorsomedial aspects of a metacarpophalangeal joint affected with eosinophilic synovitis (arthrocentesis revealed 43% eosinophils) demonstrating moderate to severe synovial proliferation and anechoic synovial effusion but no signs of a mass-like lesion. SR, Sagittal Ridge

manifestations of eosinophilic granulomas that never progressed to the chronic stage seen in the current case report. As stated above, synovial fluid analysis was not performed in these cases and peripheral blood eosinophil counts have proven to be unreliable in the diagnosis of intra-articular eosinophilic synovitis and in the current case report as well. Furthermore, since tendon sheath fluid was unfortunately not obtained for analysis in the current case report, it is unknown if eosinophils would be present within the digital flexor tendon sheath fluid or if the eosinophils would be strictly confined to within the well encapsulated granuloma.

It is interesting that the four intra-articular eosinophilic synovitis cases did not present with any masses, nodules or granulomas within

the joint (Figure 3) and responded quickly to corticosteroids, non-steroidal anti-inflammatory drugs and/or joint lavage (Climent et al., 2007; DiDomenico et al., 2021; Madison & Zimmer, 1993; Turner et al., 1990). This could be due to the more urgent attention given to effusive joints with associated severe lameness and the concern for sepsis particularly following intra-articular medication, which had been administered in three of the four reported intra-articular cases. These horses were seen within 1–2 weeks post-injection. In the current case report by Williams et al. (2023), the digital flexor tendon sheath had also been injected but was not presented for referral evaluation until approximately 3 months after the start of lameness and approximately 2 months after injection at which time severe lameness was observed as well as profound mineralisation on radiographic and ultrasonographic examination. Is this difference in presentation simply due to time and progression of the disease or does eosinophilic synovitis within the deep digital flexor tendon sheath truly present with a granulomatous appearance?

Ultimately, more diagnosed cases will be needed to answer all of these questions and will be dependent on thorough clinical examination, imaging examination, synovial fluid analysis prior to surgical intervention or joint lavage, and diligent follow-up. The current case report by Williams et al. (2022) highlights the necessity of such information and adds a new clinical differential diagnosis to our list for masses within a tendon sheath.

AUTHOR CONTRIBUTIONS

All authors have contributed to this commentary.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

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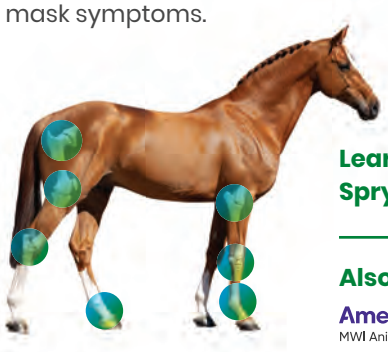

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Equine Veterinary Education

CASE REPORT

Schiff-Sherrington syndrome in a 7-year-old zebra mare (*Equus quagga*)

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SUMMARY

A 7-year-old plains zebra *(Equus quagga)* mare was presented to the Clinic for Horses, University of Veterinary Medicine Hannover as an emergency. The owner reported that the mare was unable to stand after a suspected traumatic episode at the home yard. The mare was transported in lateral recumbency in a commercial horse trailer. Initial clinical examination revealed tachycardia (up to 102 beats/min), tachypnoea (28 breaths/min), mild fever (38.7°C) and clinical dehydration with elastic skin and dry and red mucous membranes. Neurological examination showed paraplegia with a complete loss of nociception of the mid-thoracic region and caudal to it. A possible concurrent spinal shock in this area was assumed due to completely flaccid pelvic limbs. In contrast, examination of the thoracic limbs revealed marked extensor rigidity and hyperaesthesia in the area of the scapula, the withers and the left neck, seen as enhanced reaction to minimal stimulation by touch with an extended thumb (Figure 1).

Lateral radiographs of the thoracic vertebral column led to the diagnosis of a fracture of the 7th thoracic vertebra with suspected traumatic compression of the spinal cord. The classification of the fracture by adapting a three-compartment model from human and small animal medicine revealed an involvement of all three compartments. Therefore, the fracture was considered unstable, and the mare was euthanised due to very poor to hopeless prognosis. Post-mortem examination confirmed the diagnosis. Gross pathology revealed a complete comminuted fracture of the 7th thoracic vertebra with marked compression of the spinal cord. This is the first report that describes the clinical, radiological and pathological findings of a fracture of a thoracic vertebra leading to a *Schiff–Sherrington syndrome* in a zebra *(Equus quagga)* (Figure 2).

FIGURE 1 Zebra mare in right lateral recumbency. Thoracic limbs show rigid extension with concurrent pelvic limb paraplegia.

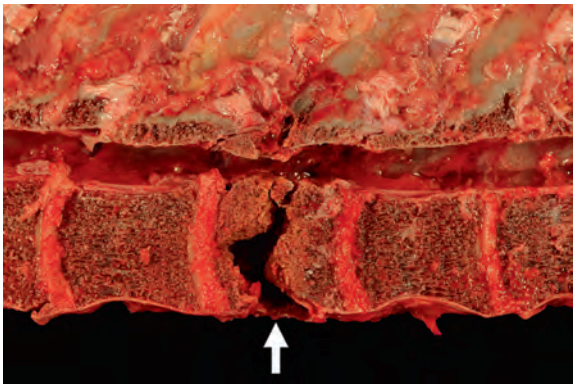

FIGURE 2 Macroscopically, a complete comminuted fracture of the vertebral body of T7 is evident (white arrow).

KEYWORDS
horse, fracture, Schiff-Sherrington syndrome, thoracic vertebrae, zebra

Key points

- *Schiff–Sherrington syndrome* is a rare, clinical condition in equids resulting in extensor rigidity of the thoracic limbs with concurrent pelvic limb paralysis
- Spinal shock can impede interpretation of neurological symptoms and result in misdiagnosis
- Radiography of the thoracic and lumbar vertebral column is essential for confirming the suspected clinical diagnosis of a *Schiff–Sherrington syndrome* and to assess the severity of the spinal cord lesion

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Equine Veterinary Education

CLINICAL COMMENTARY

Moritz Schiff, Charles Sherrington, border cells, frogs, cats and a zebra with abnormal clinical signs

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The case report presented by Frers et al. (2023) describes an interesting neurological syndrome observed in a zebra, likely to be consistent with the Schiff-Sherrington syndrome (SSS). This is well described in dogs (De Lahunta & Glass, 2014; McBride et al., 2022) and rarely described in ruminants or horses (Mayhew, 1989). The SSS, also referred to as the Schiff-Sherrington phenomenon, is an important finding during any clinical neurological evaluation that can assist in accurately defining the site of a spinal lesion.

Schiff-Sherrington syndrome is a medical eponym (person after whom something was named). Moritz Schiff, born in 1823 (Frankfurt) and died in 1896 (Geneva), was one of the pioneers and most eminent biologists (Feinsod, 2011). Schiff studied the motor outflow from the brain and the microscopic anatomy of the nerves and their regeneration. He published an important book in 1858: Lehrbuch der Physiologie des Menschen (Textbook of human physiology), which contained the first observations that highlighted signs of the SSS (Schiff, 1859).

Sir Charles Scott Sherrington was an English neurophysiologist born in 1857 (London) and died in 1952 (Sussex). He graduated in medicine in London and studied physiology at Cambridge. Sherrington devoted himself to physiological research when he accepted the position of physician-superintendent of the Brown Institution of the University of London (1891). This veterinary facility was created to encourage research into diseases of animals useful to man (Horwitz, 1997). He began to analyse the functional abnormality exhibited by the decerebrate animal, later introducing the term "decerebrate rigidity" (Breathnach, 2004; Molnár & Brown, 2010). As an experimental neurophysiologist, one of the first papers published by Sherrington showed an analysis of the spinal cord of a dog with a cerebral experimental lesion (Horwitz, 1997; Langley & Sherrington, 1884). In 1893, Sherrington coined the term "proprioceptive." He also described many other concepts in neurophysiology, including the description of the crossed extensor reflex (Pearce, 2004; Raju, 1999). His work on spinal reflexes and neuronal inhibition, which states that when a muscle contracts, there is a simultaneous inhibition of its functional antagonist, and regarded as essential for coordinated movement, was recognised with the Nobel Prize in Physiology or Medicine in 1932 (Berlucchi, 2009; Breathnach, 2004; Molnár & Brown, 2010).

More than 100 years have passed since the publication of Sherrington's important book, The Integrative Action of the Nervous System (1906), considered by many to be the bible of neurophysiologists (Levine, 2007; Sherrington, 1906). In this book, he presented an elaboration of the concept of reflex action, which was defined as the greatest single contribution of the physiologist to clinical neurology (Berlucchi, 2009; Molnár & Brown, 2010). He became a Knight Grand Cross of the most excellent Order of the British Empire (Molnár & Brown, 2010), so he is still currently named as Sir Charles Sherrington. He retired in 1936 aged 79 (Breathnach, 2005).

Schiff in 1858 observed in normal and decerebrate frogs that an increased irritability of forelimb reflexes was induced by severing the spinal cord below the brachial enlargement. He believed that the hyperreflexia produced was not due to irritation of ascending spinal tracts because it was still evident a month after the operation (Ruch & Watts, 1934). His detailed description was very interesting, as it showed for the first time that changes in reflex excitability produced by a spinal transection were not confined to the spinal cord segments below the level of injury (Ruch & Watts, 1934). Sherrington (1898), without knowledge of Schiff's experiments, described in greater detail a similar phenomenon in the cat (Barnes & Schadt, 1979; Ruch & Watts, 1934). He found that while he was unable to elicit a crossed extensor reflex in the forelimbs following cervical spinal section, a further transection at thoracic levels caused the reflex to appear (Barnes & Schadt, 1979; Sherrington, 1898). Interested in those descriptions, Ruch and Watts (1934) confirmed the Sherrington findings after interrupting conduction in the spinal cord and were the first authors to suggest: "… cephalad release of function should probably be designated the Schiff-Sherrington phenomenon" because Schiff described this syndrome in amphibian spinal cord 40 years before Sherrington.

In summary, Schiff was the first to describe the occurrence of extension of the forelimbs as a sign after thoracic spinal cord injury in frogs (Schiff, 1859). This observation in mammals was repeated by Sherrington 40 years later, and the eponym "Schiff–Sherrington reflex" was thus coined (Feinsod, 2011; Ruch & Watts, 1934; Wang, 1958).

It is thus now accepted that following a thoracolumbar lesion the SSS is characterised by increased extensor tone (depolarisation of extensor) and decreased flexor tone (hyperpolarisation of flexor motoneurons) in the forelimbs (Barnes & Schadt, 1979) and the thoracolumbar lesion also causes paraplegia due to upper motor neuron (UMN) or lower motor neuron (LMN) lesions depending on the site of the lesion, T3-L3 or L4-S2 respectively.

To correctly understand the pathophysiology of SSS, we need to consider the specific types of cells involved. During past decades, it was accepted that border cells are associated with SSS. Sherrington noted that there is a group of nerve cells, indistinguishable from motor cells, in the ventrolateral grey matter of the lumbar spinal cord of monkeys and cats as "outlying nerve cells" (Cooper & Sherrington, 1940; Molnár & Brown, 2010; Sherrington, 1889; Sprague, 1953). Sherrington called these neurons "spinal border cells" because, although there are exceptions, they tend to lie in the fringe of the grey matter bordering the ventrolateral white columns" (Cooper & Sherrington, 1940). These cell bodies are located between L1 and L7 (Burke et al., 1971; Cooper & Sherrington, 1940; Sprague, 1951, 1953). Sherrington was interested in these border cells because he suspected that they caused the sustained tonic inhibition of extensor muscle α-motor neurons in the brachial intumescence after injury.

There is a specific type of border cell whose axon presents fibres ascending and descending and crossed and uncrossed within the spinal cord. Sir Charles Sherrington first studied this network (Sherrington & Laslett, 1903a, 1903b), currently named the propriospinal system (neurons that are intrinsic to the spinal cord and whose axons terminate within its boundaries) (Conta & Stelzner, 2009). Sherrington demonstrated that axons "springing from the grey matter" of the spinal cord connect both proximal and distal spinal segments and suggested that spinal segments must communicate with each other (Flynn et al., 2011). In more specific terms, the word "propriospinal" is used in reference to spinal interneurons. The cervical and lumbar spinal cord are interconnected by ascending and descending long-axon propriospinal projections that coordinate the activity between cervical and lumbosacral enlargements during locomotion (Conta & Stelzner, 2009). Neuroanatomical evidence confirmed the presence of long ascending propriospinal connections from the rostral lumbar spinal cord to the cervical region along the ventrolateral funiculus – the fasciculus proprius or spinospinal tract (English et al., 1985; Laliberte et al., 2019; Molenaar & Kuypers, 1978) and showed the importance of quadrupedal stepping coordination of movements of the hindlimbs and forelimbs in mammals (Miller et al., 1973, 1975).

Therefore, it is accepted that lesions caudal to the cervical intumescence and cranial to border cell neurons can cause SSS. These border cells (cell bodies L1-L7) and/or their axons in the fasciculus proprius connect cranially with neurons in the C6-T2 spinal cord area and, when damaged, can cause SSS. Acute and severe spinal injuries to border cell neurons caudal to the cervical intumescence (dorsolateral border of the ventral grey column and axons running in the fasciculus proprius) result in forelimbs hyperextension (stiffness with relatively normal limb gait and postural reactions). Paraplegia (injury to the UMN or LMN) of the hindlimbs occurs due to injury to the thoracolumbar or lumbosacral spinal cord (De Lahunta & Glass, 2014; Wingfield, 2000).

Note that SSS cases in small animals are far more frequently described compared to large animals and the Schiff-Sherrington syndrome is described in dogs with a spinal cord injury anywhere from T1-L5 but is most commonly seen with T3-L3 myelopathies (De Lahunta & Glass, 2014; McBride et al., 2022). Small animals presenting SSS with thoracic limb extensor hypertonus retain a relatively normal gait and normal postural reactions on the forelimbs, whereas the hindlimbs are paralysed. Hindlimb reflexes in patients experiencing SSS can vary from normal to increased (Park et al., 2012) depending on the site of lesion and time after injury. The presence of SSS in small animals indicates severe injury but does not indicate that the patient cannot recover (De Lahunta & Glass, 2014; Park et al., 2012).

Spinal shock (another Sherrington described phenomenon) and SSS are two separate manifestations of severe spinal cord lesions but can be encountered at the same time. Spinal shock results in flaccid paralysis and loss of spinal reflexes in the hindlimbs, although the lesion is situated cranial to the lumbosacral intumescence. The clinical signs observed with spinal shock thus defy classical UMN/LMN lesion doctrine and are only associated with the acute phase of spinal damage, increasing the importance of repeated patient assessment over time (Granger & Carwardine, 2014).

There are a few other points that must be observed during the evaluation of a patient with suspected SSS:

a. Forelimbs present stiffness and increased reflexes; limb hypertonia being easier to detect in the lateral recumbent animal.
b. The forelimb gait and postural reactions are relatively normal. This is usually easier to observe in lighter patients that can be supported in a quadrupedal position.
c. There is often analgesia caudal to the severe lesion due to interruption of the nociceptive pathways.
d. There is paraplegia (due to the interruption of the UMN or LMN pathways), and the presence (UMN lesion) or suppression (LMN lesion) of reflexes in the hindlimbs, depending on the spinal cord level of the lesion and time after injury.
e. When dealing with severe thoracic spinal cord lesions, between T3-L3, the examiner needs to consider the time after the onset of injury when examination occurs. If the exam is performed soon after the injury the hindlimbs tonus may be depressed due to spinal shock and subsequently is followed by hypertonia due to the UMN lesion. Hindlimb reflexes return a few hours after a severe UMN lesion in cases of spinal shock.

f. Lesions at L4-S2 can also cause SSS, but are less frequently reported, and will result in permanently decreased or absent tonus and reflexes in the hindlimbs due to direct lesion of the LMN.
g. Patient presenting two lesions at the same time: C1-C5 AND L4-S2. These lesions will result in hypertonic and hyperreflexia (UMN signs) in the forelimbs and flaccid paraplegia (LMN signs) in the hindlimbs, mimicking SSS, but postural reactions will help to differentiate these syndromes.

