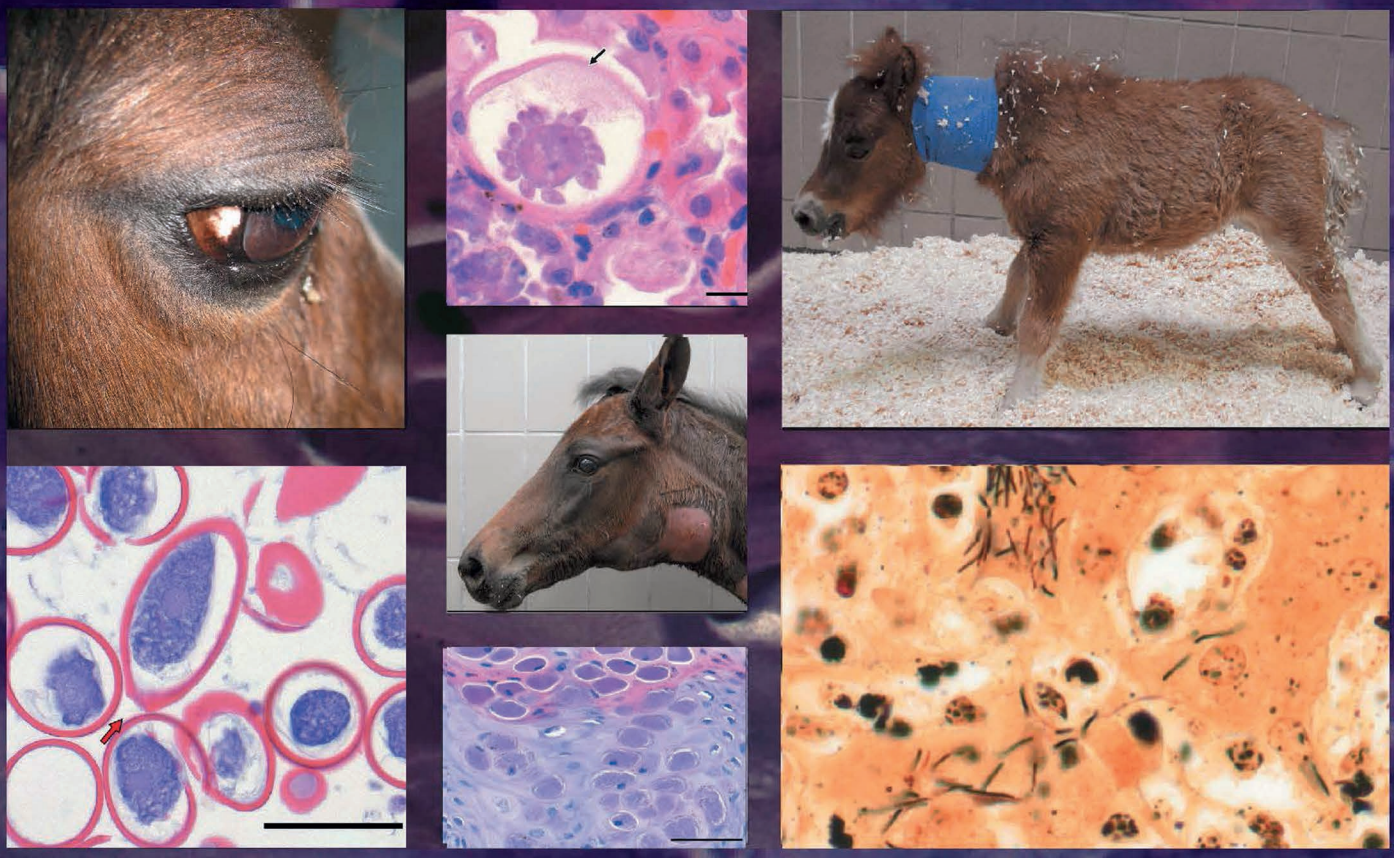
INFECTIOUS DISEASES OF THE HORSE

Diagnosis, Pathology, Management, and Public Health

SECOND EDITION



J.H. VAN DER KOLK
E.J.B. VELDHUIS KROEZE

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Infectious Diseases of the Horse

A clinician and a pathologist collaborate to create a comprehensive yet practical book about established infectious diseases of horses, categorised according to different pathogens. The book evaluates the latest diagnostic aids, including rapid developments in molecular biology, while emphasising that they are no substitute for clinical observation and skills. The majority of equine infectious diseases caused by microbes and parasites are covered—bacterial, viral, protozoan, fungal, ectoparasitic, and helminthic. Practical appendices contain a list of differential diagnoses based on clinical signs to support clinical decision-making, a list of zoonoses and reportable diseases, and an elaborate illustrated appendix on clinical pathology and haematology.

Thoroughly updated a decade after the release of the original text, the book continues to be concise and easy to understand and remains an important resource for uncommon conditions. It adds new sections on pythiosis, equine encephalosis/Peruvian horse sickness virus, *Acinetobacter baumanii*, enteric coronavirus-induced disease, and viral hepatitis, as well as updated nomenclature according to the latest reference databases. The most dynamic changes in veterinary medicine concern the development of new molecular diagnostic techniques and therapies, and these have been updated with most recent references throughout this second edition. Finally, the exceptional, full-colour clinical and microscopic images are showcased in a larger format.

Infectious Diseases of the Horse is a valuable resource for all veterinary practitioners, scientists, pathologists, students, technicians, and nurses working with horses.

PRAISE FOR THE BOOK

"I love this book! It is clear and concise, and very easy to understand. The simple format allows easy access to each disease, and the images are brilliant, and gory, and delightful! My personal favourite section is the Appendices: I love the differential diagnosis segment, allowing an easy reference for both students and clinicians without having to go through every disease to find a certain set of clinical signs. This book is brilliant for students, especially those in their clinical years or revising for their final examinations. It also encourages lateral thinking, due to the use of differential diagnoses showing other things that could be represented".

—**Sophie Neasham,** fourth-year veterinary student, University of Veterinary Medicine and Pharmacy in Kosice, Slovakia

PRAISE FOR THE FIRST EDITION

"This is an excellent review of infectious diseases in horses which occur worldwide. . . . The colour plates are stunning and really add to the text. . . . The chapters are very easy to follow so that this makes an ideal reference book for veterinary practitioners as well as veterinary students. . . . It is a must for all equine practice libraries and it is extremely well referenced so it will be well used in veterinary college libraries. . . . I strongly recommend its purchase".

—**Graham Duncanson,** in *Veterinary Practice*

"A useful overview . . . often well illustrated with colour photographs, and these photographs are a real strength of the book".

—**Robert M. Christley,** in *Veterinary Record*

"The first thing that strikes you as you browse through this book are the amazing colour plates of clinical disease . . . extremely useful to the equine clinician, but would also be of great interest as a reference for students, as well as interns and residents in equine medicine and pathology. It is a great source of information, with the same depth of knowledge for each disease and all conveniently located for the user".

—**L. Begg,** in *Australian Veterinary Journal*

INFECTIOUS DISEASES *of the* HORSE

Diagnosis, Pathology, Management, and Public Health

Second Edition

J. H. van der Kolk
DVM, PhD, dipl ECEIM
Vetsuisse Faculty
Department of Clinical Veterinary Medicine
Swiss Institute for Equine Medicine (ISME)
University of Bern
Bern, Switzerland

E. J. B. Veldhuis Kroeze
DVM, PhD, dipl ECVP
Department of Viroscience
Erasmus University Medical Center
Rotterdam, the Netherlands

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AUTHOR BIOGRAPHIES

J.H. van der Kolk graduated in Veterinary Medicine at the State University of Utrecht, the Netherlands, in 1987. Since then, he has been a member of the staff of the Faculty of Veterinary Medicine, Utrecht University. He was appointed Associate Professor in Equine Internal Medicine in 2005, with endocrinology and metabolism as areas of research. Since 2012, he has served as Head of the section Equine Metabolic and Genetic Diseases of Euregio Laboratory Services, Maastricht, the Netherlands, and was appointed director of Euregio Laboratory Services in 2015, aimed at veterinary business development. Since 2014, he has been assigned as a part-time staff member of the University of Bern, Switzerland, regarding equine research, with endocrinology and metabolism as focus areas. He was acknowledged Diplomate in Equine Internal Medicine of the European College of Equine Internal Medicine in 2003. He has also been Editor-in-Chief of the *Veterinary Quarterly* (2021 Impact Factor 8.071) since 2011. His more than 140 peer-reviewed manuscripts have been published in scientific journals, including *Am J Vet Res*, *J Am Vet Med Assoc*, *Mol Gen Metab*, *Neuromuscular Dis*, *J Appl Physiol*, and *Am J Physiol—Reg Integr Comp Physiol*.

E.J.B. Veldhuis Kroeze graduated in Veterinary Medicine at the State University of Utrecht, the Netherlands, in 2000. After a short period working as Veterinary Surgeon, he began his residency in Veterinary Pathology at the Faculty of Veterinary Medicine, Utrecht University, and passed the board examinations of the European College of Veterinary Pathology (ECVP) in 2008, becoming ECVP Diplomate. During his employment at Utrecht University, he developed profound interest in equine pathology. Since 2009, he has worked as Veterinary Pathologist at Viroclinics Biosciences BV and was engaged in a PhD project at the Erasmus University Medical Center (EMC), Rotterdam, gaining his PhD on the pathogenesis of influenza in 2017. From then on, he has started at IDEXX Laboratories as a diagnostic veterinary pathologist and has been assigned as a part-time researcher at the department of Viroscience EMC, Rotterdam, regarding comparative pathology of viral diseases on the human-animal interface. His more than 40 peer-reviewed manuscripts have been published in scientific journals, including *Lancet Infect Dis*, *Acta Neuropathol Communic, NPJ Vaccines, Vet Rec*, *Front Microbiol*, *Vaccine*, *PLoS Pathog*, *J Gen Virol*, *J Comp Path*, *Equine Vet J*, *Equine Vet Educ*, *J Vet Intern Med*, *Vet Quart*, *Vet J*, *J Vet Diagn Invest*, *Reprod Domest Anim*, and *Theriogenology*.

ABBREVIATIONS

ABLV	Australian bat lyssavirus
ABV	avian bornavirus
ADV	Aujeszky's disease virus
AGID	agar gel immunodiffusion
AHS	African horse sickness
AHSV	African horse sickness virus
AI	antibody index
AIDS	aquired immune deficiency syndrome
AST	aspartate aminotransferase
BAL	bronchoalveolar lavage
BCG	bacillus Calmette-Guérin
BCoV	bovine coronavirus
BDV	Borna disease virus
bid	twice daily
BoNT	botulinum neurotoxin
BPV	bovine papillomavirus
BW	body weight
CA-MRSA	community-associated methicillin-resistant *Staphylococcus aureus*
CDC	complement-dependent cytotoxicity (assay)
CEM	contagious equine metritis
CF	complement fixation
CFT	complement fixation test
CI	confidence interval
CK	creatine kinase
CNF	cytotoxic necrotising factor
CNS	central nervous system
CPXV	cowpox virus
CSF	cerebrospinal fluid
CT	computed tomography
CTA	cell cytotoxicity assay
DDSP	dorsal displacement of the soft palate
dpi	days post-inoculation
EAdV	equine adenovirus
EAV	equine arteritis virus
EBLV-1/2	European bat 1/2 lyssavirus
ECoV	equine coronavirus
EcPV	equine papillomavirus
EDTA	ethylenediaminetetraacetic acid
EE	equine encephalosis
EEV	equine encephalitis virus, equine encephalosis virus
EEEV	Eastern equine encephalitis virus
EGS	equine grass sickness
EHV	equine/equid herpesvirus
EIA	equine infectious anaemia, enzyme immunoassay
EIAV	equine infectious anaemia virus
EIPH	exercise-induced pulmonary haemorrhage
EIV	equine influenza virus
EL	(equine) epizootic lymphangitis
(c)ELISA	(competitive) enzyme-linked immunosorbent assay
EM	electron microscopy
EMCLV	equine molluscum contagiosum-like virus
EMG	electromyography
EPA	epidemic polyarthritis
EPE	equine proliferative enteropathy
epg	eggs per gram (faeces)
EPM	equine protozoal myeloencephalitis
ERAV	equine rhinitis A virus
ERBV	equine rhinitis B virus
ETBF	enterotoxigenic *Bacteroides fragilis*
ExPEC	extraintestinal pathogenic *Escherichia coli*
FAT	fluorescent antibody test
FEI	Fédération Equestre Internationale
FMDV	foot-and-mouth disease virus
γ-GT	γ-glutamyl transferase
GALT	gut-associated lymphoid tissue
GETV	Getah virus
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GLDH	glutamate dehydrogenase
H	haemagglutinin
HA-MRSA	hospital-associated methicillin-resistant *Staphylococcus aureus*
HCF	*Histoplasma capsulatum* var. *farciminosum*
H&E	haematoxylin and eosin
HeV	Hendra virus
HI	haemagglutination inhibition
HIV	human immunodeficiency virus
HJV	Highlands J virus
HPXV	horsepox virus
HYPP	hyperkalaemic periodic paralysis
IAD	inflammatory airway disease
IFA	immunofluorescence assay
IFAT	indirect fluorescent antibody test
IFT	immunofluorescence test
IgG(T)	immunoglobulin G induced by tetanus toxoid
IM	intramuscular
IPMA	immunoperoxidase monolayer assay
IV	intravenous
JEV	Japanese encephalitis virus
KUN	Kunjin virus
LAMP	loop-mediated isothermal amplification
LDH	lactate dehydrogenase
LPS	lipopolysaccharide

LTR	long terminal repeat
MAC	IgM antibody capture
MALDI-TOF MS	matrix-assisted laser desorption/ ionisation time of flight mass spectrometry
MAT	microscopic agglutination test
MERS CoV	Middle East respiratory syndrome-coronavirus
MHV	mouse hepatitis virus
MIC	minimum inhibitory concentration
MLST	multilocus sequence typing
MLV	modified live virus (vaccine)
MOCV	molluscum contagiosum virus
MPXV	monkeypox virus
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MVA	modified vaccinia Ankara
MVE	Murray Valley encephalitis (virus)
N	neuraminidase
NA	North America
nano-ESI-MS	nano-electrospray ionisation mass spectrometry
NASBA	nucleic acid sequence-based amplification
NiV	Nipah virus
NSAID	nonsteroidal anti-inflammatory drug
OPV	orthopoxvirus
OR	odds ratio
PAGE	polyacrylamide gel electrophoresis
PAS	periodic acid-Schiff
PBMCs	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PDD	proventricular dilatation disease
PEP	post-exposure prophylaxis
PFGE	pulsed-field gel electrophoresis
PFU	plaque-forming unit
PHEV	porcine hemagglutinating encephalomyelitis virus
PHSV	Peruvian horse sickness virus
PMT	*Pasteurella multocida* toxin
PO	per os
PPIA	pituitary pars intermedia adenoma
PRNT	plaque reduction neutralisation test
PRV	pseudorabies virus
RABV	rabies lyssavirus
RAO	recurrent airway obstruction
RAPD	random amplified polymorphic DNA
RFLP	restriction fragment length polymorphism
RLB	reverse line blot
RRV	Ross River virus
RT	reverse transcription
SARS	CoV-1/2 severe acute respiratory syndrome-coronavirus-1/2
SC	subcutaneous
SCCmec	staphylococcal cassette chromosome element carrying the *mecA* gene
SCID	severe combined immune deficiency
SDS-PAGE	sodium dodecyl sulphate polyacrylamide gel electrophoresis
SHI	synergistic haemolysis inhibition
sid	once a day
SNT	serum neutralisation test
spa	encoding gene of protein A
SRAP	sequence-related amplified polymorphism
SRH	single radial haemolysis
SSCP	single-strand conformation polymorphism
TB	tuberculosis
TCE	transarterial coil embolisation
TMP/S	trimethoprim-potentiated sulphonamide
TMP/SDZ	trimethoprim/sulphadiazine
USUV	Usutu virus
VACV	vaccinia virus
VEE	Venezuelan equine encephalitis
VEEV	Venezuelan equine encephalitis virus
VN	virus neutralisation
VSIV	vesicular stomatitis Indiana virus
VSNJV	vesicular stomatitis New Jersey virus
VSV	vesicular stomatitis virus
WBC	white blood cell
WEEV	Western equine encephalitis virus
WNV	West Nile virus

INTRODUCTION

As the first edition of this book was published a decade ago in 2013, this second edition was in need of revisions and several updates. However, these changes were made with the same objective in mind, to provide a comprehensive yet practical book about established infectious diseases of horses categorised according to the different pathogens.

