Antimicrobial prescribing guidelines for dairy cattle

Acknowledgements

Foreword – antimicrobial prescribing guidelines for dairy cattle

Antimicrobials are one of the most important medical developments of the 20th century and are used to safely treat many common infections in humans and animals. Antimicrobial resistance (AMR) occurs when the microorganisms that cause infection, such as bacteria and viruses, become resistant to medical treatment with antimicrobial agents. Australia was one of the first nations to embark on a comprehensive reform process aimed at protecting humans and animals from the harmful effects of AMR and has remained at the forefront of antimicrobial stewardship globally.

AMR is recognised as a global health priority due to its adverse effects on public health, animal health, welfare and production, and the economy. Inappropriate use of antimicrobials in humans and animals has accelerated the process. A shared One Health approach, working across the human, animal and environmental health sectors, and promoting antimicrobial stewardship across a range of industries, is a key component of how we address AMR.

As a major exporter of high-quality food products, Australia has taken a proactive approach to managing food safety issues, including the use of antimicrobials. Antimicrobials are an essential tool for dairy farmers and veterinarians to ensure the health and welfare of animals in their care. Overall, the Australian dairy industry has very low antimicrobial usage compared to other countries and holds a favourable reputation for low levels of AMR. The industry is therefore well-placed to play a leading role in how we address AMR more broadly across the animal health sector. The dairy industry's 'as little as possible, as much as necessary' method is particularly commendable and demonstrates their commitment to using antimicrobials responsibly.

In closing, I would like to recognise the important stewardship role dairy cattle veterinarians play in promoting the appropriate use of antimicrobials on dairy farms. These best-practice, evidence-based prescribing guidelines have been developed specifically for the dairy industry and will help attending veterinarians make good decisions about their use (or otherwise) of antimicrobials. I extend my sincere thanks to everyone who contributed to the development of these guidelines and urge all dairy cattle veterinarians to apply this advice. In doing so, you will help safeguard the ongoing, long-term efficacy of antimicrobials, deliver best practice veterinary service, and play an integral role in the global response to AMR.

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Australian Chief Veterinary Officer

Associate Professor John House
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John is Associate Professor of Livestock Health and Production and Head of The Livestock Veterinary Teaching and Research Unit at the University of Sydney. He is a registered specialist in livestock medicine with a keen interest in veterinary clinical practice and dairy cattle management. He completed a Bachelor of Science and Bachelor of Veterinary Medical Science at Murdoch University in 1986, became a Diplomate of the American College of Veterinary Internal Medicine in 1994 and completed a PhD in Veterinary Comparative Pathology at the University of California in 1997. As a clinical academic he gets to apply the diversity of skills and resources available in the School of Veterinary Science at the University of Sydney to investigate individual animal and herd level problems. Clinical interests include animal husbandry, medicine, surgery, and reproduction. He enjoys utilising herd records to benchmark performance and investigate herd problems. His main research areas relate to the diagnosis, treatment, management, and prevention of infectious diseases.

Dr Matthew Izzo BVSc(Hons) MVetClinStud DipHRM
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Matt completed his veterinary degree from the University of Sydney in 2004, and after spending a few years working in mixed dairy practice on the south coast of NSW, he returned to Sydney University of Sydney to undertake a residency in Ruminant health and production. Matt completed a Masters degree in the field of neonatal calf diarrhoea in 2009 and became a fellow of the Australian and New Zealand College of Veterinary Scientists in the field of dairy cattle medicine and management in in 2012. Matt is one of the few registered veterinary specialists in dairy cattle in Australia.

Since completing his residency, Matt has worked in large dairy practices in Victoria and Tasmania. Matt is a member of the Apiam Animal Health Antimicrobial Stewardship Working Group and has been active in the development of on farm treatment protocols.

Professor Jacqueline Norris
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Jacqui is Professor of Veterinary Microbiology and Infectious Diseases and Associate Head of Research at the Sydney School of Veterinary Science, at the University of Sydney. She is a registered practicing veterinarian and is passionate about practical research projects and education programs for veterinary professionals, animal breeders and animal owners. Her main research areas include: 1) Development of diagnostics and treatments for companion animal viral diseases; 2) Q fever; 3) Multidrug resistant (MDR) *Staphylococcus* species; 4) Infection prevention and control in veterinary practices; 5) Chronic renal disease in domestic and zoo Felids and 6) Factors influencing antimicrobial prescribing behaviour of vets and health professionals.

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Stephen is a consultant veterinary clinical pharmacologist and toxicologist and founder and sole director of Advanced Veterinary Therapeutics– a consulting company that provides advice on appropriate use of veterinary medicines to veterinarians, veterinary organisations (Australian Veterinary Association, World Veterinary Association, World Organisation for Animal Health), state and national government departments and statutory bodies (APVMA, Department of Agriculture, Department of Health, US Environmental Protection Agency), and global organisations (OIE, FAO, Chatham House).

He is a member of the AVA Antimicrobial of Resistance Advisory Group (ARAG), a member of the ASTAG committee on antimicrobial prioritisation; in 2017 he became President of the ANZCVS Chapter of Pharmacology, and is a Stephen is a consultant veterinary clinical pharmacologist and toxicologist and founder and sole director of Advanced Veterinary Therapeutics– a consulting company that provides advice on appropriate use of veterinary medicines to veterinarians, veterinary organisations (Australian Veterinary Association, World Veterinary Association, World Organisation for Animal Health), state and national government departments and statutory bodies (APVMA, Department of Agriculture, Department of Health, US Environmental Protection Agency), and global organisations (OIE, FAO, Chatham House).

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He has more than 100 publications on which he is author or editor, including chapters on antimicrobial stewardship, clinical pharmacology, adverse drug reactions, use of antimicrobial agents in livestock, and antimicrobial drug discovery and models of infection.

He has been a teacher and facilitator of courses at the University of Sydney on food safety, public health and antimicrobial resistance since 2003.

He is regularly invited to speak nationally and internationally at a broad range of conferences and symposia, especially on the subjects of antimicrobial use, antimicrobial stewardship and risk assessment. He gave his first presentation on veterinary antimicrobial resistance and stewardship at the AVA Conference in Perth in 2000 and remains passionate about improving the use and effective life span of antimicrobial agents.

Professor Glenn Browning BVSc (Hons I) DipVetClinStud PhD FASM

Glenn Browning is Distinguished Professor in Veterinary Microbiology, Director of the Asia-Pacific Centre for Animal Health and Director of Research at the Melbourne Veterinary School at the University of Melbourne. He completed a Bachelor of Veterinary Science with First Class Honours at the University of Sydney in 1983, a postgraduate Diploma of Veterinary Clinical Studies in Large Animal Medicine and Surgery at the University of Sydney in 1984 and a PhD in Veterinary Virology at the University of Melbourne in 1988.

He was a Veterinary Research Officer at the Moredun Research Institute in Edinburgh from 1988 to 1991, investigating viral enteritis in horses, then joined the staff of the Faculty of Veterinary Science at the University of Melbourne, and has been a member of teaching and research staff there since 1991. He teaches in veterinary and agricultural microbiology.

He is a Life Fellow of the Australian Veterinary Association, a Fellow of the Australian Society for Microbiology and Chair of the International Organisation for Mycoplasmology.

He is a co-author of 280 peer reviewed research papers and book chapters, has edited two books on recent progress in understanding the mycoplasmas, and has co-supervised 60 research higher degree students. His research interests include the molecular pathogenesis and epidemiology of bacterial and viral pathogens of animals, the development of novel vaccines and diagnostic assays to assist in control of infectious diseases, and antimicrobial stewardship in veterinary medicine.

Derived from: Page S, Prescott J and Weese S. *Veterinary Record* 2014;175:207-208.
Image courtesy of Trent Hewson, TKOAH.

Core principles of appropriate use of antimicrobial agents

While the published literature is replete with discussion of misuse and overuse of antimicrobial agents in medical and veterinary situations there has been no generally accepted guidance on what constitutes appropriate use. To redress this omission, the following principles of appropriate use have been identified and categorised after an analysis of current national and international guidelines for antimicrobial use published in the veterinary and medical literature. Independent corroboration of the validity of these principles has recently been provided by the publication[1] of a proposed global definition of responsible antibiotic use that was derived from a systematic literature review and input from a multidisciplinary international stakeholder consensus meeting. Interestingly, 22 elements of responsible use were also selected, with 21 of these 22 elements captured by the separate guideline review summarised below.

PRE-TREATMENT PRINCIPLES

1. Disease prevention

Apply appropriate biosecurity, husbandry, hygiene, health monitoring, vaccination, nutrition, housing, and environmental controls. Use Codes of Practice, Quality Assurance Programmes, Herd Health Surveillance

Programmes and Education Programmes that promote responsible and prudent use of antimicrobial agents.

2. Professional intervention

Ensure uses (labelled and extra-label) of antimicrobials meet all the requirements of a bona fide veterinarian-client-patient relationship.

3. Alternatives to antimicrobial agents

Efficacious, scientific evidence-based alternatives to antimicrobial agents can be an important adjunct to good husbandry practices.

DIAGNOSIS

4. Accurate diagnosis

Make clinical diagnosis of bacterial infection with appropriate point of care and laboratory tests, and epidemiological information.

THERAPEUTIC OBJECTIVE AND PLAN

5. Therapeutic objective and plan

Develop outcome objectives (for example clinical or microbiological cure) and implementation plan (including consideration of therapeutic choices, supportive therapy, host, environment, infectious agent and other factors).

DRUG SELECTION

6. Justification of antimicrobial use

Consider other options first; antimicrobials should not be used to compensate for or mask poor farm or veterinary practices.

Use informed professional judgment balancing the risks (especially the risk of AMR selection & dissemination) and benefits to humans, animals & the environment.

7. Guidelines for antimicrobial use

Consult disease- and species-specific guidelines to inform antimicrobial selection and use.

8. Critically important antimicrobial agents

Use all antimicrobial agents, including those considered important in treating refractory infections in human or veterinary medicine, only after careful review and reasonable justification.

9. Culture and susceptibility testing

Utilize culture and susceptibility (or equivalent) testing when clinically relevant to aid selection of antimicrobials, especially if initial treatment has failed.

10. Spectrum of activity

Use narrow-spectrum in preference to broad-spectrum antimicrobials whenever appropriate.

11. Extra-label (off-label) antimicrobial therapy

Must be prescribed only in accordance with prevailing laws and regulations.

Confine use to situations where medications used according to label instructions have been ineffective or are unavailable and where there is scientific evidence, including residue data if appropriate, supporting the off-label use pattern and the veterinarian's recommendation for a suitable withholding period and, if necessary, export slaughter interval (ESI).

DRUG USE

12. Dosage regimens

Where possible optimise regimens for therapeutic antimicrobial use following current pharmacokinetic and pharmacodynamic (PK/PD) guidance.

13. Duration of treatment

Minimise therapeutic exposure to antimicrobials by treating only for as long as needed to meet the therapeutic objective.

14. Labelling and instructions

Ensure that written instructions on drug use are given to the end user by the veterinarian, with clear details of method of administration, dose rate, frequency and duration of treatment, precautions and withholding period.

15. Target animals

Wherever possible limit therapeutic antimicrobial treatment to ill or at-risk animals, treating the fewest animals possible.

16. Record keeping

Keep accurate records of diagnosis (indication), treatment and outcome to allow therapeutic regimens to be evaluated by the prescriber and permit benchmarking as a guide to continuous improvement.

17. Compliance

Encourage and ensure that instructions for drug use are implemented appropriately

18. Monitor response to treatment

Report to appropriate authorities any reasonable suspicion of an adverse reaction to the medicine in either treated animals or farm staff having contact with the medicine, including any unexpected failure to respond to the medication.

Thoroughly investigate every treated case that fails to respond as expected.

POST-TREATMENT ACTIVITIES

19. Environmental contamination

Minimize environmental contamination with antimicrobials whenever possible.

20. Surveillance of antimicrobial resistance

Undertake susceptibility surveillance periodically and provide the results to the prescriber, supervising veterinarians and other relevant parties.

21. Continuous evaluation

Evaluate veterinarians' prescribing practices continually, based on such information as the main indications and types of antimicrobials used in different animal species and their relation to available data on antimicrobial resistance and current use guidelines.

22. Continuous improvement

Retain an objective and evidence guided assessment of current practice and implement changes when appropriate to refine and improve infection control and disease management.

Each of the core principles is important but **CORE PRINCIPLE 11 Extra-label (off label) Antimicrobial Therapy** can benefit from additional attention as veterinarians, with professional responsibility for prescribing and playing a key role in residue minimisation, must consider the tissue residue and withholding period (WHP) and, if necessary, export slaughter interval (ESI) implications of off-label use before selecting this approach to treatment of animals under their care. [2,3]

The subject of tissue residue kinetics and calculation of WHPs is very complex requiring a detailed understanding of both pharmacokinetics (PK) and statistics, as both these fields underpin the recommendation of label WHPs. Some key points to consider when estimating an off-label use WHP include the following:

1   The new estimate of the WHP will be influenced by (i) the off-label dose regimen (route, rate, frequency, duration); (ii) the elimination rate of residues from edible tissues; and (iii) the MRL.

2   Approved MRLs are published in the MRL Standard which is linked to the following APVMA website page: https://apvma.gov.au/ node/10806

3   If there is an MRL for the treated species, then the WHP recommended following the proposed off label use must ensure that residues have depleted below the MRL at the time of slaughter or at the time milk is collected for human consumption.

4   If there is no MRL for the treated species, then the WHP recommendation must ensure that no detectable residues are present at the time of slaughter or at the time of collecting milk for human consumption.

5   Tissue residue kinetics may be quite different to the PK observed in plasma – especially the elimination half-life and rate of residue depletion. The most comprehensive source of data on residue PK is that of Craigmill and colleagues.[4]

6   WHP studies undertaken to establish label WHP recommendations are generally undertaken in healthy animals. Animals with infections are likely to have a longer elimination half-life.

7   There are many factors that influence variability of the PK of a drug preparation, including the formulation, the route of administration, the target species, age, physiology, pathology, & diet.

8   The following figure provides a summary of typical effects on elimination rates associated with drug use at higher than labelled rates and in animals with infections.
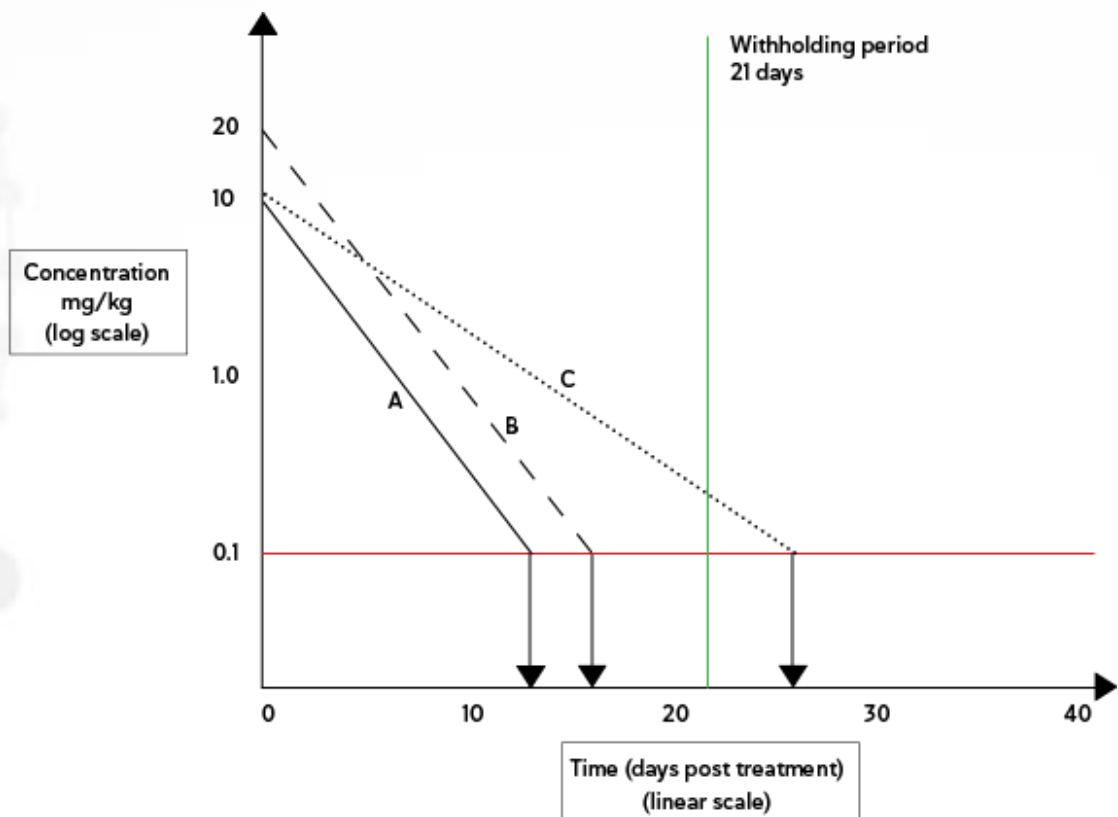
An example of the relationship between the maximum residue limit (MRL) and tissue depletion following administration of a veterinary medicine. In a healthy animal (A), tissue depletion to the MRL often occurs at a time point shorter than the withholding period (WHP) that has been established for the 99/95th percentile of the population. In such an individual animal, if the dose is doubled, tissue depletion (B) should only require one more half-life and would most likely still be within the established WHP. However, if the half-life doubles due to disease or other factors, depletion (C) would now require double the normal WHP and may still result in residues exceeding the MRL (adapted from Riviere and Mason, 2011).[5]

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Third generation cephalosporin use in dairy cattle

Third generation cephalosporins are very important in the treatment of severe and invasive infections in humans and are listed as being of high importance by ASTAG (2018).[6] Therefore, the potential for animals to act as reservoirs of organisms resistant to this category of drugs needs to be considered seriously.

There are a growing number of registered and commercially available products containing ceftiofur that are registered for used in dairy cattle in Australia:

- o Accent® Powder (50mg/mL Ceftiofur sodium) (APVMA 52092)
- o Calefur® Powder (50mg/mL Ceftiofur sodium) (APVMA 62682)
- o Cefomax® Powder (50mg/mL Ceftiofur sodium) (APVMA 64773)
- o Ceftiofur – Ketoprofen Injectable (50mg/mL Ceftiofur hydrochloride + ketoprofen 150mg/mL) (APVMA 90614)
- o Curacef® Duo (50mg/mL Ceftiofur hydrochloride and 150mg/ml Ketoprofen) (APVMA 83071)
- o Ceftiosan™ 50 (50mg/mL Ceftiofur hydrochloride) (APVMA 84894)
- o Eficur® (50mg/mL Ceftiofur hydrochloride) (APVMA 85425)
- o Excede® Sterile suspension (200mg/mL Ceftiofur crystalline free acid) (APVMA 65092)
- o Excenel® (50mg/mL Ceftiofur sodium) (APVMA 45748)
- o Excenel RTU antibiotic suspension for injection (50mg/mL Ceftiofur hydrochloride) (APVMA 50507)
- o Excenel® RTU EZ (50mg/mL Ceftiofur hydrochloride) (APVMA 82351)

All of these products are registered for the treatment of respiratory tract infections in cattle. Despite this, ceftiofur has been used empirically for other conditions, including the treatment of footrot, metritis, septic arthritis and salmonellosis.