Sometimes it is difficult to check if a true SSS is present in a horse with paraplegia due to a severe spinal cord lesion (T3-L3) with normal-appearing forelimbs during recumbency. During attempts to stand, normal horses demonstrate increased tonus in the forelimbs. Therefore, it is also important to give consideration to several components of examination of such a paraplegic patient including:

- the evolution of the clinical signs: to differentiate spinal shock distal to the lesion.
- forelimb reflexes: are hyperactive in cases of SSS.
- hindlimb reflexes: are increased after a lesion to the UMN between T3-L3, and are absent in severe lesion between L4-S2).
- pain perception: decreased below the level of the lesion.
- gait and normal postural reactions: in lighter patients, using a sling to help determine if forelimbs present a relatively normal gait and normal postural reactions despite the hypertonicity; only when feasible (and considering a possible unstable fracture).

It goes without saying that a thorough neurological examination is essential for lesion localisation and diagnosis of equids and can add important information to the literature (Mayhew, 1989), thus increasing our knowledge about interesting clinical signs previously described experimentally in reptiles, birds and mammals. Now, after reading the case report describing a zebra mare affected with SSS due to a fracture of a thoracic vertebra (Frers et al., 2023), we can complement Schiff's and Sherrington's studies with a new species affected with the syndrome they described more than 100 years ago.

CONFLICT OF INTEREST

No competing interests have been declared.

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Equine Veterinary Education

CASE IMAGE

Computed tomographic diagnosis of a fracture of the floor of the pelvis in a Thoroughbred foal

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Summary

This case report describes the clinical and diagnostic imaging findings, treatment and outcomes of a 15-day-old Thoroughbred foal referred for the evaluation of severe left hindlimb lameness of 8 days' duration. Radiographic examination of the left hindlimb and transcutaneous ultrasonographic examination of the pelvis were unremarkable. A computed tomographic (CT) examination was performed to investigate the proximal aspect of the limb and the pelvis; CT scans of the thorax were also acquired. In this case, CT images allowed detection of a closed, slightly displaced, oblique wedge-like fracture of the left caudal ramus of the pubis and medial ramus of the ischium, allowing an accurate diagnosis to guide appropriate treatment and prognostication. The foal was treated with anti-inflammatory drugs and box-rest. A follow-up by telephone interview with the trainer 3 years later revealed that the horse is in full athletic activity without any residual gait alteration related to the pelvic fracture.

KEYWORDS
horse, computed tomography, foal, pelvis fracture, pubis, ischium

INTRODUCTION

In horses, acute onset and severe hindlimb lameness caused by pelvic fractures is far more common than previously documented (Moiroud et al., 2019). Young horses, especially foals and yearlings, seem to be predisposed to traumatic pelvic fractures (Moiroud et al., 2019). Such fractures should be suspected in horses with or without a history of known trauma, crepitus, pelvic asymmetry and/or muscle atrophy and lameness (Almanza & Whitcomb, 2003; Moiroud et al., 2019). Radiography, transrectal and transcutaneous ultrasonography (US) and nuclear scintigraphy are the most commonly used imaging modalities in the diagnosis of pelvic fractures in adult horses (Almanza & Whitcomb, 2003; Geburek et al., 2009; Moiroud et al., 2019; Walker et al., 2012). Unfortunately, transrectal US does not find application in foals because of their small size. However, computed tomography (CT) can be a very effective diagnostic imaging technique in foals (Barba & Lepage, 2013). Among the differential diagnoses, septic arthritis and physeal or epiphyseal osteomyelitis of the pelvis should be considered in foals showing a sudden onset of severe lameness, neutrophilic leucocytosis and/or high plasma fibrinogen and serum amyloid A because septicaemia is one of the most common problems in neonatal foals of less than 14 days of age (Barba & Lepage, 2013). CT provides a detailed examination of bone and soft tissue changes and allow to differentiate cases of fractures, abscesses, coxofemoral luxation, bone ossification defects, osteomyelitis, septic arthritis and physitis (Barba & Lepage, 2013).

The aim of this case report was to describe the clinical and diagnostic imaging approach to a 15-day-old Thoroughbred foal presented at our Veterinary Teaching Hospital (VTH) for acute onset of severe left hindlimb lameness of 8 days' duration.

CASE HISTORY AND CLINICAL FINDINGS

The foal was born by uncomplicated delivery and consumed colostrum normally. According to the owner, the lameness and difficulty to rise were firstly noticed one week after birth and the degree of lameness was initially described as severe, but a partial improvement was observed in a few days. Despite the clinical improvement of the lameness at walk, difficulty in standing up was constantly noticed by the owner. At admission, the colt appeared bright, alert and in a good body condition (73 kg bwt). The rectal temperature was 38.9°C, heart rate was 106 beats/min, and respiratory rate was 80 breaths/min; however, the foal was very agitated and clinical parameters returned in the normal range shortly after hospitalisation. Haematology showed a mild normocytic hypochromic anaemia (5.29×10^{12}/L, reference interval [RI] 7.2–10.8×10^{12}/L) and an increase in serum amyloid A (SAA) (365.12 mg/L, RI: 0–20 mg/L) and fibrinogen (14.41 g/L, RI: 0.5–4.0 g/L) values. All other values were within normal limits. On clinical examination, the foal showed left hindlimb lameness at walk and trot in a straight line next to the mare (AAEP grading scale 4 out of 5). No significant abnormalities were detected on palpation and passive mobilisation of the hindlimb. The colt was able to obtain a standing position to feed although several attempts were necessary. Blood culture was performed to exclude the presence of septicaemia, and it was negative. Broad-spectrum antimicrobial drugs (amikacin 20 mg/kg bwt intravenously [i.v.] once a day and ceftriaxone 25 mg/kg bwt i.v. twice a day) with anti-inflammatory therapy (meloxicam 0.6 mg/kg bwt i.v. once a day) were started; gastro-protection was achieved by administration of sucralfate (30 mg/kg bwt orally every 8 h).

IMAGING FINDINGS

Radiographic and ultrasonographic findings

A radiographic screen of the left hindlimb was performed with a portable radiography machine and direct digital radiography (Fujifilm DR-ID601SE, Fujifilm Corporation). Radiographic projections included lateromedial (LM) and dorsoplantar (DPl) views of the foot, fetlock, tarsus and LM and caudo-cranial views of the stifle, which were considered unremarkable. An US examination of the pelvis, thorax and abdomen including the umbilicus was performed using an ultrasound scanner (Voluson P6, General Electric) equipped with a multifrequency convex (3–5 MHz) probe (pelvis and abdomen) and with a multifrequency linear (6–12 MHz) probe (thorax and umbilicus). The US examination of the umbilical remnants was considered unremarkable and small and diffuse comet tail artefacts were identified in the cranial portion of the lungs. The transcutaneous US of the pelvis did not reveal any significant abnormalities. Considering the risk for the presence of occult infection on the basis of the blood analysis results and the age of the foal, a CT examination was performed.

CT findings

A CT examination of the thorax, pelvis and hindlimbs was performed with the foal positioned in dorsal recumbency under general anaesthesia. Both hindlimbs were imaged simultaneously for comparison purposes with a four-slice CT scanner (Siemens Somatom Volume Zoom) using 120 kV and 100 mA. Helical acquisition (pitch 1) was performed using a 512×512 matrix with a 50-cm field of view. The thickness of the slice was collimated to 3 mm with a record index of 1.25 mm. Multiplanar reconstructed images were used in dorsal, transverse and sagittal planes, reformatted and displayed in bone and soft tissue windows. The CT examination revealed the presence of a closed, slightly displaced, wedge-like fracture involving the left caudal ramus of the pubis and medial ramus of the ischium (Figure 1, Videos S1 and S2). The first fracture line crossed the caudal ramus of the left pubis at the level of the middle part of the symphysis, close to the obturator foramen, in a craniodorsal to caudoventral and mediolateral direction. The second fracture line crossed the medial ramus of the left ischium at the level of the middle part of the symphysis, caudally to the obturator foramen, in a caudoventral to craniodorsal direction towards the obturator foramen. The two fracture lines communicated at the level of the caudal end of the obturator foramen to create an inverted V-shape fracture configuration that resulted in the development of a $0.5 \times 0.8 \times 2.6$ bone fragment (wedge-like) slightly displaced medially (Figure 2). The thoracic scans demonstrated the presence of close, transverse, moderately displaced fractures with bone callus formation at the level of the distal aspect of the sixth and seventh right ribs (Figure 3), most likely related to birth trauma. The fracture lines were simple and crossed the ribs in a craniodorsomedial to caudoventrolateral direction; the ventral parts were slightly displaced medially and proximally and a small soft tissue swelling, and pleural thickening was detected close to the fracture areas (Figure 3). Furthermore, the CT scans revealed small irregular circular hypoattenuating areas surrounded by a hyperattenuating halo (sclerosis), most likely referable to small defects of ossification, at the level of the proximal and middle axial part of the lateral trochlear ridge of the right femur. The patient recovered successfully from general anaesthesia with manual assistance.

TREATMENT AND FOLLOW-UP

Anti-inflammatory therapy (meloxicam 0.6 mg/kg bwt i.v. once a day) was continued during the entire period of hospitalisation, and antibiotic therapy (amikacin 20 mg/kg bwt intravenously [i.v.] once a day and ceftriaxone 25 mg/kg bwt i.v. twice a day) was administered for 5 days. An improvement in clinical parameters and blood analysis was observed. Repeated blood tests after 4 days revealed a decrease in the SAA value (22.07 mg/L) and fibrinogen (7.88 g/L). The foal was discharged after 9 days of hospitalisation. Mare and foal were restricted to box-rest for 3 weeks and a small paddock for an additional 3 weeks. The foal never showed signs of respiratory distress during the rehabilitation period. At a follow-up telephone

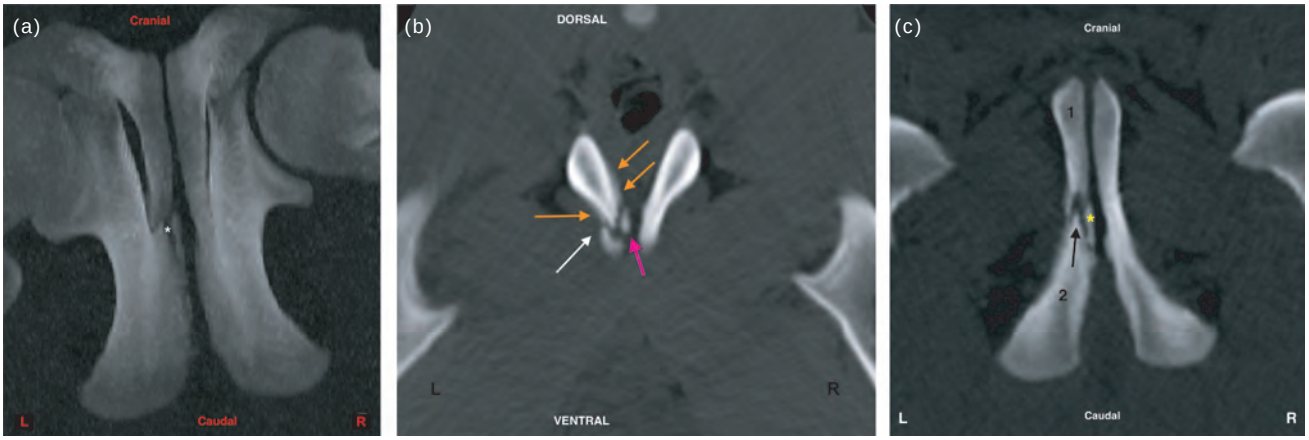

FIGURE 1 (a) Computed tomographic reconstruction of the fracture of the caudal ramus of the left pubis and involvement of the medial ramus of the left ischium (asterisk) using maximum intensity projection. (b) Transverse computed tomographic image at the level of the middle part of the pubic symphysis showing bone discontinuity and fragmentation at the level of the caudal ramus of the left pubis (white arrow); there is a mildly displaced bone fragment at the medial aspect of the left pubis (violet arrow); faint new bone formation (periosteal callus) is visible on the lateral and medial margins of the left pubis (orange arrows). (c) Dorsal multiplanar reconstruction computed tomography image of the pubic symphysis and table of the ischium showing the inverted V-fracture configuration of the left pubis and medial ramus of the ischium (black arrow) and the medial fragment (yellow asterisk). L = left side; R = right side. 1 = pubis; 2 = ischium

interview with the trainer 3 years later, the horse was in full athletic activity without any residual gait changes related to the fracture of the floor of the pelvis. Career information were achieved from a racing website (www.ippica.biz), and the colt raced 18 races during his 3- and 4-year-old racing year, when he placed first once, second twice and third six times.

DISCUSSION

In this case, CT examination was a valuable diagnostic tool used to detect a pelvic fracture involving the floor of the pelvis and excluding the presence of septic foci in the hindlimbs and pelvis, which were considered in the differential diagnosis on the basis of the history and results of the blood analyses. Furthermore, CT revealed the exact configuration (oblique and wedge-like) of the fracture of the left caudal ramus of the pubis with involvement of the medial ramus of the ischium at the level of the obturator foramen, close to the pelvic symphysis, allowing an accurate diagnosis to guide appropriate treatment and prognostication.

When a pelvic fracture is suspected, the use of traditional diagnostic imaging techniques such as radiography and US is recommended for adult horses (Almanza & Whitcomb, 2003; Geburek et al., 2009; Walker et al., 2012). Radiographic screening of the limb was performed in this case to evaluate the presence of abnormalities affecting the distal limb up to the stifle. There are several radiographic projections of the pelvis that can be obtained in the standing patient, such as ventrodorsal and lateral oblique; these projections are useful for the evaluation of the caudal part of the shaft of the ilium, acetabulum, ischium, and head and neck of the femur avoiding the use of general anaesthesia and the associated risks (Barrett et al., 2006). However, poor quality images due to small movements of the sedated patient, relatively long exposure time in foals and inability to detect fractures with mild displacement are just some disadvantages of the standing radiographic examination (Barrett et al., 2006; Geburek et al., 2009). In the authors' experience ventrodorsal view of the pelvis is not easy to obtain in neonatal foals because the positioning of the x-ray machine ventral to the abdomen is difficult in patients of small size. In addition, for both these projections there is the need of personnel for a good handling of sedated neonatal foals to minimise movement and obtain good positioning, which pose a risk of scattered radiation of persons involved in the x-ray procedure.

Considering all of these, the authors decided to perform a transcutaneous US examination of the pelvis as the second diagnostic technique, to investigate the proximal aspect of the limb and the pelvis. US examination of the pelvis using transcutaneous and transrectal approaches has been demonstrated to be very useful in detecting pelvic fractures (Almanza & Whitcomb, 2003; Moiroud et al., 2019; Walker et al., 2012). However, only the transcutaneous approach is possible in foals, and the findings were unremarkable in this particular case.