This second edition includes five newly added disorders: pythiosis, equine encephalosis/Peruvian horse sickness virus, *Acinetobacter baumanii*, enteric coronavirus-induced disease, and viral hepatitis. These emerging diseases in equine medicine are duly elaborated upon in this second edition. Furthermore, new photographs have been added to the text on Mycobacteriosis and enteric coronavirus-induced disease. In addition, throughout the book the classical veterinary term of "necropsy" to denote a postmortem examination has been replaced by the more widely used and more appropriate (Law *et al*. 2012) term of "autopsy". In a similar fashion, "gross" lesions have been replaced in favour of "macroscopic" lesions. Last but not the least, we have updated nomenclature of diseases and pathogens according to the latest recognised versions from reference databases. For bacteria, the *Bergey's Manual of Systematics of Archaea and Bacteria* was used. For virus classification and nomenclature, the digital database https://talk.ictvonline.org/taxonomy/ issued by the International Committee on Taxonomy of Viruses was consulted (King *et al*. 2018), Kassai 1999 for the classification of the helminths, and www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi proved useful for additional reference.

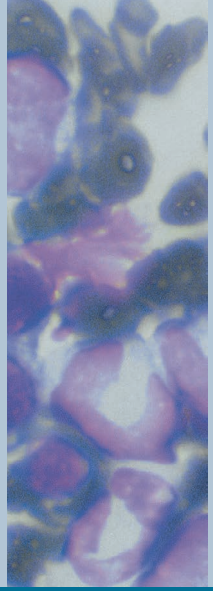
The most dynamic changes in veterinary medicine concern the development of new molecular diagnostic techniques and therapies, and these have been updated with most recent references throughout this second edition. What has not changed is the target audience of our book. It is still intended as reference work for veterinary practitioners, especially the equine clinician, as well as for students, interns, and residents in equine medicine and pathology. The practicality of the book for clinicians remains warranted by means of the included appendices containing a list of differential diagnoses based on clinical signs to support clinical decision-making, as well as a list of zoonoses and reportable diseases, and an elaborate illustrated appendix on clinical pathology and haematology. Equally dynamic is the field of emerging infectious diseases, especially in the human-animal interface. In this field, the important role of the clinical and research veterinarian at the forefront in recognising and diagnosing new emerging infectious diseases must be emphasised. Examples of these are the Hendra virus and the West Nile virus infections, in which veterinarians and veterinary pathologists played a key role in the identification of these new, emerging equine disease outbreaks with zoonotic threat to humans. Nevertheless, it must be emphasised, again, that the mere establishment of a microbe or parasite from a patient cannot be considered adequate evidence that it is the aetiological agent causing the disease (Coles 1986). Therefore, diagnostic aids must be used to supplement, not supplant, clinical observations.

JH van der Kolk
EJB Veldhuis Kroeze

We sincerely acknowledge the contributions of M Aleman, CM Butler, A van Dijk, F Giannitti, GCM Grinwis, E Gruys, M Heinrichs, D Kersten, B Malmhagen, K Matiasek, G Uilenberg (†), E Smiet, E Teske, and VM van der Veen.

DISCLAIMER

The advice and information given in this book are believed to be true and accurate at the time of going to press. However, not all drugs, formulations, and devices are currently available in all countries, and readers are advised to check local availability and prescribing regimens.



Chapter 1

Bacterial Diseases

Anaplasma phagocytophilum: EQUINE ANAPLASMOSIS

Phylum XII Proteobacteria/Class I Alphaproteobacteria/Order II Rickettsiales/Family II Anaplasmataceae/Genus I *Anaplasma*

Definition/Overview

The *Alphaproteobacteria* form one of the most abundant groups of bacteria on Earth. Of note, all mitochondria evolved from bacteria within this group (Muñoz-Gómez *et al*. 2019). Equine anaplasmosis is a noncontagious infectious disease of horses caused by *Anaplasma phagocytophilum* (formerly named *Ehrlichia phagocytophila* and *Ehrlichia equi*), identified as emerging in Europe (Vorou *et al*. 2007).

Aetiology

Equine anaplasmosis is caused by the obligate intracellular bacterium *A. phagocytophilum*. Cross-species differences in pathogenicity and ecologically separate strains within this bacterial species appear to exist (Franzén *et al*. 2005, Foley *et al*. 2009), as two unique genetic variants infecting horses in the Czech Republic were identified (Zeman & Jahn 2009). Although the overall genetic diversity of *A. phagocytophilum* in Europe is higher than in the USA, the strains responsible for the human infections are related on both continents (Matei *et al*. 2019). Having horses inoculated with the human-derived *A. phagocytophilum* agent results in clinical disease largely indistinguishable from equine anaplasmosis (Madigan *et al*. 1995). The mode of transmission is predominantly considered as tick-borne. Ticks of the *Ixodes ricinus* complex also act as vectors in the spread of *Borrelia burgdorferi* and co-infections of *A. phagocytophilum* and *B. burgdorferi* (Chang *et al*. 2000, Magnarelli *et al*. 2000) as well as *Theileria equi* have been confirmed in horses (Dos Santos *et al*. 2019).

Epidemiology

Equine anaplasmosis was first described in the USA in 1969 (Gribble 1969) and has since been reported in other countries, including Switzerland, Sweden, France, Germany, Italy, the UK, the Czech Republic, and the Netherlands (Gerhards *et al*. 1987, Butler *et al*. 2008, Zeman & Jahn 2009). Most infections develop during the late fall, winter, and spring (Madigan & Gribble 1987). *I. ricinus* is one of the vectors of *A. phagocytophilum* in Europe, in which rates of infection range from 1.9 to 34%. In 1997, only 0.4% of equine blood samples examined were found positive for antibodies to *A. phagocytophilum* in the Latium region (Lillini *et al*. 2006). Indirect immunofluorescent assay revealed 23% of healthy horses with previous tick exposure seropositive for *A. phagocytophilum* and 15% seropositive for spotted fever group *Rickettsia* spp. (with *Rickettsia conorii* being the etiologic agent of Mediterranean spotted fever) in Central Italy during the period from 2013 to 2018, whereas 4% for both agents (Ebani 2019). However, the rate of *A. phagocytophilum* antibody prevalence in healthy horses on USA farms enzootic for equine anaplasmosis can be as high as 10% (Madigan *et al*. 1990), whereas 9.8% of horses with fever of unknown origin tested positive for *A. phagocytophilum* in the Netherlands (Butler *et al*. 2008).

Transmission and propagation of *A. phagocytophilum* occur in large mammals, such as horses, cattle, sheep, goats, dogs, and cats. Small mammals and not ticks are the reservoirs of anaplasmosis (Lillini *et al*. 2006, Matei *et al*. 2019). Roe deer are the main reservoir for *A. phagocytophilum* in Central Europe and Scandinavia, with a high seroprevalence of about 95% and a variable rate of polymerase chain reaction (PCR)–proven infection ranging from 12.5% in the Czech Republic to 85.6% in Slovenia (Skarphedinsson *et al*. 2005).

The role of migrating birds in long-range tick transfer may be important, since the same *A. phagocytophilum* gene sequences were detected in infected ticks on migrating birds and in humans and domestic animals in Sweden (Bjoersdorff *et al*. 2001).

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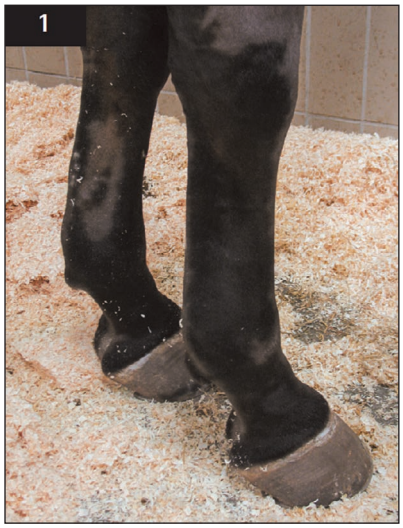
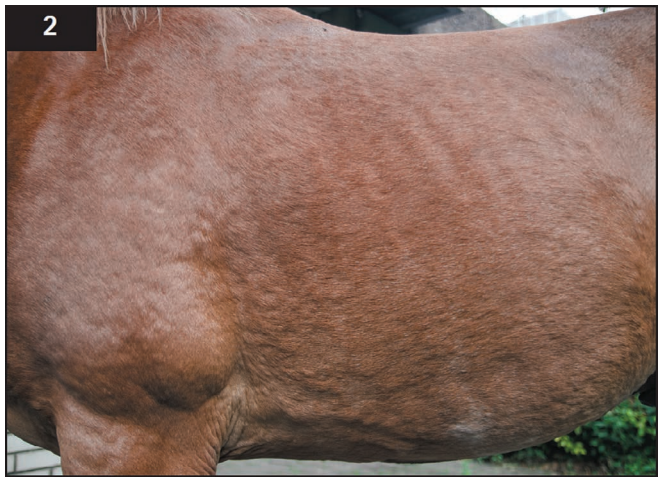
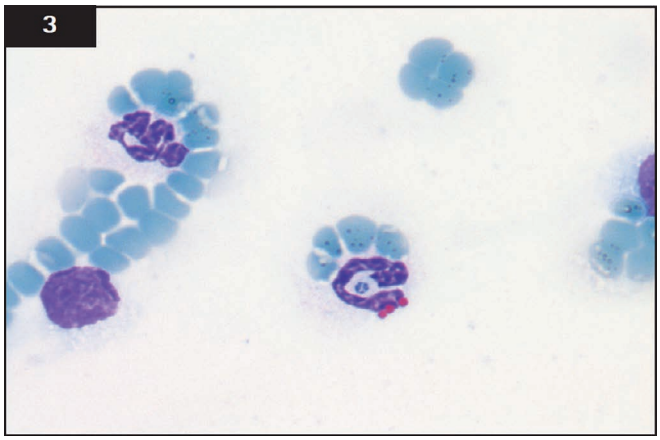


1 Legs. Equine anaplasmosis. Clinical signs include distal limb oedema.



2 Flank. Equine anaplasmosis. The integument is irregular due to generalised urticaria or hives (variably sized oedematous bumps) especially apparent on thorax, neck, and proximal extremities. A hypersensitivity reaction is implicated; this feverish horse proved positive for *Anaplasma phagocytophilum*.



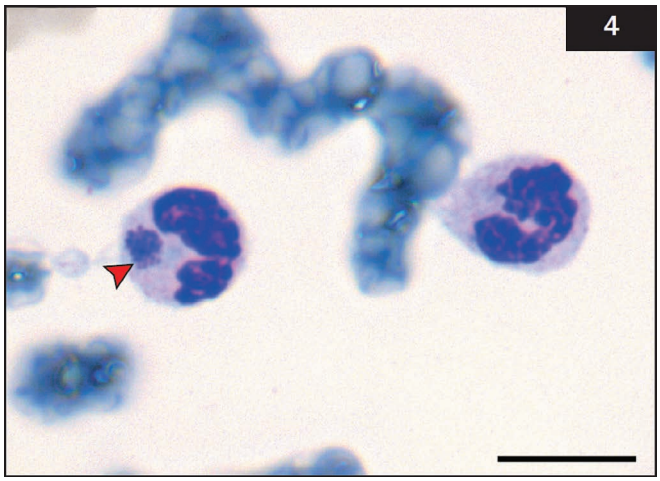
3 Equine anaplasmosis. Equine blood smear. The central neutrophilic granulocyte contains a cytoplasmic ring-shaped inclusion consistent with *Anaplasma phagocytophilum*. Inclusions may be detected predominantly in neutrophilic granulocytes and are polymorphic, round, irregular to ring-shaped, ranging from 0.75 to 3.5 µm in diameter. Round to ovoid morulae (2.5–3.5 µm in diameter) are composed of small granules. Single initial bodies measure approximately 0.5 µm in diameter. (May-Grünwald-Giemsa stain.)

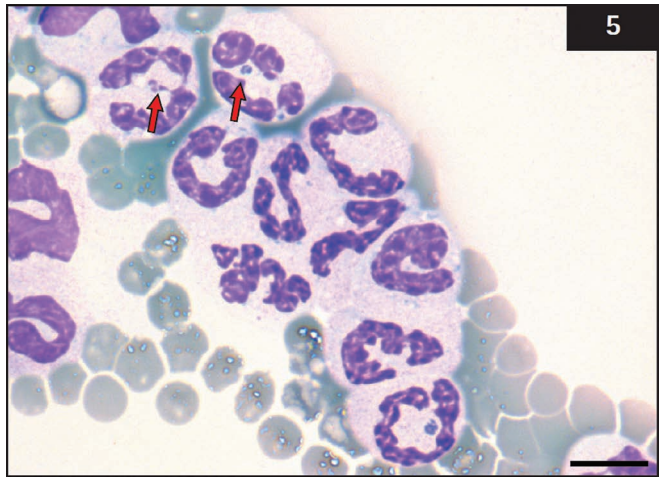
Incubation Period

The incubation period in experimentally infected horses varies from 1 to 9 days (Stannard *et al*. 1969, Franzén *et al*. 2005). One of two horses receiving high dosage of infective blood (20×10^6 infected neutrophilic granulocytes) died suddenly and unexpectedly 2 days into clinical illness (Franzén *et al*. 2005).

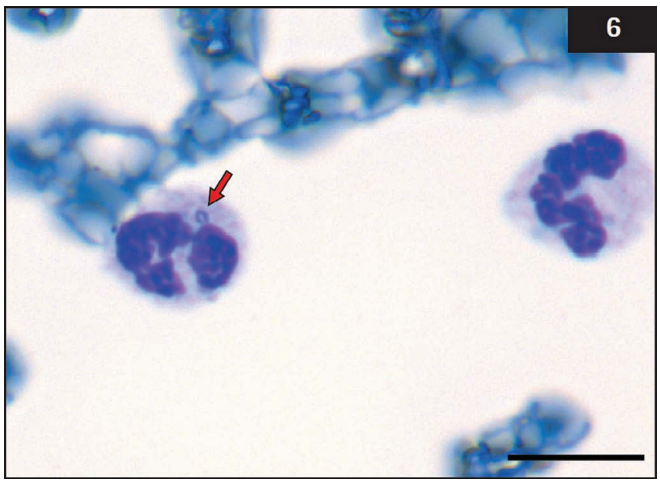
Clinical Presentation

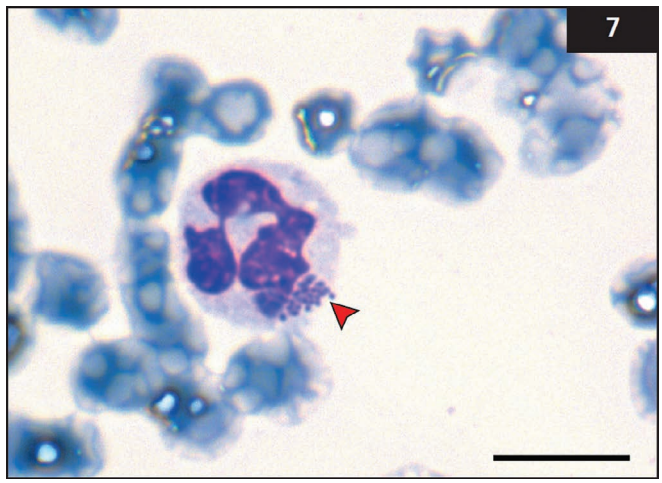
Clinical signs include inappetence, high fever, depression, petechiation, icterus, ataxia, rhabdomyolysis, and distal limb oedema (**1**) associated with lymphopenia, neutropenia, thrombocytopaenia, and anaemia (Gribble 1969, Madigan & Gribble 1987, Gerhards *et al*. 1987, Madigan 1993, Franzén *et al*. 2005, Butler *et al*. 2008, Hilton *et al*. 2008). Extensive urticaria may also be associated with equine anaplasmosis (**2**). The disease can be self-limiting when untreated, and the clinical signs abated and disappeared without specific treatment 7–14 days after onset of the disease (Gerhards *et al*. 1987, Gribble 1969). By 22 days after infection, in one study, all abnormal signs associated with equine anaplasmosis had fully abated in all surviving horses (Franzén *et al*. 2005). However, infection with *A. phagocytophilum* can persist in the horse for at least 129 days, although the continued presence of the organism is not associated with detectable clinical or pathological abnormalities (Franzén *et al*. 2009). It is unclear whether horses younger than 3 to 4 years of age generally experience less-severe clinical disease (Gribble 1969, Madigan & Gribble 1987, Butler *et al*. 2008). Occasionally, euthanasia is required because of deterioration despite treatment (Butler *et al*. 2008).