Importantly the following label information is an example of a prudent use statement approved by the APVMA (see APVMA 84894):

PRUDENT USE:

Indiscriminate use of ceftiofur can contribute to the development of antibiotic resistance. Culture and sensitivity tests should be performed when appropriate to determine susceptibility of the causative organism(s). Empirical therapy can be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly. It is also advised ceftiofur should be reserved for the treatment of clinical conditions which have responded poorly or expected to respond poorly (refers to very acute cases when treatment must be initiated without bacteriological diagnosis) to first line treatment.

Not to be used for any purpose, or in any manner, contrary to this label unless authorised under appropriate legislation.

One of the factors behind the off-label use of ceftiofur is the zero-milk withholding period (WHP) for treated animals. This has several advantages in dairy production, as treated animals contribute to saleable milk, rather than milk being discarded, and there is no risk of an antibiotic residue penalty due to the accidental addition of milk from a treated animal to the bulk milk. However, from a prudent antimicrobial use standpoint, neither factor amounts to an acceptable rationale for use.

For each of the off-label uses for ceftiofur outlined above, there are alternative treatments, including several efficacious antibiotics with a lower ASTAG importance rating that could and should be used. These are described in these guidelines. Ceftiofur should only be used in situations where culture and susceptibility testing has been performed and there are no other registered antimicrobials that are likely to be efficacious. The most likely scenarios where this will occur is in bovine respiratory disease in lactating animals due to *Mannheimia haemolytica* (for which ceftiofur is registered) and multi-drug resistant salmonellosis. Extreme care must be taken in treating multi-drug resistant salmonellosis with ceftiofur, as there is a significant zoonotic risk for in-contact humans and all necessary infection control precautions should be undertaken when handling these animals.

Table 1. Injectable antibiotic labelled dose and indication

Drug	Label indications	Label dose	Withholding period (milk) #	Withholding period (meat) #
Amoxicillin trihydrate	Amoxicillin susceptible gram-positive and gram-negative pathogenic bacteria	7 mg/kg SC or IM SID	48 h	28 d
Ceftiofur crystalline free acid	Treatment of bovine respiratory diseases caused by *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*	6.6 mg/kg Single SC injection behind the ear	Nil	14 d
Ceftiofur hydrochloride	Treatment of bovine respiratory diseases caused by *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*	1 mg/kg route product dependent SID	Nil	3 - 6 d (product dependant)
Ceftiofur Sodium	Treatment of bovine respiratory diseases caused by *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*	1 mg/kg IM SID	Nil	24 hours
Erythromycin	Treatment of organisms susceptible to erythromycin	2-4 mg/kg IM SID	72 h	14 d
Oxytetracycline dihydrate	Treatment of organisms susceptible to oxytetracycline	20-30 mg/kg Single IM dose. Some products indicate a second dose may be administered in 72 hours	7 d	21-35 d (product dependant)
Oxytetracycline hydrochloride	Treatment of organisms susceptible to oxytetracycline	3-8 mg/kg SID Multiple routes (product dependant)	72-96 h (product dependant)	11-14 d (product dependant)
Procaine penicillin	Treatment of penicillin susceptible organisms	12 mg/kg IM SID	36 h (single) or 72h (multiple)	5 d
Penethamate hydriodide	Treatment of infections due to gram-positive bacteria, mastitis, uterine infections, respiratory infections, and footrot	10-15 mg/kg IM Either 10 g on day one followed by 5 g day 2 or 5 g daily for 3 days	36 h (single) or 72 h (multiple)	5 d
Potentiated sulphonamides	Treatment of organisms susceptible to potentiated sulphonamides	2.66-4 mg/kg trimethoprim 13.3-20 mg/kg sulfadiazine/ sulfadoxine/sulfadimidine Route product dependent Most IM some products IV. SID	36 h (single) or 72 h (multiple)	14-28 d (product dependant)
Tilmicosin	Treatment of bovine respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and other organisms susceptible to tilmicosin	10 mg/kg Single SC Dose	Not to be used in lactating cattle	28 d
Tulathromycin	Treatment of bovine respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* susceptible to tulathromycin	2.5 mg/kg Single SC dose	Not to be used in lactating cattle	35 d
Tylosin	Treatment of tylosin susceptible bacterial and mycoplasmal infections in cattle	5-10 mg/kg IM or slow IV SID	72 h	21 d

All withholding periods (WHPs) are product specific. The label must be consulted to determine the product specific WHP.

PART A: NEONATAL DISORDERS

Umbilical infections

Body system/syndrome

Abdomen

Background/nature of infection/organisms involved

Infection of umbilical structures, including the umbilical arteries, veins, and/or urachus. Inflammation of the umbilical structures may lead to adhesions involving the omentum, abomasum, and small intestines. The prevalence of umbilical infections is variable. Failure of passive transfer is a common risk factor. Poor hygiene of the newborn calf environment, umbilical cord management and navel sucking by other calves also influence the risk of infection. Bacteria commonly associated with umbilical infections include *Trueperella pyogenes, Escherichia coli, Proteus* spp. and *Enterococcus* spp.

Infection may ascend from a contaminated navel or occur secondary to bacteraemia. Concurrent septic diseases that may be observed with umbilical infections include septic arthritis and meningitis. Urachal adhesions to the body wall may compromise urination, predisposing to cystitis. Umbilical hernias may be observed concurrently or develop secondary to umbilical infections and necessitate careful assessment prior to draining suspected umbilical abscesses.

Key issues

- Failure of passive transfer is a common risk factor
- Infection may occur through contamination of the navel or secondary to bacteraemia

Tests for diagnosis

1. Palpation of the umbilical stump
2. Abdominal palpation (umbilical vein, arteries and urachus)
3. Ultrasound (agreement between palpation and ultrasound is generally high (95%))

Treatment

Systemic antimicrobial therapy may be adequate to resolve cases detected early in the course of the disease. Superficial abscessation of the umbilical stump may be treated effectively with surgical drainage. Surgical resection of infected structures is often indicated. Extensive abdominal adhesions may compromise effective surgical resection and should be considered when formulating the surgical plan and prognosis for the patient. If it is not possible to resect abscesses involving the umbilical vein due to extension into the liver, the umbilical vein can be marsupialised to achieve drainage.

Antimicrobials used

- Amoxicillin trihydrate at 10 mg/kg IM every 24 h for 7 days when infection is limited to the umbilicus, and 20 mg/kg IM every 12 h for 7 days when there are concurrent joint infections (note this is an off-label dosage regimen)[7]; or
- Procaine penicillin at 20 mg/kg IM every 24 h for 7 to 10 days (note this is an off-label dosage regimen); or
- Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 7 to 10 days (note this is an off-label dosage regimen)

Prognosis

Variable depending on the structures involved, the presence and extent of adhesions and the involvement of other body systems. The prognosis ranges from good for uncomplicated cases to very poor for cases with extensive adhesions and/or meningitis.

Undifferentiated calf scours

Body system/syndrome

Gastrointestinal

Background/nature of infection/organisms involved

Diarrhoea is the most common disease syndrome in calves less than 4 weeks of age. A diversity of bacterial, viral and protozoal pathogens may be involved, with multiple pathogens frequently isolated from affected calves. A diversity of enteric pathogens is common on commercial dairies. The morbidity and mortality rates on individual farms reflect the success or failure of management to maximise host immunity and minimise pathogen challenge.

Proliferation of *E. coli* in the gastrointestinal tract is observed in calves with diarrhoea regardless of the aetiological agent.[8] Isolation of *E. coli* from faeces is not informative unless the isolate possesses defined virulence attributes, such as those of enterotoxigenic *E. coli*. Approximately one third of calves with severe diarrhoea develop bacteraemia.[9] Clinical parameters associated with an increased risk of bacteraemia include loss of the suckle reflex, dehydration of greater than 6%, weakness, an inability to stand, an age of less than 5 days and a concurrent focus of infection (umbilicus, joint).[8,10] Failure of passive transfer also increases the risk of scouring calves developing bacteraemia. Faecal *E. coli* isolates are not indicative of isolates associated with bacteraemia.

Key issues

- A diversity of bacterial, viral and protozoal pathogens
- Non-specific proliferation of *E. coli* in the gastrointestinal tract of calves with diarrhoea
- Adequate and appropriate sample selection is required to obtain a definitive diagnosis of causative agents
- Prevention has better welfare outcomes and is more productive than treatment
- Fluid therapy for management of dehydration and electrolyte losses is pivotal for effective treatment

Tests for diagnosis

The pathogens most frequently associated with calf scours include *Cryptosporidium* spp., rotaviruses, coronaviruses, enterotoxigenic *E. coli* and *Salmonella* spp. Enterotoxigenic *E. coli* is unlikely to be involved in calves greater than 1-2 weeks of age due to specific age resistance. Coccidia may cause scours in calves from 3 weeks of age. Other pathogens that have been associated with scours in calves include other pathogenic strains of *E. coli*, *Clostridium perfringens, Campylobacter* spp., enteroviruses, noroviruses, nebovirus, torovirus, bredavirus, astrovirus and *Giardia* spp.

The availability of diagnostic tests is generally limited to detection of *Cryptosporidium* spp., rotaviruses, coronaviruses, enterotoxigenic *E. coli*, *Salmonella* spp., coccidia and *Giardia* spp. Faecal flotation may be used to detect *Cryptosporidium* spp. and coccidia, culture techniques to isolate *Salmonella* spp., *E. coli*, and *C. perfringens*, and molecular diagnostics for detection of rotaviruses, coronaviruses, *Salmonella* spp. and *Cryptosporidium* spp. Several antigen-capture enzyme-linked immunosorbent assays (ELISAs) and immunochromatographic assays have been developed for rapid detection of several enteric pathogens. These assays may be useful to facilitate on-farm decision making, but their sensitivity and specificity tend to be less than the laboratory-based diagnostic assays. Diagnostic tests are not readily available for the extended spectrum of pathogens so their respective contributions to disease in Australia is unknown.

Appropriate sample selection is important to achieving a meaningful diagnosis. Healthy calves may shed enteric pathogens and disease outbreaks frequently involve multiple pathogens. Collecting samples from an individual sick calf is unlikely to provide a robust diagnosis for a herd outbreak. Sampling six or more acutely affected calves will provide a clearer indication about which pathogens have a causal relationship with the outbreak. In the context of antimicrobial therapy, bacterial culture and antimicrobial susceptibility testing is relevant for *Salmonella* spp. and enterotoxigenic *E. coli*.

Treatment

The primary treatment for calf diarrhoea is fluid therapy, a topic that is beyond the scope of these guidelines. The recommendation NOT to routinely use antimicrobials to treat undifferentiated calf scours is logical as viral and protozoal enteric pathogens are not susceptible to antimicrobial therapy. Specific indications for antimicrobial therapy include salmonellosis, enterotoxigenic *E. coli* and individual calves with a high risk of bacteraemia. In this section we will discuss antimicrobial treatment of the individual sick calf that has a high risk of bacteraemia. A blood culture may be performed on calves with severe scours and high risk of bacteraemia, but treatment should not be delayed pending bacterial isolation and antimicrobial susceptibility testing. Field research suggests Gram-negative pathogens account for 80% of the bacteraemia observed in calves with severe scours.[11] *Eschericia coli* is the most common bacterial isolate.[10,12] Empirical antimicrobial therapy should include a Gram-negative spectrum.

Antimicrobials used

Antimicrobial therapy is not recommended for scouring calves that are bright and nursing vigorously. Antimicrobial therapy should be instigated where calves are displaying signs of bacteraemia or during outbreaks of disease where a bacterial pathogen has been implicated and mortality rates are high in spite of appropriate fluid therapy. Of the first line antimicrobials available in Australia, amoxicillin has the most robust experimental evidence.[8] Potentiated sulphonamides have more varied outcomes, depending on dose and product. Oxytetracycline is not generally recommended for treatment of calf scours, although the spectrum of activity covers *E. coli* and other Gram-negatives.[8] The experimental trials that have evaluated antimicrobial treatments have been conducted in Europe and the USA, where the prevalence of resistance to tetracyclines is frequently higher. Ceftiofur has an appropriate spectrum of activity. Ceftiofur should not be used indiscriminately. Ceftiofur use should only be used when antimicrobial susceptibility testing indicates that the target pathogen is resistant to first line options.

First line

- o Amoxicillin trihydrate at 10 mg/kg IM every 12 h for 3 to 5 days (note this is an off-label dosage regimen); or
- o Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 24h for 3 to 5 days

Second line

- o Oxytetracycline hydrochloride at 10 mg/kg IM every 24h for 3 to 5 days (note this is an off-label dosage regimen)

Not generally recommended as first line antimicrobial for calves with diarrhoea, but may be utilised for susceptible organisms.

Third line

- o Ceftiofur sodium 5 mg/kg IM q24h for 3 to 5 days (note this is an off-label dosage regimen). Use should be reserved for scenarios where culture and susceptibility testing has demonstrated that resistance to first line drugs limits their use.

Prognosis

The prognosis for undifferentiated diarrhoea varies according to farm management. Failure of passive transfer of colostral antibody, poor nutrition, environmental contamination, and environmental stressors may contribute to high morbidity and mortality. Appropriate fluid therapy is the foundation for correction of dehydration, acid-base imbalances, and electrolyte and energy deficits. A high incidence of calf scours (> 20%) should trigger a review of calf management. A high mortality rate (> 20%) associated with calf scours should prompt a review of treatment protocols, particularly fluid therapy protocols.

Abomasal bloat

Body system/syndrome

Gastrointestinal

Background/nature of infection/organisms involved

This is a sporadic condition characterised by a rapid onset of abdominal distension, depressed attitude, occasional signs of colic and often death within 48 hours. Affected calves may be seen to grind their teeth and salivate. Diarrhoea may or may not accompany these signs. Severely affected calves become dehydrated and acidotic. Most affected animals are under 3 weeks of age. Risk factors include high osmolality milk replacers or oral electrolyte solutions, improper mixing of milk replacers, feeding a large volume of milk in a single daily feeding, cold milk (or milk replacer), not offering water to calves, erratic feeding schedules and failure of passive transfer.[13]

The aetiology of abomasal bloat is unknown but probably involves bacteria that produce gas as well as an event that slows down abomasal emptying. The most frequently incriminated bacterial pathogens include *Clostridium perfringens*, along with *Campylobacter* spp. and *Sarcina spp.*[14,15]

Key issues

- Acute disease of uncertain aetiology
- Calves tend to deteriorate rapidly; treatment is more effective following early intervention

Tests for diagnosis

Diagnosis is based on the history and clinical presentation.

Treatment

Treatment is aimed at relieving tympany, stopping microbial proliferation and providing supportive care. The abomasum may be deflated by paracentesis or passage of a stomach tube. Paracentesis is more effective when the calf is placed in dorsal recumbency.[16] Paracentesis with the calf in a standing position carries a higher risk of inducing peritonitis and fails to completely drain the abomasum.[16,17] If tympany recurs following paracentesis, a right flank laparotomy is performed to correct a potential abomasal torsion.[18] Passing a stomach tube with the calf in a standing position is also usually ineffective. Elevating the front of the calf until the calf is sitting or standing in a near vertical plane facilitates passage of gas out of the abomasum into the reticulorumen. The tube should be gently moved back and forth several centimetres while the calf is held in this position. Before the tube is removed, procaine penicillin (10 mL of 300 mg/mL) is administered into the tube, followed by a cup or two of warm water to wash the medication out of the tube and into the stomach. This anecdotal treatment is intended to slow bacterial proliferation, fermentation and gas production. Intravenous fluids are administered to correct dehydration, and electrolyte and metabolic derangements. Systemically administered oxytetracycline is reported to slow production of toxins more rapidly than penicillin.[19]

Antimicrobials used

- Oxytetracycline hydrochloride at 10 mg/kg by slow IV injection, followed by administration at 10 mg/kg IM every 24 h for 3 days (note this is an off-label dosage regime); or
- Procaine penicillin at 3000 mg by stomach tube (note this is an off-label dosage regimen)

Prognosis

Guarded, and influenced by the timing of the intervention. Mortality rate of 50 to 60 %.

Septic arthritis

Body system/syndrome

Musculoskeletal

Background/nature of infection/organisms involved

"Joint ill" or septic arthritis in calves is most frequently a result of haematogenous spread and infrequently secondary to extension from soft tissue wounds and penetrating wounds. Polyarthritis is common after haematogenous spread. Bacteraemia in calves may be secondary to enteritis, pneumonia or omphalitis, with failure of passive transfer an underlying risk factor. In a recent study of 64 cases, 25% of calves with septic arthritis had an umbilical infection, 23% had bronchopneumonia, and 19% had diarrhoea.[20] Septic arthritis may also be associated with septic physitis. Common bacterial isolates include *E. coli, Salmonella* spp., *Mycoplasma* spp., *Streptococcus* spp. and *Trueperella pyogenes*. *Trueperella pyogenes* is more frequently isolated from the joints of older calves.[20-23] The prevalence of the different pathogens on different farms depends on the endemicity of *Mycoplasma* spp. and *Salmonella* Dublin on the farm. On farms that are free of *Mycoplasma* spp. and *Salmonella* Dublin, Gram-positive pathogens are likely to predominate.[20]

Key issues

- Septic arthritis should normally be an infrequent sporadic disease. An increasing prevalence should trigger diagnostic investigation as it may reflect incursion of *Mycoplasma* spp. or *Salmonella* Dublin into the herd. Alternatively, it may reflect calf management failures, most frequently relating to poor colostral antibody transfer and or contamination of the calving environment.

Tests for diagnosis

Field diagnosis of septic arthritis is based on the patient history, clinical signs (joint swelling and lameness, concurrent disease) and the turbid appearance of a joint fluid aspirate. Ultrasound is useful for evaluating periarticular and tenosynovial structures prior to collecting joint fluid to avoid iatrogenic contamination of the joint during arthrocentesis. Joint fluid may be submitted for cytological analysis and bacterial culture. Aseptic collection of samples into a blood culture bottle is recommended. Cytological findings consistent with septic arthritis include a synovial fluid total protein concentration greater than 45 g/L, a nucleated cell count greater than 25,000 cells/mL with more than 80% of the cells polymorphonuclear.[24] The rate of recovery of bacteria from septic joints is reported to be around 60%.[25] Bacteria are infrequently seen on cytology, even if they are recovered by culture, so the absence of visible bacteria does not exclude a diagnosis of septic arthritis. The synovial fluid may be normal in cases of septic physitis that do not extend into the joint. Radiographs, while not commonly performed on livestock in the field, are useful for detection of bone lysis, which indicates infection. Lytic changes take 10 – 14 days to become detectable and may be missed in early cases. Radiographic features of septic arthritis include soft tissue swelling, widening or collapse of the joint space, osteoporosis and osteosclerosis.