For these reasons, the authors decided to use CT examination because of its good spatial and contrast resolution, allowing one to obtain the best information from cross-sectional images of the limbs and pelvis in the same amount of time that would be spent under general anaesthesia to obtain good radiographic images. The CT examination is faster than radiography in dorsal recumbency because retakes, and additional projections are not necessary. In the case presented here, a CT examination was proposed to the owner, considering the strong suspicion of a septic process due to the severity of the hindlimb lameness, increased serum amyloid A and the young age of the foal and with these clinical signs a septic process should be considered until proven otherwise (Lindegaard et al., 2021). As reported in the literature, CT has a number of advantages compared with other imaging modalities, such as early diagnosis related to the higher sensitivity in the

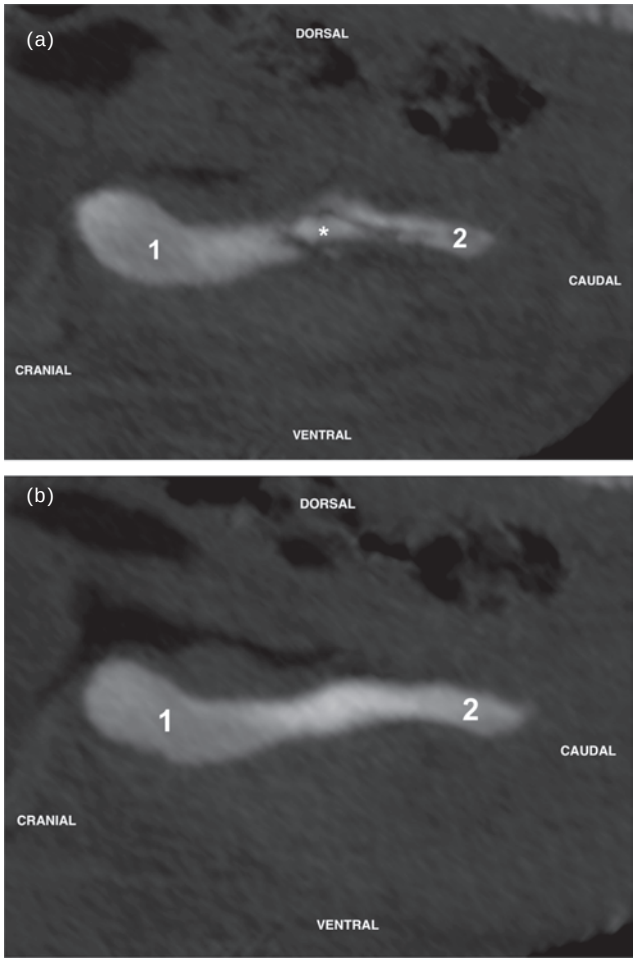

FIGURE 2 Sagittal multiplanar reconstruction computed tomographic images of the (a) left and (b) right floor of the pelvis showing the fracture lines and the medial fragment involving the left caudal ramus of the pubis and medial ramus of the ischium (asterisk). The fracture is slightly displaced compared with the right (normal) side. Cranial is to the left. 1 = pubis; 2 = ischium

detection of decreased bone density compared with radiography and should be considered the gold standard in foals (Lindegaard et al., 2021). The CT examination was an excellent diagnostic technique to exclude septic process affecting the hindlimbs and the pelvis in this foal and to identify the fracture at the level of the left caudal ramus of the pubis and medial ramus of the ischium, which was impossible to detect on the transcutaneous US. To the authors' knowledge, several studies regarding CT diagnosis of fracture in foals have been published (Barba & Lepage, 2013; Trump et al., 2011), but there are few reported cases affecting the pelvis, and fractures of the floor of the pelvis have never been described in foals with CT, specifically. This fracture involved two bones of the pelvis close to the pubic symphysis, which is a synchondrosis made by fibrocartilage that allow only small movements and after rest the foal was able to start the athletic career as soon as he reached 2 years of age. The prognosis of the pelvic fractures is affected by the involvement of the articular surface (i.e. coxofemoral joint) and the amount of the displacement leading to an early development of arthropathy (Trump et al., 2011). In our case, the prognosis was excellent because the fracture did not involve the coxofemoral joint and the amount of the displacement was mild. The configuration of the fracture of the presented case is of particular interest because fractures of the floor of the pelvis generally involve the cranial ramus of the pubis, the lateral ramus of the ischium, the ischiatic arch or table and are predominantly consequences of external trauma (fall, direct trauma) (Moiroud et al., 2019). However, in this foal, the location and shape of the fracture line and the wedge-like fragment made external trauma less likely, considering the deep and axial position of the pelvic symphysis. In long bones, wedge or butterfly fractures develop as a consequence of bending forces acting perpendicular to the long axis of the bone, resulting in a compression side, where the wedge develops, and a tensile opposite site. However, although external trauma cannot be excluded, in the author's opinion it is possible

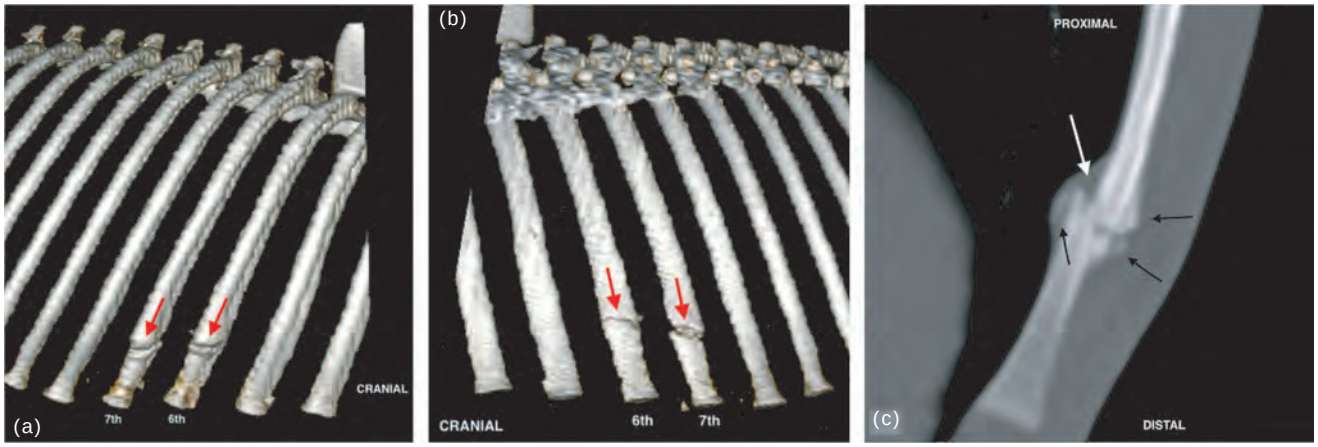

FIGURE 3 3D Volume Rendering computed tomographic image highlighting the right side of the thorax from the lateral (a) and medial (b) aspects showing the fractures (red arrows) of the sixth (6th) and seventh (7th) ribs. (c) Transverse plane multiplanar reconstruction computed tomographic image using maximum intensity projection highlighting a portion of the right sixth rib. A fracture (white arrow) of the sixth rib is detected with a mild grade of displacement just proximal to the costochondral junction. The distal part of the bone is slightly displaced medially and new bone formation (bone callus—black arrows) is observed around the fracture site

that this oblique wedge-like fracture configuration affecting flat bones was most likely an avulsion fracture of the muscles inserting on the ventral aspect of the floor of the pelvis, mainly the external obturator muscle and adductor muscles.

An additional CT scan of the thorax is included in our protocol for CT examination in foals with severe lameness and suspicion of a septic process to investigate the presence of primary site of infection, as the lungs. A previous report demonstrated that primary site of infection (i.e. abscess) can be detected by CT examination also in foals without clinical signs of pulmonary disease (Lindegaard et al., 2021; Pressanto et al., 2020). Some other abnormalities were detected by the CT examination, such as the rib fractures and the small bone lesions at the level of the lateral trochlear ridge of the right femur; the latters were considered incidental findings and not related directly to the clinical presentation. However, the detection of rib fractures merits further consideration; they were missed during the US examination of the thorax and this can be considered an 'inattentional blindness' as the foal did not show any clinical signs of respiratory distress and/or pleurodynia, and the examination was performed primarily to look for a primary site of infection. As these fractures were detected in only two ribs, were only mildly displaced and were not associated with clinical signs, they were treated conservatively, as for the fracture of the pelvis, with box-rest.

The major disadvantages of the use of CT are the limited availability in referral centres, the transport to them and the relatively high cost, which may be considered acceptable in specific cases to obtain an early diagnosis and avoid delay of appropriate treatment and prognosis in foals. Risks associated with general anaesthesia are limited in foals with a low bodyweight as they can be recovered by hand. Based on the findings identified in this foal, the authors strongly recommend the use of CT examination for foals when routine diagnostic procedures may not be adequate to localise the bone lesion and to exclude septic foci when there are suggestive blood abnormalities.

CONCLUSIONS

In conclusion, CT examination is a valid diagnostic tool in foals that allows the detection of pelvic fractures owing to its sensitivity. In this particular case, CT allowed identification of the cause of the lameness and ruled out the presence of a septic process hypothesised on the base of blood examination abnormalities, which represent a major problem in young foals with severe lameness. Equine practitioners should not overlook the pelvis as a possible site of fractures in cases of acute onset of hindlimb lameness in foals. The use of advanced diagnostic imaging techniques in foals, such as CT, is recommended when standard radiographic examination of the limb and ultrasonographic examinations of the pelvis are unremarkable.

AUTHOR CONTRIBUTIONS

Case management was performed by F. Beccati, E. Lauteri and M. Pepe. Imaging interpretation was performed by F. Beccati, G. Angeli, N. Scilimati and S. Schiavo. All authors drafted the manuscript and gave their final approval of the manuscript.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

ETHICS STATEMENT

No experimental animals were used in this case report. No submission to an ethics committee was required, and the owner signed a standard consent form upon entry to the hospital that informs the owner about permitting the use of patient data for scientific purposes.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Equine Veterinary Education

ORIGINAL ARTICLE

Ophthalmic findings in a herd of Caspian miniature horses

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SUMMARY

Background: The Caspian miniature horse (CMH) is a small horse breed, which has not previously been evaluated for ophthalmic diseases.

Objectives: The purpose of this study was to describe the ocular findings and to declare the normal ocular parameters seen in a small herd of CMH.

Study design: Cross-sectional study.

Methods: Forty-five Caspian miniature horses (25 mares and 20 stallions) were examined. Complete ophthalmic examination, commensal ocular surface microbiota culture and measurement of the horizontal and vertical fissure length were performed.

Results: Mean ± SD age of horses was 52.0 ± 33.9 months (range: 12–122 months). Nine different ocular disorders were observed: dacryocystitis, conjunctivitis, linear keratopathy, Haab's striae, corpora nigra atrophy, iris hyperpigmentation, cataract, peripapillary butterfly inactive lesions and inactive choroiditis were detected. In total, 17 eyes (18.8%) of 12 horses (26.2%) had ocular-related lesions. Two horses (4%) had more than one ocular lesion; the lesions were consistent with a diagnosis of either traumatic or recurrent uveitis. No vision loss was detected in these horses despite the identified ocular disorders.

Main limitations: Limited number of studied animals.

Conclusions: This study reported ocular findings in a small herd of CMH. A minority of horses in the herd had ocular lesions suggesting a history of glaucoma and/or equine recurrent uveitis.

KEYWORDS

horse, Caspian miniature horses, fungal flora, intraocular pressure, ocular microflora, palpebral fissure length, Schirmer tear test

Clinical relevance

- In total, 12/45 horses (26.2%) and 17/90 eyes (18.8%) had ocular related lesions. Two horses had more than one type of ocular lesion.
- Sequela that could be consistent with a past history of equine recurrent uveitis, and glaucoma were observed in Caspian miniature horses.
- Ocular disorders were not vision-threatening in these Caspian miniature horses.

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Equine Veterinary Education

ORIGINAL ARTICLE

Low-field MRI findings and follow-up of central tarsal bone fractures in four non-racehorses

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SUMMARY

Background: Central tarsal bone fractures in non-racehorses are uncommon, and their MRI appearance and follow-up have not been described.

Objectives: To describe the clinical and MRI characteristics, and follow-up of central tarsal bone fractures in non-racehorses.

Study design: Retrospective descriptive case series.

Methods: The low-field MRI appearance of central tarsal bone fractures in sport horses identified over a 9-year period was reviewed. Follow-up MRI examinations, treatment and clinical outcome were included.

Results: Four horses with five vertical fractures of the central tarsal bone were included. There were three Warmbloods, of which two were showjumpers and one a dressage horse, and one Quarter Horse was used for western performance. All fractures could consistently be visualised on low-field standing MRI and were associated with marked sclerosis in the surrounding bone, with little-to-no associated bone marrow lesion of the central tarsal bone. One horse had bilateral fractures. Three fractures were complete (full-thickness) slab fractures, and two were incomplete (partial-thickness) slab fractures. Fractures occurred in a consistent dorsomedial-to-plantarolateral oblique orientation and were nondisplaced. Incomplete fractures occurred at the dorsomedial proximal aspect of the central tarsal bone. All horses were treated conservatively initially. The dressage horse with bilateral fractures and the Quarter Horse remained lame after conservative treatment and were subsequently treated surgically. Three horses returned to their previous level of performance, one horse in spite of persistent MRI evidence of a fracture line (nonunion), while the Quarter Horse returned to a lower level of reining.

Main limitations: Small number of horses.

Conclusions: Standing low-field MRI is helpful in the diagnosis of central tarsal bone fractures. Central tarsal bone fractures occur in a dorsomedial-to-plantarolateral orientation in sport horses, can be complete or incomplete, unilateral or bilateral, and remain nondisplaced. The prognosis is good for return to performance.

KEYWORDS

horse, low-field MRI, tarsus, sport horses

Clinical relevance

- Central tarsal bone fractures occur in a dorsomedial-to-plantarolateral orientation in sport horses; standing MRI is useful to identify the fracture and determine the optimal radiographic angle for visualisation of the fracture and follow-up.
- Fractures can be complete or incomplete, unilateral or bilateral, and are nondisplaced.
- Prognosis for return to performance is good.

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Equine Veterinary Education

ORIGINAL ARTICLE

A survey of non-steroidal anti-inflammatory drug use in the post-operative period following equine colic surgery

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SUMMARY

Background: There is currently a lack of evidence surrounding the factors that contribute towards a clinician's decision to discontinue non-steroidal anti-inflammatory drug (NSAID) administration during the post-operative period following equine colic surgery, and the drugs and dosages commonly administered to these patients.

Objectives: To survey clinicians involved in the care of colic patients as to their use of NSAIDs and to investigate the factors associated with the decision to discontinue their administration.

Study design: An online questionnaire was created using Jisc Online Surveys, designed to record information about the use of NSAIDs by equine clinicians who regularly manage post-operative colic patients.

Methods: The questionnaire was distributed to boarded equine veterinarians from the American College of Veterinary Internal Medicine (ACVIM), the European College of Equine Internal Medicine (ECEIM) and the European College of Veterinary Surgeons (ECVS).

Results: Responses were obtained from 60 clinicians. Flunixin and phenylbutazone were the most administered NSAIDs and were also the most widely available drugs. 83% of clinicians ranked the absence of active colic signs as an important factor to consider when deciding the timepoint for NSAID discontinuation following colic surgery, in addition to 81% for pain score evaluation and 78% for the absence of fever. NSAIDs were typically discontinued 5–7 days post-operatively in the absence of complications but were often continued for longer where complications occurred.

Main limitations: Free text answer boxes provided in the questionnaire meant that some answers were difficult to interpret alongside the rest of the data, and therefore, had to be omitted. The case scenarios were fictitious, potentially altering the clinicians' treatment decisions compared with real-life cases, where more clinical information would be available.

Conclusions: There is variation in NSAID usage in the post-operative colic patient but agreement among clinicians about which factors are influential when considering NSAID discontinuation.

KEYWORDS
horse, colic, NSAIDs, post-operative, surgery

Clinical relevance

- NSAIDs are commonly used by clinicians in the management of the post-operative colic patient, and in the immediate post-operative period, flunixin remains the most commonly administered NSAID.
- The factors perceived to be most important by treating clinicians in discontinuing NSAID administration include the absence of colic signs, absence of fever and pain score evaluation.
- Post-operative patients with complications pertaining to the celiotomy or the underlying disease process generally received NSAID administration for a longer duration post-operatively.

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Equine Veterinary Education BEVA AAEP

ORIGINAL ARTICLE

Evaluation of a subcutaneously implanted biodegradable matrix with and without cisplatin in horses

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SUMMARY

Objective: To determine the biodegradability and platinum release profile of a calcium sulfate matrix (Matrix III) implanted subcutaneously in horses.

Study design: Matrix III with and without cisplatin was implanted subcutaneously in the cervical region of five horses with normal cervical skin.

Methods: Five 3-mm beads of Matrix III alone and ten 3-mm beads containing 7% cisplatin were implanted subcutaneously in the cervical region. Tissues were harvested every 7 days for 35 days. Biodegradability and histologic tissue reaction were determined. Inductively coupled plasma mass spectrometry was used to determine platinum concentration 3, 6, 9, 12 and 15 mm from each implantation site. Plasma and distant skin biopsies were harvested every 7 days. Repeated-measures ANOVA was performed to determine the differences between the 5 weeks and the five distances from the implant.

Results: Matrix III alone caused local inflammation that resolved early, and the implant had absorbed completely by 28 days leaving only focal fibrosis. Matrix III containing 7% cisplatin incited persistent histologically evident inflammation that appeared to be clinically insignificant. The implants had not been completely absorbed by 35 days. Platinum tissue concentration decreased with time after implantation and as the distance from the implant increased. Therapeutic concentrations remained in the tissue at 35 days.