4, 5 Equine anaplasmosis. Cytology specimen from a blood smear containing several small bacterial polymorphic cytoplasmic morulae (**4**, arrowhead) or single initial bodies (**5**, arrows) within neutrophilic granulocytes. *Anaplasma phagocytophilum*. (May-Grünwald-Giemsa stain. Bars 10 µm.)





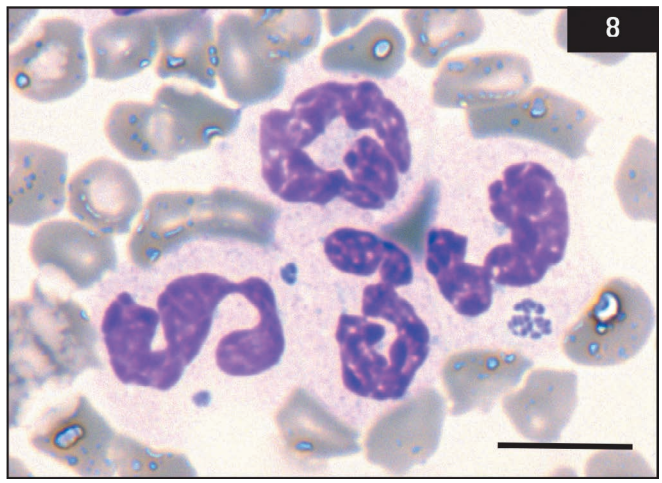
6, 7 Equine anaplasmosis. Cytology specimens from a blood smear with infected neutrophilic granulocytes containing an intracytoplasmic ring form (**6**, arrow) and clustered initial bodies (**7**, arrowhead) of *Anaplasma phagocytophilum*. (May-Grünwald-Giemsa stain. Bars 20 µm.)

Differential Diagnosis

Clinical signs are similar to those caused by infections with other pathogens such as *Borrelia. burgdorferi*, *Babesia caballi*, *Theileria equi*, equine herpesvirus, equine infectious anaemia virus, equine arteritis virus, viral encephalitides, Leptospiraceae (Butler *et al*. 2008), and *Anaplasma bovis* (Seo *et al*. 2019). Fever, anorexia, lethargy, and severe dehydration in a 23-year-old male Thoroughbred was associated with *A. bovis* infection (Seo *et al*. 2019). In addition, potential tick-borne fever of unknown origin might also be associated with *Rickettsia rickettsia* infection, the causative agent of Rocky Mountain spotted fever. Clinical signs include fever (39.2 °C), anorexia, and lethargy in a 20-year-old paint gelding (Freese & Sheats 2019).

Diagnosis

Diagnosis of equine anaplasmosis is usually based on the detection of characteristic cytoplasmic inclusion bodies in peripheral blood (**3–7**); either morulae or elementary bodies are seen. In the neutrophilic and, occasionally, eosinophilic granulocytes on a Wright-Giemsa- or haematoxylin and eosin (H&E)–stained smear of peripheral blood (8) obtained during days 3–5 of fever during peak anaplasmosis (Gribble 1969, Madigan & Gribble 1987, Madigan 1993). Morulae (<4



8 Equine anaplasmosis. Cytology specimen from a blood smear with three infected neutrophilic granulocytes each containing different forms of *A. phagocytophilum* inclusions. (May-Grünwald-Giemsa stain. Bar 20 µm.)

μm in diameter) consist of elementary bodies (<1 μm in diameter). Microscopic interpretation of a buffy coat smear of H&E-stained peripheral blood is a sensitive and practical diagnostic tool for the veterinarian considering possible infection with *A. phagocytophilum* in horses with pyrexia, but some cases may require PCR testing for diagnosis (Butler *et al*. 2008, Hilton *et al*. 2008). The best diagnostic tool for the detection of EGA is PCR assay (Saleem *et al*. 2018) with the PCR signal detected 2–3 days before appearance of clinical signs and persisted 4–9 days beyond abatement of clinical signs, whereas diagnostic inclusion bodies (varying from 0.5 to 16% of neutrophilic granulocytes) were first noted on average 2.6±1.5 days after onset of fever (Franzén *et al*. 2005).

Horses seroconverted by 12–16 days after inoculation, reaching maximal indirect immunofluorescence assay (IFA) titres (up to 1:5,120) within 3–7 days from when seropositivity was identified (Franzén *et al*. 2005). The indirect fluorescent antibody titre to *A. phagocytophilum* persists for approximately 300 days after inoculation of the organism (Nyindo *et al*. 1978).

Genomic DNA extraction from blood samples subjected to shotgun next-generation sequencing might also be considered regarding diagnosis of equine anaplasmosis (Subbiah *et al*. 2021)

Pathology

Macroscopically, oedema of the ventrum and limbs may be present, including subcutaneous petechiae. Histopathologically, there is evidence of vasculitides in the affected subcutis (Jubb *et al*. 2007). During fever, rickettsial inclusions can be detected in granulocytes of a blood smear and are polymorphic, round, irregular to ring-shaped, ranging from 0.75 to 3.5 μm in diameter. Round to ovoid morulae (2.5–3.5 μm in diameter) are composed of small granules. Single initial bodies measure approximately 0.5 μm in diameter (Jubb *et al*. 2007).

Management/Treatment

The treatment of choice is oxytetracycline 7 mg/kg BW IV sid for 3–7 days to hasten recovery and alleviate clinical signs (Madigan & Gribble 1987). Clinical immunity in experimental horses was shown to last 2 years (Gribble 1969).

Public Health Significance

Despite the apparently ubiquitous presence of the pathogen *A. phagocytophilum* in ticks and various wild and domestic animals from Europe, up-to-date published clinical cases of human granulocytic anaplasmosis (HGA) remain rare compared to the worldwide status (Matei *et al*. 2019). However, HGA was first identified during 1994 and is now an emerging public health threat in the United States. The New York State has experienced a recent increase in the incidence of anaplasmosis (Russell *et al*. 2021). Although five Anaplasmataceae members, including *A. phagocytophilum*, *Ehrlichia chaffeensis*, *E. ewingii*, *E. canis*, and *Neorickettsia sennetsu*, infect humans, only the first three species have been investigated fully. All forms of human ehrlichiosis share many clinical and laboratory manifestations, including fever, headache, myalgia, arthralgia and malaise, thrombocytopaenia, leucopaenia, and indices of hepatic injury (Dumler *et al*. 2007, Matei *et al*. 2019).

Neorickettsia risticii: EQUINE NEORICKETTSIOSIS

Phylum XII Proteobacteria/Class I Alphaproteobacteria/Order II Rickettsiales/Family II Anaplasmataceae/Genus *V Neorickettsia*

Definition/Overview

Equine neorickettsiosis (also known as Potomac horse fever or equine monocytic ehrlichiosis) is an acute and potentially fatal equine disease associated with depression, anorexia, fever, dehydration, laminitis, abortion, and watery diarrhoea (Holland *et al*. 1985, Rikihisa *et al*. 1985, Arroyo *et al*. 2021) caused by *Neorickettsia risticii* (formerly *Ehrlichia risticii*) and *N. findlayensis*.

Aetiology

N. risticii is an obligate intracellular bacterium of the Anaplasmataceae family in the order Rickettsiales. The organism has a unique affinity for monocytes, and during the course of the disease and among horses, monocyte counts are variable, but they increase to 13% in some horses (Dutta *et al*. 1988). Characteristic cytoplasmic inclusion bodies (either morulae or elementary bodies) occur in the monocytes from peripheral blood during peak neorickettsiaemia. Morulae (less than 4 µm in diameter) consist of elementary bodies (less than 1 µm in diameter) (Holland *et al*. 1985). The complete genome sequence of *N. risticii* consists of a single circular chromosome of 879,977 base pairs and encodes 38 RNA species and 898 proteins. Comparison with its closely related human pathogen, *N. sennetsu*, showed that 88.2% of proteincoding genes are conserved between *N. risticii* and *N. sennetsu* (Lin *et al*. 2009). Both *N. risticii* and *N. findlayensis* show similar characteristic intramolecular repeats within strain-specific antigen 3 (Teymournejad *et al*. 2020).

Epidemiology

It has been shown that the trematode *Acanthatrium oregonense* is a natural reservoir and probably a vector of *N. risticii*, as *N. risticii* is vertically transmitted (from adult to egg) in *A. oregonense* (Gibson *et al*. 2005). In addition, caddisflies were reported as second intermediate hosts of *N. risticii*–infected trematodes by carrying infected metacercariae (Madigan *et al*. 2000, Mott *et al*. 2002). Furthermore, *N. risticii* can also be transmitted horizontally from trematode to bats (Gibson *et al*. 2005). The freshwater snail *Planorbella subcrenata* is regarded as a natural reservoir, and probably a vector of *N. risticii* also (Pusterla *et al*. 2013). *N. risticii* has not been reported outside the American continent yet. An evolutionary model showed that the *N. risticii* clade was composed of three distinct subclades each identified as genotype. The genetic divergence of *N. risticii* sequences seemed to be related to the geographical location, since a new, third genotype from South America, which diverged from the two genotypes from North America, was recently reported (Paulino *et al*. 2020).

Incubation Period

The incubation period varies from 3 to 9 days. Major clinical and haematological features of induced *N. risticii* infection are biphasic increase in rectal temperature (with peak increases to 38.9°C and 39.3°C on post-inoculation days 5 and 12, respectively), depression, anorexia, decreased white blood cell (WBC) count (maximal decrease of 47% on post-inoculation day 12), and diarrhoea from post-inoculation days 14 to 18. Increased WBC count was an inconsistent feature, with a maximal increase of 52% on post-inoculation day 20 (Dutta *et al*. 1988).

Clinical Presentation

Under field conditions, *N. risticii* infection is characterised by fever, anorexia, depression, and leucopaenia, eventually followed by diarrhoea (**9**). Occasionally, horses develop profound ileus and severe colic (**10**) (Whitlock & Palmer 1986, Palmer *et al*. 1986, Long *et al*. 1992, Madigan *et al*. 2000). Diarrhoea developed in 73% of horses, and mortality was 9% (Dutta *et al*. 1988). Laminitis and limb oedema are often seen as a sequel to *N. risticii* infection, and mortality is 10–20% (Whitlock & Palmer 1986). However, clinically undetectable infections exist (Ristic *et al*. 1986). *In utero* infection (Dawson *et al*. 1987) has also been reported, as well as abortion (81 days post-infection), with recovery of the organism from the bone marrow of a foetus on the 200th day of gestation (Long *et al*. 1992).

Differential Diagnosis

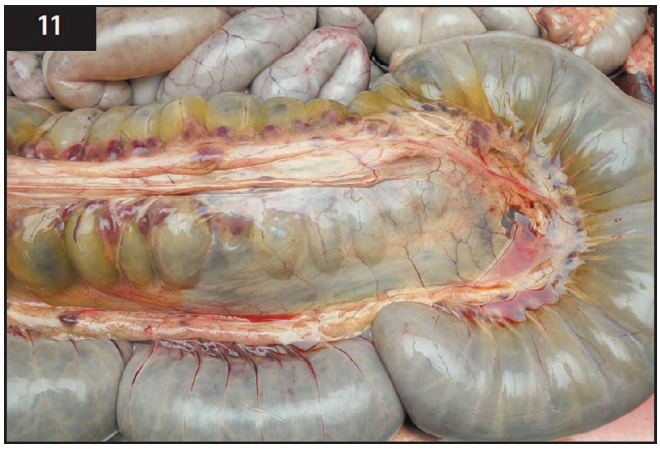
The differential diagnosis includes various causes of acute diarrhoea (see p. 267–268).

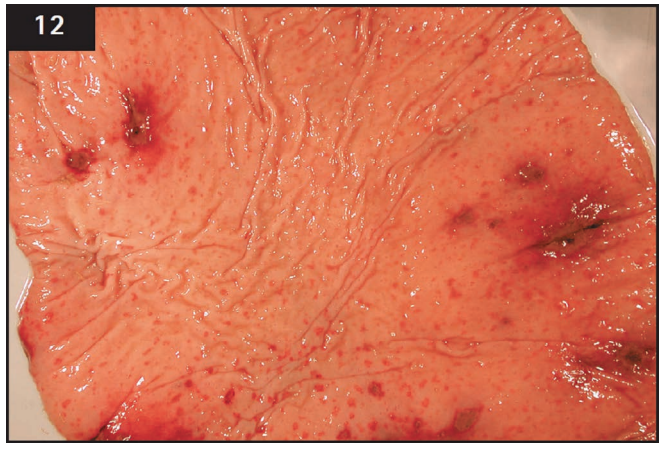
9 Diarrhoea develops in the majority of horses suffering from equine neorickettsiosis.

Diagnosis

Using mice inoculation, *N. risticii* was first detected in the blood on post-inoculation day 10, peaked on post-inoculation day 19, and was not detectable after post-inoculation day 24. The *N. risticii* titre was maximal

10 Colic can be noticed as an initial sign of equine neorickettsiosis.





11, 12 Colon. Ulcerative colitis postmortem. The colon is severely congested with prominent distended mesocolonic lymph vessels (**11**). The mucosa is thickened and oedematous, with multiple mucosal ulcerations and haemorrhages (**12**). These lesions may be indicative of equine neorickettsiosis.

during the peak increase in rectal temperature, and infected horses seroconverted, as detected by IFA assay and enzyme-linked immunosorbent assay (ELISA), with antibody titres between 1:160–1:640 and >1:5,000, respectively (Dutta *et al*. 1988).

For diagnosis, preference is given to culture or PCR. PCR was successfully used to detect the organism directly from the blood buffy coat cells of infected horses. It was estimated that buffy coat cells obtained from less than 1 ml of blood from infected horses was adequate for the detection of *N. risticii* (Biswas *et al*. 1991). *N. risticii* was detected in the blood by nested PCR in 81% of the culture-positive clinical specimens, indicating that the nested PCR is as sensitive as culture for detecting infection with *N. risticii* (Mott *et al*. 1997). Agreement between two different laboratories for detection of *N. risticii* using PCR assay was excellent for faeces (κ = 0.932, 95% confidence interval [CI]: 0.80 to 1), and fair for blood samples (κ = 0.494, 95% CI: 0.13 to 0.85) (Arroyo *et al*. 2021). In addition, characteristic cytoplasmic inclusion bodies (either morulae or elementary bodies) can be visualised in the monocytes on a Wright-Giemsa- or H&E-stained smear of peripheral blood obtained during peak ehrlichiaemia (Holland *et al*. 1985). In accord, microscopic interpretation of a buffy coat smear of H&E-stained peripheral blood is a sensitive and practical diagnostic tool for the veterinarian considering possible infection with *N. risticii*.