Treatment

Effective joint lavage may be achieved using aseptically placed needles in acute joint infections. Joint lavage is often compromised by accumulations of fibrin in more chronic disease.[26] Alternative strategies for joint lavage include using a teat canula, arthroscopy or arthrotomy.[27]

Antimicrobial selection will be influenced by the specific pathogens isolated. Sporadic cases in young calves are most likely to be caused by Gram-negative organisms (*E. coli*), whereas *Truperella pyogenes* is a more common isolate in older calves. Disease outbreaks are most likely to reflect infection with *Mycoplasma* spp. or, less frequently, *Salmonella* Dublin. Establishing a diagnosis in disease outbreaks is important. *Mycoplasma* spp. and *Salmonella* Dublin have significant management implications and, in the case of *Mycoplasma* spp., significant treatment implications. Prolonged (4 – 8 weeks) antimicrobial therapy is commonly required for treatment of septic arthritis. Continuing antimicrobial therapy for a minimum of 2 weeks following clinical improvement in lameness is recommended.[20]

Significant inflammation and pain are associated with septic arthritis. Treatment with non-steroidal anti-inflammatory drugs and application of supportive bandages following joint lavage may mitigate joint swelling and discomfort.

Antimicrobials used

Amoxicillin, TMS and ceftiofur are treatment options for septic arthritis that is not caused by *Mycoplasma* spp. *Mycoplasma* spp. do not possess a cell wall, so beta-lactam antimicrobials are ineffective, and they do not synthesise folic acid and are therefore intrinsically resistant to sulfonamides and trimethoprim. Tulathromycin and oxytetracycline are treatment options for infection with *Mycoplasma* spp. in non-lactating dairy replacements.

- o Amoxicillin trihydrate at 10 mg/kg IM every 12 h for a minimum of 14 days (note this is an off-label dosage regimen); or
- o Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 24 h for a minimum of 14 days; or
- o Ceftiofur sodium at 5 mg/kg IM every 24 h for a minimum of 14 days (note this is an off-label dosage regimen). Use should be reserved for scenarios where culture and susceptibility testing has demonstrated that resistance to first line drugs limits their use.

For *Mycoplasma* spp.

- o Tulathromycin at 2.5 mg/kg SC every 5 days (note this is an off-label dosage regimen); or
- o Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for a minimum of 14 days (note this is an off-label dosage regimen)

At a group level, septic tenosynovitis/arthritis caused by mycoplasmas is commonly associated with otitis media and pneumonia. In the authors' experience, tulathromycin has been more efficacious than oxytetracycline in treating calves with mycoplasmosis.

Prognosis

Poor – the prognosis is influenced by the timing of treatment relative to the onset of disease. The recovery rate reported for septic arthritis ranges from 40 – 70%,[20,28] but these reports originate from veterinary teaching hospitals following intensive care and prolonged antimicrobial therapy. Septic arthritis is a painful condition. Cases are often presented with chronic disease following irreversible damage to the joint/s. Euthanasia is likely to be the best welfare outcome when treatment options are limited.

Neonatal sepsis

Body system/syndrome

All

Background/nature of infection/organisms involved

Septicaemia is most frequently observed in calves less than 4 weeks of age. Infection may be via the gastrointestinal tract or secondary to bacterial colonization of another site such as the umbilicus. Failure of passive transfer is a common risk factor. Calving cows in a contaminated environment and environmental stressors (cold, heat, wet), inadequate nutrition, and micronutrient deficiencies may also contribute to an increased risk.

Depressed mentation and a lack of suckling ability or interest in nursing are early non-specific clinical signs. Fever is inconsistent. Tachycardia, tachypnoea, hyperaemia of the mucous membranes and scleral injection are frequently observed. Uveitis and hypopyon are observed in some cases. Capillary fragility may result in petechiae on mucous membranes. Severely affected calves become hypotensive, manifested by a slow capillary refill, diminished peripheral pulse and cold extremities. Diarrhoea and dehydration are common. Bacteraemia may lead to focal infections in joints, meninges, heart valves or growth plates. Eighty percent of bacterial isolates are Gram-negative, with *E. coli* the most common species.[12] Other common causes include *Salmonella, Campylobacter, Klebsiella* and *Staphylococcus* species.

Key issues

- Sepsis in neonates progresses rapidly.
- Early antimicrobial treatment is more likely to be successful. Gram negative organisms are likely to be involved, requiring broad spectrum antimicrobial cover.

Tests for diagnosis

Laboratory findings consistent with septicaemia include neutrophilia or neutropenia and increased band cells. Hyperfibrinogenaemia is common. Thrombocytopaenia may be present in severe cases. Metabolic acidosis may be observed in severe cases following circulatory collapse. Definitive diagnosis of septicaemia is based on a positive blood culture, which is infrequently performed in clinical practice. Aseptic collection of two samples into a blood culture bottle is recommended. Bacterial isolation enables antimicrobial susceptibility testing.[29] Cultures of other body fluids, such as joint or cerebrospinal fluid, when indicated, provide alternative options for bacterial isolation.

Treatment

The goals of treatment are to control the infection, attenuate the inflammatory cascade and to provide supportive care to maintain hydration, acid-base and electrolyte balance, and thermoregulatory and nutritional status.

Antimicrobial therapy should be initiated as soon as possible. Intravenous administration is recommended for the initial treatment if an appropriate preparation is available. Initial broad-spectrum antimicrobial cover with robust Gram-negative cover is indicated. Procaine penicillin does NOT have an appropriate Gram-negative spectrum to treat sepsis in neonates. Ideally the antimicrobial selected should be bactericidal. Performing a culture permits antimicrobial susceptibility testing to be performed, allowing for adjustment of antimicrobial therapy should there be a poor response to the initial antimicrobial selected.

Ancillary treatments include non-steroidal anti-inflammatory drug therapy to mitigate the inflammatory cascade associated with endotoxemia, and fluid therapy to correct dehydration, and electrolyte and acid-base derangements. Environmental and nutritional support are important. Providing nutritional support can be difficult, as septic calves are often inappetent and/or nurse poorly. Tube feeding is an option, but it is important to check for abdominal distension prior to tubing calves as ileus can be a problem and overloading a poorly functioning gastrointestinal system can lead to abdominal pain and excessive fermentation, leading to acidosis. The objective is to feed 10% to 15% of the calf's body weight of milk each day. Feeding small amounts 3 to 4 times per day is generally tolerated better than larger infrequent feeds.

Antimicrobials used

- o Amoxicillin trihydrate at a loading dose of 20 mg/kg, followed by 10 mg/kg IM every 12 h for 10 days (note this is an off-label dosage regimen); or
- o Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 24 h for 10 days; or
- o Oxytetracycline hydrochloride at 10mg/kg IV initially, then 10 mg/kg IM every 24 h for 10 days (note this is an off-label dosage regimen); or
- o Ceftiofur sodium at 5 mg/kg IM every 24 h for 10 days (note this is an off-label dosage regimen). Use should be reserved for scenarios where culture and susceptibility testing has demonstrated that resistance to first line drugs limits their use.

Prognosis

Guarded to poor – treatment success is influenced by the timing of treatment. If affected calves are treated quickly, favourable outcomes are possible. The prognosis is compromised when infection disseminates into sites such as the meninges.

Meningitis

Body system/syndrome

Neurological

Background/nature of infection/organisms involved

Calves with meningitis often present with a history of prior treatment for diarrhoea or sepsis. Affected calves are often described as "dumb", as they have a depressed, ineffectual suckle reflex. Calves may appear to have a stiff neck and resist flexion of the neck. Neurological signs may include depressed mentation, tremor, hyperaesthesia, opisthotonos, convulsions and coma. Affected calves often have evidence of a septic process, such as omphalophlebitis, septic arthritis or hypopyon. Meningitis is frequently a sequela of generalised sepsis, with failure of passive transfer a significant risk factor. The Gram-negative enteric bacteria, such as *E. coli, Enterobacter* spp., and *Salmonella* spp. that are associated with sepsis in calves also cause meningitis.

Key issues

- Most commonly seen following sepsis or diarrhoea
- Poor prognosis – euthanasia is often the most appropriate option

Tests for diagnosis

A presumptive diagnosis of bacterial meningitis is usually based on the clinical presentation. A definitive diagnosis is based on an abnormal cerebrospinal fluid (CSF). Collection of CSF from the lumbosacral space is easy and safe in calves. Increased turbidity and an elevated CSF protein and white blood cell count are consistent with meningitis. Cytologically, neutrophils predominate in the CSF of calves with acute disease. Mononuclear cells may be observed in calves with chronic disease. Bacteria may be observed in the CSF of approximately 50% of cases.

Treatment

The prognosis for meningitis in calves is poor. Treating calves in commercial farming operations is unlikely to be successful. Euthanasia is the best option for calves where ongoing intensive care cannot be provided.

If treatment is to be attempted, antimicrobial therapy should include an agent with a Gram-negative and Gram-positive spectrum. The major determinant of CSF penetration is lipid solubility. Lipophilic drugs distribute more readily into the CSF, although in cases of meningitis the blood-brain barrier may be compromised, and drug access enhanced. Distribution of polar drugs into the CSF is based on a diffusion gradient. Drugs that have a high safety margin may be administered at a higher dose.

Antimicrobials used

- Amoxicillin trihydrate at a loading dose of 20 mg/kg, followed by 10 mg/kg IM every 12 h for 10 days (note this is an off-label dosage regimen); or
- Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 24 h for 10 days; or
- Oxytetracycline hydrochloride at 11.1 mg/kg IM every 24 h for 10 days (note this is an off-label dosage regimen); or
- Ceftiofur sodium at 5 mg/kg IM every 24 h for 10 days (note this is an off-label dosage regimen). Good antimicrobial spectrum Use should be reserved for scenarios where culture and susceptibility testing has demonstrated that resistance to first line drugs limits their use.

Prognosis

Poor – aggressive early treatment can be successful, but even with good supportive care the mortality rate is high. Euthanasia is indicated for calves where intensive supportive care is not available.

Vertebral body abscess

Body system/syndrome

Musculoskeletal - neurological

Background/nature of infection/organisms involved

Osteomyelitis and vertebral body abscesses may be a sequel of bacteraemia following neonatal septicaemia or pneumonia.[30] The frequent isolation of *Trueperella pyogenes* from vertebral body abscesses in cattle suggests that chronic respiratory tract infections may be a source of infection.[31,32] Vertebral body abscesses may also be observed secondary to inappropriate needle placement of vaccines in the neck of calves. Clinical presentations may include neck stiffness, ataxia, and partial or complete paralysis. Involvement of cervical vertebrae may be palpable in affected calves.

Vertebral body abscesses tend to present following impingement on the spinal cord. Pressure on the cord may reflect soft tissue swelling in the area, distortion, or pathological fracture of the affected vertebrae. Compromised neurological function is frequently a determinant of patient outcome.

Key issues

- Uncommon sequelae following bacteraemia
- Prognosis generally poor despite treatment due to neurological deficits

Tests for diagnosis

Establishing a definitive ante-mortem diagnosis can be difficult without access to radiographic equipment. A tentative diagnosis based on characteristic clinical signs and a history of sepsis or recent vaccination in the neck is supported by a finding of hyperfibrinogenaemia and/or hyperglobulinaemia. Vertebral abscesses do not usually infiltrate the meninges, so the CSF is either normal or has only a mild elevation of protein and/or a mild pleocytosis.[30,31]

Treatment

Successful treatment of individual cases has been described with surgical drainage and antimicrobial therapy. The probability of treatment success is low. Euthanasia is recommended for commercial animals. Valuable animals may be referred for a more comprehensive workup to evaluate opportunities for drainage and curettage. If access to the site is limited, long term antimicrobial therapy may be attempted. The efficacy of antimicrobials in treatment of osteomyelitis in cattle is limited. The beta-lactams have limited bone penetration, and *Trueperella pyogenes*, the organism most commonly implicated in vertebral body infections, has variable susceptibility to oxytetracycline, which has better bone penetration. Usually the site of the infection precludes sample collection for antimicrobial susceptibility testing in a field setting.

Antimicrobials used

- Procaine penicillin at 20 mg/kg every 24 h for 14 days (note this is an off-label dosage regimen); or
- Amoxicillin trihydrate with a loading dose of 20 mg/kg, followed by 10 mg/kg IM every 12 h for 10 days (note this is an off-label dosage regimen); or
- Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 14 days (note this is an off-label dosage regimen).

Prognosis

Poor - most cases present with neurologic deficits. Euthanasia is recommended for commercial animals.

Necrotic laryngitis (calf diphtheria)

Body system/syndrome

Respiratory

Background/nature of infection/organisms involved

Necrotic laryngitis is a common cause of inspiratory dyspnoea and stridor in cattle, predominantly affecting calves less than 6 months of age. Calves are often febrile, anorexic, have a foul breath and often exhibit open mouth breathing. Stridor is initially most pronounced on inspiration. The disease is postulated to be initiated by mechanical irritation of the laryngeal mucosa causing ulceration. Necrosis is associated with colonisation by and proliferation of *Fusobacterium necrophorum* in the mucosa and arytenoid cartilages.

Key Issues

- Inflammation leads to swelling of soft tissue in the larynx, compromising the airway, and can result in severe dyspnoea.
- Infection and necrosis of the arytenoid cartilage can lead to prolonged clinical signs requiring protracted treatment.
- Several surgical options are described for managing cases refractory to medical management.

Tests for diagnosis

Diagnosis of necrotic laryngitis is based on the clinical presentation. Application of gentle pressure across the larynx exacerbates the stridor and may occlude the airway, confirming the origin of the stridor. Endoscopy is useful, but it is not commonly used in livestock practice.

Treatment

Necrotic laryngitis is frequently detected when clinical signs of dyspnoea with stridor are evident. Airway compromise induced by necrotic laryngitis may cause asphyxiation and death. As the airway becomes narrowed, turbulence increases, further contributing to inflammation and narrowing of the airway. Short acting corticosteroids, rather than NSAIDs, are indicated with acute presentations to reduce laryngeal oedema and assist breathing. A tracheotomy with insertion of a tracheostomy tube may be required in very compromised calves.

Fusobacterium necrophorum is generally sensitive to penicillin. Necrosis of the laryngeal cartilage is common. Necrotic cartilage is slow to heal so treatment needs to be continued for several weeks. Heat stress exacerbates clinical signs. Affected calves should be provided with shade during hot weather.

Calves that show no improvement after 2 to 3 weeks of antimicrobial therapy are unlikely to respond and may be managed surgically. Surgical options to provide symptomatic relief for severe dyspnoea include tracheostomy, laryngotomy or tracheolaryngostomy.[33]

Antimicrobials used

Penicillin has good activity against *Fusobacterium necrophorum*. Penicillin is less tissue reactive than most oxytetracycline formulations, which is desirable when longer term therapy is needed, as there is the potential to cause significant muscle soreness.

- Procaine penicillin at 20 mg/kg IM every 24 h for 2 to 3 weeks (note this is an off-label dosage regimen); or
- Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 2 to 3 weeks (note this is an off-label dosage regimen).

Prognosis

Fair if detected early, but poor if there is significant dyspnoea/stridor on presentation. Failure of medical management generally reflects the presence of necrotic cartilage rather than antimicrobial resistance.

PART B: POST WEANING

Coccidiosis

Body system/syndrome

Gastrointestinal

Background/nature of infection/organisms involved

Coccidiosis is caused by the protozoan *Eimeria spp*. There are at least 13 different *Eimeria* species that infect cattle, but the most common and pathogenic are *Eimeria zurnii*, *Eimeria bovis* and *Eimeria alabamensis*. These intracellular pathogens primarily infect the epithelium of the distal ileum and large intestine.

Factors that predispose to the development of coccidiosis include nutritional, climatic and management stressors, and inter-current disease. Coccidiosis is most commonly observed in young stock kept in calf rearing/weaner paddocks that have become heavily contaminated because of multiple years of use or when a coccidiostat is omitted from supplementary concentrates fed to calves/weaners.

Coccidiosis usually presents as a high morbidity, moderate mortality outbreak in animals between 3 and 6 months of age. Clinical signs include profuse foetid diarrhoea, dysentery and haematochezia. Severe tenesmus with partial eversion of the rectal mucosa and rectal prolapse are common features. Chronic diarrhoea is often seen, with affected animals becoming cachectic and anorexic. Necropsy findings are haemorrhagic enteritis of the distal ilium, caecum and colon.

Key issues

- Common cause of diarrhoea post-weaning.
- Several risk factors are usually required for disease to occur.

Tests for diagnosis

1. Faecal flotation using a hypertonic salt flotation method. Oocysts can be present in normal calves, so semi-quantitative methods are best for presumptive diagnosis of disease. Oocysts are first detected in faeces 2 to 4 days after the onset of diarrhoea. A count of 5000 oocysts per gram is considered significant. Counts over 100,000 oocysts/g are common in acute infections. The output of oocysts following an acute infection falls rapidly after the peak, so clinically affected animals may have low oocyst counts.[34]
2. Mucosal scrapings or impression smears of the large intestine to visualize protozoa.
3. Histopathology findings of loss of epithelium, villous atrophy and the presence of intra-cellular parasites. Small, white cyst-like bodies are formed by large schizonts on the tips of the villi of the terminal ileum.

Treatment

Affected animals should be moved from heavily infected paddocks as soon as possible. Where possible, sick calves should be isolated from healthy animals. Supportive therapy, such as oral or parenteral fluid therapy, should be used as required. Anti-coccidial treatment should be commenced on all affected animals.[35]

Anticoccidial/Antimicrobials used

- Toltrazuril at 15 mg/kg orally as a single treatment; or
- Sulfadimidine at 140 mg/kg orally every 24 h for 3 to 5 days

Prevention

Anti-coccidial drugs are effective in preventing clinical disease and decreasing oocyte excretion when used prophylactically.

- Toltrazuril at 15 mg/kg orally as a single treatment will prevent excretion of oocysts for approximately 21 days; or

- o   Ionophores (monensin sodium or lasalocid) can be provided in-feed. Medicated feed should be provided for a minimum of 28 days prior to the expected period of exposure and continued until active immunity develops at approximately 6 months of age. Recommended dose rates for prevention of coccidiosis for monensin are 16-33 g/tonne of feed and for lasalocid 1 mg/kg of bodyweight, which equates to approximately 40 mg/kg of feed.

Prognosis

The overall prognosis is good for animals that are treated early in the disease process. Prognosis is guarded for severely affected cases

Yersiniosis

Body system/syndrome

Gastrointestinal

Background/nature of infection/organisms involved

Yersinia pseudotuberculosis, and less commonly *Yersinia enterocolitica*, are responsible for sporadic cases of enteritis in post-weaning and yearling cattle. The Gram-negative bacteria are a common inhabitant of the intestine of many domestic species.

Predisposing risk factors, such as environmental, nutritional or management stressors, are usually required for disease to occur. Disease is more common in cold, wet weather, and is seen more frequently in winter and spring. Concurrent intestinal parasitism and infection with bovine viral diarrhoea virus (BVDV) can also predispose animals to disease.

Clinical signs of disease include chronic diarrhoea, which may contain mucous or blood, depression, dehydration, decreased growth rates, anorexia and cachexia. Lesions seen at necropsy include ulcerative enterocolitis, villous atrophy and micro-abscessation in the intestinal wall.

Key issues

- Predisposing stressors are usually required for clinical disease.
- A cause of chronic diarrhoea in yearling cattle.