Conclusions: Matrix III with 7% cisplatin resulted in chemotherapeutic platinum concentrations sustained for 35 days.

KEYWORDS

horse, cisplation, local chemotherapy, biodegradable, neoplasia

Clinical relevance

- To offer information regarding an alternative localised treatment for equine skin tumours sensitive to the chemotherapeutic drug cisplatin.
- The calcium sulfate matrix is solid enough for ease of implantation, and has a consistent release profile of cisplatin.
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ORIGINAL ARTICLE

Equine Veterinary Education

The mesotendineum of the superficial digital flexor tendon (SDFT)

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SUMMARY

Background: It is a common assumption that the mesotendineum of the SDFT creates an extrasynovial space within the tendon sheath. Thus, an incision of the palmar/plantar annular ligament (PAL) in this area should not result in the opening of the digital flexor tendon sheath (DFTS).

Objectives: To identify differences in the conformation of the mesotendineum of the SDFT, that do not allow for an extrasynovial midline desmotomy of the PAL in every horse.

Study design: A prospective study on horse cadaver limbs.

Methods: A total of 60 cadaver limbs from 15 horses were taken and divided into two groups. A midline or a lateral desmotomy of the PAL was performed. An opening of the DFTS in the course of midline desmotomy was investigated, and the attachment of the mesotendineum at the SDFT and the PAL was measured. A correlation between the conformation of the mesotendineum and the opening of the DFTS was investigated.

Results: Four different types of the mesotendineum could be detected. Type 1 and type 2 both include a continuous mesotendineum, but differ in their width. Type 3 and type 4 show a discontinuous attachment of the mesotendineum. In type 3, there is no attachment in its distal part, and in type 4, the interruption of the attachment is seen in its central part. Using the conventional desmotomy in the midline, the DFTS was entered in 50% of the limbs because of a thin, interrupted or a missing attachment at the distal part of the mesotendineum.

Main limitations: The relatively low number of cases and the heterogenous distribution of breeds did not allow for substantial statistical analysis.

Conclusions: This study shows that an extrasynovial midline dissection of the PAL is not always guaranteed due to different anatomical conformations of mesotendineum.

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KEYWORDS

horse, annular ligament, extrasynovial desmotomy, fetlocktunnel syndrome, mesotendineum

Clinical relevance

- The study shows that by using the so-called extrasynovial midline desmotomy of the PAL for the fetlock tunnel syndrome (FTS), the digital flexor tendon sheath is opened in 50% of the cases.
- Four different types of the mesotendineum could be detected according to morphological aspects of its attachment. The relation between the different types of the mesotendineum and the opening of the DFTS during a midline desmotomy is shown.
- The existence of four different types may play a role in the aetiopathogenesis of FTS.

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Equine Veterinary Education

REVIEW ARTICLE

Review of two viral agents of economic importance to the equine industry (equine herpesvirus-1, and equine arteritis virus)

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Summary

Equine herpesvirus type-1 (EHV-1) and equine arteritis virus (EAV) are infectious agents that cause serious health risks to horse populations and are disbursed worldwide, which can lead to significant financial losses. In addition to being responsible for abortion and neonatal death, these viruses are associated with respiratory illness. Although previous research and reviews have been written on these viruses, both viruses still affect horse populations around the world and the vaccines currently available are not completely protective, especially against EHV-1 and equine herpes myeloencephalopathy (EHM). Moreover, EAV is considered a threat to the $102 billion equine industry in the United States. As a result, these viruses represent a huge threat to the horse industry and efforts geared towards preventing the outbreak of the disease are strongly encouraged. For this reason, updates about these viruses are necessary and require more and more discussion on the nature and characteristics of these viruses to know how to overcome them. Prevention and control of abortion and neonatal foal death caused by each of the two viruses depend on appropriate management strategies coupled with prophylactic vaccination. This review presents the latest detailed information on EHV-1 and EAV from several aspects such as transmission, clinical signs, pathogenesis, latest developments on the treatment of the diseases, vaccination, and finally challenges and future perspectives. The information presented herein will be useful in understanding EHV-1 and EAV and formulating policies that can help to limit the spread of these viruses within horse populations.

KEYWORDS
horse, equine herpesvirus, equine arteritis virus, mechanism of abortion

THE EQUINE HERPESVIRUS TYPE-1 (EHV-1)

Introduction

The equine herpesvirus type-1 (EHV-1) belongs to the *Alphaherpesvirinae* subfamily of the *Herpesviridae* family and is characterised by double-strand DNA. This virus threatens the equine industry by causing significant economic losses resulting from both sporadic and epidemic outbreaks (Harless & Pusterla, 2006; Hedges et al., 1998).

Several abortions, multiple occurrences of equine respiratory disease, and sporadic outbreaks of myeloencephalopathy caused by EHV-1 have an economic effect on the horse industry. Between 1994 and 2012, outbreaks occurred in southern Brazil. During this outbreak, one pregnant mare out of 50 had an abortion (Estima-Silva et al., 2019). The prevalence of EHV-1 in mares and foals was 26.2%

and 11.4%, respectively, while the seropositivity for EHV-1 was 52.48% in Turkey (Yildirim, et al., 2015).

Recently, a report from Normandy showed the progress of a major EHV-1 outbreak that took place in 2009, during which the three forms of disease were observed (Sutton et al., 2019). Moreover, a collection of EHV-1 strains was isolated in France and Belgium from 2012 to 2018 (Sutton et al., 2019). Furthermore, a study carried out by Stasiak et al. (2020) describe an outbreak of abortions in Arabian mares at a well-managed State stud farm in Poland. Multiple abortions due to EHV-1 infection can occur in well-managed groups of horses. Reactivation of latent EHV-1 in one of the resident mares followed by a horizontal spread was considered the most likely explanation for the outbreak. In Middle East countries, EHV-1 infection was widespread among horses in Egypt at Monufia province (apparent prevalence rate 64% and true prevalence rate 28%) (Pagamjav et al., 2011). Recently, a study carried out in Morocco demonstrated that EHV-1 is endemic in the horse populations in the north of Morocco, with prevalence differences between regions (El Brini et al., 2021).

Transmission

Equine herpesvirus is mainly transmitted by inhalation of the infected droplets or ingestion of contaminated material by nasal secretions and aborted fetuses (Hebia et al., 2007). The principal reservoir of infection for EHV is latently infected horses. It can spread directly from horse to horse and indirectly via an object contaminated by nasal secretions and aborted fetuses. Latent infection and its reactivation play an important role in the epidemiology of EHV1 abortion and neurologic disease (Figure 1).

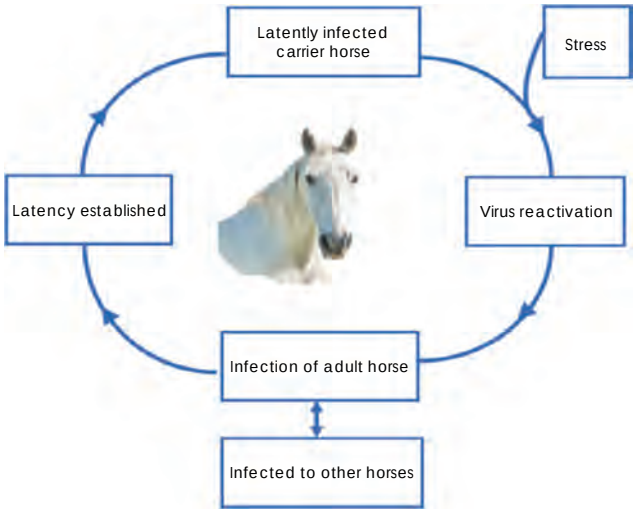

FIGURE 1 Transmission cycle of EHV-1 in horses

Clinical signs

Equine herpesvirus type-1 has different forms which includes respiratory infection, neurological disease (neurologic form), and abortion in pregnant mares (abortogenic form) (Kapoor et al., 2014; Loh et al., 2015). Equine herpes myeloencephalopathy (EHM) may result from neurological dysfunction (Kapoor et al., 2014). Horses older than 2 years are susceptible for EHV-1 infection (Oladunni et al., 2019). The major initial signs of EHV-1 involve fever, nasal discharge, cough, swollen legs, red eyes and congested mucous membranes (Oladunni et al., 2019). The major clinical signs of EHM involve multifocal myeloencephalopathy, ischaemic neuronal injury, haemorrhage and thrombosis (Wilson, 1997). Abortion as a result of EHV-1 infection usually occurs after 2–12 weeks in late gestation. However, the infection does not affect the mare's reproductive tract. Infection during gestation can also cause the death of the foal within a limited period after birth (Perkins et al., 1999).

Pathogenesis

It is well known that two pathotypes of EHV-1 strains are circulating in the field: neurovirulent (N) and non-neurovirulent (NN). For both strains, CD172a$^+$ monocytic cells are one of the main carrier cells of EHV-1 during primary infection, allowing the virus to invade the horse's body. Recently, it was reported that EHV-1 NN strains showed a restricted and delayed replication in CD172a$^+$ cells. A study performed by Laval et al. (2017) aimed to characterise the in vitro replication kinetics of two EHV-1N strains in CD172a$^+$ cells. It was found that EHV-1N replication was restricted to 7%–8% in CD172a$^+$ cells compared with 100% in control RK-13 cells. Approximately 0.04% of CD172a$^+$ cells produced and transmitted infectious EHV-1 to neighbour cells compared with 65% of RK-13 cells. Overall, these results show that the EHV-1 replication of N strains in CD172a$^+$ cells differs from that observed for NN strains, which may contribute to their different pathogeneses in vivo. In a trial to identify the most neurovirulent EHV-1 strains, a recent study evaluated the pathogenesis of two neurovirulent EHV-1 strains (A4/72 or A9/92) in mice, and characterised the inflammatory cells and expression of chemokines and the apoptosis marker caspase-3 in the brain of infected mice (Mesquita et al., 2021). Results showed that severe neurological signs were discovered in EHV-1-infected mice at 3 days post inoculation (DPI). The authors concluded that neurovirulent EHV-1 strains induced a fulminant necrotising lymphohistiocytic meningoencephalitis in mice, with microgliosis and expression of chemokines and caspase-3. This model will be useful for understanding the mechanisms underlying the extensive neuropathology induced by these viral infections.

Another study (Cymerys et al., 2018) investigated EHV-1 replication (wild-type Jan-E strain and Rac-H laboratory strain) during long-term infection and during the passages of the virus in cultured neurons. Results indicated a high level of virus DNA in cultured neurons, and during long-term infection, these neurons were still able to

transmit the virus to the other cells. The study compared the neurovirulence of Rac-H and Jan-E EHV-1 strains after multiple passages of these strains in neuron cell culture. The results showed that multiple passages of EHV-1 in neurons lead to the inhibition of viral replication as early as in the third passage. Finally, it is concluded that certain balance between EHV-1 and neurons has been established during in vitro infection allowing neurons to survive long-term infection. However, the mechanisms of the neuronal damage of EHV-1 are still mysterious. Therefore, a study (Cymerys et al., 2020) was carried out to define the phosphorylation status of tau protein in neuronal cell culture infected with EHV-1. The authors illustrated for the first time that EHV-1 infection causes accumulation of hyperphosphorylated tau in primary murine neurons. The results showed that non-neuropathogenic and neuropathogenic EHV-1 strains specifically stimulate hyperphosphorylation of tau-ser199/ser202, tau-ser404 and tau-thr205 during long-term infection and after a controlled activation of productive infection.

Although the neuropathogenic strain of EHV-1, T953, was reported to suppress the host cell's antiviral type-I interferon (IFN) response in vitro, it is undetermined whether or not this is unique to EHV-1 strains possessing the neuropathogenic genotype. Thus, Oladunni et al. (2018) examined whether there is any direct relationship between neuropathogenic genotype and the induced IFN-β response in equine endothelial cells (EECs) infected with 10 different strains of EHV-1. Then, a comparison was made between IFN-β and the total type-I IFN protein suppression between T953, an EHV-1 strain that is neuropathogenic and T445, an EHV-4 strain mainly associated only with respiratory disease. Results revealed no relationship between the neuropathogenic genotype of EHV-1 and the induced IFN-β mRNA by the host cell. However, while the T953 strain of EHV-1 was able to suppress IFN-β mRNA and type-I IFN biological activity at 12 h post-infection (hpi), EHV-4 weakly induces both IFN-β mRNA and type-I IFN biological activity. This finding correlated with a statistically significant difference in the mean plaque sizes produced by the two EHV subtypes in EECs. These data help to illuminate how EHV-1, irrespective of its genotype, evades the host cell's innate immune response thereby enabling viral spread to susceptible cells.

Mechanism of abortion

Equine herpes virus is the most harmful infectious agent that causes abortion in the mare. The virus induces premature detachment of the fetus from the placenta, stillbirth, or weak neonatal foals (Reed & Toribio, 2004). Pregnant mares infected with EHV-1 may also abort before exhibiting clinical signs of the upper respiratory tract infection (Mumford et al., 1994). The essential roles exerted with the aid of host immune, inflammatory responses and vascular coagulation cascades mediating EHV-1 caused abortion have not been entirely elucidated (Allen et al., 2004). However, infection of the endothelium of a pregnant uterus by EHV-1 influences vasculitis especially the small vascular networks of the glandular endothelia of micro cotyledons (Smith et al., 1993). Within 9–13 days post-infection, endothelial cell infection turns to substantial resulting in multifocal vasculitis of the affected blood vessels (Allen et al., 2004). Occasionally, the appearance of micro thrombosis within blood vessels may additionally promote thrombo-ischaemic necrosis of the cotyledons and intercotyledonary stroma causing the fetus to detach from the placenta (Smith et al., 1993) (Figure 2). The aborted fetus dies of anoxia following an unexpectedly progressive separation of the placenta-endometrium immediately earlier than fetal expulsion (Allen, 2002). Here are different factors that indicate the severity of the diseases causing abortion such as the virulence of the EHV-1 strain involved, the stage and magnitude of viraemia, and the hormonal state of the pregnant mare. More virulent strains of EHV-1 such as Ab4 have been pronounced to produce a higher rate of abortion in pregnant mares than the less virulent strains such as V592 (Mumford et al., 1994).

Mare infected with EHV-1 during conception may bear live infected fetuses which become ill within 1–2 days of birth (McCartan et al., 1995) and rapidly deteriorate then die.

Treatment

There is no particular medicine that can be used to treat EHV-1 infection. However, symptomatic treatment with non-steroidal anti-inflammatory drugs may be beneficial (Lunn et al., 2009; Reed & Toribio, 2004).

The neurological variant of the disease, known as equine herpesvirus-1 myeloencephalopathy (EHM) is seen as a clinical consequence to EHV-1 respiratory diseases (Pusterla et al., 2009; Wilson, 1997). In these cases of EHM, corticosteroids and immunomodulatory drugs can also be utilised to treat early clinical signs. However, there is no evidence-based study demonstrating the efficacy of either treatment type, so caution should be used to avoid reactivating viral shedding in horses who are latently infected (Lunn et al., 2009; Rybachuk, 2009). Corticosteroids are thought to protect against the cellular response to CNS infection, reducing bleeding, oedema, vasculitis and thrombosis, which are all prominent early indications of EHM. However, they should only be used in severe instances of EHM (Lunn et al., 2009).

Vaccination

No currently registered vaccine for EHV-1 has claimed to be completely effective in preventing either infection or disease that may result from exposure. The primary beneficial effects derived from vaccination of horses against EHV-1 are reduction in the severity, duration of respiratory disease in the young vaccinated animal, and reduction of the overall incidence of fetal loss during outbreaks of abortion.

However, authors still try to develop vaccines providing improved immunity and protection. Recent studies carried out by Perkins et al.