Pathology

Pathological features usually observed are mild to moderate typhlitis and colitis, with congested and ulcerated mucosae (**11**, **12**), most prominent in the right dorsal colon, and mesenteric lymphadenopathy. Similar, less-grave lesions may be present in the stomach and small intestine. Subcutaneous oedema, small oral vesicles, epicardial

and pulmonary haemorrhages, and laminitis may be accompanying macroscopic features. Microscopically, intestinal lesions are composed of mucosal congestion and haemorrhages with superficial epithelial erosive to necrotising lesions and fibrin deposits. Furthermore, crypt abscesses and mixed inflammatory hypercellularity of the lamina propria may be present. Neorickettsial clustered organisms of <1 µm can be identified in special silver stains within the apical cytoplasm of cryptal enterocytes and in macrophages in the lamina propria (Maxie 2016).

Management/Treatment

The only effective treatment is the administration of tetracycline in the early stages of the disease (Dutta *et al*. 1998, Rikihisa *et al*. 2004). IV administration of oxytetracycline (6.6 mg/kg BW sid for 5 days) is an effective treatment when given early in the clinical course (Palmer *et al*. 1992). There is protective immunity against *N. risticii* infection, as evidenced by clinical resistance to reinfection for as long as 20 months after the initial infection (Palmer *et al*. 1990). Despite treatment with oxytetracycline (6.6 mg/kg BW bid IV beginning 14 hours before inoculation and continuing for 10 days) before inoculation, the antigenic stimulation was sufficient to induce such protective immunity (Palmer *et al*. 1988).

Although monocomponent vaccines are available against equine neorickettsiosis, clinical protection with vaccination has been reported to be inconsistent (McKenzie *et al*. 2019).

Public Health Significance

Not convincing as yet.

Bartonella henselae: BARTONELLOSIS

Phylum XII Proteobacteria/Class I Alphaproteobacteria/Order VI Hyphomicrobiales/Family II Bartonellaceae/Genus I *Bartonella*

Definition/Overview

Bartonella spp. are associated with an extended animal host range (including equines) and are identified as emerging in Europe (Vorou *et al*. 2007). A carrier state might occur in the equine species, and as a consequence, associated zoonotic transmission cannot be excluded.

Aetiology

Bartonella (formerly *Rochalimaea* species) spp. are members of the α-proteobacteria group that also includes the genera *Rickettsia*, *Ehrlichia*, and *Brucella*. They are fastidious, Gram-negative, short-to-spirillar bacteria that occur in the blood of man and other mammals; they are usually vector-borne but can also be transmitted by animal scratches and bites from haematophagous insects, such as sandflies (*Lutzomyia* spp.), fleas, and lice (Maguiña *et al*. 2009).

Epidemiology

Horses in the South-Eastern USA are naturally infected with *B. henselae*, *B. vinsonii* subsp. *berkhofii* genotypes I and III, and a bacterium most similar to *Candidatus Bartonella volans*. Antibodies were not detectable by indirect fluorescent antibody assay (IFA) testing in infected horses (Cherry *et al*. 2012). In contrast, IFAT detected 58% healthy horses in Central Italy positive to *B. henselae* antigen with antibody titres ranging from 1:64 (cut-off) to 1:512. PCR assay revealed 12% positive reactions specific for *Bartonella* sp. in the same horse population. All PCR-positive horses were serologically positive (Magni *et al*. 2017).

Incubation Period

Transient mild clinical signs occurred in some horses inoculated intradermally with *B. henselae*, but neither haematological alterations nor fever did occur. An injection-site reaction, including mild oedema, sensitivity, and pruritus, was obvious. Transient limb oedema, mild to moderate in severity and sensitivity and mild in warmth, was observed in most horses inoculated intradermally on days 4–33 post-inoculation with some horses seroconverting. Of note, no long-term effects were noted for 2 years post-inoculation (Palmero *et al*. 2012).

Clinical Presentation

B. henselae was isolated from the blood of a horse with chronic arthropathy, a horse with presumptive vasculitis (Jones *et al*. 2008), and a horse with haemolytic anaemia (PCV 5.5%) (Cherry *et al*. 2011). A 3.5-month-old Thoroughbred colt suffered from severe suppurative cholangiohepatitis and associated dermatitis of the

pasterns and muzzle with identification of *B. henselae* in the liver (Setlakwe *et al.* 2014).

Diagnosis

Blood samples or fresh-frozen tissue can be tested for the presence of *Bartonella* spp. by a combination of real-time PCR and enrichment culture technique facilitated by prior use of Bartonella alpha-Proteobacteria Growth Medium to increase likelihood of diagnosis, considering the difficulties in identifying the organism (Jones *et al.* 2008, Cherry *et al.* 2012, Palmero *et al.* 2012, Setlakwe *et al.* 2014).

Pathology

B. henselae infection caused abortion of a foal exhibiting necrosis and vasculitis in multiple tissues, with intralesional, Gram-negative, short-to-spirillar bacteria (Johnson *et al.* 2009). Hepatic infection of *B. henselae* in a Thoroughbred foal induced a severe suppurative cholangiohepatitis and associated dermatitis (Setlakwe *et al.* 2014).

Management/Treatment

Human *Bartonella* isolates are highly susceptible to antibiotics, including most of the beta-lactams, the aminoglycosides, the macrolides, doxycycline, and rifampicin (rifampin) (Maurin *et al.* 1995).

Public Health Significance

The bartonelloses of medical importance comprise Carrión's disease, trench fever, cat-scratch disease, bacillary angiomatosis, and peliosis hepatis. The *Bartonella* spp. are considered emerging human pathogens (Maguiña *et al.* 2009). *B. henselae* has been identified as the causative agent of cat-scratch disease. On the other hand, *B. quintana*, which causes the body lice–mediated trench fever in humans and has no known animal reservoir, was shown to infect a domestic cat (Vorou *et al.* 2007). Furthermore, *Bartonella* spp. were first recognised to cause endocarditis in humans in 1993 when cases caused by *B. quintana*, *B. elizabethae*, and *B. henselae* were reported. Since the first isolation of *B. vinsonii* subsp. *berkhoffii* from a dog with endocarditis, this organism has emerged as an important pathogen in dogs and an emerging pathogen in people (Chomel *et al.* 2009). *B. henselae* as a zoonotic disease is illustrated by the case of co-infection with *Bartonella henselae*, *Anaplasma platys*, and Candidatus *Mycoplasma haematoparvum* in a veterinarian (Maggi *et al.* 2013). In line, zoonotic transmission of *Bartonella* spp. from the equine species cannot be excluded.

Brucella spp.: BRUCELLOSIS

Phylum XVII Proteobacteria/Class I Alphaproteobacteria/Order VI Hyphomicrobiales/Family IV Brucellaceae/Genus I *Brucella*: Gram-negative aerobic rods and cocci

Definition/Overview

Coincidental infection in horses caused by various bacteria of the genus *Brucella* is especially associated with abortion and fistulous withers. Brucellosis has important public health significance and is a reportable disease.

Aetiology

Brucellae are facultative intracellular, Gram-negative, partially acid-fast coccobacilli. The bacterium is 0.5–0.7 µm in diameter and 0.6–1.5 µm in length. They are oxidase, catalase, and urease positive. *Brucella* species considered important agents of human disease include *B. melitensis*, *B. abortus*, and *B. suis* (Ekers 1978, Mohandas *et al.* 2009). Isolation of *B. suis* biotype 1 (Cook & Kingston 1988) and *B. abortus* biotypes 1, 2, and 4 (Ekers 1978, Carrigan *et al.* 1987, De Massis *et al.* 2019) was reported from horses.

Epidemiology

The epidemiology of human brucellosis, the commonest zoonotic infection worldwide, has drastically changed over the past decade because of various sanitary, socioeconomic, and political reasons, together with the evolution of international travel. Several areas traditionally considered to be endemic, such as France, Israel, and most of Latin America, have achieved control of the disease. On the other hand, new foci of human brucellosis have emerged, particularly in central Asia, while the situation in certain countries of the Near East (e.g. Syria) is rapidly worsening (Pappas *et al.* 2006). *B. melitensis* biovar 3 is the most commonly isolated species from animals in Egypt, Jordan, Israel, Tunisia, and Turkey (Refai 2002). The seroprevalence of *Brucella* species among horses in Jordan was 1%, and 8.5% in donkeys. Contact with small ruminant herds with a history of brucellosis was associated with a high odds ratio (20 and 81 for horses and donkeys, respectively) for *Brucella* seropositivity in equids (Abo-Shehada 2009). It has been suggested that equines with a seroprevalence rate of 0.2% are not a reservoir of brucellosis and do not play an important role in the epidemiological patterns of this disease in northeastern Mexico (Acosta-González *et al.* 2006), with horses in Latin America mainly infected with *B. abortus* and *B. suis* (Lucero *et al.* 2008).

In horses admitted for evaluation of fistulous withers, 38% tested for antibody to *B. abortus* were seropositive. Horses that tested seropositive were significantly more likely to have been pastured with cattle that were seropositive for *B. abortus* and were also significantly more likely to have had radiographic evidence of vertebral osteomyelitis than were horses that tested seronegative (Cohen *et al.* 1992).

Pathophysiology

These bacteria do not produce classical virulence factors (Roop *et al*. 2009), and their pathogenic ability relies on their stealthy strategy and their capacity to replicate within host cells and to induce long-lasting infections. They promote the premature death of neutrophilic granulocytes with neutropenic *Brucella*-infected animals developing cachexia in the early phases of the disease. It has been suggested that *Brucella*-infected polymorphonuclear neutrophilic granulocytes (PMNs) function as "Trojan horse" vehicles for bacterial dispersal (Moreno & Barquero-Calvo 2020). Extensive replication of the Brucellae in placental trophoblasts is associated with reproductive tract pathology in natural hosts, and prolonged persistence in macrophages leads to the chronic infections that are a hallmark of brucellosis in both natural hosts and humans (Roop *et al*. 2009).

Incubation Period

Experimental intraconjunctival infection of horses with *B. abortus* revealed no appreciable clinical signs up to 30 months except mild pyrexia (MacMillan *et al*. 1982, MacMillan & Cockrem 1986).

Clinical Presentation

The clinical signs of the disease are variable but include fistulous withers (Cohen *et al*. 1992), abortion (Shortridge 1967, McCaughey & Kerr 1967), arthritis (Carrigan *et al*. 1987), and vertebral osteomyelitis (Collins *et al*. 1971).

Differential Diagnosis

The differential diagnosis predominantly includes various causes of abortion and fever (see p. 267).

Diagnosis

The diagnosis is based on a positive culture of the bacterium and/or seroconversion as assessed by a complement fixation test eventually combined with a positive reaction to the intradermal skin test. However, an intradermal skin test was positive in infected adults only, and negative in all foals tested (MacMillan & Cockrem 1986).

Antibodies to *B. abortus* became detectable from the second week after inoculation. Titres in the serum agglutination and complement fixation tests declined substantially after 6–8 weeks, but reactions to the Coombs antiglobulin, 2-mercaptoethanol, and immunodiffusion tests were maintained (MacMillan *et al*. 1982). Of interest, genus-specific, real-time PCR assays, e.g. based on the bcsp31 gene, will lead to an early diagnosis, but for the purpose of epidemiological surveillance, a species-specific, real-time PCR deriving from the conventional AMOS (AbortusMelitensisOvisSuis)–PCR is necessary (Al Dahouk *et al*. 2004).

Pathology

Postmortem examination of a foal suffering from brucellosis disclosed granulomatous lesions in the lungs, liver, testes, and metatarsophalangeal synovial membranes. *B. abortus* identical with strain 544 was recovered from lymphoid and other tissues (MacMillan & Cockrem 1986).

Management/Treatment

Horses with a tentative diagnosis of brucellosis should be isolated to prevent possible human exposure. Treatment should not be attempted as the pathogen has important public health significance and brucellosis is a reportable disease. The most commonly used veterinary vaccines are *B. abortus* S19 and *B. melitensis* Rev.1 vaccines. *B. abortus* RB51 vaccine is used in some countries on a small scale. Vaccination is limited to cattle and small ruminants (Refai 2002). Five horses that were seropositive for *B. abortus* were administered strain 19 *Brucella* vaccine SC (n = 1) or IV (n = 4). The horse treated by SC injection of vaccine improved during hospitalisation but was lost to follow-up evaluation. Three of four horses treated by IV injection died, but one horse recovered within 4 weeks of treatment (Cohen *et al*. 1992).

Public Health Significance

Brucellosis has important public health significance (Mohandas *et al*. 2009, De Massis *et al*. 2019). Brucellosis, especially caused by *B. melitensis*, particularly biovar 3 (Refai 2002), remains one of the most common zoonotic diseases worldwide, with more than 500,000 human cases reported annually (Seleem *et al*. 2010). Involvement of the musculoskeletal system is the most common complication of human brucellosis, while neurobrucellosis (like meningitis) and endocarditis are life-threatening complications (Ranjbar *et al*. 2009).

Cardiovascular complications occur in <2% but account for most of the mortality. *Brucella* endocarditis usually involves normal native aortic valves in 75% of cases. A combination of antibiotics and valve replacement is the most acceptable treatment (Mohandas *et al*. 2009). Cutaneous manifestations, including erythema nodosum, are not specific and affect 1–14% of patients with brucellosis (Mazokopakis *et al*. 2003). Uveitis is also seen (Rolando *et al*. 2009). The standard treatment for acute and chronic brucellosis is a combination of doxycycline with a second drug, such as rifampicin or gentamicin, in order to treat and to prevent complications and relapse (Sakran *et al*. 2006).

Burkholderia mallei: "GLANDERS"

Phylum XVII Proteobacteria/Class II Betaproteobacteria/Order Burkholderiales/Family Burkholderiaceae/Genus I *Burkholderia*: Gram-negative aerobic rods and cocci

Definition/Overview

Glanders is an ancient, highly fatal, and usually chronic respiratory disease of solipeds caused by *Burkholderia mallei* (formerly *Pseudomonas mallei*), with humans being accidental hosts. The diagnosis is based on the presence of characteristic stellate scars in the nasal septum and a positive reaction to the mallein test, combined with a positive culture of *B. mallei*. Human infections are often fatal if untreated.

Aetiology

B. mallei is a facultative, rod-shaped, Gram-negative, nonspore-forming, nonmotile, intracellular pathogen that can invade, survive, and replicate in epithelial and phagocytic cell lines (Ribot & Ulrich 2006). It is an obligate animal pathogen whose natural hosts are horses, donkeys, and mules, but infections can also occur in felines, camels, and goats. Virulence in *B. mallei* is multifactorial, and several virulence determinants have been identified and characterised (Schell *et al*. 2007). Seventeen distinct ribotypes were identified from human and equine infections (Harvey & Minter 2005). Multilocus variable-number tandem-repeat analysis showed seven outbreak area–related genotypes in nine districts in India (Singha *et al*. 2021).

Epidemiology

Glanders is endemic in Africa, Asia, the Middle East, and Central and South America. Carriers that have made an apparent recovery from the disease are the most important source of infection, as the pathogen does not survive for more than 6 weeks outside the host (Lehavi *et al*. 2002).

Pathophysiology

Equines are generally infected orally (Schell *et al*. 2007). Following penetration of the mucosae, the pathogen is spread via the lymphatic tissues.

Incubation Period

The incubation period varies from 1 to 2 days following intratracheal deposition, with rectal temperatures increased to above 40°C (Lopez *et al*. 2003).

Clinical Presentation

Clinical signs include febrile episodes, cough, blood-encrusted material on nostrils, inflammatory nodules and ulcers developed in the nasal passages with a sticky yellow discharge, characteristic stellate scars in the nasal septum, purulent nasal discharge, enlargement of submaxillary lymph nodes, chronic lymphangitis, skin abscessation, progressive debility, orchitis, and dyspnoea associated with interstitial pneumonia. Furthermore, apparent neurological degeneration is seen in acute glanders (Lopez *et al*. 2003). Life expectancy was judged likely to have been less than 12 hours in *B. mallei*–inoculated horses due to subsequent pulmonary oedema (Lopez *et al*. 2003).