Tests for diagnosis

1. Faecal culture in live animals.
2. Culture of jejunum, ileum, colon and mesenteric lymph node samples collected at necropsy
3. Histopathological examination of samples of the jejunum, ileum, colon and mesenteric lymph nodes

Treatment

For individual animals, correction of dehydration with parenteral and oral fluid therapy and antimicrobial therapy are required. For large outbreaks, providing ample high-quality feed and antimicrobial therapy are recommended.

Antimicrobials used

Most isolates show *in vitro* susceptibility to aminoglycosides, tetracyclines, sulphonamides and trimethoprim/sulphonamide. The trimethoprim/sulphonamide combination has been reported to be ineffective in a clinical setting

- o   Oxytetracycline dihydrate at 20 mg/kg IM once.

Prognosis

Prognosis is generally good except in severely debilitated cases.[36]

Infectious bovine keratoconjunctivitis (IBK, pink eye)

Body system/syndrome

Ocular

Background/nature of infection/organisms involved

Infectious bovine keratoconjunctivitis is the most common ocular disorder of cattle. The primary aetiological agent is the Gram-negative rod-shaped organism, *Moraxella bovis*. In recent years, a secondary agent, *Moraxella bovoculi*, has been isolated from cattle with clinical disease but the role of this organism in the pathogenesis of keratoconjunctivitis is unclear, as experimental infection studies have failed to induce disease.

The disease is most commonly seen in young stock. Outbreaks can be significant, with up to 100% morbidity in some mobs. Several risk factors are important in the pathogenesis of infectious bovine keratoconjunctivitis, including flies, ultraviolet radiation and mechanical trauma from dust and mature forage.

Despite the efficacy of antimicrobial therapy, treatment of affected cattle has many disadvantages and the prevention of IBK is therefore preferable. Minimising spread of disease in an outbreak could include isolation of affected animals, reducing exposure to dust and the use of fly control products such as insecticidal pour-on or impregnated ear tags. If possible, exposure to environmental irritants such as grass awns and dust should be limited. A *Moraxella bovis* vaccine, which provides protection from the majority of strains that cause disease, is useful in preventing disease if administered at least 4 weeks prior to the key risk period. The commercial vaccine is targeted at the pili of *Moraxella bovis*. As the pili expressed by different *M. bovis* strains can vary, vaccination failure can occur if an outbreak is caused by an *M. bovis* strain that has pili that are not included in the vaccine.

Clinical signs of infectious bovine keratoconjunctivitis include corneal ulceration and oedema, photophobia, blepharospasm, lacrimation and epiphora. In more severe cases, corneal rupture can occur, resulting in permanent blindness.

Key issues

- Most common ocular disease of young cattle.
- Risk factors are important in the pathogenesis.

Tests for diagnosis

1. Aerobic culture of ocular swabs from affected eyes.

Diagnostics are generally only performed if there is a poor response to treatment or during an investigation of an apparent breakdown in vaccination.

Treatment

Treatment of individual clinical cases includes systemic, sub-conjunctival or topical antimicrobial therapy and cloth patching of affected eyes to reduce dissemination by flies and to provide patient comfort, as affected stock are photophobic.

Treatment with NSAIDs can be used to reduce ocular inflammation and improve comfort. The addition of dexamethasone in sub-palpebral injections has not been shown to improve recovery compared to antimicrobial therapy alone and may increase the risk of corneal perforation.[37]

The efficacy of sub-conjunctival penicillin administration is variable, with a notable difference in outcome reported between superior palpebral subconjunctival and bulbar conjunctival routes of administration. Superior palpebral subconjunctival injection of penicillin is not effective.[37]

Two doses of bulbar subconjunctival penicillin (300 mg) administered 48 hours apart provides a similar reduction in corneal ulcer healing time to parenteral administration of long-acting oxytetracycline (20 mg/kg IM), however corneal ulcer recurrence is higher following bulbar subconjunctival treatment.[38,39]

Surgical treatment options including third eyelid flaps and temporary tarsorrhaphy are commonly used, but there is no evidence to support the benefits of either option.

Antimicrobials used

Moraxella bovis and *Moraxella bovoculi* are generally considered to be susceptible to a variety of antimicrobials *in vitro*.

The primary antimicrobials that should be considered are:

Small number of animals affected:

- o Benzathine cloxacillin 250 mg topically, (treatment of the affected and unaffected eye is recommended with treatment of the unaffected eye first) twice over a 72 h period; or
- o Procaine penicillin at 300,000 IU deposited into the bulbar conjunctiva, twice over a 48-72 h period.

Herd outbreak, large number of animals affected with rapid spread of disease and or in situations where facilities preclude topical treatmen:.

- o Oxytetracycline at 20 mg/kg IM, twice over a 72 h period; or
- o Tulathromycin at 2.5mg/kg S/C once

Variables that should be considered when choosing the most appropriate antimicrobial are the number of animals affected and the facilities available to administer the treatment. Repeatedly congregating affected cattle in dusty yards to identify and treat new cases can facilitate disease transmission by promoting ocular irritation and fly activity. In scenarios where the disease is getting away, blanket treatment of the group with a long acting systemic medication can mitigate shedding, yarding and subsequently disease spread. The topical or subconjunctival treatment of large numbers of animals in poor facilities can be very difficult and time consuming and poses significant risk of injury to the person administering the treatment or iatrogenic eye injury (bulbar sub-conjunctival).

Prognosis

Prognosis for recovery is good if animals are treated early in the disease process. Calves may resolve without treatment however a small percentage of eyes will perforate and compromised welfare is a significant concern. [40,41]

Sporadic bovine encephalomyelitis

Body system/syndrome

Neurological

Background/nature of infection/organisms involved

Sporadic bovine encephalomyelitis (SBE) is caused by *Chlamydia pecorum*, an obligately intracellular Gram-negative bacterium. *C. pecorum* commonly inhabits the gastrointestinal and reproductive tracts. Transmission of *C. pecorum* is believed to be via the faecal-oral route or via ingestion/inhalation of infective secretions.

Clinical disease is most often seen in calves under the age of 6 months. Sporadic cases, as well as outbreaks with up to 50% morbidity, have been reported. Mortality rates in affected animals often reach 30%. Clinical signs associated with SBE include pyrexia, depression, ptyalism, anorexia, diarrhoea, limb stiffness, incoordination, circling, opisthotonos, recumbency and death. In untreated cases, progression from initial clinical signs to death is approximately 10-14 days.

Lesions consistent with sporadic bovine encephalomyelitis include leptomeningeal hyperaemia and oedema with exudative meningitis, severe diffuse mononuclear meningoencephalomyelitis, and fibrinous polyserositis involving the pleural, peritoneal and pericardial cavities.

Key issues

- Commonly seen in cattle under 6 months of age.
- Morbidity and mortality rates can be significant.
- Untreated cases have high mortality rates.

Tests for diagnosis

1. Serology using a complement fixation test has been used but lacks sensitivity and specificity due to cross reactions between different chlamydial species.
2. Histopathological examination of brain sections collected at necropsy.
3. Detection of *C. pecorum* in brain tissue or fluid from the pericardium, pleura or peritoneum using polymerase chain reaction assays (PCR).

Treatment

Early antimicrobial treatment is important for a positive outcome. There are no studies that have examined the efficacy of treatment in clinical settings. Treatment of infected animals may result in chlamydial persistence rather than cure, with reoccurrence of clinical signs 3-6 weeks after treatment.

Antimicrobials used

Tetracyclines and macrolides have been used in veterinary and human medicine for the treatment of chlamydial infections.

- Oxytetracycline dihydrate at 30 mg/kg IM once a week for 2 weeks; or
- Tilmicosin at 10 mg/kg SC once; or
- Tulathromycin at 2.5 mg/kg SC once.

Prognosis

Prognosis for animals is good if they are treated early in the disease process (prior to recumbency).[42]

Actinobacillosis ('wooden tongue')

Body system/syndrome

Gastrointestinal

Background/nature of infection/organisms involved

Actinobacillosis is caused by *Actinobacillus lignieresii*, a Gram-negative, facultatively anaerobic coccobacillus that is a normal inhabitant of the gastrointestinal tract of cattle and is widespread in soil and manure.

The most frequent presentations are single or multiple granulomatous or pyogranulomatous lesions of the tongue or subcutaneous tissue in the head and neck. Sporadic cases are normally seen, although outbreaks can occur in cattle exposed to rough, stemmy forage.

Clinical signs include a firm swelling of the tongue, dysphagia, drooling and tongue protrusion. Granulomas of the head and neck are also commonly seen. Atypical manifestations of the disease have been reported associated with lacerations.

Key issues

- Firm painful swelling of the tongue or subcutaneous tissue of head/neck
- Associated with cattle grazing rough, coarse feed

Tests for diagnosis

Actinobacillosis is generally diagnosed based on clinical assessment of the lesions. In atypical cases, diagnosis may be confirmed by performing an impression smear or biopsy of the lesion, to microscopically identify club-like rosettes with a central mass of bacteria.

Treatment

Medical management with antimicrobials should result in resolution of disease in the majority of cases. Literature refers to debulking of some lesions but this may lead to profuse blood loss and therefore should not be routinely performed.

Antimicrobials used

Treatment should be continued until the lesions have returned to normal. A combination of intravenous sodium iodide and parenteral antimicrobials (either procaine penicillin or oxytetracycline dihydrate) at initial presentation will often lead to a reduced treatment duration compared to use of the individual parenteral antimicrobials alone. Oxyetetracyline dihydrate is the main antibiotic selected for combination with sodium iodide as the treatment interval is similar with both products.

First line

- Sodium iodide at 70 mg/kg IV and oxyetracycline dihydrate at 30 mg/kg IM at weekly intervals.

Second line

- Sodium iodide at 70 mg/kg IV in several treatments 5 to 10 days apart; or
- Oxytetracycline dihydrate at 30 mg/kg IM at weekly intervals; or
- Procaine penicillin at 20 mg/kg IM every 24 h for 7 to 10 days (note this is an off-label dosage regimen).

A combination of intravenous sodium iodide and parenteral antimicrobials at initial presentation will often lead to a reduced treatment duration compared to parenteral antimicrobials alone.

Note: label recommendations for the administration of sodium iodide state that it should be diluted in sterile water for injection and administered slowly intravenously. Use in pregnant animals is contraindicated due to the risk of abortion. Treatment should be discontinued if signs of toxicity, such as excessive lacrimation, dyspnoea, tachycardia or exfoliation of skin, occur.

Prognosis

Response to treatment is generally rapid and dramatic, although several weeks of treatment may be required for complete elimination of the lesions.[43]

Actinomycosis ('lumpy jaw')

Body system/syndrome

Gastrointestinal

Actinomycosis is a localised bacterial infection caused by *Actinomyces bovis*, a Gram-positive, filamentous, anaerobic bacterium. *Actinomyces bovis* is a normal commensal organism of the oral and upper respiratory tract of cattle.

Lesions tend to be locally proliferative, with bone infected following a break in the oral mucosa. The most common presentation is osteomyelitis of the mandible or maxilla. The lesion is a slow growing, firm, non-painful mass that is firmly attached to or part of the bone. It usually occurs sporadically, but common risk factors, such as rough, coarse feed, may result in multiple animals being affected in the same herd.

Key issues

- Slow growing, firm, non-painful mass associated with bone.
- Injury to the oral mucosa by rough, coarse feed is often the initiating factor.
- Lesions involving extensive bone involvement have a poor response to therapy.

Tests for diagnosis

Diagnosis is routinely based on clinical signs. The observation of club colonies associated with Gram positive rods upon microscopic examination of the lesion can be used to confirm the diagnosis.

Treatment

Optimal treatment involves surgical debridement and antimicrobial therapy. If the lesion involves the tooth root, teeth should be removed. Surgical debridement is difficult, with extensive haemorrhage often resulting in a requirement for a blood transfusion, so surgery should be reserved for animals of high value and be performed with appropriate supportive therapy. Resolution of the lesion is uncommon, with recrudescence following treatment a typical outcome.

Antimicrobials used

Whilst isolates are susceptible to both penicillin and oxytetracycline *in vitro*, penetration of penicillin into bone is poor, so oxytetracycline is a more appropriate choice in most cases. A combination of intravenous sodium iodide and parenteral antimicrobials at initial presentation will often lead to a reduced treatment duration compared to use of the individual parenteral antimicrobials alone.

First line

- Sodium iodide at 70 mg/kg IV and oxytetracycline dihydrate at 30mg/kg IM at weekly intervals.

Second line

- Sodium iodide at 70 mg/kg IV in several treatments 5 to 10 days apart; or
- Oxytetracycline dihydrate at 30 mg/kg IM at weekly intervals.

Note: label recommendations for the administration of sodium iodide recommend that it should be diluted in sterile water for injection and administered slowly intravenously. Use in pregnant animals is contraindicated due to the risk of abortion. Treatment should be discontinued if signs of toxicity, such as excessive lacrimation, dyspnoea, tachycardia or exfoliation of skin, occur.

Prognosis

Cases have a good prognosis if treatment is initiated early. If there is extensive bone involvement, complete resolution is unlikely even with prolonged treatment, so euthanasia of the animal should be considered in these cases.[43]

Abomasal ulceration

Body system/syndrome

Gastrointestinal tract

Background/nature of infection/organisms involved

Abomasal ulceration most commonly occurs in mature dairy cattle within the first 6 weeks of lactation and in young dairy calves.

The condition tends to occur in intensive management systems where dairy cows are fed significant amounts of concentrates such as grain or corn silage. Higher producing animals tend to be at greater risk of disease, potentially due to higher feed intakes and relative under perfusion of the abdominal viscera.

Young, rapidly growing calves are also at greater risk of disease, with an association often made with the feeding of milk replacer, high volumes of milk/milk replacer feeding or inconsistent feeding times.

Clostridium perfringens Type A and *Campylobacter jejuni* have been associated with abomasal ulceration in young calves, however the role of microbial agents in the formation of abomasal ulcers is limited and potentially indirect.[44]

Clinical signs associated with abomasal ulceration include abdominal pain, pyrexia, inappetence, bruxism, gastrointestinal ileus and dilatation of the abomasum.

Ulcers that penetrate major blood vessels can lead to severe blood loss and melaena. Perforating ulcers can lead to either localised or generalised peritonitis. Death may occur in animals due to either severe blood loss or generalised peritonitis.

Key issues

- More common in high production lactating cows in early lactation on higher levels of concentrates.
- Localised peritonitis is a common sequela.

Tests for diagnosis

- Haematology and biochemistry. Evidence of inflammation, such as increased fibrinogen and globulins, and/or blood loss.
- Abdominocentesis.
- Transabdominal ultrasound.

Treatment

Treatment of abomasal ulceration is dependent on the degree of damage caused by the ulceration.

For ulcers that cause significant blood loss, blood transfusions and intravenous fluid therapy will be required to stabilise the animal.

Antacid and alkalinising agents, such as magnesium oxide, magnesium hydroxide and aluminium hydroxide can be used to increase abomasal pH and decrease the proteolytic action of pepsin in the stomach, but their efficacy is questionable especially in adult ruminants. Kaolin and pectin have been used with limited efficacy.

Histamine H2 antagonists, such as cimetidine (50 – 100 mg/kg orally every 8 h) and ranitidine (10 – 50 mg/kg orally every 8 h), or the proton pump inhibitor omeprazole (4 mg/kg orally once per day) may be used to increase abomasal pH in calves. Ranitidine may be used intravenously or intramuscularly (1.5 mg/kg and 6.6 mg/kg, respectively) in adult ruminants as oral products are generally destroyed by the rumen.[44]

The use of these ancillary treatments is generally limited to high value animals due to their significant cost and these treatments are all off-label.

Antimicrobials used

As localised peritonitis is a common sequela of abomasal ulceration, broad spectrum antimicrobial therapy is generally indicated. There are limited studies to determine appropriate antimicrobial treatment regimens, so the recommendations provided are empirical.

- o Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 7 to 10 days (note this is an off-label dosage regimen); or
- o Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 24 h for 7 to 10 days (note this is an off-label dosage regimen).

Prognosis

The prognosis is dependent on the type of abomasal ulceration.

Non-perforating ulcers and ulcers that cause localised peritonitis generally have a good prognosis. A more guarded prognosis is associated with ulcers that cause significant blood loss and a poor prognosis is associated with perforation that leads to diffuse peritonitis.

Vaccination with commercial clostridial vaccines is unlikely to aid in the prevention of abomasal ulceration due to *Clostridium perfringens* Type A, as Type A is not included in commercial vaccines and there is limited cross protection amongst clostridial strains.

Ruminal acidosis and sequelae

Body system/syndrome

Gastrointestinal/rumen acidosis and sequelae

Background/nature of infection/organisms involved

Ruminal acidosis is a very common disease in all cattle when they are fed excess levels of rapidly fermentable carbohydrates, especially in animals that are unaccustomed to a high carbohydrate diet.

The pathogenesis of ruminal acidosis involves the proliferation of ruminal bacteria that digest starches and sugars, resulting in a significant increase in volatile fatty acids (VFA) and lactic acid. When the production of VFA and lactic acid exceeds the buffering capacity of the rumen, the ruminal pH declines and VFA and lactic acid are absorbed into the circulation.

The bacterium primarily implicated in clinical disease is *Streptococcus bovis*, which rapidly divides at moderately low pH and produces lactate, which potentiates the pH drop. As the pH continues to decline, lactic acid production and growth of *S. bovis* is slowed, and at this point *Lactobacillus* spp. become the dominant microorganisms in the rumen.

Lactic acid causes damage to the ruminal epithelium, resulting in the development of mycotic rumenitis and omasitis. In addition, bacteria such as *Fusobacterium necrophorum* colonise the damaged rumen wall, leading to bacterial emboli that can spread to the liver, resulting in liver abscessation. Colonisation of the liver can also lead to haematogenous dissemination of bacteria to the lungs, heart and kidneys, resulting in abscesses in these organs. Erosion of lung abscesses into an artery and airway may lead to acute haemoptysis and death due to exsanguination. Polioencephalomacia is another potential sequela of ruminal acidosis due to the lack of production of thiamine as a result of the disturbance of microbial fermentation.

Key issues

- Excess starch in diet leading to proliferation of *Streptococcus bovis.*
- Lactic acid production damages the ruminal wall and allows dissemination of bacteria to the liver and lungs.
- Antimicrobial therapy is used to prevent liver and pulmonary abscessation.

Treatment

Therapy is focused on restoration of hydration status, correction of ruminal and systemic acid-base disturbances, restoration of a normal ruminal environment and treatment/prevention of potential secondary complications. Thiamine should be administered to prevent the development of polioencephalomalacia.

Antimicrobials used

Parenteral antibiotics may have some benefit in reducing the development of liver and pulmonary abscesses.

- Procaine penicillin at 20 mg/kg IM every 24 h for 3 to 5 days (note this is an off-label dosage regimen).

Prognosis

The prognosis depends on the degree of acidosis and the presence of secondary complications. Mild cases generally have very good recovery rates, whereas severe cases with profound dehydration, ruminal atony and recumbency generally have very poor survival rates.