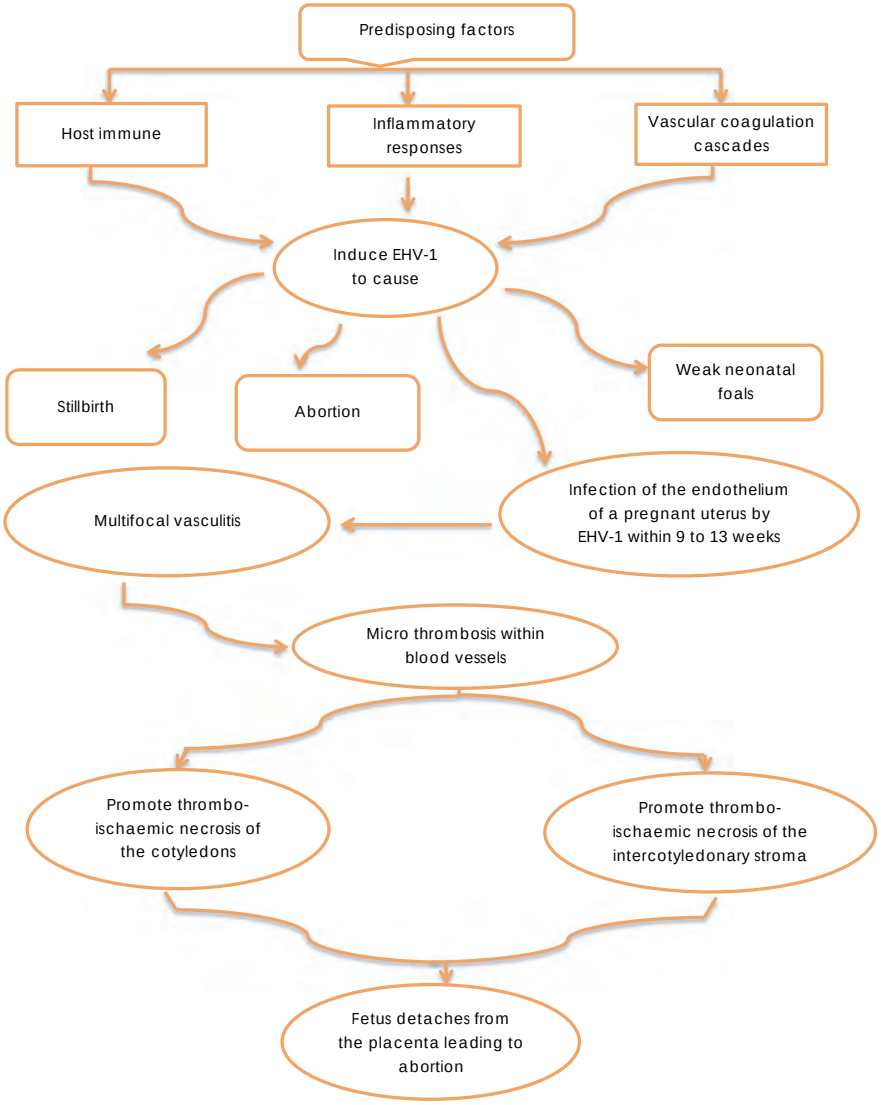

FIGURE 2 Mechanism of abortion by EHV-1

(2019) and Schnabel et al. (2019) aimed to confirm protection against EHV-1 challenge 9 months after intranasal infection with the vaccine candidate Ab4ΔORF2 and characterised key parameters of local and systemic immunity in EHV-1-susceptible and -protected horses. The authors reported that intranasal infection with Ab4ΔORF2 or Ab4 9 months prior to EHV-1 challenge protected the majority of horses from clinical disease, virus shedding and cell-associated viraemia after challenge infection. The attenuated vaccine candidate Ab4ΔORF2 protected a higher number of horses completely from EHV-1 infection, clinical disease, virus shedding and viraemia than infection with its parent strain Ab4. Improved protection was linked to a stronger, rapidly increasing nasal IgG4/7 response and the absence of inflammatory mediator upregulation in the upper respiratory tract after challenge. Pre-existing EHV-1-specific IgG4/7 antibodies in serum were found to be robust markers of protection from challenge infection. These data support EHV-1-specific IgG4/7 antibodies as valuable biomarkers and correlates of protection for improving vaccination and management strategies to limit EHV-1 outbreaks.

Challenges and future perspectives

Horses shed EHV for up to 21 days after infection. Quarantine durations may also be mandated for up to one month following the resolution of viral shedding and fevers in affected horses. The virus survived for up to 7 days at ambient temperatures. Herpes viruses are susceptible to many disinfectants, but before disinfection, all areas must be thoroughly cleaned with detergent to decrease the organic matter. In a trial of detection of the environmental persistence of EHV-1, recent research (Saklou et al., 2021) indicated that viable EHV-1 was recovered up to 48 h from all material-environmental condition combinations, which represented a transmission risk. In general, outdoor environment had the greatest impact followed by indoor environment and 4°C. On average, wood shavings had the greatest impact on persistence, followed by leather, straw, fabric and polystyrene. This means that environmental factors had variable effects on environmental persistence. Barrier precautions should be used to prevent spread of EHV-1 from unrecognised environmental reservoirs.

Another aspect was indicated by Pusterla et al. (2021) who reported that a close clinical monitoring of at-risk horses has remained the main strategy in disease prevention. The detection of EHV-1 early in the outbreak allowed medical intervention with the goal to prevent myeloencephalopathy. Specifically, the use of valacyclovir in all horses was successful at reducing and preventing viraemia and nasal shedding. Furthermore, regular testing of blood and nasal secretions by qPCR allowed closely monitoring individual infection status and documenting the resolution of the outbreak.

EQUINE ARTERITIS VIRUS (EAV)

Introduction

Equine arteritis virus (EAV) is a major economic threat to the horse industry due to its responsibility for causing reproductive and respiratory diseases (Balasuriya et al., 2013; Balasuriya & MacLachlan, 2013). It is considered a threat to the $102 billion equine industry in the United States. It causes economic losses mainly due to abortions in pregnant animals and reduces the income from stud fees due to carrier males shedding virus in their semen (Balasuriya et al., 2018). EAV has been reported to belong to a species Alpha arterivirus equid in the genus Alpha arterivirus of the family Arteriviridae in the order Nidovirales (King et al., 2018). The EAV genome is composed of a single-stranded-positive RNA molecule of almost 12,700 bp. EAV is differentiated into two types of groups, the first one belonging to the North American (NA), while the second is known as the European group. Moreover, the European one is lately divided into other two subgroups known as European subgroup 1 (EU-1) and European subgroup 2 (EU-2) (Gaudaire et al., 2019).

The virus causes major economic losses which appeared after its implication in cases of abortions, neonatal death reached 23% of the infected cases, fatal broncho-interstitial pneumonia or pneumoenteric syndrome in foals (Balasuriya et al., 2018; Timoney & McCollum, 2000), and establishment of persistent infection in stallions (Bażanów et al., 2014). The abortion rates in mares during field outbreaks was found to vary from approximately 10% to 70%, depending on the virus strain (Timoney & McCollum, 1993).

The virus recently detected in Serbia based on the serological evidence and phylogenetic analysis (Lazić et al., 2017). While another study monitored the spread of EAV with different EqCXCL16 genotypes among Polish Hucul horses (Socha et al., 2020).

Transmission

Respiratory or venereal routes are the methods of transmission of the virus between horses (Laabassi et al., 2014; Lazić et al., 2017; Pagamjav et al., 2011). In this respect, the spreading of the infection occurs through contact among infected and susceptible animals. Besides, acutely infected horses represent an important source of infection through their infectious droplets of respiratory secretions which leads to horizontal transmission of the virus (Balasuriya et al., 2013; Holyoak et al., 2008) (Figure 3).

Maintenance of the virus in the equine population occurs by the presence of the virus in carrier stallions for the short-term and long-term which may extend from several weeks to years. Colts infected with the virus before the peripubertal development do not suffer from long-term infections. Long-term infections do not occur in mares (Hedges et al., 1999; Holyoak et al., 1993; Timoney & McCollum, 1987). It is believed that the venereal route is the primary method of infection. Carrier stallions used for breeding transmit the infection to the mares. The embryo transfer technique can also transmit the virus to the naïve recipient mares if the used embryo resulted from a donor mare inseminated with semen contaminated with the virus (Broaddus et al., 2011a, 2011b) (Figure 3).

Clinical signs

The clinical signs of the disease vary from severe clinical signs to subclinical infections. The incubation period in the case of venereal transmission is 6–8 days. In acute infection, the animal suffers from a fever (40.6°C/105°F) for 1–5 days which leads to making the animal depressed, anorectic and may have a cough. Other clinical signs include a serous nasal discharge, congestion of the nasal mucosa, intermandibular lymphadenopathy, conjunctivitis, lacrimation, and less frequently, corneal opacification. Oedema of the sheath, scrotum, ventral midline, limbs and eyelids occurs because of vasculitis (Balasuriya, 2014; Glaser et al., 1996).

Abortion also may occur if pregnant mares get infected. Infection of young foals leads to severe interstitial pneumonia or pneumoenteric syndrome. The severity of the infection in foals depends on the age at the time of infection (Balasuriya et al., 2013). A period of temporary sub-fertility was noticed in stallions that had been acutely affected by the disease. This temporary sub-fertility resulted from increased testicular temperature rather than a specific side effect of the virus. Therefore, the reduced libido during the acute phase of infection is accompanied by a reduction in sperm motility, concentration and percentage of morphologically normal sperm in ejaculates, which persist for up to 6–7 weeks (Neu et al., 1992).

Pathogenesis

The respiratory tract epithelium and the alveolar macrophages are invaded by the virus after the intranasal challenge (aerosolisation). The virus is replicated and can be detected after 3 days of infection in the bronchopulmonary lymph nodes, endothelium and circulating macrophages (Timoney & McCollum, 1987). The virus also causes necrotising arteritis and panvasculitis after its localisation in the endothelium and medial myocytes of blood vessels 6–8 days after infection (Del Piero, 2000).

After respiratory infection of horses by EAV, the virus infects alveolar macrophages (AMF) which in spite of being susceptible to

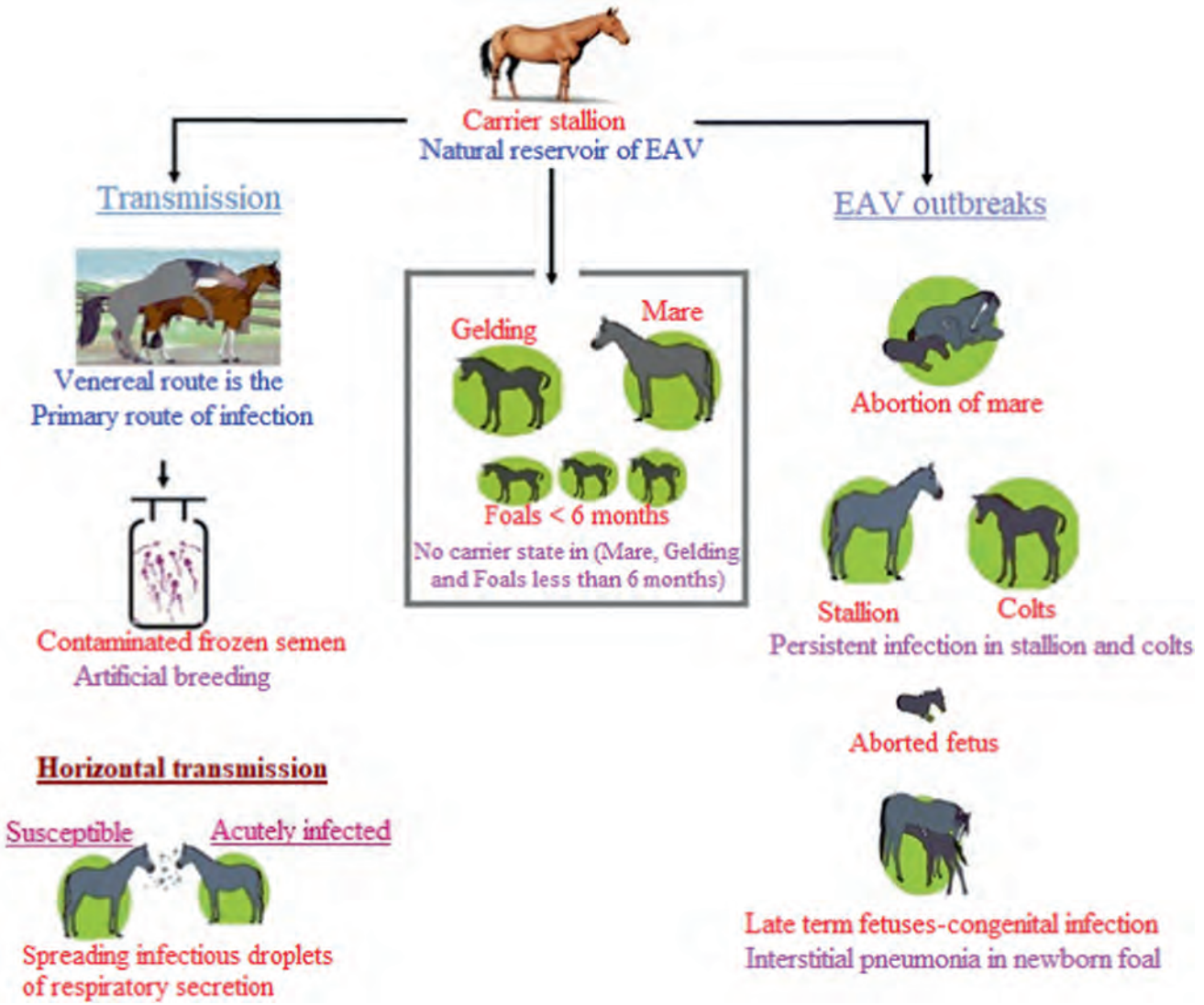

FIGURE 3 Transmission and outbreaks of EAV in equine species

infection are refractory to productive replication of EAV. These data were confirmed by recent in vitro studies using cultured equine AMF (Moore et al., 2003). In contrast, cultured blood-derived equine macrophages (BMF) were reported to be responsible for productive replication that occurred following EAV infection (Moore et al., 2003). The transcription of genes encoding pro-inflammatory mediators, such as IL- 1b, IL-6, IL-8 and TNF-a was increased by EAV infection of both equine AMF and BMF; in addition, there was a release of substantial quantities of TNF-a into the culture medium (Moore et al., 2003). Moreover, different quantities of TNF-a and other pro-inflammatory cytokines (IL-1b, IL-6, and IL-8) were induced by virulent and avirulent strains of EAV. Therefore, the virulence of the infecting virus strain was reflected by the magnitude of the cytokine response of equine AMF and BMF to EAV infection (Moore et al., 2003). Additionally, it was reported that EAV infection upregulates the expression of leukocyte adhesion molecules. Therefore, the importance of these factors is not restricted to inciting inflammation to limit initial virus replication, but also may participate in the vascular and tissue injury that distinguish EVA. In synopsis, these in vitro studies obviously highlighted that EAV infected equine cells produce those cytokine mediators which perhaps can be used to determine the nature and severity of the outcome of the infection.

Equine arteritis virus (EAV) has unparalleled ability to cause long-term persistent infection in the reproductive tract of stallions and be sexually transmitted. Previous studies illustrated that long-term persistent infection is accompanied by a specific allele of the CXCL16 gene (CXCL16S) and that persistence is maintained despite the presence of local inflammatory, humoral and mucosal antibody responses. Recent study carried out by Carossino et al. (2019) aimed to perform a transcriptomic analysis of the ampullae, the primary site of EAV persistence in long-term carrier stallions, to investigate the molecular signatures of viral persistence. The authors elucidated that the local $CD8^+$ T lymphocyte response is predominantly orchestrated by the transcription factors eomesodermin (EOMES) and nuclear factor of activated T-cells cytoplasmic 2 (NFATC2), which is likely modulated by the upregulation of

inhibitory receptors. Most importantly, EAV persistence is accompanied by consolidated expression of CXCL16 and CXCR6 by infiltrating lymphocytes, proving the implication of this chemokine axis in the pathogenesis of persistent EAV infection in the stallion reproductive tract.

Trials have been performed to attempt to explain the mechanism that allows EAV to be maintained in the horse populations through persistently infected stallions. Socha et al. (2020) carried out a study to monitor the spread of EAV among Polish Hucul horses, to analyse the variability of circulating EAVs both between- and within-horses, and to identify allelic variants of the serving stallions EqCXCL16 gene that had been previously shown to strongly correlate with long-term EAV persistence in stallions. The results showed that the EAV genomes from different stallions were 94.7%–99.6% identical to each other. A number of single nucleotide variants were identified within EAV sequences from infected stallions. Four stallions possessed EqCXCL16S genotype that correlated with development of long-term carrier status, three of which were persistent shedders and the shedder status of the remaining one was undetermined. None of the remaining 12 stallions with EqCXCL16R genotype was identified as a persistent shedder.