Differential Diagnosis

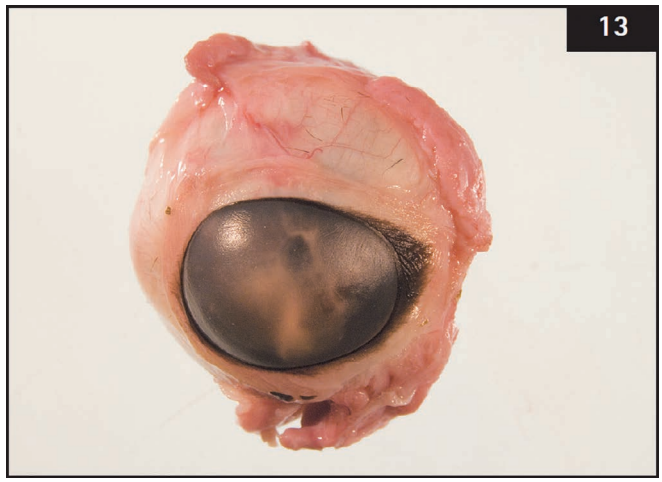
The differential diagnosis includes various causes of fever and dyspnoea (see p. 267).

Diagnosis

The presence of stellate scars in the nasal septum is regarded as pathognomonic. *B. mallei* can be cultured easily from purulent nasal discharge, and the complement fixation test can be used for serology (Arun *et al*. 1999). However, false-negative results are reported in the CFT (Laroucau *et al*. 2020). Furthermore, the mallein test can also be used to identify infected horses; purulent exudate in the eye associated with blepharospasm of a glanderous animal 24–48 hours following subconjunctival inoculation is regarded as a positive test result. Alternatively, the intracutaneous mallein test can be used with an increase in rectal temperature, and a swelling at the point of injection regarded as a positive test result (Arun *et al*. 1999). When tested comparatively with Dutch PPD mallein as standard, trichloroacetic acid–precipitated proteins were comparable to Dutch PPD mallein in potency and innocuity, whereas ammonium sulphate–precipitated proteins elicited nonspecific reactions (Verma *et al*. 1994).

Competitive enzyme-linked immunosorbent assay (cELISA) test specificity for *B. mallei* was 99%. Concordance and kappa value between the complement fixation (CF) and the cELISA procedures for the serodiagnosis of *B. mallei* infection in experimentally exposed horses were 70% and 0.44, respectively (Katz *et al*. 2000). The cELISA offers the possibility for automatisation, can be applied to noncomplement fixing sera, and is used for various host species, although the complement fixation test (CFT) is internationally mandatory for testing of equine sera for the absence of glanders to date (Sprague *et al*. 2009). In general, Western Blot and ELISAs are more specific than the CFT (Elschner *et al*. 2019).

Hydrolysis probe–based, real-time PCR using the uneven distribution of type III secretion system genes afforded considerable improvements in the specificity and rapidity of the diagnosis of *B. pseudomallei, B. mallei*, and *B. thailandensis* and allows rapid discrimination from opportunistic pathogens, such as members of the *B. cepacia* complex (**13**), that routine diagnostic laboratories are more likely to encounter (Thibault *et al*. 2004). The efficiencies for the qPCR Bmallei.fiP.121, Bmallei.hypprot.61, and Bmallei.hypprot.89 on equine tissue samples were 96%, 96%, and 97%, respectively. Cq values were considered positive if less than 36. The three qPCRs showed similar results for the detection limit, about 3–10 copies of genomic DNA per microliter. None of the qPCRs were positive for *B. pseudomallei*, and all amplified the DNA of *B. mallei* (Fonseca Júnior *et al*. 2021). PCR assay for the molecular diagnosis of glanders have been advocated,



13 Eye. Hypopyon, suppurative uveitis. The anterior eye chamber is blurred with pale yellowish specks of a fibrinopurulent exudate. From this foal, *Burkholderia cepacia* was isolated. Members of the *B. cepacia* complex are regarded as opportunistic pathogens.

especially in regions where the circulating *B. mallei* strains have not yet been fully genetically characterised (Laroucau *et al.* 2021). Although bacterial isolation is considered the gold standard for glanders diagnosis, it is necessary to perform complementary tests, such as PCR, since PCR is more sensitive than isolation independent of the viability of the agent and can detect *B. mallei* even in a sample with secondary contamination (Abreu *et al.* 2020).

Pathology

B. mallei infection may incite pyogranulomatous and necrotic pulmonary nodules and ulcerative nodular skin and respiratory mucosal lesions with characteristic white stellate scars in the nasal septum. Histologically, lung lesions comprise liquefactive necrosis, including neutrophilic granulocytes and surrounding epithelioid macrophages and fibrosis. The dermal disease of ulcerations, including purulent lymphangitis, is named "farcy" (Maxie 2016). Remarkably, *Streptococcus equi* subsp. *zooepidemicus* was isolated from the brain of all *B. mallei*–inoculated horses (Lopez *et al.* 2003). Immunohistochemistry using a monoclonal antibody to *B. mallei* BpaB showed localisation of the bacterial antigen in the cytoplasm of neutrophilic granulocyte, macrophages, epithelioid cells, and multinucleated giant cells in the pyogranulomas and abscesses in target organs. Some alveolar type II cells and bronchiolar epithelial cells also contained the antigen (Erdemsurakh *et al.* 2020).

Management/Treatment

Horses with a tentative diagnosis of glanders should be isolated to prevent possible human exposure. Treatment should not be attempted, as the pathogen has important public health significance and glanders is a reportable disease.

Public Health Significance

Humans are accidental hosts of *B. mallei*, and the majority of cases have been the result of occupational contact with infected horses. Whereas equines are generally infected orally, the primary route of infection in humans is contamination of skin abrasions or mucous membranes with nasal discharge or skin lesion exudate from an infected animal (Schell *et al.* 2007). Person-to-person spread of *B. mallei* is extremely rare (Mandell *et al.* 1995). However, *B. mallei* is infectious by the aerosol route (Waag *et al.* 2021). In humans, glanders is characterised by initial onset of fever, rigors, and malaise, culminating in a rapid onset of pneumonia, bacteraemia, pustules, and abscesses, leading to death in 7–10 days without antibiotic treatment. The course of infection is dependent on the route of exposure. Direct contact with the skin can lead to a localised cutaneous infection. Inhalation of aerosol or dust containing *B. mallei* can lead to septicaemic, pulmonary, or chronic infections of the muscle, liver, and spleen. The disease has a 95% case fatality rate for untreated septicaemia infections, and a 50% case fatality rate in antibiotic-treated individuals (Mandell *et al.* 1995). *Burkholderia* infections are difficult to treat with antibiotics, and no vaccine exists (Whitlock *et al.* 2007, Waag *et al.* 2021). Continuous serological surveillance and monitoring of human glanders under one health concept might be of value (Singha *et al.* 2020).

Burkholderia pseudomallei: MELIOIDOSIS

Phylum XVII Proteobacteriales/Class II Betaproteobacteria/Order Burkholderiales/Family Burkholderiaceae/Genus I *Burkholderia*: Gram-negative aerobic rods and cocci

Definition/Overview

Melioidosis is a rare disease caused by *Burkholderia pseudomallei* (formerly *Pseudomonas pseudomallei*) characterised by an intracellular life cycle. Both humans and animals (including birds, crocodiles, and kangaroos) are susceptible to melioidosis with both latency and a wide range of clinical manifestations. Some species may develop melioidosis only if immunocompromised. Sheep, goats, and horses are particularly susceptible, but zoonotic transmission to humans is extremely unusual (Neubauer *et al*. 1997, Choy *et al*. 2000). Melioidosis has important public health significance and is a reportable disease.

Aetiology

B. pseudomallei is a Gram-negative, bipolar-staining, pleomorphic, motile bacillus, which is principally an environmental saprophyte responsible for melioidosis.

Epidemiology

This saprophyte inhabitant of telluric environments is mainly encountered in Southeast Asia and Northern Australia but is sporadically isolated in subtropical and temperate countries (White 2003). Melioidosis has become an increasingly important disease in endemic areas, such as Northern Thailand and Australia (Currie *et al*. 2000*a*). In endemic areas, the positive rates of antibodies against *B. pseudomallei* in humans, horses, oxen, and pigs were 4–15%, 9–18%, 7–33%, and 35%, respectively (Li *et al*. 1994). Of note, closely related *B. mallei* strains are circulating in the Middle East (Laroucau *et al*. 2021).

Pathophysiology

Following ingestion via contaminated soil or faeces, a diverse assortment of virulence factors (quorum sensing, type III secretion system, lipopolysaccharide, and other surface polysaccharides) allows *B. pseudomallei* to become an effective opportunistic pathogen; its intracellular life cycle also allows it to avoid or subvert the host immune system (Adler *et al*. 2009, Wiersinga & van der Poll 2009). The BoaA and BoaB genes specify adhesins that mediate adherence to epithelial cells of the human respiratory tract. The BoaA gene product is shared by *B. pseudomallei* and *B. mallei*, whereas BoaB appears to be a *B. pseudomallei*–specific adherence factor (Balder *et al*. 2010).

Incubation Period

Fever up to 40°C occurred 4–14 days following subcutaneous inoculation, and nasal discharge from 6 to 13 days following oral inoculation. Subsequent abscessation at the site of injection developed from 4 days post-inoculation on. Three out of six animals showed weight loss post-inoculation. Most prominent postmortem findings were pulmonary and renal abscesses, whereas no abnormalities were detected in the nasal septum and conchae (Wernery *et al*. 2019). The incubation period in man from defined inoculating events was previously ascertained as 1–21 (mean 9) days (Currie *et al*. 2000*b*).

Clinical Presentation

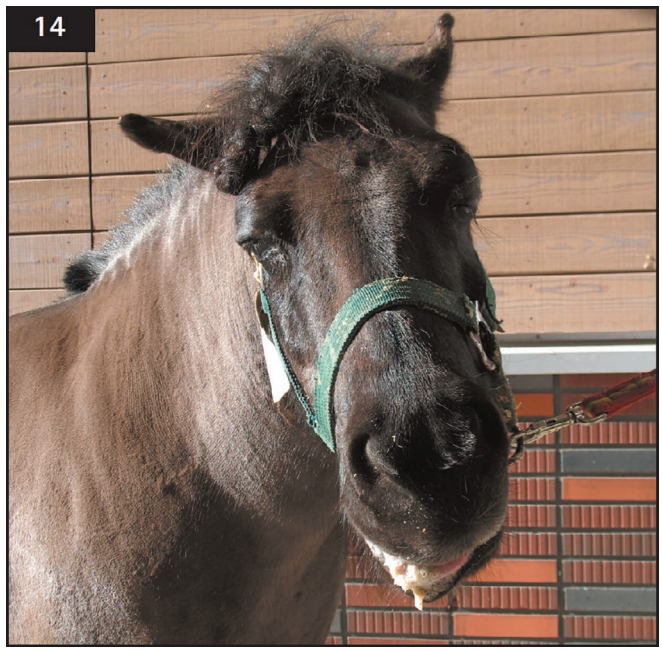
Clinical signs include fever, skin nodules (some of them ulcerated), oedema and lymphangitis (especially of the legs), septicaemia, oedema, colic, diarrhoea, nasal discharge, enlarged (retropharyngeal) lymph nodes, dyspnoea, and emaciation (Ladds *et al*. 1981, Laroucau *et al*. 2021). A case of acute meningoencephalomyelitis caused by infection with *B. pseudomallei* has been described associated with inability to stand, opisthotonus, facial paralysis (**14**), and nystagmus, rapidly progressing to violent struggling (Ladds *et al*. 1981).

Differential Diagnosis

The differential diagnosis includes various causes of internal abscessation (without characteristic stellate scars in the nasal septum as seen in *B. mallei*) (see p. 267). Listeriosis should be considered in a case of meningitis.

Diagnosis

B. pseudomallei can be cultured from purulent nasal discharge on specific agar within 72 hours, as well as other Burkholderia species, including *B. pseudomallei* and *B. thailandensis*, but non-Burkholderia species derived from horses cannot (Kinoshita *et al*. 2019). All three subcutaneously infected (starting from day 7) and one out of three orally infected horses developed antibodies



14 Head, neck. Right-sided proximal facial nerve paralysis resulting in muzzle deviation contralateral of the affected side and dropped right ear is associated with equine melioidosis.

detected by CFT and/or ELISA (Wernery *et al*. 2019). The diagnosis is based on a positive reaction to the mallein test combined with a positive culture.

Hydrolysis probe–based, real-time PCR methods using the uneven distribution of type III secretion system genes afford considerable improvements in the specificity and rapidity of the diagnosis of *B. pseudomallei*, *B. mallei*, and *B. thailandensis* and allow rapid discrimination from opportunistic pathogens, such as members of the *B. cepacia* complex (**15**, **16**), that routine diagnostic laboratories are more likely to encounter (Thibault *et al*. 2004). However, while PCR systems targeting the Burkholderia pseudomallei complex gave positive signals, the species-specific PCR systems targeting B. mallei (fliP-IS407A) and B. pseudomallei (orf11)—the OIE recommended targets—resulted in negative signals (Laroucau *et al*. 2021). Of note, an aroA PCR system has been developed, allowing the detection of the Burkholderia strains included in the B. pseudomallei complex (i.e. *B. mallei*, *B. pseudomallei*, *B. thailandensis*, *B. oklahomensis*, and *B. humptydooensis*) (Laroucau *et al*. 2021).

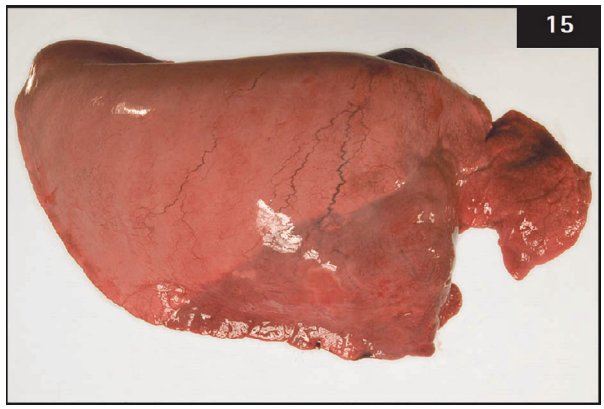
Pathology

Multiple abscesses in most organs are characteristic of the disease. The encapsulated nodules with caseous centres are composed of necrosis, neutrophilic granulocytes, lymphocytes, and epithelioid macrophages. In a case of acute meningoencephalomyelitis, macroscopic examination revealed malacia and haemorrhage in the medulla oblongata and adjacent spinal cord. Microscopically, there were disseminated focal neutrophilic granulocyte accumulations in affected areas, perivascular cuffing with mononuclear cells and lymphocytes, and marked oedema. Intracellular bacteria were identified in sections stained by the Giemsa method (Ladds *et al*. 1981).

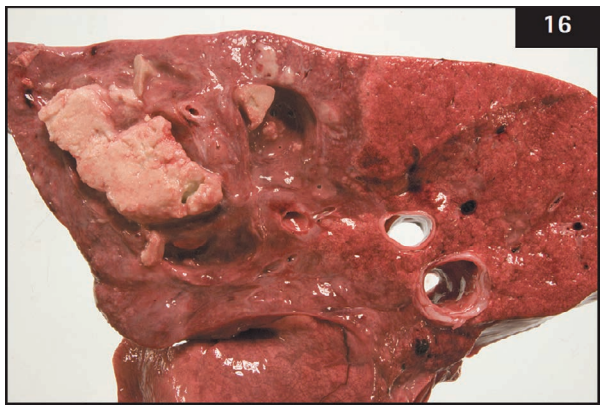
Management/Treatment

Horses with a tentative diagnosis of melioidosis should be isolated to prevent possible human exposure. Treatment should not be attempted as the disease has important public health significance. Furthermore, the ubiquitous bacterium is characterised by remarkable insensitivity to antimicrobial drugs. For instance, *B. pseudomallei* is intrinsically resistant to aminoglycosides and macrolides, mostly due to AmrAB-OprA efflux pump expression (Trunck *et al*. 2009) and to β-lactams due to possession of ambler class A Pen β-lactamase. In line, the β-lactam-β-lactamase inhibitor combination sulbactam-durlobactam may be useful as a treatment for *Burkholderia* infections (Papp-Wallace *et al*. 2021).