The use of antimicrobial rumen modifiers for prevention of rumen acidosis

Feed components high in starch are commonly fed to dairy cattle to promote milk production. The risk of acidosis is largely influenced by feed and stock management. Before antimicrobial rumen modifiers are considered the following practices should be adopted:

1. Supply adequate levels of fibre in the diet
   a. Ensure a minimum of 32% non-digestible fibre in diet with adequate effective fibre levels
   b. Offer high quality hay or silage during high risk periods when pastures are lush
   c. Ensure optimal chop length in cows fed a mixed ration to avoid compromising effective fibre or predisposing to sorting and selective consumption of ration components.
2. Ensure gradual adaptation to starch-rich feeds
   a. Ensure grain is not over processed
   b. Avoid rapid feed changes
3. Ensure forage is provided close to concentrate feeding and ensure constant pasture access
4. Use rumen buffers and neutralising agents
   a. Sodium bicarbonate (200-300 g per head)
   b. Magnesium oxide (30-45 g per head)

The three main antimicrobial ruminal modifiers used for the prevention of ruminal acidosis are ionophores (monensin and lasalocid), virginiamycin and tylosin.

Ionophores

Ionophores aid in the prevention of acidosis by reducing the numbers of lactic acid producing strains of bacteria, such as *Streptococcus bovis* and *Lactobacillus spp.*, and by maintaining consistent dry matter intake. Sodium monensin is the ionophore most commonly used in the dairy industry for prevention of acidosis. Ionophores are considered of low importance in the Australian Strategic and Technical Advisory Group on Antimicrobial Resistance (ASTAG) ratings[6] and are not used in humans. Although research has shown that monensin has some benefit in controlling acidosis,[45] results are variable, and it is not registered by the APVMA for the prevention or control of ruminal acidosis.

Virginiamycin

The streptogramin class of antimicrobials (to which virginiamycin belongs) are highly important in human medicine as they are used for treatment of infection with vancomycin-resistant staphylococci and enterococci. Accordingly, there is a risk of selection for AMR of significant concern to human health arising from the inclusion of virginiamycin in animal feeds, particularly if this is done on a routine or long-term basis. The APVMA review of the registration of products containing virginiamycin and their labels found that there was an unacceptable risk that the use of virginiamycin for undefined periods of time will select for streptogramin resistance in *Enterococcus faecium* in animals and poultry. Such resistant bacteria may colonise humans directly, or transfer genetic determinants of resistance to human pathogens, with *Staphylococcus aureus* the greatest concern.

With good nutritional management, virginiamycin should only need to be used in rare circumstances. The main justifications for the use of virginiamycin are limited to drought feeding or the introduction (or reintroduction) of cattle to grain-based diets when it is not possible to manage a progressive induction, scenarios that are not typical in dairy production. Virginiamycin is currently the only registered antimicrobial agent for the prevention of rumen acidosis in cattle (the label claim is 'reduce acidosis due to high grain diets').

Dose rate, and frequency and duration of administration - *risk management framework:*

- Any directions for virginiamycin use in cattle must limit administration for a **specified purpose and duration** and include a statement that any medicated feed must not be fed to any animal other than those authorised by the prescription.
  - Best practice use of virginiamycin is for a period no longer than 28 days, no more frequently than once per year, and specifically for transitioning animals to a high grain diet or during periods with a high risk of acidosis.
  - The recommended dose rate for use in lactating dairy cow is 200 mg per cow per day

- Virginiamycin must only be prescribed for a specific group of cattle that are identifiable in the clinical records of the veterinarian.
- Any veterinarian prescribing virginiamycin must undertake a retrospective review of farm records on the use of the product containing virginiamycin to ensure compliance with prescribing instructions.
- **Virginiamycin carries a label restraint that prohibits off-label use.**

Tylosin

Tylosin is a macrolide antibiotic that has been shown to reduce lactic acid production *in vitro* and in the rumen. Tylosin has been shown to reduce the prevalence of liver abscesses, which are common sequelae of acidosis. Tylosin is considered of low importance in the ASTAG ratings[6] and is not used in humans (although it will select for resistance to erythromycin, which is used in humans). Tylosin is registered by the APVMA for the prevention of liver abscess, but is not registered for the prevention of acidosis. The use of tylosin in combination with monensin is as effective as virginiamycin in the prevention of ruminal acidosis.[46,47]

Other agents

Yeasts

Studies have demonstrated increases in rumen pH with yeast supplementation, increased numbers of lactic acid utilizing bacteria and decreased numbers of *S. bovis*.[48,49] Yeast products are not interchangeable and vary greatly in form, being live (with differing organism concentrations) or in the form of yeast cell culture or yeast extracts, such as cell wall enriched fractions. Veterinarians should acquaint themselves with the information available on different commercial products.

Flavophospholipol (bambermycin)

There are limited data on the action of flavophospholipol on rumen function, but there may be increased stability of rumen function through increased fibre digestion and enhanced protein metabolism in the rumen and intestine.

Recommendation for rumen modifier usage

Antimicrobials should only be used when the risk of acidosis is high (moderate to high levels of starch, low availability of effective fibre) and other preventive measures are inadequate. All in-feed antimicrobials should be introduced gradually into the diet to minimize ruminal disruption and should be continued to be fed during the highest risk periods. Similarly, caution should be exercised when removing rumen modifiers from the diet, as the removal of inhibition of the growth of bacteria can trigger acidosis.

- Sodium monensin at 250 mg per cow per day; or
- Sodium monensin at 250 mg and tylosin at 150 mg per cow per day.

Traumatic reticuloperitonitis (TRP)

Body system/syndrome

Gastrointestinal

Background/nature of infection/organisms involved

Traumatic reticuloperitonitis develops following ingestion of metallic objects that then perforate the reticulum. Ingested objects are moved into the cranioventral part of the reticulum by ruminal contractions. Perforation of the reticular wall results in a localised peritonitis. In some cases, the object can penetrate the diaphragm, entering the thoracic cavity and the pericardial sac.

Acute clinical cases typically involve a mixed gastrointestinal tract bacterial flora, whilst more chronic cases are associated with *Trueperella pyogenes* and significant anaerobic bacteria.

Clinical signs are dependent on the stage of the disease process. Initially, when the object pierces the reticulum, there is a sudden onset of ruminoreticular atony and pyrexia, and a marked drop in milk production. Affected animals will display signs of abdominal pain, such as an arched back, reluctance to move and an uneasy gait. Chronic cases may develop vagal indigestion.

Cattle with pleuritis or pericarditis are depressed, tachycardic, tachypnoeic and pyrexic. Effusive pericarditis causes cardiac tamponade and congestive heart failure, leading initially to jugular distension and brisket oedema. Submandibular oedema may also be observed with severe or more chronic cases.

Thoracic auscultation may reveal muffled lung sounds, pleural friction ribs and a washing machine murmur due to fluid and gas in the pericardial sac.

Key issues

- Ingestion of metallic objects that pierce the rumen, leading to localised peritonitis, pleuritis and pericarditis.

Tests for diagnosis

1. Positive withers test (failure to arch back) or xiphoid test (grunting when force is applied to the xiphoid process).
2. Haematological findings range from a normal haemogram to severe leukopaenia with a degenerative left shift. Hyperfibrinogenaemia is present in most cases.
3. Biochemical analyses reveal elevated serum proteins caused by elevated globulins.
4. Abdominocentesis and pericardiocentesis. If ultrasound is not used, peritoneal fluid may not be obtained, as most fluid accumulation is localised.
5. Ultrasonography of the ventral abdomen is the most accurate way to identify localised peritonitis near the reticulum. Ultrasonography can also be used to confirm the presence of a pericardial or pleural effusion.

Treatment

Conservative treatment is generally attempted first with the use of a rumen magnet and parenteral antimicrobial therapy.

A rumenotomy may be performed to remove foreign bodies in animals that do not respond to medical management. If intraperitoneal abscesses are detected during surgery, they may be drained into the reticulorumen when they are adhering to the rumen wall. In cattle with thoracic and pericardial involvement, fluid may be drained using a thoracic or pericardial drain.

Both procedures are reserved for animals of high value, as the prognosis is poor.

Euthanasia is the best option for advanced cases.

Antimicrobials used

Acute clinical cases benefit from broad spectrum antimicrobial treatment targeted at the gastrointestinal flora found in the lesions, whilst more chronic cases, which typically involve *Trueperella* pyogenes and anaerobic bacteria can be treated with narrower spectrum antimicrobials.[50]

Acute

- o Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 5-7 days (note this is an off-label dosage regimen); or
- o Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 24 h for 5-7 days.

Chronic

- o Procaine penicillin at 20 mg/kg IM every 24 h for 10-14 days (note this is an off-label dosage regimen); or
- o Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 10-14 days (note this is an off-label dosage regimen).

Prognosis

The prognosis for uncomplicated cases with simple localized peritonitis is good, but poor for cows that have generalised peritonitis and or pericarditis. Vagal indigestion may also develop following otherwise successful treatment of localised peritonitis, limiting productive capacity.
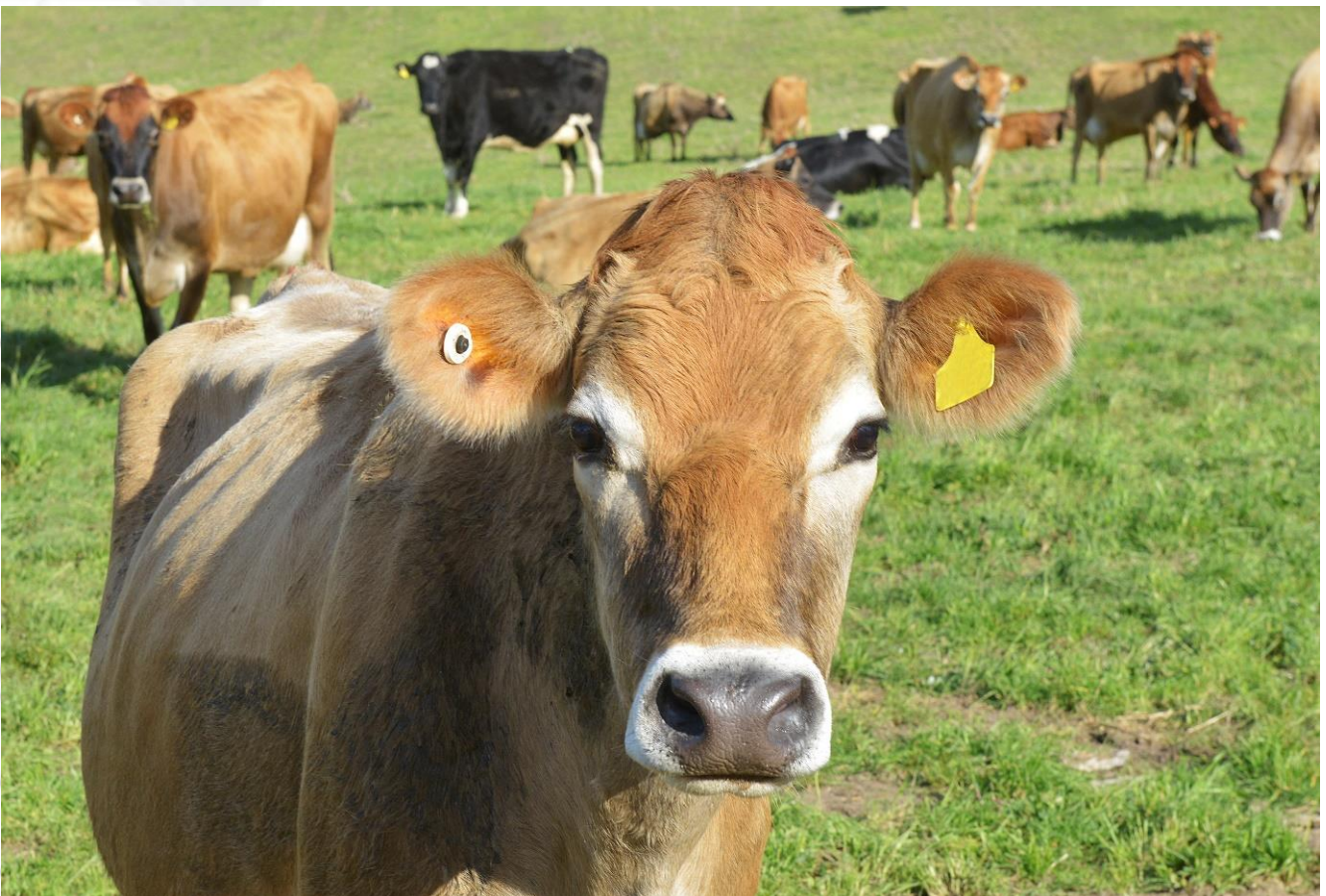
Haemorrhagic bowel syndrome

Body system/syndrome

Gastrointestinal

Background/nature of infection/organisms involved

Haemorrhagic bowel syndrome is an acute and often fatal condition of cattle characterised by segmental intraluminal haemorrhage in the small intestine. While the exact aetiology has not been determined, a tentative association has been identified with *Clostridium perfringens* Type A expressing the alpha and beta 2 toxins[51] and the fungus, *Aspergillus fumigatus*.

The disease occurs sporadically and is mainly seen in mature lactating cows on high concentrate diets. Morbidity is low, but mortality rates are almost 100%. Several risk factors for disease have been identified, including high amounts of fermentable carbohydrates in the diet, high dry matter intake and milk production, feeding a total mixed ration, higher parity, larger herd size and early lactation.[52]

Clinical signs of disease include sudden anorexia, depression, marked decrease in milk production, dehydration, abdominal pain and distension, weakness leading to recumbency, bloody to dark red scant faeces and finally death. Single or multiple sections of the small intestine, mainly the jejunum and ileum, are filled with blood clots. Histologically, there is a multifocal submucosal oedema, segmental necrosis, ulceration, and mucosal and transluminal haemorrhage.

Key issues

- Definitive causative agent unknown but associated with *Clostridium perfringens* Type A and *Aspergillus fumigatus.*
- Characterised by single or multiple sections of the small intestine being filled with blood clots.
- High mortality rate.

Tests for diagnosis

1. Abdominal ultrasound revealing intraluminal blood clots.[53]
2. Exploratory laparotomy.
3. Histopathology at necropsy.

Treatment

Treatment of affected animals is generally unsuccessful. Medical therapy alone has been associated with lower survival rates than when surgical intervention combined with medical therapy are instigated. Surgical intervention involves either exploratory laparotomy with intestinal resection or manual breakdown of clots. Medical therapy includes aggressive parenteral fluid therapy and antimicrobial treatment. No specific antitoxin is available for *Clostridium perfringens* Type A and there is limited cross protection from the antitoxin against *Clostridium perfringens* Types C and D.

Antimicrobials used

- Procaine penicillin at 20 mg/kg every 6-8h IM for 7-10 days[54] (note this is an off-label dosage regimen).

Prognosis

Even with aggressive surgical and medical therapy, survival rates are generally low.

Dermatophilosis (rain scald)

Body system/syndrome

Integumentary

Background/nature of infection/organisms involved

Dermatophilosis is caused by the actinomycete, *Dermatophilus congolensis*, a Gram-positive, non-acid fast, branching, filamentous, facultatively anaerobic bacterium. *D. congolensis* is an obligate parasite of the skin; it may occur transiently in soil but does not multiply there. It usually requires moisture and skin damage to establish infection. Mechanical transmission can be facilitated by both biting and non-biting insects, as well as fomites. Disease caused by *D. congolensis* is usually seen in the wettest months of the year. When disease is seen in young stock, the severity tends to be greater when there are concurrent stressors, such as inadequate or poor-quality nutrition. Dermatophilosis may also be seen in housed milking cows during the summer when cows are spending significant time under sprinklers used for cooling.

Early lesions are pustules, with hair over the infected site matted, and a greasy exudate that forms crusts that are difficult to remove. Infection is usually confined to the epidermis and does not penetrate the dermis. As disease progresses, the crusts become scabs that cover granulation tissue. The scabs are painful to remove. Lesions typically occur along the backline, extending from the neck to the back of the udder.

Key issues

- Damage to the skin is usually required for infection.
- Occurs frequently during prolonged wet periods.
- Lesions typically occur along the top line of the animal.

Tests for diagnosis

1. Clinical observations (environmental conditions, location of lesions, hair clumped and pulls away with scab).
2. Cytology on stained skin scrapings and crusts shows characteristic bacterial morphology.
3. Culture of skin scraping, scab or biopsy of affected skin.

Treatment

Most cases are self-limiting and do not require treatment. Treatment of more severe cases includes careful removal of crusts and washing with iodine detergents. Systemic antimicrobial therapy is rarely used but may be indicated where lesions are extensive.

Antimicrobials used

1. Procaine penicillin at 20 mg/kg IM every 24 h for 3 days (note this is an off-label dosage regimen).
2. Oxytetracycline dihydrate at 20 mg/kg IM once.

Prognosis

Prognosis for recovery is good.[55]

Peritonitis

Body system/syndrome

Abdominal cavity

Background/nature of infection/organisms involved

Peritonitis may occur as a primary disease or secondarily as part of an aetiologically-specific disease. Primary disease occurs most commonly following injury of the serosal surfaces of the alimentary tract (e.g. traumatic reticuloperitonitis), but may also occur following perforation of the abdominal wall, injury to the reproductive tract during parturition, or infection after abdominal surgery.

Peritonitis can be classified as peracute, acute/subacute or chronic. In the peracute form, clinical signs are more severe, with profound toxaemia. Cattle display severe depression, weakness, often have a subnormal temperature, and die within a short time frame. In acute/subacute peritonitis clinical signs are often mild, with inappetence, pyrexia, abdominal pain (indicated by an arched stance), reluctance to walk or grunting, and decreased intestinal motility, leading to reduced faecal output and faeces that is drier than normal. Cattle with chronic peritonitis often display non-specific signs of disease, although marked abdominal fluid accumulation may occur. Peritonitis may also be localised or diffuse. Ruminants have a propensity to produce fibrin to wall off leaks from damaged bowel or a compromised reproductive tract. If this process is successful, adhesions will contain the inflammation to a compartment within the peritoneal cavity. Diffuse peritonitis reflects a failure of this process, with infection disseminated throughout the peritoneal cavity. Cows with localised peritonitis may have localised pain that can be elicited by withers pinch tests, or bending the cow down, to the left or to the right. Alternatively, the site of pain may be elicited by striking over the area of inflammation. Localising the site of pain can help to discern if peritonitis is secondary to traumatic reticuloperitonitis or an abomasal ulcer. In contrast to localised peritonitis, cows with diffuse peritonitis usually have a significant accumulation of peritoneal fluid in the abdomen and will appear round when observed from behind. Abdominal fill should be interpreted in the context of the cows reported appetite.

A diversity of bacteria may be associated with peritonitis, reflecting the mixed flora of the potential sources of infection (gastrointestinal tract, post-partum uterus, surgical sites). *Enterobacteriaceae*, anaerobes and *Trueperella pyogenes* are likely to be involved.