In another study (Nam et al., 2019), sequential viruses isolated from nasal secretions, buffy coat cells and semen of seven experimentally infected and two naturally infected EAV carrier stallions were deep sequenced to elucidate the intrahost microevolutionary process after a single transmission event. The study illustrated that during persistent infection, extensive genome-wide purifying selection shaped variant diversity in the stallion reproductive tract. Overall, the nonstochastic nature of EAV evolution during persistent infection was driven by active intrahost selection pressure. Among the open reading frames within the viral genome, ORF3, ORF5, and the nsp2-coding region of ORF1a accumulated the majority of nucleotide substitutions during persistence, with ORF3 and ORF5 having the highest intrahost evolutionary rates. The findings presented in this study provide a novel insight into the evolutionary mechanisms of EAV and identified critical regions of the viral genome likely associated with the establishment and maintenance of persistent infection in the stallion reproductive tract.

Mechanism of abortion

Equine arteritis virus causes abortion of pregnant mares if the infection occurs from 2 months of pregnancy to term (Balasuriya et al., 1998; Paweska, 1997; Szeredi et al., 2005).

Viral myometritis with degeneration of myocytes and infiltration of mononuclear cells leads to transplacental infection of the fetus (Wada et al., 1996). The placenta becomes oedematous while the sub-villous layers contain degenerated fibroblasts.

Equine arteritis virus antigen can be detected in the dam (myometrium and the endometrial glands) and the aborted fetus, in addition to the sub-villous layer of the placentae using immunofluorescence. The virus may be recovered from the uterus and fetus, but the placenta is probably providing the major quantity of the virus (Balasuriya, 2014).

Vertical transmission of the EAV was evidenced by the presence of the high viral titres and abundance of viral antigen in diverse fetal tissues, chorioallantoic membrane and other fetal membranes; specifically in trophoblastic, amniotic, and allantoic epithelium, chorioallantoic mesenchyma, pneumocytes, alveolar macrophages, thymic epithelium and lymphocytes, splenic reticular cells and mononuclear cells in the white and red pulp, renal interstitial cells and tubular epithelium, extramedullary hemopoietic cells in the liver and rare hepatocytes, endothelial cells, vascular smooth muscle cells and enterocytes.

Although the time of abortion is known, the mechanism of abortion is still unknown and abortion may occur with or without preceding clinical evidence of infection (Timoney et al., 1996). Teratological abnormalities do not occur in fetuses aborted due to EAV infection; however, sudden death may occur in neonates or neonates may suffer firstly from respiratory distress then causes death (Del Piero et al., 1997; Timoney & McCollum, 1987).

Treatment

Antivirals and other therapeutics

Phosphorodiamidate morpholino oligomers (PMOs) were evaluated as an antiviral potential against EAV (Van den Born et al., 2005; Zhang et al., 2010a, 2010b). PMOs are DNA analogues that are single-stranded (Summerton & Weller, 1997). PMO delivery into cells is improved greatly through Peptide-conjugation to the PMO (P-PMO) (Abes et al., 2006). The EAV genome contains the 5′ UTR which is the most sensitive target for inhibition with P-PMOs (Van den Born et al., 2005).

In other studies, it was discovered that treatment of horse cells by 100 U/ml recombinant equine IFN-g after its infection by 100 TCID50 of infectious EAV causes prohibition against this infection (Sentsui et al., 2010). Plant and nonplant lectins, which are carbohydrate-binding agents, have also been reported to have antiviral activities against Nidoviruses (Van der Meer et al., 2007). Despite, in vitro experiments showed that antiviral agents have a promising effect but, in vivo, the results differ as the usage of antiviral agents as a therapy against the virus is still limited due to the large mass of horses and the inherent costs involved.

When the infected stallion with EAV converts to the carrier state, this state is mainly related to the testosterone hormone. Therefore, tentative inhibition of testosterone secretion in carrier animals may provide a therapeutic method in the excretion of EAV infection (Glaser et al., 1996; Holyoak et al., 1994; Timoney & McCollum, 1993).

Recent studies carried out by Valle-Casuso et al. (2020) presented a high-throughput in vitro assay suitable for testing candidate antiviral molecules in equine dermal cells infected by EAV. The authors identified three molecules that impair EAV infection in

equine cells: the broad-spectrum antiviral and nucleoside analogue ribavirin, and two compounds previously described as inhibitors of dihydroorotate dehydrogenase (DHODH), the fourth enzyme of the pyrimidine biosynthesis pathway. These molecules effectively suppressed cytopathic effects associated with EAV infection, and strongly inhibited viral replication and production of infectious particles. The results of the study demonstrate that this antiviral activity extends to Arteriviridae, suggesting that pyrimidine biosynthesis inhibitors may act as pan-nidovirales inhibitors. The authors believed that IPPA17-A04 is an interesting molecule for developing a therapy against EAV and nidovirales and should be further evaluated in vivo. These results open new perspectives for the management of EAV outbreaks.

Vaccination

In North America, a modified live virus (MLV) vaccine, ARVAC (Fort Dodge Animal Health, Fort Dodge, IA [now Zoetis Animal Health, Kalamazoo, MI]) is widely used for vaccination against EAV, while in several European countries, an adjuvant killed virus vaccine, ARTERVAC, is approved for usage.

Unfortunately, the MLV vaccine has variant contraindication in its usage, as it is not used for pregnant mares, especially during 8 months of gestation. Furthermore, foals less than 6 weeks of age are not allowed to be vaccinated with MLV unless they are at high risk of natural exposure (Balasuriya & MacLachlan, 2004; Broaddus et al., 2011; Timoney & McCollum, 1993).

Both structural proteins (GP5, M, and N) and nonstructural proteins (nsp2, nsp4, nsp5, and nsp12) induce humoral immunity (Go et al., 2011; MacLachlan et al., 1998).

In vivo studies carried out on experimentally immunised horses revealed that the cloned vaccine virus is safe and induces high titres of neutralising antibodies against EAV. However, when evaluated with the heterologous KY84 strain of EAV, the rMLVB vaccine proved its ability to give protection to immunised animals by reducing the severity of the disease which occurs by reducing the magnitude and duration of viremia and virus shedding. But unfortunately, the rMLVB vaccine failed to prevent clinical signs of EAV. Whereas the recognisable serotypes of EAV is only one, field strains obviously varied in their neutralisation phenotype (Balasuriya et al., 2004; MacLachlan & Balasuriya, 2006; Miszczak et al., 2012; Zhang et al., 2010a, 2010b).

Challenges and future perspectives

It is essential in the procedures undertaken for controlling EAV to prevent further spread of the virus in the breeding populations and reduce the risk of outbreaks of virus-related abortion, death in young foals, and establishment of the carrier state in stallions and post-pubertal colts. Despite EAV sometimes being responsible for outbreaks of disease at racetracks, shows, sales, and veterinary hospitals, these were intermittent due to absence of specific control programmes applied to prevent such crises. EVA is considered a manageable and preventable disease that can be controlled by application of sound management procedures in association with a targeted vaccination program. The application of sound management includes a trial carried out by Fidler et al. (2021) and aimed to develop an experimental set-up for testing the spread of viruses by ultrasonic scaler (USS) generated dental spray and evaluate its mitigation by antiviral coolants. The trial evidenced that a simple substitution of the USS coolant with sodium hypochlorite (NaOCl) or electrolysed oxidising water (EOW) managed to mitigate the spread of the virus. The use of vaccines aims to prevent the establishment of carrier states. Furthermore, vaccination leads to rapidly formed immunity which lasts for 1–3 years (Timoney & McCollum, 1987). However, reinfection was not prevented by primary vaccination. Mares which will be used for breeding with carrier stallions should be vaccinated 3–4 weeks before the time of breeding and should be isolated for 3 weeks after being bred to a carrier stallion for the first time (Timoney et al., 1996). It is not recommended to vaccinate pregnant mares or foals less than 6 weeks of age. The antibodies to EAV of foals born to seropositive mares are reduced to undetectable amounts by 8 months after delivery. Therefore, vaccination can be carried out at this time if necessary (Hullinger et al., 1998).

Conclusions

Equine herpesvirus type-1 and equine arteritis virus infect horses around the world and the vaccines currently available are not completely protective, especially against EHV-1 and EHM. As a result, the two viruses represent a huge threat to the horse industry and efforts geared towards preventing the outbreak of the disease are strongly encouraged. Detailed information on both the host and the certain environmental factors that enable the recent incidence of EHV-1 myeloencephalopathy and EAV are still elusive. Further research is necessary to detect potent epidemiological factors that promote the diseases. Most research on how EHV-1 modulates host immune responses has been carried out in vitro with only a few studies investigating the immunomodulatory effects of EHV-1 in vivo. More in vivo studies focusing on viral properties that are important for the evasion of host immunity will help to expose putative therapeutic targets of EHV-1. Advances and progress in treatment and control of EHV-1 and EAV depend on the combined application of detailed epidemiological data and in-depth knowledge of how the sophisticated viral biology promotes pathogenesis.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

AUTHOR CONTRIBUTIONS

Y. Amin and H. Mahmoud wrote the manuscript and Y. Amin, H. Mahmoud and S. Fouad revised it. All authors gave their final approval of the manuscript.

ETHICS STATEMENT

This review had approval from the Faculty of Veterinary Medicine, South Valley University.

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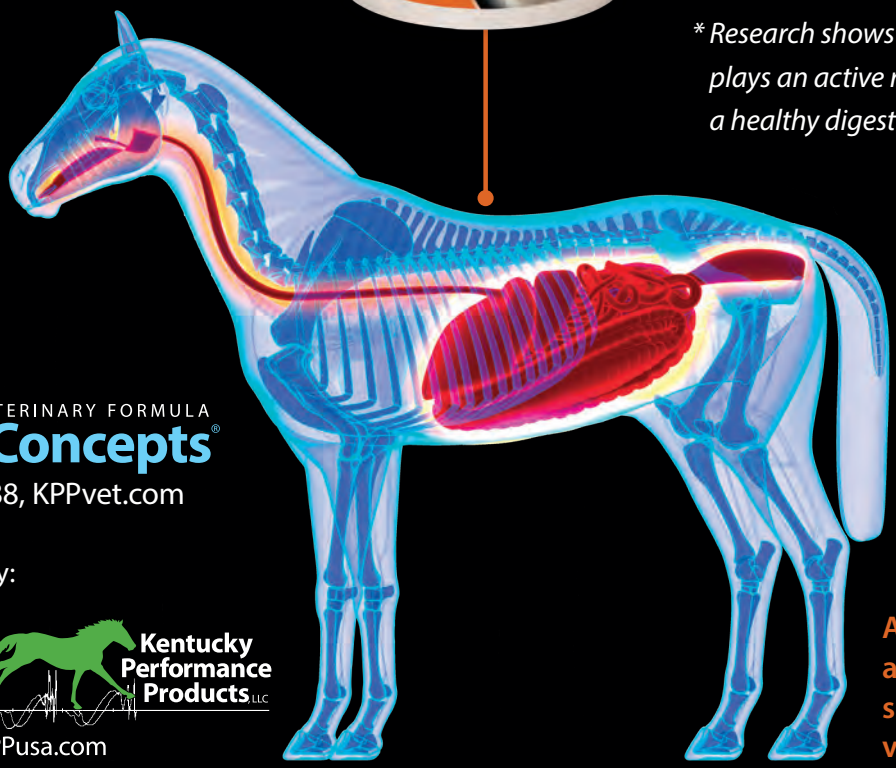

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Equine Veterinary Education

REVIEW ARTICLE

Can the use of antimicrobials in adult equine patients with acute colitis be justified in the era of antimicrobial stewardship?

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Summary

The use of antimicrobials in adult horses with acute colitis is controversial and clear antimicrobial guidelines are lacking. It is generally accepted that antimicrobials should be reserved for patients with specific bacterial enterocolitis such as *Neorickettsia risticii* or *Clostridium difficile*; however, in practice, horses show similar clinical signs independently of the underlying aetiology. The clinician is therefore often confronted with the dilemma of rapid initiation of treatment to avoid mortality vs. delayed and selective targeted antimicrobial treatment based on faecal diagnostic testing. The risk of antibiotic associated diarrhoea and the emergence of antimicrobial resistance are other important considerations.

KEYWORDS
horse, antimicrobial, diarrhoea

INTRODUCTION

Acute colitis is a potentially life-threatening condition characterised by hypersecretion of fluid, altered motility and an impaired mucosal barrier resulting from direct injury, inflammation and/or dysbacteriosis (Sanchez, 2017). It is responsible for approximately 5% of admissions to equine veterinary hospitals with a mortality of about 40% (Prescott, 2020). Horses with acute colitis present with diarrhoea and potentially other signs such as fever, depression, and colic. It is commonly associated with severe dehydration and electrolyte abnormalities. They can develop SIRS (systemic inflammatory response syndrome) secondary to bacterial translocation, absorption of endotoxin or other bacterial products in the blood stream through a compromised gastrointestinal mucosa (Sanchez, 2017). A variety of infectious and non-infectious aetiologies exist, yet many of the clinical and clinicopathological features are similar regardless of the underlying cause (Sanchez, 2017). In addition, the underlying aetiology remains undetermined in over 50% of the cases (Prescott, 2020).

Furthermore, therapeutic principles are similar regardless of the cause and include (1) replacing fluid and electrolyte losses, (2) minimising colonic inflammation and sepsis, (3) promoting mucosal repair and (4) re-establishing normal flora. Some horses require specific therapy aimed at the underlying aetiology (Sanchez, 2017).

The routine use of antimicrobials in equine colitis is controversial as antimicrobials may further alter the already compromised normal protective gastrointestinal flora. Additionally, high-level evidence supporting antimicrobial therapy in equine colitis has been previously reported to be lacking (Dunkel & Johns, 2015; Sanchez, 2017). The objectives of this paper are to provide a comprehensive overview of the current evidence regarding the use of antimicrobials in the different types of acute colitis in adult horses.

GENERAL CONSIDERATIONS

Categorisation of antimicrobials from AMEG (Antimicrobial Advice Ad Hoc Expert Group)

The AMEG has categorised antimicrobials according to their critical use in humans. Following antimicrobial stewardship principles, one should attempt to select an antimicrobial from the non-critical classes (https://www.ema.europa.eu/en/documents/report/categorisation-antibiotics-european-union-answer-request-european-commission-updating-scientific_en.pdf; EMA categorisation of antimicrobials for use in animals: https://www.ema.europa.eu/en/documents/report/infographic-categorisation-antibiotics-use-animals-prudent-responsible-use_en.pdf).

ANTIBIOTIC-ASSOCIATED DIARRHOEA

Antimicrobial therapy can disrupt the enteric flora and induce antibiotic-associated diarrhoea (AAD). AAD can occur with all antimicrobials and several studies have shown greater mortality risk compared with other causes of diarrhoea (Cohen & Woods, 1999; Herholz et al., 1999). Cohen and Woods (1999) showed that horses with acute diarrhoea previously treated with antimicrobials were 4.5 times less likely to survive than those not treated with antimicrobials. Reported prevalence of AAD varies a lot (0.6%–54%) (Barr et al., 2013; Båverud et al., 1997, 1998; Gustafsson et al., 1997; Johns & Barnet, 2016) and there seems to be geographical variation regarding the antimicrobials implicated in development of AAD (Båverud et al., 1998; Gustafsson et al., 1997).