Immunisation with heat-inactivated *B. pseudomallei* cells provided the highest levels of protection against either melioidosis or glanders, indicating longer-term potential for heat-inactivated bacteria to be developed as vaccines against melioidosis and glanders (Sarkar-Tyson *et al*. 2009).



15 Lung. Necrosuppurative bronchopneumonia in a foal. The cranioventral lung field is hyperaemic, consolidated, and firm. Lesions resemble pulmonary lesions in melioidosis. From this foal *Burkholderia cepacia* was isolated.



16 Lung cross section. Necrosuppurative bronchopneumonia in a foal. The cranioventral lung lobes show on cut section a well-delineated hyperaemic area enclosing pale-yellow, variably sized, caseating, coagulative, necrosuppurative sequesters of remnant pulmonary parenchyma. Lesions resemble pulmonary lesions in melioidosis. From this foal *Burkholderia cepacia* was isolated.

Public Health Significance

Melioidosis has important public health significance and is a reportable disease. It is a life-threatening disease that is mainly acquired through skin lesions or inhalation, although other routes of infection have been documented (Neubauer *et al*. 1997). Primary skin melioidosis occurred in 12% of human patients. Secondary skin melioidosis (multiple pustules from haematogenous spread) was present in 2%. Patients with primary skin melioidosis were more likely to have chronic presentations (duration of a minimum of 2 months) (Gibney *et al*. 2008). Severe septicaemia secondary to melioidosis carries a high mortality. Although melioidosis can involve most tissues and organs, pericardial involvement is rare (De Keulenaer *et al*. 2008). Of human cases, 46% were bacteraemic and 19% died (Currie *et al*. 2000*a*).

Bordetella bronchiseptica

Phylum XVII Proteobacteriales/Class II Betaproteobacteria/Order Burkholderiales/Family III Alcanigenaceae/Genus III *Bordetella*: Gram-negative aerobic rods and cocci

Definition/Overview

The opportunistic bacterium *Bordetella bronchiseptica* is a rare cause of acute respiratory disease and abortion/infertility.

Aetiology

Pasteurellaceae are Gram-negative bacteria with an important role as primary or opportunistic, mainly respiratory, pathogens in domestic and wild animals. Some species of Pasteurellaceae cause severe diseases with high economic losses in commercial animal husbandry and are of great diagnostic concern (Dousse *et al*. 2008). Sixteen distinct ribotypes were identified in *B. bronchiseptica* strains (Register *et al*. 1997). Four main types of variation of the *B. bronchiseptica* lipopolysaccharide (LPS) are apparent: (1) heterogeneity of the core, (2) presence or absence of 0-chains, (3) differences at the level of the hinge region between the 0-chain and the core, and (4) differences in the association with other cell surface constituents. Isolates from different animal species did not show significant differences in their patterns of reactivity with monoclonal antibodies (LeBlay *et al*. 1997). Equine strains belong to group A classified using PCR-RFLP and sequence analysis of flagellin typin (flaA gene) (Khayer *et al*. 2014).

Epidemiology

Glucose nonfermenting Gram-negative bacilli have been recognised as opportunistic pathogens of humans. The most common veterinary glucose-nonfermenting Gram-negative bacilli were *Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*, *B. bronchiseptica*, and *P. pseudoalcaligenes*. Of all clinical veterinary specimens submitted for cultures, 10% contained nonfermenters (Mathewson & Simpson 1982). In addition, *Streptococcus equi* subspecies *zooepidemicus*, *Pseudomonas aeruginosa*, *Pasteurella* species, *Escherichia coli*, and *Bordetella bronchiseptica* are the most frequently isolated species from the equine respiratory tract (Fonseca *et al*. 2020), with *B. bronchiseptica* isolated from bronchial lavage specimens in distal respiratory tract disease (nasal discharge, cough, pneumonia) in 13% of foals (1–8 months old) (Hoffman *et al*. 1993).

Pathophysiology

Either *B. bronchiseptica* does not persist inside animals or susceptible animals possess specific receptors for smooth-type LPSs, in contrast to man (Le Blay *et al*. 1997).

Incubation Period

Not established in the equine species yet.

Clinical Presentation

Clinical presentation includes respiratory disease in foals (**17**) (Koehne *et al*. 1981), coughing in Thoroughbred racehorses (Christley *et al*. 2001), bronchopneumonia (Saxegaard *et al*. 1971), abortion (Mohan & Obwolo 1991), and infertility (Mather *et al*. 1973). *B. parapertussis* did not grow in tracheobronchial washing from a horse (Porter & Wardlaw 1994).

Differential Diagnosis

The differential diagnosis includes various causes of fever and dyspnoea (see p. 267).

Diagnosis

Diagnosis primarily depends on culture of the bacterium from tracheobronchial washing samples combined with clinical signs. Analysis of tracheobronchial washing samples for known *Bordetella* nutrients revealed concentrations of amino acids and nicotinic acid averaging 0.35 mM and 0.56 µg/ml, respectively (Porter & Wardlaw 1994).

Pathology

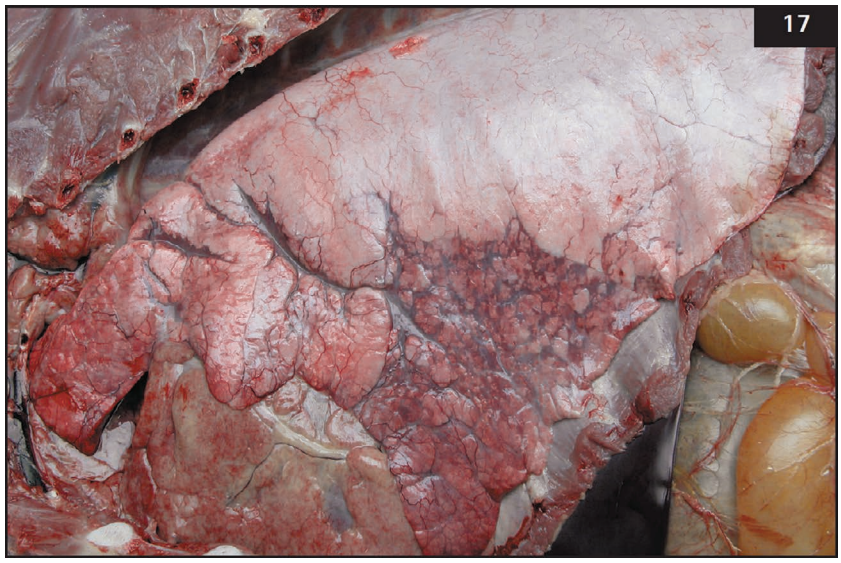
Common lesions caused by *B. bronchiseptica* include a catarrhal to suppurative bronchopneumonia and a (sero)fibrinous pleuropneumonia. These are usually opportunistic secondary infections preceded by viral infections in juvenile animals.

Management/Treatment

Treatment of diseased animals is supportive, and specific treatment should be based on *in vitro* antimicrobial susceptibility testing.

Public Health Significance

The absence of smooth-type LPSs appears to be rather frequent in human isolates, since long-chain LPSs were detectable in only 52% of human isolates, whereas 94% of animal isolates contained molecules of that type (Le Blay *et al*. 1997). *B. bronchiseptica* might have some public health significance, and its zoonotic risk should be minimised.



17 Lung postmortem. Suppurative bronchopneumonia in a foal. Cranioventral pulmonary hyperaemia and consolidation. A primary viral respiratory infection (herpesvirus, influenza virus) may be complicated by opportunistic infections with bacteria like *Streptococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Rhodococcus equi*, and *Bordetella bronchiseptica*.

Taylorella equigenitalis: CONTAGIOUS EQUINE METRITIS

Phylum XVII Proteobacteriales/Class II Betaproteobacteria/Order Burkholderiales/Family III Alcanigenaceae/Genus XI *Taylorella*: Gram-negative, microaerophilic, fastidious, slow-growing coccobacilli

Definition/Overview

Contagious equine metritis (CEM) caused by *Taylorella equigenitalis* is a highly contagious disease that is transmitted venereally. The carrier state occurs in the mare and the stallion, and carrier animals are frequently the source of infection for new outbreaks (Timoney 1996).

Aetiology

T. equigenitalis is a Gram-negative, microaerophilic, fastidious, slow-growing coccobacillus with streptomycin-sensitive and streptomycin-resistant biotypes (Timoney 1996). Isolates of *T. equigenitalis* obtained from European horses analysed by pulsed-field gel electrophoresis (PFGE) were classified into 18 genotypes (Kagawa *et al*. 2001). High sequence similarity (99.5% or more) was observed throughout isolates from Japan, Australia, and France, except from nucleotide positions 138 to 501, where substitutions and deletions were noted (Matsuda *et al*. 2006). Three major and three minor clonal complexes (CCs), and 11 singletons, were identified using MLST (Duquesne *et al*. 2020). A phylogenetic analysis revealed a position of *T. equigenitalis* in the beta subclass of the class Proteobacteria apart from the position of *Haemophilus influenzae*, which belongs in the gamma subclass of Proteobacteria. A close phylogenetic relationship among *T. equigenitalis*, *Alcaligenes xylosoxidans*, and *Bordetella bronchiseptica* was detected (Bleumink-Pluym *et al*. 1993).

Epidemiology

CEM has given rise to international concern since it was first recognised as a novel venereal disease of equids in 1977. The first known outbreak of CEM in the USA was in Kentucky in 1978. For some time, none of the subsequent outbreaks impacted significantly on the horse industry. That changed dramatically in 2008, however, after the discovery of some 1,005 exposed and carrier stallions and mares in 48 states. Neither clinical evidence of CEM nor decreased pregnancy rates were reportedly a feature in infected or exposed mares. In light of these findings, the question arose as to whether or not the considerable expense incurred in investigating the latest CEM occurrence was warranted (Timoney 2011). Among stallions examined in Slovenia, 92% were negative to *T. equigenitalis* by either PCR or culture (Zdovc *et al*. 2005). In comparison, from 1999 through 2001, 4 out of 120 imported European stallions tested positive for CEM at a quarantine facility in Darlington, MD, USA (Kristula & Smith 2004). Samples from mares with no clinical signs of CEM submitted for conventional culture were negative for *T. equigenitalis*, but in the PCR assay, 49% were positive for *Taylorella* DNA. The high incidence of *Taylorella* in horse populations without apparent clinical signs of CEM, the occurrence of incidental clinical cases, and the known variability between strains indicate that *Taylorella* was endemic in the horse population (Parlevliet *et al*. 1997, Duquesne *et al*. 2020).

Pathophysiology

CEM is transmitted by direct or indirect venereal contact. The invasiveness of *T. equigenitalis* strains seemed to be associated with the contagiousness of the infection, whereas the replication index seemed to be associated with the severity of the symptoms of CEM (Bleumink-Pluym *et al*. 1996).

Incubation Period

Horses challenged with *T. equigenitalis* showed seroconversion from day 11 post-inoculation (Katz & Geer 2001).

Clinical Presentation

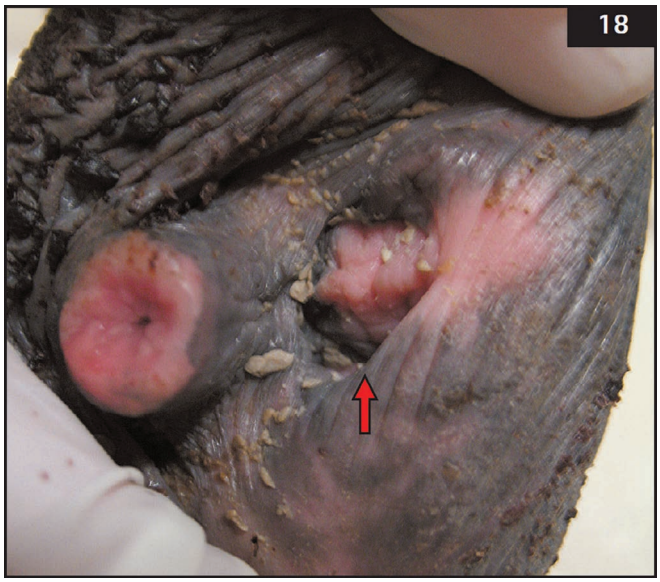
CEM can be the cause of short-term infertility sometimes associated with mucopurulent discharge and, very rarely, abortion in mares (Fontijne *et al*. 1989). Unlike the mare, stallions exposed to *T. equigenitalis* do not develop clinical signs of disease (Timoney 1996). It has been concluded that *T. equigenitalis* is of limited significance in horse breeding (Parlevliet *et al*. 1997).

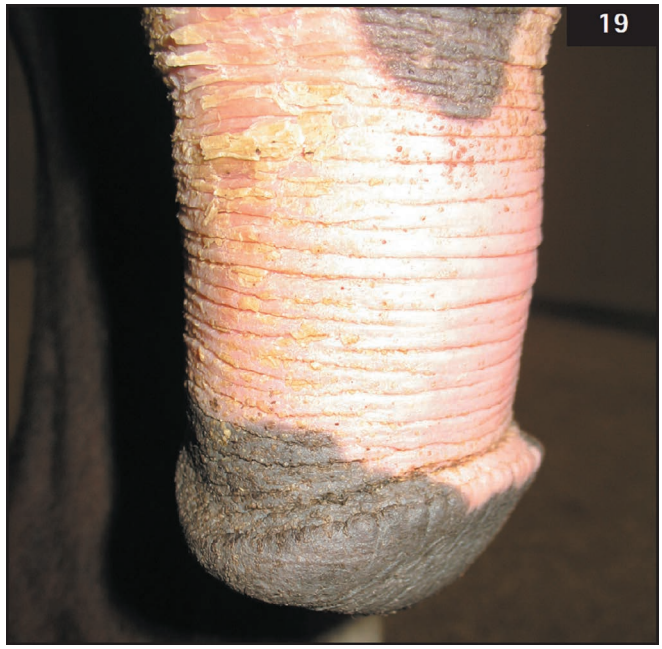
Differential Diagnosis

Atypical (donkey-origin) *Taylorella* spp. infections should be considered as a differential diagnosis of equine infertility in mares (Katz *et al*. 2000, Brooks *et al*. 2010). Furthermore, *T. asinigenitalis* might cause severe venereal infection in horses (Båverud *et al*. 2006, Wilsher *et al*. 2021). A lower minimum inhibitory concentration (MIC) of gentamicin (≤1 µg/ml) but a higher MIC of streptomycin (>16 µg/ml) has been reported in a *T. asinigenitalis* strain (Båverud *et al*. 2006).

Diagnosis

Diagnosis is based primarily on culture of the bacterium from its predilection sites in the reproductive tract of the mare and the stallion (**18**, **19**) (Timoney 1996). However, the rate of *T. equigenitalis* detection was higher with PCR than with the classic bacteriological examination. PCR is especially valuable in cases of intensive bacterial and fungal contamination of swabs, where the isolation of *T. equigenitalis* usually fails (Zdovc *et al*. 2005). A direct-PCR assay was developed for the rapid detection of *T. equigenitalis* in equine genital swabs without need for a preliminary step of DNA extraction or bacterial isolation (Duquesne *et al*. 2007). The assay is also able to discriminate between *T. equigenitalis* and *T. asinigenitalis* (Wakeley *et al*. 2006). Although the usefulness of MALDI-TOF MS as a differential diagnostic tool between *T. equigenitalis* and *T. asinigenitalis* has been demonstrated additionally, for *T. asinigenitalis*, which has slower growth





18, 19 Urethral fossa *in vivo*. *Taylorella asinigenitalis* resembling *T. equigenitalis* might be isolated from the urethral fossa (arrow) in horses.

than *T. equigenitalis*, direct spotting of 48-hour colonies turned out to be reliable as well (Petry *et al*. 2019).