Key issues

- Identifying whether disease is primary or secondary.
- Peritonitis may be localised, or diffuse, diffuse peritonitis has a poor prognosis.
- Peritonitis may be peracute, acute/subacute and chronic

Tests for diagnosis

1. Normal haemogram to severe leukopaenia with degenerative left shift, increased globulin and fibrinogen concentrations.
2. Abdominal ultrasound to detect increased abdominal fluid or abscess.
3. Abdominal paracentesis – peritoneal fluid may contain fibrinogen and clot after collection. Normal bovine peritoneal fluid is clear with a protein content less than 6.3 g/dL, and a nucleated cell count less than 10^6 cells/mL, the majority of which are macrophages.[56] Paracentesis of normal cattle typically yields a low volume of peritoneal fluid (0 – 1 mL). The volume of peritoneal fluid is often increased with peritonitis, as is the turbidity, protein content and cell count. Neutrophils are the predominant cell type with bacterial infections. Samples can be submitted for culture and susceptibility testing. Most veterinary diagnostic laboratories do not routinely perform anaerobic cultures. If anaerobic cultures are not available or performed, the requirement for inclusion of an antimicrobial with a spectrum that includes anaerobes should be assumed.

Treatment

Medical therapy includes systemic antimicrobial therapy, non-steroidal anti-inflammatory drugs (if the peritonitis is not secondary to abomasal ulceration), and parenteral or oral electrolyte and fluid therapy.

Oral administration of a magnet into the rumen is indicated in cases of traumatic reticuloperitonitis. Surgical intervention, including peritoneal lavage and drainage, are of limited value because of the difficulty in maintaining drain patency, as fibrin deposits often compartmentalise the abdomen and block drains.

Antimicrobials used

There are minimal published reports of clinical trials to evaluate the effectiveness of treatment of peritonitis in cattle, so empirical recommendations for broad spectrum antimicrobials are used. Ideally, antimicrobial choice should be based on culture of peritoneal fluid and susceptibility testing of isolates.

Administration of antimicrobials into the peritoneal cavity has been attempted, but there is no evidence to support their use, with some studies showing a more inconsistent antimicrobial distribution compared to systemic therapy, probably because of the compartmentalisation within the abdominal cavity that occurs during peritonitis. The ideal antimicrobial spectrum for treatment of peritonitis in cattle includes the *Enterobacteriaceae*, anaerobes and *Trueperella pyogenes.* None for antimicrobial drugs registered for cattle provide this spectrum at labelled doses. Oxytetracycline will cover some anaerobes, the *Enterobacteriaceae* and some *Trueperella pyogenes* isolates (antimicrobial resistance is reportedly common). Penicillin has a better anaerobic spectrum and is effective against *Trueperella pyogenes*, but not the *Enterobacteriaceae*. Ceftiofur has an appropriate spectrum when administered at a higher, off-label dose. The MIC for anaerobes and the *Enterobacteriaceae* is higher than the MIC for the respiratory pathogens that are the target of its registered use. The most common antimicrobials used to treat peritonitis include oxytetracycline and penicillin, accepting that neither is ideal.

- o Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 7 to 10 days (note this is an off-label dosage regimen); or
- o Procaine penicillin at 20 mg/kg IM every 24 h for 7 to 10 days (note this is an off-label dosage regimen); or
- o Ceftiofur at 2 mg/kg IM every 24 h for 7 to 10 days (note this is an off-label dosage regimen). Should only be used in individual cases where the response to the first line antimicrobials is poor (if there is no response to initial treatment within the first 48 – 72 hours).

Prognosis

The prognosis is dependent on the form of peritonitis. It is better for localised peritonitis and for animals with acute/sub-acute forms. Peracute and/or diffuse peritonitis have a poor prognosis. Cows with chronic peritonitis and extensive adhesions may survive, but their productivity is typically limited.

Digital dermatitis (hairy foot warts)

Body system/syndrome

Musculoskeletal

Background/nature of infection/organisms involved

Bovine digital dermatitis is a painful, erosive papillomatous-like lesion of the skin of the lower limb. Definitive identification of the aetiological agent has not been established, but it is most probably caused by a group of spirochetes, *Treponema* spp. The disease is extremely contagious and can be spread between farms by infected cattle and contaminated fomites used by veterinarians and hoof trimmers.

Digital dermatitis is characterised by erosion of the superficial layers of the epidermis, epithelial hyperplasia and hypertrophy, pain and swelling. Large numbers of spirochetes can be identified in the dermis and cause destruction of the epidermis. Lesions are typically present on the hind feet. More acute lesions appear moist, reddened and prone to bleeding. Chronic lesions develop papillary proliferation.

Clinical disease is more often seen in younger lactating cows that are housed or kept for prolonged periods in areas that are very muddy. International reports of infected herds have described a prevalence of infection of 20 to 80%. Prevalence within and between herds in pasture-based systems (as is most seen in Australia) is much lower.

Key issues

- Contagious disease that can be spread between farms by veterinarians and hoof trimmers.
- Wet and muddy conditions are major risk factors.
- More common in housed cattle.

Tests for diagnosis

1. Biopsy of lesion for histopathological examination and silver staining to identify spirochetes.

Treatment

Topical antimicrobial treatment is indicated. Several non-antibiotic treatments, including copper and zinc sulphate, formalin and peracetic acid, have been used. The efficacy of these products is uncertain, as there are limited peer reviewed studies and the use of some of the products (formalin and copper sulphate, in particular) has significant human and/or environmental concerns.[57]

Antimicrobials used

The required concentration at the site of infection for treatment of *Treponema* isolates is unlikely to be achieved by systemic therapy, but this has not been evaluated in the field. The use of medicated footbaths is common overseas, but antimicrobials are rapidly neutralised in footbaths by excessive contamination with mud and manure, so direct topical application is preferred in Australia because of the lower incidence and prevalence of disease. The efficacy of several topical antimicrobials (oxytetracycline, lincomycin and spectinomycin) has been evaluated for the treatment of digital dermatitis. Oxytetracycline has been shown to be at least as effective as the other antimicrobials[57] and is considered of lower ASTAG importance, so should be the only antimicrobial that is used.

Topical therapy

- Oxytetracycline hydrochloride in a 25 mg/mL solution applied every 24 h for 5 days.[58] Commercially available oxytetracycline hydrochloride powder is mixed with clean water to make this solution. Ideally, this should be applied after the area has been cleaned using a high-pressure hose. Bandaging of affected animals following treatment has not been shown to improve treatment outcomes.

Prevention

Where possible, spending prolonged periods in muddy areas should be avoided. All hoof care equipment should be disinfected between individual cows and biosecurity protocols should be developed for veterinarians and hoof trimmers who visit the property. Screening of individual cows and herds via visual assessment should occur prior to the introduction of cattle onto the property.

Prognosis

Recovery following treatment is usually very good, although periodic recurrence is common in infected herds.

Interdigital necrobacillosis (footrot)

Body system/syndrome

Musculoskeletal

Background/nature of infection/organisms involved

Interdigital necrobacillosis is an infectious disease that is a significant cause of lameness in both pastured and housed cattle. The condition is caused primarily by the gram-negative anaerobes *Fusobacterium necrophorum, Prevotella melaninogenica* and *Porphyromonas levii.* Wet, muddy and rough environmental flooring or laneways are important factors predisposing to disease.

The condition is characterised by significant inflammation and tissue necrosis of the soft tissues of the interdigital space. Deeper structures, such as the interphalangeal joint, flexor tendons and phalanges, can be affected in more severe cases. Affected cattle develop swelling and heat in the affected limb, followed by soft tissue swelling, necrosis and fissure formation. A characteristic foul smell accompanies the necrotic tissue. Affected feet are painful and cattle become lame. In more severe cases, infection extends into the distal interphalangeal joint and flexor tendon sheath.

Key issues

- Disease is commonly seen when cattle spend prolonged periods in wet, muddy conditions.
- Rapid improvement is observed in cases that are treated at the onset of swelling and lameness.
- Delayed treatment may lead to disease progression, with infection of the deeper structures of the foot, including the distal interphalangeal joint, flexor tendons, and phalanges.

Treatment

Therapy includes manual removal of necrotic tissue and antimicrobial therapy. In severe cases with involvement of the distal interphalangeal joint or flexor tendons, amputation of the affected claw may be required. *Fusobacterium necrophorum* is very sensitive to penicillin.

Antimicrobials used

- Procaine penicillin at 20 mg/kg IM every 24 h for 3 days (note this is an off-label dosage regimen); or
- Long acting combination product benzathine penicillin (150 mg/ml) and procaine penicillin (150 mg/ml) at 6.6 ml/kg IM once; or
- Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 3 days or oxytetracycline dihydrate at 20 mg/kg IM once.

The response to treatment is largely influenced by the timing of treatment relative to the onset of disease. If treatment is delayed, resulting in infection of deeper structures, the duration of treatment may need to be extended. In complicated cases, antimicrobial therapy may need to be continued for 2-3 weeks.

Prognosis

The prognosis for early cases is very good. Complicated cases may require surgical intervention. If infection has extended above the fetlock, claw amputation is often not effective, as the tendon sheath of the medial and lateral claw communicate at this level. Euthanasia may be necessary if the cow is left without a healthy claw to walk on.[58]

Listeriosis

Body system/syndrome

Neurological

Background/nature of infection/organisms involved

Listeriosis is an acute meningoencephalitis caused by the Gram-positive intracellular rod *Listeria monocytogenes*. *L. monocytogenes* also causes a range of other diseases, including neonatal septicaemia, abortion, mastitis and ophthalmitis (silage eye). Usually only one form of disease is seen during an outbreak. Meningoencephalitis is the most common disease manifestation. Neurological listeriosis usually affects individual animals, rather than causing a herd outbreak. *L. monocytogenes* is ubiquitous in soil, silage, vegetable and faecal matter.

Listeriosis is usually a sporadic disease in cattle. *L. monocytogenes* is able to survive and proliferate in spoiled silage and outbreaks may be associated with the feeding of spoiled silage. Close examination of the patient may reveal an oral lesion. as *L. monocytogenes* often gains access via a breach in the mucosa. It crosses the blood-brain barrier by ascending the trigeminal nerve or may disseminate haematogenously.

Clinical signs of listeriosis include fever, anorexia, depression, proprioceptive deficits, head pressing, blindness, circling, nystagmus, cranial nerve deficits (e.g. unilateral facial paralysis), recumbency, convulsions and death. The lesions in the brain are most common in the pons and trapezoid region, but can be located anywhere in the brainstem. Microscopic lesions include perivascular cuffing with mononuclear cells, multifocal asymmetric brainstem microabscesses, and mononuclear cell meningoencephalitis.

Key issues

- Infection results in an acute meningoencephalitis.
- The organism is ubiquitous in the environment, but is commonly linked with the feeding of poorly fermented silage.

Tests for diagnosis

Definitive diagnosis of listeriosis is difficult in the live animal as culture of the organism from the cerebrospinal fluid is difficult.

1. Cerebrospinal fluid analysis reveals increased nucleated cell content (mainly mononuclear cells).
2. Histopathological findings of microabscessation in the brain.
3. Bacterial culture of the brainstem (this is rarely performed because of the difficulty of recovering the organism from brain tissue and the prolonged enrichment time required for growth of the organism)

Treatment

Antimicrobials used

L. monocytogenes is susceptible to most antimicrobials *in vitro*, except the cephalosporins, although some reports have identified isolates that are resistant to oxytetracycline and the macrolides. Retrospective studies of clinical cases of encephalitic listeriosis showed no significant differences in the survival rates of cattle treated with different antimicrobial regimens.[59] The success rate of antimicrobial therapy *in vivo* is often reduced because of the intracellular habitat of the bacterium within the CNS.

- Procaine penicillin at 20-40 mg/kg IM every 12 h for 7 days, followed by 20 mg/kg IM every 24 h for 7-14 days (note this is an off-label dosage regimen); or
- Oxytetracycline hydrochloride at 10 mg/kg IV/IM every 24 h for 14 days (note this is an off-label dosage regimen); or
- Amoxicillin at 7-15 mg/kg IM every 12 h for 14 days (note this is an off-label dosage regimen).

Prognosis

The prognosis is good for animals treated early in the course of disease. Animals that are recumbent or comatose rarely survive despite aggressive antimicrobial therapy.[59,60]

Endocarditis

Body system/syndrome

Cardiovascular

Background/nature of infection/organisms involved

Bacterial endocarditis is the most common valvular disease in adult cattle. The condition is often secondary to other chronic infections, such as traumatic reticuloperitonitis, soft tissue abscesses, ruminal acidosis, chronic pneumonia, metritis, or mastitis. *Trueperella pyogenes* is the most common bacterial species isolated from endocarditis cases, but *Streptococcus* spp., *Staphylococcus* spp., and aerobic Gram-negative bacteria have also been isolated.

The right atrioventricular (AV) valve is most commonly affected, followed by the left AV valve. Affected animals present with recurrent fever, weight loss, anorexia and poor milk production. Clinical signs include pyrexia, tachycardia and a systolic heart murmur. In advanced stages of disease, heart failure may develop, resulting in distension of the jugular veins and brisket oedema.

Key issues

- Most common valvular disease in cattle.
- Echocardiography is the definitive means for diagnosis.
- Prognosis for treatment is guarded.

Tests for diagnosis

1. Echocardiography.
2. Blood culture – this is a relatively insensitive diagnostic tool, with multiple samples (3 x 10 mL samples over a 3 - 6 hour period) often required, but may be useful when positive to enable selection of the appropriate antimicrobials.

Treatment

Long term antimicrobial therapy is required to cure bacterial endocarditis. In addition, if animals are showing signs of heart failure, then treatment with furosemide is indicated. Penetration of antimicrobials into the vegetative heart valve lesions can be poor.

Antimicrobials used

If culture is not available, then, given that *Trueperella pyogenes* and *Streptococcus* spp. are the bacterial species most commonly isolated from cases of endocarditis, penicillin is the best option for empirical therapy.

- Procaine penicillin at 20 mg/kg IM every 12 h for a minimum of 3 weeks (note this is an off-label dosage regimen).

If culture indicates Gram-negative involvement:

- Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 24 h for a minimum of 3 weeks.

Resolution of the heart murmur and tachycardia, combined with the echocardiographic appearance of the heart valves, are good prognostic indicators.

Prognosis

The prognosis for cattle with endocarditis is guarded at best. Cattle that are displaying signs of heart failure have a very poor prognosis and euthanasia should be considered prior to treatment.[61]

Retained placenta/retained foetal membranes

Body system/syndrome

Reproductive

Background/nature of infection/organisms involved

Retained placenta commonly affects periparturient dairy cattle and is defined as the failure to pass the foetal membranes within 24 h after parturition. Retained placenta has a deleterious effect on fertility (including delayed uterine involution, prolonged time to first service and decreased pregnancy rates). The condition has also been associated with higher risks for endometritis, metritis, ketosis and mastitis.

Risk factors associated with retained placenta include induction of parturition, decreased gestation, abortion, twinning, dystocia, nutritional deficiencies and immunosuppression.

Key issues

- Failure to pass foetal membranes within 24 h of parturition.
- Multiple risk factors for disease.
- Antimicrobial therapy only indicated if pyrexia is present.

Treatment

There are relatively few effective treatment options for retained placenta in cattle. Manual removal of the placenta is contraindicated and can result in more severe uterine infection.

Intrauterine antimicrobial therapy has been shown to reduce pyrexia but has not been found to improve subsequent reproductive performance. Some intrauterine antimicrobials (e.g. oxytetracycline) interfere with normal placental detachment mechanisms and therefore should not be used. Systemic antimicrobial therapy is indicated when pyrexia is present and has been shown to have beneficial effects on reproductive performance.

Hormones such as prostaglandin and oxytocin have also traditionally been used, but there is no evidence to support their efficacy in the treatment of retained placenta in cattle.

Antimicrobials used

If pyrexia is present:

- Procaine penicillin at 20 mg/kg IM every 24 h for 3 to 5 days (note this is an off-label dosage regimen); or
- Oxytetracycline hydrochloride at 10 mg/kg IV/IM every 24 h for 3-5 days (note this is an off-label dosage regimen).

Prognosis

Prognosis for survival is very good if no secondary complications, such as metritis, occur.[62]

Metritis (acute puerperal metritis)

Body system/syndrome

Reproductive system

Background/nature of infection/organisms involved

Acute puerperal metritis is a systemic illness with pyrexia and signs of toxaemia due to infection of the uterus and occurs within the first 21 days after parturition.

Disease is characterised by an enlarged uterus and a watery-brown discharge that has a foetid odour. Systemic signs of disease include decreased milk production, inappetence, pyrexia, tachycardia and dehydration.

Whilst bacterial contamination of the lumen of the uterus is normal following parturition, specific bacterial species have been isolated in cases of acute puerperal metritis, including *E. coli, Trueperella pyogenes*, *Fusobacterium necrophorum*, *Prevotella* spp. and *Bacteroides* spp.

Key issues

- Common disease occurring in the first 21 days after calving.
- Several bacterial species have been associated with clinical disease.

Treatment

Treatment consists of antimicrobial and supportive therapy (non-steroidal anti-inflammatory drugs, parenteral/oral fluids). Several hormones, including oestrogens, prostaglandins and gonadotropin releasing hormones, have been used previously, but the benefits of these hormones are equivocal. Intrauterine therapy using antiseptic solutions has also been used, but this is not recommended, as there is a risk of iatrogenic trauma to the genital tract.

Antimicrobials used

There has been a variety of both intrauterine and systemic antibiotics used in the treatment of metritis. Intrauterine use of antibiotics results in incomplete tissue distribution and variable residues, therefore, is not recommended.

- Procaine penicillin at 20 mg/kg IM every 24 h for 3 to 5 days (note this is an off-label dosage regimen); or
- Oxytetracycline hydrochloride at 10 mg/kg IV/IM every 24 h for 3 to 5 days (note this is an off-label dosage regimen).

Prognosis

The prognosis is generally good for animals with mild to moderate clinical disease receiving appropriate antimicrobial therapy. Animals with severe signs of toxaemia have a more guarded prognosis.[63]

Endometritis

Body system/syndrome

Reproductive

Background/nature of infection/organisms involved

In dairy cattle, clinical endometritis is defined as inflammation of the endometrium associated with a purulent vaginal discharge more than 21 days after parturition in the absence of systemic clinical disease. The predominant bacterial species associated with clinical endometritis is *Trueperella pyogenes.*

Clinical endometritis has a significant adverse impact on reproductive performance, resulting in an increased number of services per conception, increased calving to conception intervals and reduced likelihood of pregnancy. The adverse reproductive impacts result in economic losses due to increased culling, decreased milk production and infertility treatment costs. Risk factors for the development of endometritis include dystocia, twins, stillbirth, abortion, metritis, male offspring and ketosis.

Key Points

- Inflammation of the endometrium in the absence of systemic disease.
- High apparent self-cure rate, but adverse effects on reproduction if treatment is not instigated.

Treatment

The apparent self-cure rate of infected animals is very high without treatment, but the treatment of infected animals does improve the reproductive performance over that of untreated animals.

Several agents have been used as treatments for clinical endometritis, including systemic and intrauterine antimicrobials, intrauterine antiseptics and reproductive hormones (such as prostaglandins, oestrogens and gonadotrophin releasing hormones).

Intrauterine antiseptics should not be used as there is a risk of causing chemical damage and infection of the deeper layers of the uterus. There is minimal scientific evidence to support the use of reproductive hormones in the treatment of endometritis.

Antimicrobials used

As the disease does not cause systemic illness, and intrauterine antimicrobial therapy has been shown to be efficacious, parenteral antimicrobial therapy is not recommended.