Different mechanisms contribute to AAD. The most important is antimicrobial-mediated disruption of the normal enteric microflora and ecosystem (Costa et al., 2015; Harlow et al., 2013; Högenauer et al., 1998; McGorum & Pirie, 2009; Sanchez, 2017). The normal large intestinal flora in the horse is complex and poorly characterised, yet it is thought to be mainly composed of obligate anaerobes (Clostridia class) and Streptococci (Harlow et al., 2013). Through the process of colonisation resistance, those normal bacteria compete with pathogenic bacteria for space and nutrients and protect the host (Högenauer et al., 1998; McGorum & Pirie, 2009). Antimicrobials can disrupt the normal enteric flora and consequently decrease colonic resistance, allowing pathogenic bacteria to overgrow (Gustafsson et al., 2004; Harlow et al., 2013). Intestinal colonisation and overgrowth of pathogenic bacteria, such as *Clostridium difficile* or *Salmonella*, together with release of toxins, will subsequently result in mucosal damage and inflammation (Gustafsson et al., 2004; Harlow et al., 2013; Högenauer et al., 1998; House et al., 1999; McGorum & Pirie, 2009; Sanchez, 2017). Additionally, antimicrobials can disrupt the flora's metabolic functions with numerous consequences on carbohydrate, volatile fatty acid, and bile acid metabolism (Högenauer et al., 1998; McGorum & Pirie, 2009). Certain antimicrobials, such as macrolides, also have a direct prokinetic effect which may influence faecal consistency (Roussel et al., 2000, 2003).

Different factors such as the antimicrobial's spectrum and the active drug concentration achieved in the hindgut are believed to influence the impact of individual antimicrobials on the enteric microflora (Costa et al., 2015; McGorum & Pirie, 2010). It is, for example, assumed that anaerobic activity is an important feature linked to the development of AAD (Båverud et al., 1997; Gustafsson et al., 2004; McGorum & Pirie, 2010), yet the relative risks of individual antimicrobials to induce AAD in horses have not been evaluated systematically. Moreover, several reports suggest that oral antimicrobial administration might increase the risk of AAD as large amounts of active drug are delivered directly to the intestinal tract (Costa et al., 2015; McGorum & Pirie, 2010; Papich, 2003). However, Gustafsson et al. (1999) found no evident differences in the hindgut flora of horses treated with intravenous versus oral trimethoprim/sulfadiazine and scientific reports comparing the incidence of AAD for others drug delivered orally compared to parenterally are lacking (Table 1).

Overall, the pathophysiology of AAD in horses is still poorly understood. Nevertheless, the risk of AAD and its impact on outcome are an important consideration for clinicians.

Antimicrobials as treatment of a specific aetiology

It is generally accepted that antimicrobials can be used in patients with acute colitis due to a specific bacterial aetiology (Dunkel & Johns, 2015; Papich, 2003; Sanchez, 2017; Shaw & Staempfli, 2018). In practice, however, horses present with similar clinical signs regardless of aetiology. Distinguishing between causes and deciding on the need for antimicrobials can be challenging. Diagnostic testing can assist, but results are often unavailable for 48–72 h (Dunkel & Johns, 2015; Sanchez, 2017), and interpretation sometimes challenging (Sanchez, 2017). However, for certain aetiologies, fast initiation of treatment is important to improve outcome (Bertin et al., 2013).

Clostridiosis

Clostridium difficile

C. difficile associated disease (CDAD) is believed to be the most important infectious cause of antibiotic-induced diarrhoea in humans (Cho et al., 2020) and horses (Diab et al., 2013; Sanchez, 2017). Risk factors for CDAD development in adult horses are diet changes, hospitalisation (nosocomial infection), colic and/or antimicrobial treatment (Båverud et al., 1997, 1998, 2003; Diab et al., 2013; Gustafsson et al., 2004; Madewell et al., 1995, Sanchez, 2017; Schoster et al., 2019). CDAD has been associated with several antimicrobials including beta-lactams, tetracyclines, gentamicin, trimethoprim sulfonamides, macrolides, and rifampicin (Båverud et al., 1997, 1998, 2003; Diab et al., 2013; Madewell et al., 1995; Papich, 2003; Shaw & Staempfli, 2018). Occasionally, CDAD occurs without a history of antimicrobial treatment or hospitalisation (Båverud et al., 2003). A smaller retrospective study found that antimicrobial treatment preceded CDAD only in 26% of horses and no difference in incidence of antimicrobial therapy between CDAD and non-CDAD groups (Weese et al., 2006). Unlike in human medicine, testing for *C. difficile* is therefore still strongly recommended in horses with non-AAD (Weese et al., 2006). It is generally accepted that confirmation of CDAD requires faecal detection of toxin A and B (by cell cytotoxicity assay or ELISA) or toxin A/B genes (by PRC) (Sanchez, 2017; Shaw & Staempfli, 2018). Although it is common for CDAD to develop as a sequel of antimicrobial administration, some antimicrobial agents have paradoxically been found to be useful as treatment. As *C. difficile* remains intra-luminal (Koenigsknecht et al., 2015), antimicrobials should exert their effect in the intestinal lumen.

Metronidazole

Metronidazole has a narrow antibacterial spectrum against protozoa and anaerobic bacteria (Baggot et al., 1988; Davis, 2017; Papich, 2003).

Metronidazole can induce ADD (Båverud et al., 1997; Weese et al., 2006) but has historically been associated with a low incidence of AAD in adult horses (McGorum & Pirie, 2009; Sweeney et al., 1991). Nevertheless, a recent study characterised changes in caecal and faecal microbiome in healthy caecal canulated horses treated with metronidazole (Arnold et al., 2020). It showed decreases in diversity and altered bacterial composition in caecal and faecal samples and concluded that metronidazole administration could be a risk factor for diarrhoea (Arnold et al., 2020).

Intravenous formulations of metronidazole are costly and rarely used for adult horses (Davis, 2017). Absorption is good after oral administration (bioavailability 75%–85%; Steinman et al., 2000; Sweeney et al., 1986), but lower after rectal administration (bioavailability 30%–40%; Garber et al., 1993; Steinman et al., 2000). However, its intraluminal distribution and therefore its effects against *C. difficile* are unclear. In humans without gastrointestinal inflammation, metronidazole is absorbed from the proximal small intestine and does not reach high levels in the remaining part of the intestinal tract (Bolton & Culshaw, 1986). Therefore, potentially subinhibitory concentrations are reached in the large intestine (Bolton & Culshaw, 1986; Weese et al., 2006). This is suggested to explain its low incidence of AAD in horses (McGorum & Pirie, 2010), but also its reported occasional lack of efficacy in human CDAD (Musher et al., 2005). It is also unclear if following rectal administration adequate luminal concentrations are reached in the colon and caecum. Moreover, there is a lack of information on how intestinal inflammation and diarrhoea affect its bioavailability through changes in ionisation grade; intestinal acidosis could potentially capture metronidazole in the intestinal lumen. Perhaps, this contributes to higher intraluminal concentration in the large intestine and enhanced efficacy against CDAD in cases with intestinal acidosis. There is a disparity between clinical results and evidence of antimicrobial resistance in vitro, possibly because antimicrobial concentrations used for in vitro susceptibility (based on plasma drug concentrations) are not reflecting concentrations achieved in the intestinal lumen (Jang et al., 1997; Magdesian et al., 2006).

Despite the possible side effects and the doubts on distribution, metronidazole is reported as an effective first-line treatment of CDAD in horses (Papich, 2003; Shaw, 2018; Weese et al., 2001). However, strong evidence based on randomised controlled trials or metanalyses is currently lacking. Despite the improved outcome in horses with confirmed CDAD treated with metronidazole reported in one study (Wees et al., 2006) and the generally good sensitivity of *C. difficile* strains to metronidazole (Båverud et al., 2003; Thean et al., 2011; Weese et al., 2001), some doubts remain on the clinical benefits of metronidazole treatment for CDAD. *Metronidazole resistance* has namely been reported in 18% (Magdesian et al., 2006) to 19% (Jang et al., 1992) of equine isolates. Metronidazole treatment also predisposed to colonisation with resistant strains; a horse infected with a metronidazole resistant strain was 10 times more likely to have been treated with metronidazole prior to the onset of diarrhoea compared with horses infected with non-resistant strains (Magdesian et al., 2006). More importantly, horses infected with metronidazole-resistant strains had more severe clinical disease with more significant SIRS, higher mortality rate and longer hospitalisation. Beyond its antimicrobial properties, metronidazole has been suggested to reduce intestinal inflammation (Bjarnason et al., 1992).

Vancomycin

In humans with CDAD, metronidazole is recommended for mild to moderate disease and vancomycin for severe disease or metronidazole-resistant infection (Cho et al., 2020). Vancomycin has a poor tissue distribution and tends to stay within the gastrointestinal tract when given orally (Wijesekara et al., 2017). Little information is available on the use of vancomycin in horses (Wijesekara et al., 2017). Two equine studies showed that all equine isolates of *C. difficile* showed excellent susceptibility (Båverud et al., 2003; Weese et al., 2001), including metronidazole-resistant strains (Jang et al., 1997; Magdesian et al., 2006). However, as vancomycin is a highly critical antimicrobial in humans, its use in horses is inappropriate.

Bacitracin

Bacitracin is rarely used in veterinary medicine. It is active primarily against Gram-positive bacteria and it is not absorbed from the intestine (Papich, 2003). Despite previous reported efficacy for equine colitis (Staempfli et al., 1992), widespread in vitro resistance of *C. difficile* strains to bacitracin is reported (Båverud et al., 2003; Jang et al., 1997; Weese et al., 2001). Similar as for metronidazole, it is possible that susceptibility to bacitracin is underestimated as it reaches high intestinal concentrations.

Other antimicrobials for CDAD

Antimicrobial susceptibility studies on *C. difficile* isolates from hospitalised horses show high resistance to gentamicin, ceftiofur (Rodrigez et al., 2014), cefotaxime and trimethoprim-sulfonamides (Weese et al., 2001).

In human medicine, there are concerns regarding hypervirulent strains of *C. difficile* (called PCR ribotype 027 in Europe and NAP1 in the US) that are associated with high morbidity and mortality (Riley, 2006). Once exposed to fluoroquinolones, rapid genetic mutations cause these strains to develop resistance against this group of antimicrobials. Little information is available on the prevalence of these hypervirulent strains in horses; however, Thean et al. (2011) reported two isolates from horses with diarrhoea in Australia to be resistant to moxifloxacin.

Conclusion CDAD:

- Metronidazole can be used as treatment of equine CDAD; however, clinicians should be aware of the lack of strong evidence of its clinical benefits, the uncertainty around drug distribution and the possibility of adverse effects. If elected to use metronidazole, antimicrobial susceptibility testing is warranted as resistant strains occur.

TABLE 1 Antimicrobials previously suggested for acute diarrhoea in adult horses and the current recommendation around their use

Drug	WHO classification	AMEG classification	Restriction for use in veterinary medicine	Recommended dose
Metronidazole	Important	D	Avoid unnecessary use and unnecessarily long treatments	15–25 mg/kg bwt q6–8h 30–50 mg/kg bwt q6–8h
Vancomycin	Highest priority critical important	A	Use restricted to human use	5–10 mg/kg bwt q12h, or 125 mg per horse q6H
Bacitracin	Important	D	Avoid unnecessary use and unnecessarily long treatments	25–50 gram q12h
Fluoroquinolones	Highest priority critical important	B	Only used when no alternative effective antimicrobials in a lower category, and based on antimicrobial susceptibility testing	Enrofloxacin:5 mg/kg bwt q24h
TMS	Important	D	Avoid unnecessary use and unnecessarily long treatments	15–30 mg/kg bwt q12h
Cephalosporins (3rd and 4th generation, such as ceftiofur)	Highest priority critical important antimicrobials	B	Only used when no alternative effective antimicrobials in a lower category, and based on antimicrobial susceptibility testing	Ceftiofur: 2.2 mg/kg bwt q24h
Aminoglycosides	Critically important antimicrobials	C	Only when no effective Category D available	Gentamicin: 6.6 mg/kg bwt q24h
Tetracyclines	Important	D	Avoid unnecessary use and unnecessarily long treatments	6.6 mg/kg bwt (range 5–15 mg/kg bwt) q12–24h

Abbreviations: AAD, antimicrobial associated diarrhoea; CDAD, clostridium difficile associated disease; IM, intramuscular; IV, intravenous; PO, per os.

- Other antimicrobials (including vancomycin and bacitracin) are inappropriate.

Clostridium perfringens

C. perfringens type A is considered part of the normal flora (Tilotson et al., 2002), but it is also the most cultured isolate from adult horses with diarrhoea (Gohari et al., 2014). Currently, it is poorly understood how it causes disease, study results regarding the role of enterotoxin, beta2 toxin and NetF toxin are conflicting, and therefore an important need to define criteria to establish a diagnosis of *C. perfringens* exists (Donaldson & Palmer, 1999; Gohari et al., 2014, 2020; Herholz et al., 1999; Prescott, 2020; Weese et al., 2001).

Antimicrobial considerations for *C. perfringens* colitis are similar as to *C. difficile*, yet because of the poor understanding of its role in acute colitis, and lack of evidence of clinical benefits of antimicrobial treatments, recommendations are even less well established than for *C. difficile*. Aminoglycosides have been suggested to induce beta2 toxin production in equine strains (Herholz et al., 1999; Vilei et al., 2005). In one study, removing gentamicin from the standard post-laparotomy treatment decreased the incidence and mortality of postoperative typhlocolitis in an equine referral hospital (Vilei et al., 2005).

Conclusion C. perfringens

Because of poor understanding of the role of *C. perfringens* and its different toxins in acute colitis, the author scan currently not give clear recommendations regarding antimicrobial treatment.

Equine Neorickettsiosis (Potomac Horse fever)

Equine Neorickettsiosis (EN) is a form of acute enterocolitis in horses caused by the Gram-negative, obligate, intracellular, bacterial organism *Neorickettsia risticii* (Bertin et al., 2013; Sanchez, 2017). It is mostly recognised in the United States and South America, yet some cases have been reported in Europe. In the host, *N. risticii* infects macrophages and peripheral blood monocytes, colonises intestinal epithelial cells and mainly resides intracellularly. Clinical signs of acute enterocolitis have a high predictive value in summer months

Administration route	Spectrum of activity	Distribution	Side effects	For which type of diarrhoea advised
PO rectal	Protozoa and anaerobic bacteria	Low	Rare, dislike bitter taste, anorexia, AAD	CDAD; no additional value against *N. ristici* in combination with oxytetracycline
PO	Gram-positive bacteria, incl clostridium	Low, remains in intestinal lumen	Ototoxic, nephrotoxic	Found inappropriate for CDAD
PO (zinc bac - premix feed additive)	Gram-positive bacteria			Found inappropriate for CDAD due to high levels of resistance
IV	Broad-spectrum, excellent against Gram-negatives (like *Salmonella*), minimal against streptococci and anaerobic bacteria	High, intracellular	Drive the development of hypervirulent strains of *C. difficile*; arthropathy in young animals; variable AAD risk	Severe adult Salmonellosis or extra-intestinal Salmonellosis; NOT for not-severe Salmonellosis
PO or IV	Broad-spectrum; high resistance *C. difficile*	Low, poor intracellular	AAD	Bacteraemia
IV or IM	High resistance *C. difficile*	Low, poor intracellular	CDAD or AAD; emergence of multidrug resistant *Salmonella* spp	Young horse Salmonellosis (alone or in combination with aminoglycoside), but efficacy questioned and found inappropriate
IV	Gram negative; limited efficacy against anaerobics, high resistance C. difficile	Low, poor intracellular	Variable risk of AAD; might promote beta2 toxin production by *Clostridium perfringens*	Young horse Salmonellosis in combination with cephalosporins, but efficacy questioned and found inappropriate; bacteraemia
IV	Broad spectrum, incl *N. risticii*	High, intracellular	Nephrotoxic, AAD	EN; bacteraemia

in endemic areas (Sanchez, 2017). Diagnosis is usually established by PCR from whole blood or faeces (Bertin et al., 2013; Sanchez, 2017).

Tetracyclines have good intracellular penetration (Davis, 2017), making them the drug of choice for EN (Bertin et al., 2013; Davis, 2017; Papich, 2003; Shaw & Staempfli, 2018). Rapid initiation of oxytetracycline treatment of affected horses is associated with *survival* (Bertin et al., 2013). Adding metronidazole to oxytetracycline does not improve the outcome (Bertin et al., 2013). Bertin et al. (2013) recommend a treatment duration of 5 days. The authors have not found any reports regarding tetracycline resistance in *N. risticii* isolates. Tetracyclines are potentially nephrotoxic, so fluid resuscitation in hypovolemic and/or dehydrated horses before or in conjunction with tetracycline treatment is critical (Davis, 2017; Shaw & Staempfli, 2018). They can also induce *AAD* (Andersson et al., 1971; Diab et al., 2013; Papich, 2003; Shaw & Staempfli, 2018).