In chronically infected mares, the organism was detectable in the clitoral swabs of nearly 93%, but in the cervical swabs of only 31%. In contrast, in acutely infected mares, the organism was detectable in the clitoral swabs of nearly 69%, but in the cervical swabs of 84% (Wood *et al*. 2005).

There was close agreement between CFT and ELISA methodologies during the post-exposure time period used to detect CEM serodiagnostically in regulatory animal health testing programmes. Unlike the CFT, which requires an overnight incubation step, the ELISAs are more convenient and can be completed in 3 hours (Katz & Geer 2001).

Pathology

Macroscopically, no vaginal lesions are apparent; the endometrial mucosa may be swollen and corrugated, with a scant mucopurulent exudate. Histology of uterine biopsies might reveal a mild purulent endometritis, characterised by interstitial mucosal oedema and a mild inflammatory infiltrate composed of neutrophilic granulocytes; later plasma cells may be more evident (Maxie 2016).

Management/Treatment

Aggressive systemic antibiotic therapy accompanied by routine topical therapy might be required to treat CEM-positive stallions (Kristula & Smith 2004).

Intrauterine immunisation with killed *T. equigenitalis* did not induce absolute protection from infection (Widders *et al*. 1986).

Public Health Significance

Not convincing yet.

Francisella tularensis: TULAREMIA

Phylum XII Proteobacteria/Class III Gammaproteobacteria/Order V Thiotrichales/Family II Francisellaceae/Genus I *Francisella*: Gram-negative aerobic rods and cocci

Definition/Overview

Tularemia caused by *Francisella tularensis* (formerly *Pasteurella tularensis*) is identified as emerging in Europe (Vorou *et al*. 2007), although the pathogenicity of *F. tularensis* for the horse appears to be extremely low.

Aetiology

F. tularensis is a Gram-negative, arthropod-borne coccobacillus (Petersen *et al*. 2009).

Epidemiology

The serological response in burros and horses to the viable LVS strain of *F. tularensis* generated high-titred agglutinating antisera and fluorescent antibody conjugates in both groups of animals. Maximum titres were obtained in horses 14–21 days (up to 1:1,024 and 1:360, respectively) and in burros 21–28 days (up to 1:1,024 and 1:160, respectively) after the start of vaccination. The use of so-called Woodhour's adjuvants or booster inoculations did not result in increased titres (Green *et al*. 1970).

Pathophysiology

Free-living amoebae feed on bacteria, fungi, and algae. However, some microorganisms have evolved to become resistant to these protists. These amoeba-resistant microorganisms include established pathogens, such as *F. tularensis*, *Legionella* spp., *Chlamydia pneumoniae*, and *Listeria monocytogenes*. Free-living amoebae represent an important reservoir of amoeba-resistant microorganisms and may, while encysted, protect the internalised bacteria from chlorine and other biocides. On the other hand, free-living amoebae may act as a "Trojan horse", bringing hidden amoeba-resistant microorganisms within the human or animal "Troy", and may produce vesicles filled with amoeba-resistant microorganisms, increasing their transmission potential (Greub & Raoult 2004).

Incubation Period

Not established in the equine species yet.

Clinical Presentation

Not established in the equine species yet.

Pathology

Not established in the equine species yet.

Public Health Significance

Tularemia is regarded as an important (tickborne) zoonosis with two primary disease manifestations, ulceroglandular and glandular. Two subspecies of *F. tularensis* cause most human illness, namely, subspecies *tularensis*, also known as type A, and subspecies *holarctica*, referred to as type B. The equine species is not regarded as a main reservoir for human infection in contrast with rodents and lagomorphs (Petersen *et al*. 2009).

Legionella pneumophila

Phylum XII Proteobacteria/Class III Gammaproteobacteria/Order VI Legionellales/Family I Legionellaceae/Genus I *Legionella*: Gram-negative aerobic rods and cocci

Definition/Overview

Febrile lymphadenopathy can be experimentally induced by *Legionella pneumophila*. It has been concluded that there is no evidence to support a role for the horse in the maintenance of these organisms in nature (Cho *et al*. 1983).

Aetiology

The pathogenicity of *L. pneumophila* serogroups 1 and 3 for the horse appears to be low (Cho *et al*. 1983).

Epidemiology

Seroconversions in horses provided additional evidence that horses become naturally exposed to *Legionella* spp. Nineteen per cent of horses seroconverted to at least one serogroup (out of four) of *L. pneumophila* (Cho *et al*. 1984). With 58% of the sera tested negative, 35% had end point titres of 1:2, 7% end point of 1:16, and 0.3% an end point of 1:256. South African serological results revealed a much lower exposure rate than that reported in the USA (Wilkins & Bergh 1988). In addition, a high percentage of seropositivity suggested that horses are commonly infected with *L. pneumophila* or related organisms, and the age-specific rates of occurrence indicated that infection was related directly to duration of exposure. The occurrence of positive (1:64) equine sera (31%) was significantly higher than the occurrence of positive sera in cattle (5%), swine (3%), sheep (2%), dogs (2%), goats (0.5%), wildlife (0%), and humans (0.4%) as assessed by means of microagglutination. The highest titre measured in horses was 1:512. Of the positive sera in horses, 44% reacted to a single serogroup (III or I most commonly), and 56% reacted to multiple serogroups (II and III or I, II, and III most commonly) (Collins *et al*. 1982).

Pathophysiology

Not established in the equine species yet.

Incubation Period

A transient decrease in circulating lymphocytes occurred 2 days after inoculation (Cho *et al*. 1983).

Clinical Presentation

Signs of clinical illness were restricted to a transient febrile response and lymphadenopathy (Cho *et al*. 1983).

Diagnosis

Agglutinating antibodies persisted at least 4 months after infection (Cho *et al*. 1983), with a high correlation (r = 0.89) found between titres measured by either the indirect fluorescent antibody test or the microagglutination test (Cho *et al*. 1984). All horses exhibited a marked increase in agglutinating antibodies to *L. pneumophila* serogroups 1 and 3 as early as 4 days after experimental challenge (Cho *et al*. 1983).

Pathology

At autopsy following experimental inoculation, only moderate generalised lymphadenopathy was noted, with lymph nodes showing evidence of reactive hyperplasia. Histologically, the lungs contained evidence of a low-grade inflammatory response characterised by focal proliferation of alveolar lining cells, with few neutrophilic and eosinophilic granulocytes (Cho *et al*. 1983).

Management/Treatment

Not appropriate yet.

Public Health Significance

Not convincing yet, as it has been stated that the horse could not be considered to be a source of infection but that both humans and animals were probably exposed to a common source of infection. Serological testing of people closely associated with horses showed that out of 22 people, 3 had a positive end point titre of 1:64, and only 1 person showed an end point titre of 1:256 (Wilkins & Bergh 1988).

Coxiella burnetii: Q FEVER

Phylum XII Proteobacteria/Class III Gammaproteobacteria/Order VI Legionellales/Family II Coxiellaceae/Genus I *Coxiella*

Definition/Overview

Coxiella burnetii, the causative agent of Q fever, is not currently reported to affect horses. Seropositivity was mentioned in horses ranging from 5.5 to 21.7% in Uruguay (Somma-Moreira *et al*. 1987). In addition, *C. burnetti* DNA was detected from blood samples using the transposon-like repetitive region (*IS1111*) by PCR method, revealing a prevalence of 5.2% in Korean horses (Cho *et al*. 2021). Similarly, IgG antibodies were detected in 5.6% of equine sera samples, and *C. burnetii* DNA was detected in 7.8% of equine vaginal samples in the east of Iran in a highly endemic region without significant difference in seroprevalence between sex, age, and breed groups (Jaferi *et al*. 2021). Nested PCR based on the presence of the transposable gene IS1111 revealed an overall *C. burnetti* DNA prevalence of 7.5% in equine sera from the north of Iran, with a higher prevalence in horses aged over 6 years (7–20 versus 1–8%) (Khademi *et al*. 2020). As a consequence, it cannot be excluded that the equine species plays a role in the transmission of infection.

Moraxella spp.

Phylum XII Proteobacteria/Class III Gammaproteobacteria/Order VI Moraxellales/Family II Moraxellaceae/Genus I *Moraxella*: Gram-negative aerobic rods and cocci

Definition/Overview

Moraxella spp. are a frequent isolate in ocular and pharyngeal flora of clinically normal horses and horses suffering from lymphoid follicular hyperplasia and conjunctivitis.

Aetiology

A Gram-negative, aerobic, oxidase-positive diplococcus that may colonise the conjunctiva and the pharynx in horses. In ocular flora of clinically normal horses (**20**), *Corynebacterium* spp., *Staphylococcus* spp., *Bacillus* spp., and *Moraxella* spp. are the bacteria most frequently isolated (Andrew *et al*. 2003), with *Moraxella* spp. comprising 28% of Gram-negative bacteria involved (Gemensky-Metzler *et al*. 2005). In addition, within healthy subgingival (below the gumline) niches in the horse oral cavity, phylotypes corresponding to Gammaproteobacteria were abundant using 16S rRNA gene amplicon pyrosequencing, including *Actinobacillus* spp. (8.8%), unclassified *Pasteurellaceae* (9.9%), and *Moraxella* spp. (9.6%) (Gao *et al*. 2016).

Epidemiology

There were no significant differences between the number or type of organisms cultured during the sampling seasons in ocular flora of clinically normal Florida horses, whereas the likelihood of detecting an organism depended on the horse's age (Andrew *et al*. 2003).

Pathophysiology

Unknown in the equine species yet.

Incubation Period

Not established in the equine species yet.

Clinical Presentation

Moraxella spp. are associated with lymphoid follicular hyperplasia (**21**) (Hoquet *et al*. 1985) and conjunctivitis (Hughes & Pugh 1970, Huntington *et al*. 1987), although their clinical significance remains unclear in the equine species. Of note, *Moraxella bovoculi* was isolated and identified in ocular fluid samples collected from racehorses with infectious keratoconjunctivitis (Liu *et al*. 2014).

Diagnosis

Diagnosis primarily depends on culture of the bacterium in diseased animals combined with clinical signs compared to negative controls.

Pathology

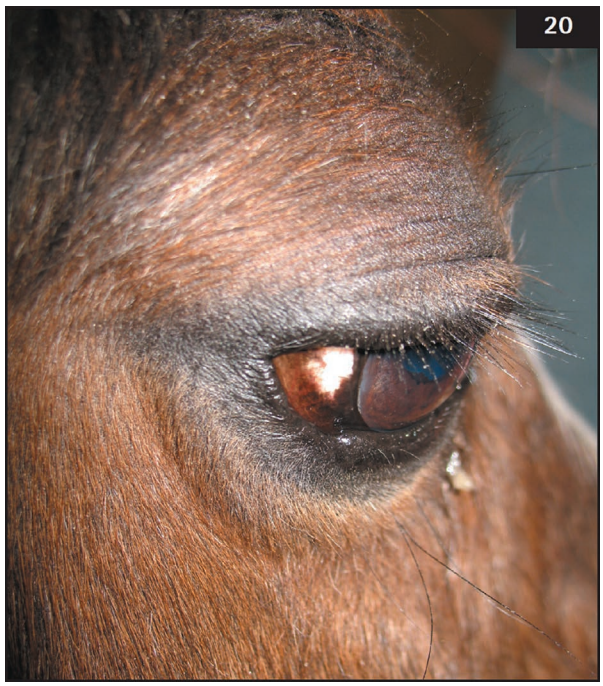
Moraxella spp. were isolated in 88% of horses with pharyngitis of grades III and IV, followed by *Streptococcus equi* subsp. *zooepidemicus*, *Pseudomonas aeruginosa*, coagulase-negative staphylococci, and *Enterobacter* spp. (Hoquet *et al*. 1985).

Management/Treatment

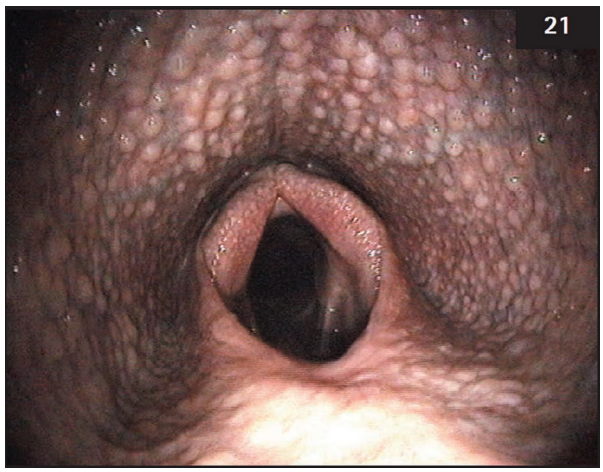
Treatment of diseased animals is supportive.

Public Health Significance

Not convincing yet. *Moraxella catarrhalis* is an exclusively human pathogen and is a common cause of otitis media in infants and children, causing 15–20% of acute otitis media episodes. *M. catarrhalis* causes an estimated 2–4 million exacerbations of chronic obstructive pulmonary disease in adults annually in the USA. Most strains produce beta-lactamase and are thus resistant to ampicillin but susceptible to several classes of oral antimicrobial agents (Murphy & Parameswaran 2009).



20 Eye. *Moraxella* spp. are one of the bacteria most frequently isolated in ocular flora of clinically normal horses, with the likelihood of detecting it depending on the horse's age.



21 Pharynx *in vivo*. The isolation of *Moraxella* spp. and *S. equi* subsp. *zooepidemicus* in large numbers is frequent in horses with lymphoid follicular hyperplasia grades III and IV. However, *Moraxella* spp. are one of the bacteria also most frequently isolated in pharyngeal flora of clinically normal horses. Illustration shows lymphoid follicular hyperplasia grade IV associated with dorsal displacement of the soft palate (DDSP).

Acinetobacter baumannii

Phylum XII Proteobacteria/Class III Gammaproteobacteria/Order VI Moraxellales/Family *Moraxellaceae*/Genus *Acinetobacter*

Definition/Overview

A. baumannii represents nowadays an important veterinary nosocomial pathogen. However, it seems that the majority of *A. baumannii* infections in veterinary medicine are secondary and, as a sequela, might be fatal or lead to euthanasia in some cases (van der Kolk *et al.* 2019). However, clear evidence demonstrating the role of animals for the dissemination of *Acinetobacter* spp. to humans is lacking yet.

Aetiology

The genus *Acinetobacter* comprises more than 50 validly named species of aerobic, rod-shaped, Gram-negative bacteria. Of note, many comprise only one strain, and their ecology is not well-known. They comprise a group of genetically related sugar-non-fermenting, oxidase-negative, Gram-negative, and strictly aerobic cocco-bacilli (Perez *et al.* 2007, Doi *et al.* 2015, Jung & Park 2015). The clinically relevant species are mostly confined to the ACB complex: *A. baumannii*, *A. calcoaceticus*, *A. pittii*, *A. nosocomialis*, and the recently added species *A. seifertii* and *A. dijkshoorniae*, of which *A. baumannii* is the most important one (Ahmed & Alp 2015, Marí-Almirall *et al.* 2017).

An *A. baumannii* isolate recovered from a horse with conjunctivitis comprised a size of 3,839,365 bp and a G+C content of 38.93% and was predicted to contain 3,529 coding sequences. The isolate belonged to sequence type 462 (ST462) according to the Oxford scheme (Abaumannii1) and to ST46 according to the Pasteur scheme (Abaumannii2) (Wareth *et al.* 2019).