The efficacies of several intrauterine antibiotics (including cephapirin benzathine, penicillin G, oxytetracycline and ampicillin) have been reviewed. Of these, only cephapirin benzathine has been shown to improve reproductive performance.

- Intrauterine cephapirin benzathine at 500 mg once.

Prognosis

As the disease has a very high self-cure rate, the prognosis for survival is excellent. The treatment of infected animals does improve reproductive performance over that of untreated animals, but it is still below that of unaffected animals.[64]

Seminal vesiculitis or vesicular adenitis

Body system/syndrome

Male accessory sex glands

Background/nature of infection/organisms involved

Inflammation of the seminal vesicle accessory sex glands is most common in young bulls 1 to 2 years of age. The majority of affected bulls do not show any overt signs of disease. The condition is typically detected during bull breeding soundness examinations. Rectal palpation reveals enlargement of one or both vesicular glands and leukocytes may be detected in the ejaculate.

The pathogenesis of vesiculitis is unknown. Proposed routes of infection include ascending or descending urogenital tract infection or haematogenous invasion. A diversity of bacteria have been isolated from inflamed seminal vesicles, including *Trueperella pyogenes*, *Histophilus somni*, *Acinetobacter* spp., *Streptococcus* spp., *Pasteurella* spp. and *Corynebacterium* spp..

Some bulls with seminal vesiculitis may produce semen with few or no sperm, the semen has a higher pH than normal and sperm motility is low.

Key issues

- Common in young bulls.
- Several treatment protocols have been described.
- Spontaneous resolution is common in young bulls, and re-evaluation in 4 to 6 weeks is recommended.

Tests for diagnosis

Seminal vesiculitis is normally detected on rectal palpation when one or both glands is determined to be enlarged and/or more nodular than the other. Leukocytes may be observed in the semen of affected bulls.

Treatment

Systemic and local antimicrobial treatment options have been described. Treatment with tulathromycin at the labelled dose, three injections of tilmicosin two days apart, and intra-glandular injection of procaine penicillin (1.5 mg diluted in 6 mL of saline) have been reported to be effective.

In an experimental treatment trial, 76% of young bulls with seminal vesiculitis treated with tilmicosin resolved. However, 76% of the untreated control group also resolved during the 28 – 70 day interval between treatment and follow-up.[60,65]

In contrast, in an experiment conducted with mixed age bulls, none of 17 untreated bulls recovered while 22/25 (88%) bulls treated with tulathromycin and 11/23 (48%) bulls treated with tilmicosin recovered.[65]

Antimicrobials used

1. Tulathromycin at 2.5 mg/kg SC once.
2. Procaine penicillin at 1.5 mg dissolved in 6 mL of saline injected into the affected seminal gland (note this is an off-label dosage regimen).

Prognosis

Spontaneous resolution is common for young bulls. The prognosis for older bulls is more guarded.

Bovine venereal campylobacteriosis (vibriosis)

Body system/syndrome

Urogenital/sexually transmitted disease

Background/nature of infection/organisms involved

Campylobacter fetus subspecies *venerealis* is an obligate parasite of the bovine reproductive tract that causes asymptomatic infections in bulls with no changes in semen quality or gross genital abnormalities. Infection in cows is associated with reproductive failure, irregular oestrus, transient infertility, and, in pregnant cows, embryonic or foetal death. Bulls and cows become infected by breeding with infected animals. *C. fetus* ss *venerealis* colonises the crypts of the preputial and penile mucosa of older bulls and the reproductive tract of some cows. Young bulls (yearling to 3 years of age) clear the infection within 4 to 6 weeks and do not normally become persistently infected. Older bulls have deeper crypts in the preputial and penile mucosa, do not eliminate the infection and remain long term carriers. *C. fetus* ss *venerealis* also persists for 6 to 24 months) in the vagina of cows, facilitating persistence from one breeding season to next.

Clinical scenarios consistent with vibriosis include a high number of heifers and cows returning to service at irregular intervals and a high empty rate at pregnancy check in natural service herds. Abortions may be observed, mostly at 2 to 5 months of gestation.

Key issues

- Sexually transmitted disease
- Older bulls more likely to be infected and remain infected than young bulls
- Vaccination highly effective in treating and preventing disease
- Can persist in infected cows for 24 months

Tests for diagnosis

Diagnostic investigation is typically triggered by a clinical scenario consistent with vibriosis. Diagnostic methods include culture, PCR and demonstration of specific antibodies.

The most efficient method of sampling vaginal and preputial secretions for culture and/or PCR involves insertion of an infusion pipette into the vaginal fornix or preputial cavity and performing short strokes while concurrently aspirating secretions. A portion of the sample is placed in pre-warmed campylobacter enrichment transport medium (CETM). To collect samples to measure pathogen specific antibodies, a long guarded swab is rotated against the wall of the vaginocervix until moist, placed in 4.5 mLs of phosphate buffered saline, chilled and shipped to the laboratory.

Isolating *C. fetus* ss *venerealis* requires transport of samples from preputial or vaginal secretions, foetal stomach contents, lungs and liver, and placentomes (in abortion investigations) to the laboratory in CTEM at room temperature. Culturing *C. fetus* ss *venerealis* is challenging and has a low sensitivity. PCR has a higher sensitivity and specificity than culture. It is recommended that the vaginal mucus IgA ELISA be used at a herd level rather than at the individual level as individual titres may vary from week to week.

Treatment

Campylobacter fetus ss *venerealis* infections in bulls may be cleared by vaccination.[66] Bulls are administered two doses of the vaccine a month apart. Isolated cases of vaccine failures are reported,[67] but, when combined with vaccination of the breeding herd, it is a highly effective treatment regimen.[68] Diagnostic testing should be performed to assess the efficacy of treatment prior to re-introducing bulls into the breeding herd. Culling of infected bulls may be the lowest risk option in most situations.

Ancillary strategies used to manage herds infected with *C. fetus* ss *venerealis* include replacement of older bulls with young virgin bulls and avoiding the use of shared or rented bulls.

Antimicrobials used

There is no evidence suggesting that combining antimicrobial therapy and vaccination is superior to vaccination alone in the treatment of vibriosis.

Reported antimicrobial therapies for bulls with vibriosis include local or systemic streptomycin,[69] local penicillin/streptomycin combination,[69] systemic oxytetracycline[70] and local cephapirin.

Streptomycin is reported to have the most clinical success but is not available in Australia and should not be used in food producing animals. The remaining antimicrobial therapies have limited efficacy data.

Prognosis

Treatment via vaccination is generally successful in younger bulls, with older bulls being at higher risk of treatment failure.

Urinary tract infection

Body system/syndrome

Urinary

Background/nature of infection/organisms involved

The most common urinary tract diseases in cattle are bacterial pyelonephritis and cystitis. Pyelonephritis in cattle results in a chronic, purulent inflammation of the bladder and ureters, as well as the kidneys. Infection of the bladder also occurs secondary to bladder paralysis following dystocia.

In the majority of cattle, pyelonephritis is caused by the ascension of *Corynebacterium renale*, which is a common inhabitant of the lower urogenital tract. Other bacteria that have been isolated from cases of pyelonephritis in cattle include *Escherichia coli*, *Trueperella pyogenes*, *Corynebacterium cystitidis*, *Corynebacterium pilosum*, *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp., *Klebsiella* spp., and *Pseudomonas* spp. These bacteria are also the most common cause of uncomplicated cases of cystitis.

Pyelonephritis is mainly seen in cows, with approximately 75% of cases occurring after abortion, dystocia or puerperal infection. The disease occurs sporadically. Clinical signs in the acute stage of infection include pyrexia, anorexia, colic, stranguria, polyuria and haematuria. Once disease has become chronic, cattle also display weight loss, a poor hair coat, anorexia, decreased milk production and anaemia.

Key issues

- Pyelonephritis is mainly seen in cows following abortion, dystocia or puerperal infection
- Chronic manifestations are the most common presentation
- Prolonged antimicrobial therapy is required for resolution of disease

Tests for diagnosis

1. Urine culture and susceptibility testing to confirm the aetiological agent(s).
2. Ultrasonography to determine bladder and/or renal involvement.

Treatment

Treatment of urinary tract disease may require the administration of antimicrobials for prolonged periods, with the duration of treatment based on clinical response.

Most cases of urinary tract infection are secondary to calving injury or damage to bladder innervation. Animals with permanent bladder dysfunction may improve whilst on antimicrobial therapy, but often relapse due to incomplete voiding of urine.

Antimicrobials used

Antimicrobial treatment recommendations for pyelonephritis reported in the literature are empirical, with minimal data supporting efficacy.

If culture and susceptibility testing has not been performed, given the high prevalence of infection with *Corynebacterium renale* in cases of pyelonephritis, procaine penicillin is the primary antimicrobial of choice.

Treatment of Gram-negative bacterial pyelonephritis is dependent on susceptibility testing. As cases are initially treated with penicillin, if the animal shows signs of clinical improvement whilst awaiting culture then penicillin can be continued. If not, then an alternative antimicrobial should be commenced.

- o Procaine penicillin at 20 mg/kg IM every 12 h for 2 to 3 weeks (note this is an off-label dosage regimen).[71]

If Gram negative organisms are involved:

- o Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 12 h for 2 to 3 weeks (note this is an off-label dosage regimen); or
- o Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 2 to 3 weeks (note this is an off-label dosage regimen).

Treatment of uncomplicated cases of cystitis usually requires a shorter treatment period (3 to 5 days).

Urine culture should be repeated 7 to 10 days after conclusion of treatment to assess cure.

Prognosis

The prognosis for cows with acute pyelonephritis is good unless functional damage to the kidney occurs.

The prognosis for chronic pyelonephritis is guarded.

The prognosis for cows with cystitis is good, although recurrence is likely in cows with bladder paralysis resolves. Culling should be considered for cows with chronic tail and bladder paralysis.[72-74]
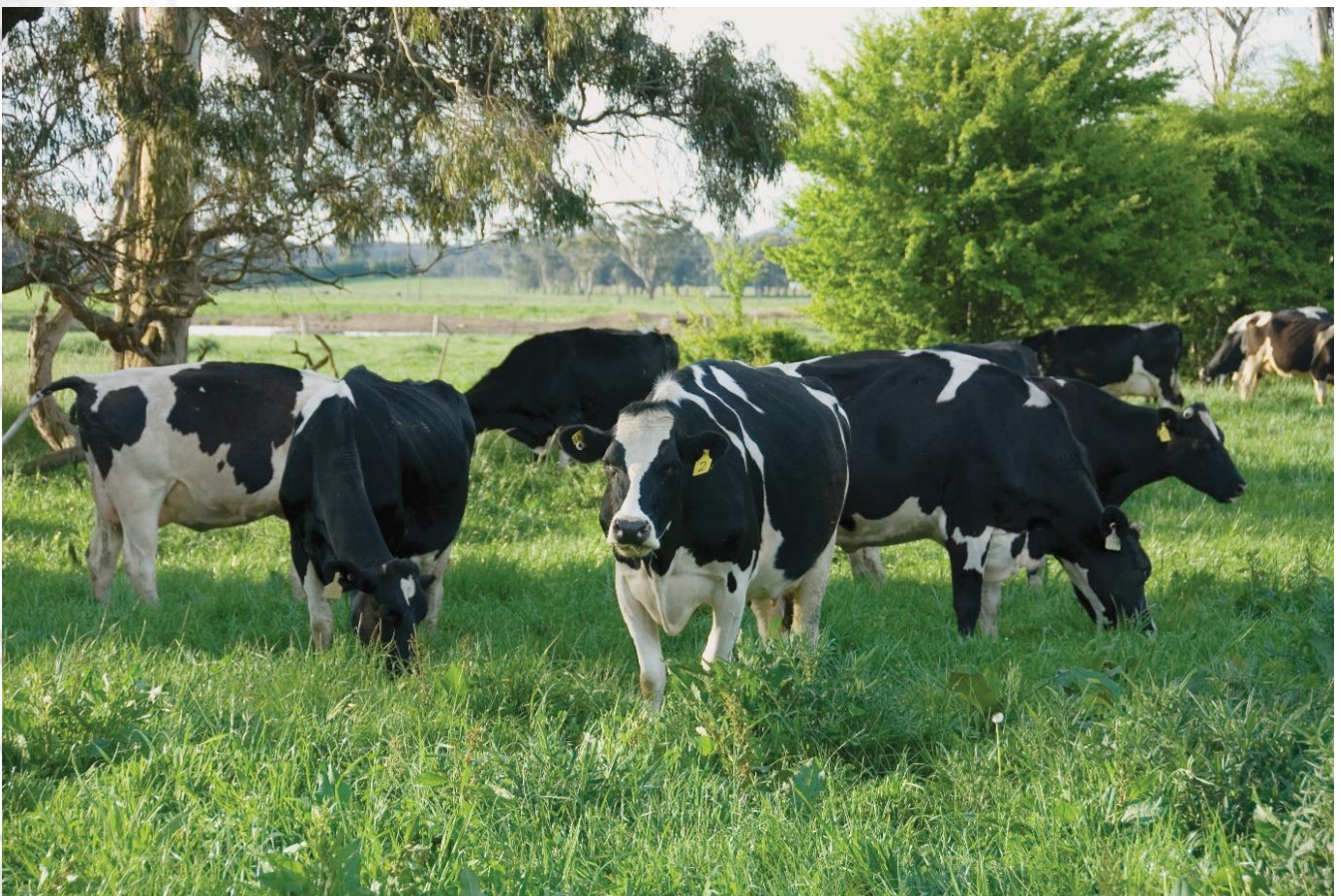
Salmonellosis

Body system/syndrome

Gastrointestinal, diarrhoea, sepsis, joint infections, meningitis/salmonellosis

Background/nature of infection/organisms involved

There are over 2500 *Salmonella* serovars, with most of the disease in a specific region being associated with 20 or fewer serovars, although the serovars causing disease in different regions may vary. In Australia, serovars Typhimurium, Dublin, and Bovismorbificans are frequently associated with disease in livestock. Disease manifestations include diarrhoea, sepsis, joint infections, meningitis, respiratory disease (*Salmonella* Dublin), abortion, and gangrene of the distal extremities (*Salmonella* Dublin).

The most frequent route of infection is faecal-oral, with spread occurring directly between livestock, and between livestock and other animal species, and via fomites and contaminated feed and water. Subclinical infections are also common, so isolation of *salmonellae* from the faeces of a single animal does not constitute a robust diagnosis of a herd disease outbreak. On farms experiencing salmonellosis in dairy calves, the infections often occur within 24 hours of birth. Recent research suggests calves may also be infected *in utero*.[75] *Salmonella* Dublin is the only host-adapted serovar in cattle, and has a propensity to cause chronic infections. *Salmonella* Dublin may be shed in the colostrum, milk and faeces of infected cows. Pooling colostrum or waste milk on an infected farm should be avoided as it can promote disease transmission. The number of organisms required to cause disease is typically in the order of 10^7 to 10^9 Neonates are typically more susceptible than adults. Compromised host immunity contributes to the risk of disease. Failure of passive transfer and inadequate nutrition contribute to disease risk in calves. Compromised feed intake, ruminal acidosis, compromised feed quality (spoiled silage), feeding magnesium oxide and feeding brewers' grain may contribute to risk in cows. Concurrent disease (e.g. fascioliasis or pestivirus infection) and environmental stress (heat or cold) may also contribute to disease risk.

Key issues

- Salmonellosis can result in a range of disease manifestations, including diarrhoea, sepsis, joint infections, meningitis, respiratory disease, abortion, and gangrene of the distal extremities (*Salmonella* Dublin).
- *Salmonella* Dublin is the only host-adapted serovar in cattle.

Tests for diagnosis

A diagnosis of salmonellosis is usually based on isolating the organism from the faeces or tissues of an animal showing clinical signs consistent with salmonellosis. A diversity of serovars may be present on a farm, but during disease outbreaks one serovar tends to predominate in the stock that are sick. During disease outbreaks when animals are dying, it is useful to culture tissues of animals that have died to identify the serovar associated with disease. Establishing a robust diagnosis when animals are sick, and a necropsy is not available, requires collection of samples from multiple affected animals, with testing for all relevant enteric pathogens to establish causality.

The most common test used to diagnose *Salmonella* is enrichment culture. This process involves inoculating the sample into a selective broth which, following incubation, is then sub-cultured on a selective-differential culture medium. Multiple molecular tests have been developed including PCR, qPCR and loop-mediated isothermal amplification (LAMP) assays. The sensitivity of molecular tests is typically lower than that of enrichment culture unless the molecular testing protocol includes a pre-enrichment step.

Bacterial isolation is required to perform antimicrobial susceptibility testing.

Treatment

As with other causes of diarrhoea, fluid therapy is fundamental to the treatment of salmonellosis. Antimicrobial treatment is useful, but it will not be effective if animals are dying from dehydration before the antimicrobial has time to inhibit the growth of the infecting salmonella. Conducting culture and antimicrobial susceptibility testing is useful, as attempting to treat salmonellosis with an antimicrobial in

the face of resistance to that antimicrobial has the potential to exacerbate disease. Non-steroidal anti-inflammatory drug therapy is likely to be beneficial.

The key outcome of antimicrobial prophylaxis/treatment trials in calves is that antimicrobial use may improve or compromise clinical outcomes. This contradiction has been observed with prophylactic use of antimicrobials in calves. There are a number of epidemiological studies reporting a lower incidence of salmonella shedding by calves fed prophylactic antimicrobials,[76-79] but conversely, in an experimental challenge study, prophylactic feeding of chlortetracycline exacerbated disease when the challenge organism was resistant to chlortetracycline.[80]

This finding underlies the importance of prudent antimicrobial use. When producers observe resolution of calf scours following antimicrobial treatment, they may see routine administration of antibiotics as a safeguard against scours. Antimicrobial use should be directed at resolving acute problems, pending correction of the underling predisposing conditions. Attempts at ongoing disease management using antimicrobials are likely to fail and will limit future treatment options.

Antimicrobials used

Numerous antimicrobial treatment trials have been conducted in calves, providing an evidential basis for antimicrobial treatment in young stock. Treatment decisions for adult stock are empirical, as there are no published controlled clinical treatment trials in adult cattle.

Antimicrobials of relevance in Australia that have been evaluated in experimental salmonella challenge trials in dairy calves include amoxicillin, neomycin, sulphonamides, trimethoprim/sulphonamides, oxytetracycline[77] and ceftiofur. Neomycin and sulphonamides were not effective treatments and neomycin has been associated with increased scouring in calves. Neomycin is not absorbed from the gut, so it would not be anticipated to protect against invasive infections when administered orally. Therapeutic efficacy has been reported with amoxicillin, trimethoprim/sulphonamides, oxytetracycline and ceftiofur. In all cases except trimethoprim/sulphonamides, the dose administered in these trials exceeded the labelled dose for the product in Australia.

While ceftiofur is listed as an effective treatment for salmonellosis, it should only be used as a last resort (and resistance to it has been detected in salmonellae isolated from dairy cattle in Australia). Third generation cephalosporins are the drug of choice to treat children. If antimicrobial resistance to ceftiofur develops on-farm and the antimicrobial resistant salmonellae enter the human food supply leading to disease in children, the therapeutic options for treating affected children will be compromised.