Conclusion EN

Oxytetracycline is the treatment of choice for EN. In endemic areas during summer months, antimicrobial treatment should be considered even before a definitive diagnosis is reached.

Salmonella

Salmonellosis is an important cause of infectious colitis (Ernst et al., 2004; Hird et al., 1986; House et al., 1999; Kim et al., 2001; Sanchez, 2017; Smith, 1981). *Salmonella enterica* is a species of Gram-negative, facultative anaerobic bacteria.

Carrier horses can serve as environmental reservoirs and a potential source of infection to susceptible horses (Sanchez, 2017). Several environmental and host factors, such as transport, hospitalisation, antimicrobial treatment, general anaesthesia, and surgery have been associated with faecal shedding of *Salmonella* and with clinical *Salmonellosis* (Ernst et al., 2004; Hird et al., 1986; House et al., 1999; Kim et al., 2001; Sanchez, 2017). After oral ingestion, the organism attaches to and invades caecal and colonic epithelial cells, and an intracellular infection establishes (Foley & Linne, 2008). Clinical signs of *Salmonella* infection in adult horses range from depression, fever, and anorexia without diarrhoea to severe, profuse diarrhoea (Sanchez, 2017; Shaw & Staempfli, 2018). In neonatal foals *Salmonella* can cause severe sepsis, yet this is uncommon in adult horses (Sanchez, 2017; Shaw & Staempfli, 2018). Profound

neutropenia is usually present in horses with Salmonellosis (Dallap Shaer et al., 2012; Manship et al., 2019; Shaw & Staempfli, 2018). Manship et al. (2019) showed that horses with Salmonella were more likely to be leukopenic compared with horses with an unknown diagnosis when investigating horses presented with fever and colic. Yet the same study showed no difference in haematologic abnormalities when comparing horses diagnosed with equine coronavirus to those that had Salmonella. Diagnosis is made by collecting between 3 and 5 serial faecal samples for faecal culture or PCR (Sanchez, 2017; Shaw & Staempfli, 2018).

Several sources recommend that antimicrobial therapy should be considered in patients with Salmonella enterocolitis, especially those with severe leukopenia/SIRS or with extraintestinal Salmonella infections (Papich, 2003; Sanchez, 2017; Shaw & Staempfli, 2018), yet evidence supporting these recommendations is lacking. When choosing to treat Salmonellosis with antimicrobials, it is important to consider the aim of the treatment; (1) killing intracellular intestinal Salmonella bacteria, (2) killing bacteria circulating in the blood stream after translocation (bacteraemia; this can be Salmonella but also other translocating bacteria), (3) killing bacteria in extra-intestinal Salmonella lesions. Little is known regarding the incidence of bacteraemia in adult horse with colitis; Johns et al.(2009) showed that 29% had a positive blood culture within 24 h of admission. Additionally, it is often unknown which bacteria are circulating following translocation over intestinal lesions. Therefore, it is the authors opinion that if one would choose to treat because of a suspicion of bacteraemia, a first-line, non-critical, broad-spectrum antimicrobial is most likely the best option, for example tetracyclines, trimethoprim-sulphonamides, or the combination of penicillin-gentamicin. This topic will be further discussed in the next paragraph.

If one would choose to use antimicrobials against intracellular intestinal or extra-intestinal Salmonella, an antimicrobial with intracellular penetration is required. Commonly proposed antimicrobials are fluoroquinolones, 3rd generation cephalosporines and aminoglycosides (Dunkel & Johns, 2015; Papich, 2003; Sanchez, 2017; Shaw & Staempfli, 2018). Fluoroquinolones are mentioned to be the drug of choice in adult horses, while an extended spectrum cephalosporin, alone or in combination with an aminoglycoside, in young horses (Dunkel & Johns, 2015; Papich, 2003; Sanchez, 2017; Shaw & Staempfli, 2018).

Fluoroquinolones have a relatively broad spectrum, with excellent activity against Gram-negative organisms (like *Salmonella)* but minimal activity against Streptococci and anaerobic bacteria (Davis, 2017). Fluoroquinolones are concentration-dependent bactericidal and highly lipid soluble (Davis, 2017), leading to excellent intracellular penetration. Resistance of Salmonella strains against fluoroquinolones has been described in equine samples (Leon et al., 2018). They have a negative effect on cartilage metabolism reported in young animals (Davis, 2017). There are few reports documenting diarrhoea associated with enrofloxacin administration; however, one recent study showed the prevalence of AAD with enrofloxacin to be as high as 5.4% (Barr et al., 2013).

Third- and fourth-generation cephalosporines are broad-spectrum antimicrobials. Some considerations regarding the use of cephalosporines for treating Salmonella enterocolitis should, however, be made. Cephalosporines have a low volume of distribution and weak acid characteristics (implicating the drug is highly ionised in plasma) leading to poor intracellular penetration (Davis, 2017). This makes it unlikely that they reach intracellular Salmonella. Additionally, their broad-spectrum antibacterial activity may cause overgrowth or superinfection by inherently resistant bacteria, including *Clostridium difficile*, which benefits from the reduced colonisation resistance from the normal microbial flora. This can lead to *CDAD or AAD* (Båverud et al., 1997, 1998, 2003; Diab et al., 2013; Madewell et al., 1995; Papich, 2003; Shaw & Staempfli, 2018).

Aminoglycosides (including gentamicin) have a broad antimicrobial spectrum (Davis, 2017; Papich, 2003; Shaw & Staempfli, 2018). Gentamicin is a large, hydrophilic molecule, is highly ionised in plasma, has a low volume of distribution and hence poor intracellular penetration (Davis, 2017). Therefore, similar as to cephalosporins, gentamicinis not a suitable choice to treat intestinal Salmonellosis. Regarding the risk of gentamicin to induce AAD, results are conflicting. Madewell et al. (1995) reported that hospitalised horses developed CDAD most commonly while receiving gentamicin treatment, while in a recent study, gentamicin monotherapy resulted in diarrhoea in only two horses (Barr et al., 2013). On the other hand, gentamicin can promote beta2 toxin production by *Clostridium perfringens* (Herholz et al., 1999; Vilei et al., 2005), thereby increasing the clinical severity of colitis.

Using antimicrobials to treat intestinal Salmonellosis in horses remains highly controversial. Currently, no controlled clinical studies have been performed demonstrating the benefit of antimicrobial treatment in equine Salmonellosis in terms of *clinical severity and duration of shedding* (Dunkel & Johns, 2015). On the contrary, in experimentally infected ponies, oxytetracycline therapy prolonged shedding of Salmonella (Owen et al., 1983). As comparison, in children and adults with non-severe *Salmonella* gastroenteritis, a meta-analysis demonstrated no evidence of clinical benefit of antimicrobial therapy (Onwuezobe et al., 2012). Antimicrobial treatment might, however, be indicated in severely ill horses, as often suggested in the literature. The main aim to treat these critically ill cases is mostly treating bacteraemia rather than intestinal lesions. However, in high-risk human patients with enteric Salmonellosis, there is no consensus on antimicrobial treatment with the aim of preventing bacteraemia and extraintestinal infections (Gordon, 2008; Sanchez-Vargas et al., 2011).

Besides whether antimicrobial treatment has positive effects on the affected horse, the clinician also needs to consider potential drug hazards. Antimicrobial treatment could further alternate the already compromised normal gastrointestinal flora, which is considered an important line of defence against colonisation by Salmonella. As a matter of fact, an *association between antimicrobial drug treatment and Salmonellosis* infection in hospitalised horses has been reported in different studies (Ernst et al., 2004; Hird et al., 1986; House et al.,

1999; Kim et al., 2001; Sanchez, 2017). Secondly, the emergence of *multidrug-resistant Salmonella* isolates is concerning with regards to nosocomial and zoonotic infections (Bustos et al., 2021; Dor et al., 2020; Leon et al., 2018). Based on this lack of evidence on positive effects, but clear risks for negative effects, one could conclude that there is currently no scientific data supporting the routine use of antimicrobials in adult horses with Salmonellosis. Finally, the typically recommended antimicrobials for Salmonellosis, fluoroquinolones, and 3rd-generation cephalosporines, are critical human antimicrobials, and clinicians should restrict their use to cases where the efficacy has been demonstrated.

Conclusion Salmonellosis

Antimicrobials should be used with great caution in equine patients with Salmonellosis. The routine administration of antimicrobials in adult horses with Salmonellosis is not indicated. First-line, broad-spectrum antimicrobials could potentially be considered to treat bacteraemia. Enrofloxacin can be considered to treat extra-intestinal Salmonellosis or severe cases of intestinal Salmonellosis, however, only after confirmation of Salmonella and antimicrobial efficacy. It is the authors' opinion, there is no logic rationale to use third generation cephalosporines and/or aminoglycosides in the treatment of intracellular intestinal Salmonellosis.

Antimicrobials for undifferentiated diarrhoea: treatment of bacteraemia

In horses with enterocolitis, it is assumed that antimicrobial treatment may lessen the risk of dissemination and severity of disease (Sanchez, 2017). Fatality rates increase in horses with SIRS, with a left shift leukogram (Sanchez, 2017) and with a positive blood culture (Johns et al., 2009). Therefore, antimicrobial treatment is often considered in horses with acute diarrhoea demonstrating severe leukopenia or neutropenia and/or evidence of septic foci (such as pneumonia or thrombophlebitis) or bacteraemia (Sanchez, 2017; Shaw & Staempfli, 2018). Horses with acute diarrhoea due to enteric coronavirus do not require antimicrobials to treat the viral aetiology; however, it has been suggested that severely affected horses might require antimicrobials to treat bacteraemia (Pusterla et al., 2018).

During enterocolitis, severe mucosal injury can lead to breach of the mucosal barrier and subsequently bacterial translocation, bacteraemia, and SIRS (Sanchez, 2017). Even though different bacteria can reach the blood stream, *E. coli* is often assumed to be the most likely cause of sepsis secondary to mucosal barrier injury in horses (Papich, 2003). However, there is no scientific evidence to support this. In a prospective study in the United States, 9/31 of adult horses with acute enterocolitis had a positive blood culture within 24 h of admission (Johns et al., 2009). The following organisms were isolated: *Corynebacterium* spp ($n = 6$), *Streptococus* spp ($n = 2$), *Pantoea agglomerans* ($n = 1$), Gram-negative rod ($n = 1$), *Bacillus* spp ($n = 1$) and yeast ($n = 1$). The frequent culture of *Corynebacterium* spp was believed to be clinically relevant and no contaminant, since horses with *Corynebacterium* spp were 25.3 times less likely to survive compared with a 6.3 increased likelihood of non-survival with other isolates. It is not known if similar bacteria would be found in other clinics, or in other geographic areas. Horses with a positive blood culture were clinically more severely affected and were less likely to survive compared to those with a negative blood culture. As not all blood culture positive horses met the criteria for SIRS in this study, it remained unclear why bacteraemia contributed to increased mortality. Bacteria circulating in the blood stream can namely be acting as markers of disease severity and mucosal injury or can act as true pathogens and cause sepsis. Although the study (Johns et al., 2009) did not assess the effect of antimicrobial therapy on outcome, it did conclude that prior antimicrobial therapy (before hospitalisation) had no significant effect on blood culture status. Therefore, one can argue that antimicrobial administration may not prevent bacteraemia.

As far as the authors are aware, no literature exists investigating a *link between antimicrobial treatment and positive outcome* in equine patients with undifferentiated colitis. Even so, studies exploring detrimental outcomes for those not treated with antimicrobials are lacking. Nevertheless, if one would choose to administer antimicrobial treatment in an adult horse with undifferentiated diarrhoea with the purpose of decreasing the risk of bacteraemia but in absence of blood culture results, it is the authors' opinion that a first line, non-critical broad-spectrum antimicrobial that can be administered intravenously (or reaches rapidly high plasma levels following IM or PO administration) should be selected. A high volume of distribution and intracellular distribution are not required. Suggestions could for example be a penicillin/aminoglycoside combination, tetracyclines or trimethoprim sulphonamides. If results of the above study from Johns et al. (2009) can be extrapolated to other settings, a good activity against *Corynebacterium* spp. could be beneficial. Antimicrobial choice can be adapted to blood culture results when they become available. Clinicians should be aware that all the mentioned antibiotics have a possible risk of inducing AAD (Andersson et al., 1971; Barr et al., 2013; Båverud et al., 1997; Diab, 2013; McGorum & Pirie, 2010; Papich, 2003; Shaw & Staempfli, 2018; Wilson et al.1996).

Conclusion Bacteraemia

Bacteraemia can occur in mature horses with enterocolitis but there is lack of evidence on positive and negative effects of antimicrobial treatment of horses with bacteraemia. A first line, non-critical broad-spectrum antimicrobial could be considered, but the authors believe that many horses can be managed without antimicrobials.

Antimicrobials and other treatments: How are they influencing one another?

Clinicians often use a broad range of treatments for adult horses with colitis. It is very common for horses to receive different

products orally like probiotics/prebiotics, DTO smectite, psyllium, sucralfate, and activated charcoal (Sanchez, 2017; Shaw & Staempfli, 2018). Oral antimicrobial treatment (such as metronidazole) can be affected by other oral treatments and vice versa. In vitro DTO smectite had no effect on the action of metronidazole (Weese et al., 2003), but no information is available on how other oral treatments could affect metronidazole's absorption and efficacy, potentially leading to suboptimal dosing and possibly resistance development. Oral antimicrobials could affect survival of probiotics and their success of colonising the gut. No clear data is available, however, spacing all oral treatments as much as possible might help to optimise the therapeutic plan.

Faecal microbial transplantation (FMT) has re-emerged as a treatment for human *Clostridium difficile* (Cammarota et al., 2014) and for equine acute colitis (McKinney et al., 2020; Mullen et al., 2018). In humans with CDAD, FMT is often combined with either metronidazole or vancomycin (Cammarota et al., 2014; Cho et al., 2020). Also, in equine practice, FMT is often combined with antimicrobial treatment. Even though negative effects on the transplant can be expected, no data are currently available in horses. Yet in a recent human study, antimicrobial pre-treatment significantly reduced bacterial engraftment after FMT in patients with irritable bowel syndrome (Singh et al., 2022).

Conclusion

The broad range of oral medications, including (oral) antimicrobials, might influence each other, often in a negative way. Spacing the different drugs as much as possible is recommended.

OVERALL CONCLUSION

The different causes of acute diarrhoea in horses require slightly different therapeutic approaches, yet clinically cannot be distinguished from each other. Treating acute diarrhoea with antimicrobials is a risk to further destabilise the intestinal flora and induce AAD. In addition, high resistance to cephalosporines and gentamicin in *C. difficile* isolates, emergence of hypervirulent *C. difficile* strains caused by fluoroquinolones and aminoglycosides driven production of *C. perfringens* beta2 toxin are reported. These negative effects should be carefully balanced against any potential positive effects of antimicrobial treatment. For most scenarios, the literature shows no or very limited convincing evidence on those positive clinical effects.

In summary, the following recommendations for antimicrobial treatment in horses with acute diarrhoea can be made:

- Viral colitis (coronavirus) does not require antimicrobial treatment.
- During summer months in EN endemic areas, it is indicated to start treatment with oxytetracycline in cases with signs compatible to EN even before laboratory confirmation.
- Metronidazole can be used to treat CDAD, but strong evidence is lacking. This could be extended to all horses with AAD as AAD is commonly CDAD. AAD can also be caused by *Salmonella* or unspecific dysbacteriosis, and in that case, metronidazole could, however, contribute to further destabilisation of the flora.
- For Salmonellosis in adult horses the routine administration of antimicrobials is NOT indicated. Fluoroquinolones can be considered to treat extra-intestinal Salmonellosis or severe cases of intestinal Salmonellosis, however, considering the criticality of this antimicrobial, only after confirmation of the causative agent and antimicrobial susceptibility testing.
- Bacteraemia can occur in mature horses with enterocolitis of any cause, for which treatment without antimicrobials or a first line, non-critical broad-spectrum antimicrobial could be considered.

AUTHOR CONTRIBUTIONS

Both authors contributed to all aspects of this review article.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

ETHICS STATEMENT

Not applicable to this review article.

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