Epidemiology

Originally, three international *A. baumannii* clones (the so-called International or European clones I, II, and III with preference of the use of international clones [IC]) have been reported from hospitals (Ecker *et al.* 2006, Peleg *et al.* 2008, Antunes *et al.* 2014, Zarrilli *et al.* 2013). With the introduction of the multilocus sequence typing (MLST) (Higgins *et al.* 2017), these clones I, II, and III have been shown to belong to specific sequence types (STs), which mainly cluster into three clonal complexes (CC), CC1, CC2, and CC3. There are two MLST approaches, the Pasteur (Diancourt *et al.* 2010) and Oxford (Tomaschek *et al.* 2016) schemes, and both of them can identify IC (van der Kolk *et al.* 2019).

Pathophysiology

Bacterial factors known to play a role in the pathogenesis of *A. baumannii* are numerous and versatile, with the virulence factors comprising porins, surface structures like capsular polysaccharides and lipopolysaccharide, phospholipases, iron acquisition systems, outer membranes vesicles, protein secretions systems, regulatory proteins, biofilm-associated proteins, as well as several different types of binding proteins and metabolitic and survival profiles, like utilising peptide nitrogen sources more efficiently and the thickness of biofilms formed, respectively (Cerqueira & Peleg 2011, Peleg *et al.* 2012, Lee *et al.* 2017).

Incubation Period

Not established in the equine species yet.

Clinical Presentation

The organism was isolated from a case of thrombophlebitis (Vaneechoutte *et al.* 2000) and conjunctivitis (Wareth *et al.* 2019). However, several reports indicated that the occurrence of *A. baumannii* in horses has not always been associated with disease (Kester *et al.* 1993, Wood *et al.* 1993, Moore *et al.* 1995, Vaneechoutte *et al.* 2000, Endimiani *et al.* 2011). On the other hand, *Acinetobacter* spp. sepsis and systemic inflammatory response syndrome–associated severe thrombocytopaenia resulting in coagulopathy have been reported in a 48-hour-old orphan Thoroughbred colt (Bentz *et al.* 2002).

Diagnosis

Acinetobacter of the ACB complex can be identified to species level by the use of the MALDI-TOF MS, whereas molecular techniques are still necessary to ensure unambiguous species identification (Rim *et al.* 2015), like PCR detecting of the $bla_{\text{OXA-51-like}}$ carbapenemase gene (Turton *et al.* 2006, Wareth *et al.* 2019, van der Kolk *et al.* 2019).

Pathology

Aspecific inflammatory lesions may be present.

Management/Treatment

Treatment of diseased horses is supportive with treatment preferably based on *in vitro* antimicrobial susceptibility testing as the emergence of carbapenem resistance in clinical *A. baumannii* isolates from animals is obvious (van der Kolk *et al.* 2019).

It is important to avoid the selection and spread of multidrug-resistant *A. baumannii* in animals as it is in humans, use targeted antimicrobial therapy, as well as implement infection control. Among effective control procedures of antimicrobial-resistant *A. baumannii* infections in veterinary hospitals, proper hand hygiene practice is the key (van der Kolk *et al.* 2019).

Public Health Significance

Due to the association of multidrug-resistant *A. baumannii* infections with high mortality, the bacterium has also been classified as an ESKAPE organism (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), a group of pathogens with a high rate of antimicrobial resistance that are responsible for an important part of human nosocomial infections (Rice 2008, Jung & Park 2015). Although the role of animals is still not clear in the dissemination of specific clones into the human community and hospitals, studies have demonstrated that similar or even identical *A. baumannii* clones have been identified in both settings (van der Kolk *et al.* 2019).

Escherichia coli

Phylum XII Proteobacteria/ Class III Gammaproteobacteria/ Order XIII Enterobacteriales/Family I Enterobacteriaceae/ Genus I *Escherichia*: Facultatively anaerobic Gram-negative rods

Definition/Overview

Escherichia coli can cause acute, highly fatal septicaemia of newborn foals. *E. coli* is the most common pathogen isolated from foals with sepsis (**22**) (Wilson & Madigan 1989). In foals, enteropathogenic *E. coli* and subsequent neonatal diarrhoea are very rare (in contrast with pigs and calves) as compared with extraintestinal pathogenic *E. coli* (ExPEC). In the near future, real-time PCR might facilitate fast confirmation of a diagnosis of septicaemia, thereby improving the therapeutic management of neonatal foals.

Aetiology

E. coli are Gram-negative rods belonging to the family Enterobacteriaceae. ExPEC strains carrying distinct virulence attributes are known to cause diseases in humans and animals and infect organs other than the gastrointestinal (GI) tract (**23–25**) (DebRoy *et al*. 2008).

Epidemiology

Gram-positive isolates, predominantly *Streptococcus/ Enterococcus* spp., were obtained in 41% of foals less than 7 days of age admitted to an intensive care unit. Gram-negative isolates were predominantly of the Enterobacteriaceae family, in particular *E. coli* (Russell *et al*. 2008). *E. coli* was also the organism most commonly isolated (in 44% of cases) from foals with bacteraemia in another report, followed by *Actinobacillus* spp. (25%), of which 62% were *A. equuli* (Corley *et al*. 2007). Furthermore, *E. coli* was consistently isolated most frequently in bacteraemic neonatal Thoroughbreds (Sanchez *et al*. 2008). In addition, the most common intraoperative culture isolates from horses undergoing abdominal surgery were *E. coli*, *Streptococcus* spp., and *Enterococcus* spp. (Rodriquez *et al*. 2009), with $bla_{CTX\text{-}M\text{-}1}$ (60%) being the dominant extended-spectrum β-lactamase (ESBL) gene (Kauter *et al*. 2021). In another study dealing with hospitalised horses, $bla_{CTX\text{-}M\text{-}1}$ was the major β-lactamase (79%) (Shnaiderman-Torban *et al*. 2021). ESBL-producing Enterobacteriaceae shedding rate was 12% in Thoroughbred racehorses, with *E. coli* as the main species (91%). The major ESBL gene was CTX-M-1 (55%), with 64% of total isolates defined as multidrug-resistant. Overall, antibiotic treatment in the previous month was found as a prevalence factor for ESBL-producing Enterobacteriaceae shedding (OR = 27.72, 95% CI 1.845–416.555) (Shnaiderman-Torban *et al*. 2020).

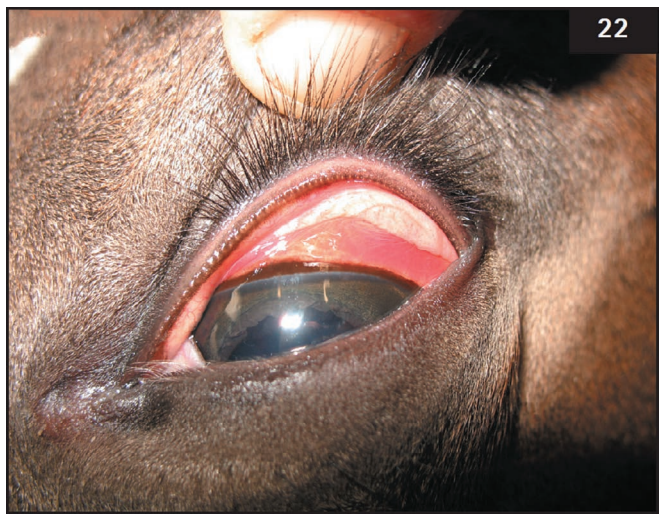
For horses, there was not a significant interaction between populations of the indicator organisms and manure type (fresh versus dry). The population size of faecal streptococci (5.47 and 6.14 log10/g in fresh and dry, respectively) in horse manure was higher than the population size of *E. coli* (4.79 and 5.08 log10/g in fresh and dry, respectively) (Weaver *et al*. 2005). However, *E. coli* of equine faecal origin are commonly resistant to antibiotics used in human and veterinary medicine (Ahmed *et al*. 2010).

Pathophysiology

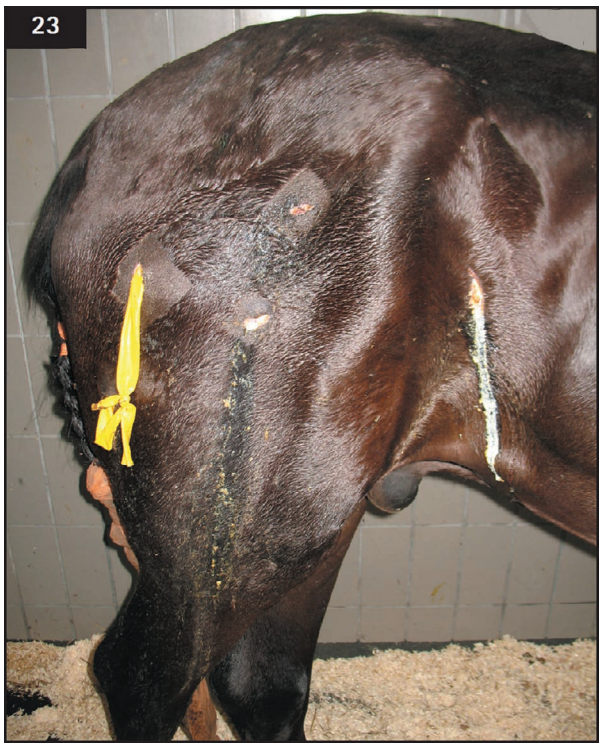
A carbohydrate metabolic operon (frz) that is highly associated with extraintestinal pathogenic *E. coli* strains promotes bacterial fitness under stressful conditions, such as oxygen restriction, late stationary phase of growth, or growth in serum or in the intestinal tract (Rouquet *et al*. 2009).

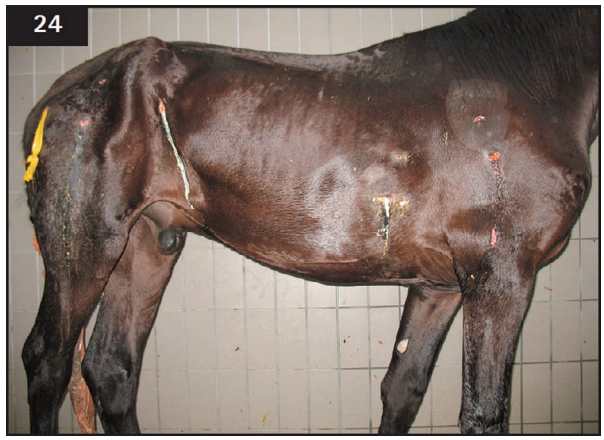
Incubation Period

Not established in the equine species yet but may be as short as several hours.



22 Eye *in vivo*. Marked episcleral haemorrhage and fibrinous conjunctivitis secondary to endotoxaemia in a foal.





23, 24 Hindquarter. External abscessation associated with *E. coli* in a yearling Friesian stallion. Note the yellow drain in one of the abscesses.

25 Eyes. Hypopyon, *E. coli* septicaemia. The anterior eye chamber is filled with a pale yellowish purulent exudate due to a suppurative uveitis. (Formalin fixed specimens.)

Clinical Presentation

Clinical signs include fever (or hypothermia associated with shock), anorexia, and depression/coma. Polyarthritis, polyserositis (including meningoencephalitis), and pneumonia might develop as the most important sequelae in neonatal foals, reflecting a poor prognosis (Corley *et al.* 2007). Of note, *E. coli*, *Rhodococcus equi*, and *Klebsiella pneumoniae* were reported as the most common bacterial pathogens associated with acute interstitial pneumonia in foals (Punsmann *et al.* 2021).

Foals with Gram-negative bacteraemia had lower total WBC and lymphocyte counts at admission than did those from which only Gram-positive bacteria were cultured. Mixed organism bacteraemia was associated with tachycardia, increased serum concentrations of sodium, chloride, and urea nitrogen, acidosis, respiratory distress, recumbency on admission, and nonsurvival (Corley *et al.* 2007). *E. coli* is usually not associated with diarrhoea in foals (Netherwood *et al.* 1996).

ExPEC might also occur in other opportunistic settings in the immunocompromised host. For instance, ExPEC O2H21 has been associated with fatal bronchopneumonia in a 12-year-old Quarter Horse mare in association with *Enterococcus* sp. and *Klebsiella pneumoniae* (DebRoy *et al.* 2008).

Differential Diagnosis

The differential diagnosis includes other causes of foal septicaemia (see p. 267).

Diagnosis

Bacterial culture of blood is the current gold standard test with which to diagnose sepsis in foals. Detection frequency of *E. coli* from equine blood was significantly greater by use of the resin-containing blood culture system (61%) than that achieved by use of the conventional blood culture system (30%) or the lysis-centrifugation-based blood culture system (0%) (Lorenzo-Figueras *et al.* 2006). Furthermore, culturing endometrial biopsy tissue or uterine fluids is a more sensitive method for identifying *E. coli* than culture swab, while endometrial cytology identifies twice as many mares with acute inflammation than uterine culture swab (LeBlanc 2010). Comparison between conventional blood culture and real-time PCR in septic foals revealed a sensitivity of 82%, a specificity of 99%, a positive predictive value of 90%, and a negative predictive value of 97% for real-time PCR (results for the universal bacterial 16S rRNA gene, including *E. coli*, in broth). However, for the foreseeable future, PCR-based testing (able to detect as few as 15 colony-forming units) will not replace conventional culture due to the requirement for purified culture isolates in antimicrobial susceptibility testing (Pusterla *et al.* 2009).

With the increasing prevalence of Gram-positive microorganisms and their unpredictable sensitivity patterns, blood cultures remain important in the diagnosis and treatment of equine neonatal septicaemia (Russell *et al.* 2008).

Pathology

Usually, *E. coli* infections induce a suppurative and fibrinous inflammation, such as in placentitis, pyometra (**26**), cholangitis (**27**, **28**), and (neonatal) septicaemic (lepto)meningitis, serositis, uveitis, and (poly)arthritis.

Management/Treatment

Treatment of diseased foals is supportive (including antibiotic therapy), with special reference to improvement of antibody status by means of the administration of hyperimmune serum. In addition, it is of importance to provide good hygiene, including antiseptic treatment of the umbilical cord stump in neonatal foals.

The MIC of ceftiofur required to inhibit growth of 90% of isolates of *E. coli*, *Pasteurella* spp., *Klebsiella* spp., and beta-haemolytic streptococci was <0.5 µg/ml. Intravenous administration of ceftiofur sodium at the rate of 5 mg/kg BW every 12 hours would provide sufficient coverage for the treatment of susceptible bacterial isolates (Meyer *et al.* 2009). However, the significance of third-generation, cephalosporin-susceptible *Enterobacterales* infections in equine medicine, and their independent detrimental impact on cure rates and mortality, is obvious (Shnaiderman-Torban *et al.* 2021).

Both hospitalisation and antimicrobial drug administration were associated with the prevalence of antimicrobial resistance among *E. coli* strains isolated from the faeces of horses. Resistance to sulfamethoxazole and to trimethoprim-sulfamethoxazole was most common, followed by resistance to gentamicin and tetracycline. Use of a potentiated sulphonamide, aminoglycosides, cephalosporins, or metronidazole was positively associated with resistance to one or more antimicrobial drugs, but use of penicillins was not associated with increased risk of resistance to antimicrobial drugs (Dunowska *et al.* 2006). Prevalence of multidrug resistance (MDR) for *E. coli* was 31.7% in clinical bacterial isolates from horses in the UK (Isgren *et al.* 2021).

On the other hand, a close spatiotemporal relationship between isolates sharing a particular sequence type was revealed by genome analysis, strongly indicating local spread within a veterinary hospital, thereby challenging the local hygiene management system and workplace safety of veterinary staff (Kauter *et al.* 2021).

Public Health Significance

Its potential zoonotic risk should be minimised as, for instance, 46% of the *E. coli* isolates from diarrhoeagenic foals were classified as extraintestinal pathogenic *E. coli* (ExPEC) and hence considered to be potentially pathogenic to humans and animals (Kennedy *et al.* 2018).