- o Amoxicillin trihydrate at loading dose of 20 mg/kg, followed by administration of 10 mg/kg IM every 12 h for 4 days (note this is an off-label dosage regimen); or
- o Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 24 h for 5 days[81]; or
- o Oxytetracycline hydrochloride at 11.1 mg/kg IM every 24 h for 3 days[82] (note this is an off-label dosage regimen); or
- o Ceftiofur sodium at 5 mg/kg IM every 24 h for 5 days.[83] (note this is an off-label dosage regimen). Use should be reserved for scenarios where resistance to all first line drugs limits their use so that selection for antimicrobial resistance to antimicrobials of high human significance is minimised.

Prognosis

The prognosis for salmonellosis is dependent on the virulence of the infecting serovar, the challenge dose and host immunity. High morbidity (> 20%) indicates significant exposure to the pathogen. High mortality (> 20%) suggests ineffective treatment and/or compromised host immunity. Bacteraemia associated with joint infections and/or meningitis has a more guarded prognosis. Gangrene of the distal limbs, as may be seen with *Salmonella* Dublin, is grounds for euthanasia.

Bovine respiratory disease

Body system/syndrome

Respiratory

Background/nature of infection/organisms involved

Most bacterial pneumonia in cattle reflects adverse host, pathogen and environmental interactions. The opportunistic bacterial pathogens (*Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*) associated with pneumonia are part of the normal flora of the nasopharynx. *Pasteurella multocida* is the species most commonly isolated from cases in dairy calves. Disease occurs secondary to host compromise that results in proliferation and dissemination of these bacteria into the lung. Host stressors may include viral pathogens (pestivirus, infectious rhinotracheitis virus (bovine herpesvirus 1), parainfluenza 3, bovine coronavirus, and bovine respiratory syncytial virus), dietary change, transport, stress and environmental conditions. Contagious bacterial pathogens that cause several disease manifestations including pneumonia include *Mycoplasma* spp. (predominantly *Mycoplasma bovis*) and *Salmonella* Dublin*.

The peak risk period for opportunistic bacterial pneumonia in dairy calves is just prior to and following weaning. Opportunistic bacterial pneumonia in adult cows is more common during early lactation. Pneumonia in post-partum cows may also reflect iatrogenic aspiration pneumonia induced by poor drenching technique.

Mycoplasma bovis and *Salmonella* Dublin also cause disease just prior to and following weaning, but they may also cause disease in young calves fed pathogen-contaminated milk.

Bacterial pathogens cause bronchopneumonia with cranioventral lung consolidation. Lung abscessation may be observed with chronic disease. *Trueperella pyogenes and Fusobacterium necrophorum* are common bacterial isolates from lung abscesses. *Trueperella pyogenes* and *Fusobacterium necrophorum* may also be isolated from cases of embolic pneumonia when a septic focus randomly showers the lung with septic emboli. Pleuropneumonia may be observed with severe cases of bronchopneumonia. Pleuropneumonia is more common with *Mannheimia haemolytica* and *Histophilus somni*.

Early clinical signs of pneumonia include tachypnoea, depressed mentation, anorexia, fever and reduced gut fill. Signs of toxaemia may develop, including scleral injection, hyperaemic mucous membranes and tachycardia. Coughing, mucopurulent nasal discharge and dyspnoea tend to occur as the disease progresses.

Key issues

- Pneumonia is largely caused by opportunistic pathogens in a compromised host.
- Response to treatment is largely influenced by correction of underlying stressors and the timing of treatment relative to the onset of disease.
- *Mycoplasma bovis* may cause outbreaks of disease in calves fed contaminated milk. Mycoplasmosis should be considered when pneumonia is associated with head tilts (otitis media interna) and tenosynovitis (swollen legs/joints).

Tests for diagnosis

Thoracic auscultation is an inexact method for identifying the area of lung involved. Abnormal lung sounds are audible on both inspiration and expiration. Increased bronchovesicular sounds may be auscultated in the cranioventral lung fields with or without crackles indicative of bronchiolar exudation. Absence of lung sounds ventrally may be detected with pleural effusion secondary to pleuropneumonia. Extensive lung consolidation may increase the audibility of the lung sounds. Percussion may be used to delineate the area of consolidated lung. The sensitivity of thoracic auscultation for diagnosis of bronchopneumonia in dairy calves is reported to be 73% (50–96%) and its specificity to be 53% (43–64%).

Thoracic ultrasound has similar sensitivity (77%, 60.–89%) to auscultation for diagnosis of bronchopneumonia, but a higher specificity (93%; 87–97%). In young calves, bronchopneumonia most commonly localizes to the cranial aspect of the right cranial lung lobe, followed by the right cardiac lung

lobe, and the caudal aspect of the left cranial lung lobe. It is important to scan both sides of the thorax because consolidation is unilateral in approximately 30% of cases.

The three options for collecting samples for virological and bacteriological examination include deep guarded nasopharyngeal swabs, transtracheal washes and bronchoalveolar lavages. Transtracheal aspiration and bronchoalveolar lavage obtain samples from the lower respiratory tract, avoiding the risk of contamination from the nasopharynx. Wash samples are also suitable for cytological examination, in addition to microbiological evaluation. Deep nasopharyngeal swabs are the easiest sample to collect, but they have a greater risk of contamination and do not provide a sample of the lower airway. Despite these limitations a recent study[84] reported good agreement between these methods for detecting bacterial pathogens. Amies transport medium is appropriate for bacterial culture and phosphate buffered glycol saline as a viral transport medium.

Thoracocentesis is of value for sampling pleural fluid when excessive fluid is detected in the pleural cavity. It can be carried out with or without ultrasound guidance by inserting a needle in the 6th or 7th intercostal space, below the fluid line determined by percussion or ultrasonography.

Treatment

Treatment outcomes are largely influenced by the timing of treatment relative to the onset of disease. Mortality and treatment failure are reduced by early treatment. Conversely, mortality, treatment failure, ill thrift and culling for chronic disease are more common when treatment is delayed.

Establishing a definitive diagnosis is useful for guiding antimicrobial therapy, particularly in dairy calves where *Mycoplasma bovis* and *Salmonella* Dublin are more likely to be found. Oxytetracycline, trimethoprim/sulphadiazine and amoxicillin are first line options. Therapy should be continued for a minimum of 5 days. Longer term therapy may be required. If the response to treatment is poor, consideration should be given to the timing of treatment and the possible involvement of *Mycoplasma bovis* or *Salmonella* Dublin. Procaine penicillin is NOT recommended for treatment of pneumonia due to the greater efficacy of alternative antimicrobials. All newer generation antimicrobials (ceftiofur, tilmicosin, tulathromycin, and florfenicol) developed for cattle are labelled for treatment of respiratory disease. The use of florfenicol, tilmicosin and tulathromycin is restricted in lactating dairy cattle. Tulathromycin is useful for treating calves with mycoplasmosis. Ceftiofur, trimethoprim/sulphadiazine, amoxicillin and procaine penicillin are NOT effective against mycoplasmas.

Non-steroidal anti-inflammatory drugs are commonly used to treat bovine pneumonia to promote animal welfare. The evidence supporting their use is limited to the short-term benefit of reducing fevers. Controlled clinical trials have failed to show significant differences in longer term outcomes, such as relapse rate, weight gain and mortality, compared to treatment with antimicrobials alone. Commonly used NSAIDs include flunixin, ketoprofen, meloxicam and tolfenamic acid. Use of corticosteroids to treat pneumonia is controversial and has the potential to exacerbate disease due to immunosuppression.

Antimicrobials used

- o Oxytetracycline hydrochloride at 10 mg/kg IM every 24 h for 5 to 7 days (note this is an off-label dosage regimen); or
- o Tulathromycin at 2.5 mg/kg SC once. Not to be used in lactating cows; or
- o Trimethoprim (4 mg/kg) and sulphonamide (20 mg/kg) combination IM every 24 h for 5 to 7 days; or
- o Ceftiofur sodium at 2 mg/kg IM every 24 h for 5 to 7 days (note this is an off-label dosage regimen). Use should be reserved for cases where demonstration of resistance to all first line drugs limits their application.

Prognosis

Good to poor - largely influenced by the timing of treatment and the ongoing level of concurrent stressors. Acute cases usually respond favourably to treatment. Animals that have failed to respond to treatment have a propensity to develop chronic pneumonia. Chronic cases tend to remain ill thrifty and grow poorly.

Surgical Prophylaxis

Body system/syndrome

Surgeries commonly performed in dairy practice include eye enucleation, umbilical hernia repair, claw amputations, exploratory laparotomy (often to correct abomasal displacement) and Caesarean section.

Background/nature of infection/organisms involved

Sepsis is the most significant complication following surgery. Human health guidelines for prevention of surgical site infections have been developed to guide antimicrobial use. These guidelines have been adapted and adopted in veterinary medicine. An example of bovine adapted guidelines is presented in Table 2, derived from Dumas and colleagues.[85] This table also provides indications of the incidence of surgical site infections (SSI) associated with the different surgical classifications in cattle.

Table 2. Classification of types of surgery and associated risks for surgical site infection (SSI)

Classification	Criteria	Risk of SSI
Clean	Non-traumatic, elective procedure where the surgical site is not inflamed or contaminated. No break in aseptic technique.	10.1 %
Clean - contaminated	Elective opening of respiratory, gastrointestinal, biliary or urogenital tract with minimal spillage. Minor break in aseptic technique.	15.4 %
Contaminated	Gross contamination is present at the surgical site without active infection, including spillage of the GIT , incision into acute non-purulent inflammation. Major break in aseptic technique.	26.7 %
Dirty	Active infection at the surgical site (purulent exudate is encountered), surgery of a traumatic wound with retained foreign bodies or faecal contamination, ruptured viscus	50 %

The incidence of SSI is largely influenced by the environment under which surgery is conducted. There are several case studies from teaching hospitals in Europe and the USA in which cattle enter a room for surgical preparation prior to entering a surgical theatre, where the cow is draped, and surgeons wear surgical gowns and sterile gloves. This environment is inconsistent with on-farm surgery, where the quality of facilities is variable and manure, dust and flies are part of the surgical environment. A report from the University of Montreal illustrates the implications of different surgical environments.[86,87] The incidence of incisional infections following "clean" flank laparotomies conducted in the hospital environment was up to 4.3%, compared to 10.5% for field surgeries performed by the same institution. The incidence of incisional infections reported following eye enucleations and laparotomies for correction of abomasal displacement, rumenotomy or Caesarean section ranges from 2.4 to 33%.[86,88-90] The reported incidence of more serious complications, such as peritonitis and mortality, are variable and influenced by the type of procedure.[91-93] Caesarean section generally carries a higher risk than exploratory laparotomy. In field-based studies, 5 – 10 % of cows developed peritonitis and mortality ranged from 3 – 24 %.[92,94-96] Even when SSI does not cause mortality, incisional complications increase the risk of a cow being removed from the herd compared to animals with uninfected incisions (48 % and 21 %, respectively, P=0.018).[94]

Most field surgeries are conducted on patients that have underlying or concurrent diseases, such as metritis, ketosis or mastitis in cows with a displaced abomasum, or infected umbilical structures in a calf with an umbilical hernia. When surgery is performed in the face of concurrent disease, antimicrobial choice is largely dictated by the type of concurrent disease. For conditions such as negative energy balance, where the concurrent disease may compromise immune function, the antimicrobial use decision often relates to the need and duration of use. Given the relatively high rate of SSI in field settings and the risk of serious life-threatening complications, prophylactic use is indicated in most cattle patients.

The risk of SSI is also influenced by the circumstances under which surgery is performed. This is illustrated well by Caesarean sections. In a case series of 412 Caesareans, wound infections were observed more commonly in dairy cattle (33%) than double muscled beef cows (13%). The surgeries conducted on the double muscled beef cattle were performed as elective surgeries, whereas the surgeries performed on dairy cattle were in response to dystocia. Peritonitis and mortality were similarly more common in the

dairy cattle than the beef cattle.[92] The risk of complications following Caesarean section is significantly greater when the uterus is not exteriorised. Difficulties exteriorising the uterus is a common problem when performing a Caesarean.[94,97] Foetal fluids are contaminated with a diversity of bacteria, including *Enterobacteriaceae*, anaerobes and *Trueperella pyogenes*.[98] The number of bacteria significantly increases following rupture of the amniotic membrane.[98] *Trueperella pyogenes, Enterobacteriaceae* and anaerobes, such as *Bacteroides, Fusobacterium* and *Prevotella* species, are commonly associated with surgical site infections and post-operative peritonitis.

Patient selection is an important consideration when considering surgical intervention. Examples of patient selection that are likely to result in poor outcomes include:

1. Performing a Caesarean as an option of last resort following a prolonged attempt to deliver a calf per vagina when the cow and surgeon are both exhausted and the uterus heavily contaminated.

2. Amputating a claw when the infection has travelled up the flexor tendon sheath above the level of the excision.

3. Correcting an LDA in a cow that is icteric secondary to a fatty liver. Surgeon experience is also a significant risk factor for surgical outcomes.[97]

Key issues

- The incidence of surgical site infections is influenced by the environment, patient selection and circumstances under which surgery is conducted
- Given the high risk of surgical site infections under field conditions and the serious life-threatening complications following infection, prophylactic use of antibiotics is recommended in most patients.
- Steps should be taken to minimize the risk of sepsis. There is no ideal antimicrobial available for surgical prophylaxis in cattle.

Treatment

Research conducted across multiple species indicates that prophylactic antimicrobial therapy is not required for clean elective surgeries where there is no break in asepsis and no trauma or inflammation encountered. The reality for on-farm surgery is that it is not conducted in a clean environment, with asepsis often breached by flies, dust and chaff, reflecting the working conditions. Avoiding prophylactic use to practice prudent drug use is unlikely to lead to good surgical or animal welfare outcomes. A short course of antimicrobial therapy translating to a live healthy cow is better than a protracted course of antimicrobial therapy and a debilitated or dead cow as an outcome. The greatest opportunity to reduce the risk of surgical complications and subsequently surgery-related antimicrobial use is through good preparation and planning. While prophylactic antimicrobial therapy has the potential to contribute to a successful outcome, it will frequently fail to compensate for poor preparation and or surgical technique.

Preparation tips that help to reduce the risk of sepsis include:

1. **Gently scrub the surgical field.** A scrubbing brush, warm water and surgical scrub are useful for removing gross contamination from the surgical site and surrounds.
2. **Clipping an appropriate surgical field.** What constitutes appropriate will vary between surgeons according to their experience and skill. A margin of 20 - 30 cm is recommended in all directions around the proposed site of the incision[99]. It is wise to anticipate that the unexpected may occur and clip an area that enables a clean surgical field to be maintained should the incision need to be extended. Washing the cow removes sand, which blunts clippers. Clippers also work better on wet hair than on dry hair, and the detergent in the surgical scrub also serves as a lubricant. Clipping in the opposite direction to the lay of the hair (ventral to dorsal on the flank of the cow) reduces the chance of hair getting caught between the clipper blades, which will compromise their function, and it also provides for a closer clip.
3. **Clean parts of the crush that are near the incision.** It is likely that the cow will move during the surgery and may rub the incision on adjacent bars. If bars are contaminated with manure, an incisional infection and/or peritonitis are more likely to occur.
4. **Consider the microbial status of the water used to wash and prepare the cow.** Experienced veterinarians who frequently perform surgery on cows have often experienced the scenario where surgeries on a particular farm are more likely to develop septic complications than surgeries performed on other farms. One potential cause of this is the use of contaminated water. One way to mitigate this risk is to use water from the hot water service. As the water is hot, it is important to think ahead and fill the buckets early so the water can cool while other preparations are underway.
5. **Provision of good analgesia.** Achieving good regional analgesia is important for the cow's welfare, surgeon safety and to maintain an aseptic surgical field. When performed correctly, a paravertebral nerve block provides good analgesia for exploratory laparotomies. The epaxial and flank muscles on the side of the surgery relax, causing the cow to bend toward the surgeon, this widens the surgical field and the muscles of the flank do not pull as obliquely, making it simpler to close the incision. Comfortable cows are much less likely to kick, which helps to maintain asepsis. When a cow kicks during surgery, the stifle is usually raised above the level of the incision and frequently impacts the surgeon's arms, contaminating the surgeon and the surgical site.
6. **Sedation.** Most dairy cows are relatively calm and do not require sedation. If the cow does not pose an immediate safety risk, it is preferable to wash and prepare the cow prior to sedation to get a better assessment of temperament. Sedation is useful if the cow will not settle. If the cow is agitated and has calved recently, consider the possibility of nervous ketosis. Managing ketosis and hypocalcaemia prior to surgery is important to reduce the risk of the cow going down during surgery. Sedation is associated with an increased risk of cows lying down during surgery and with increased uterine tone during a Caesarean, which can make it difficult to exteriorise the uterus[97].
7. **Carry a headlamp and a couple of torches.** The ones with magnets that stick to the crush are good. It is easier to do a good job when you can see what you are doing.
8. **Time, Trash and Trauma increase the risk of sepsis.** Having a plan of action before you start that includes a check of instruments and suture material prior to surgery mitigates risk of delays during the surgery. Ideally carry autoclaved instrument packs in the car. If you run out of autoclaved packs then you can revert to cold sterilisation. Carrying a small foldout table is useful for keeping instruments and equipment clean and accessible during surgery.

Antimicrobial use for surgical prophylaxis in dairy cattle should be targeted to cover *Trueperella pyogenes, Enterobacteriaceae* and anaerobes such as *Bacteroides, Fusobacterium* and *Prevotella* spp., which are the organisms most frequently associated with surgical site infections and post-operative peritonitis. Ideally antimicrobial therapy is initiated prior to surgery to achieve therapeutic drug levels at the time of surgery. The nature of clinical practice and additional economic implications to the producer often preclude this from occurring in most situations, except where postponing surgery may significantly improve surgical outcome - for example delaying LDA surgery by 24 h in dairy cattle with concurrent metritis and ketosis.

Unfortunately, none of the low importance antimicrobials labelled for use in cattle provide an ideal antimicrobial spectrum for surgical prophylaxis. This is particularly true if they are used at labelled doses. Penicillin and oxytetracycline are the antimicrobials most frequently used for surgical prophylaxis.[100,101] Neither is ideal.

Antimicrobials used

- o Procaine penicillin at 20 mg/kg IM, with the first dose ideally administered 2 h prior to surgery, or otherwise before preparing the cow for surgery. This is followed with doses of 20 mg/kg every 24 h for 3-5 days, with the duration depending on the conditions of surgery and concurrent disease.

Good spectrum of activity against the most common cause of SSI in cattle, *Trueperella pyogenes* and the anaerobes. No coverage for *Enterobacteriaceae*, which will be required if contamination occurs following leakage during Caesarean surgery or incomplete closure of an abdominal organ.

- o Oxytetracycline hydrochloride at 10 mg/kg IV 30-60 minutes before surgery. This is followed with doses of 10 mg/kg IM every 24 h for 3 – 5 days, with the duration dependent on the conditions of surgery and concurrent disease.

This therapy has a variable spectrum of activity against the *Enterobacteriaceae* and resistance frequently seen in *Trueperella pyogenes*.

Prognosis

The prognosis for surgical patients varies with the indication for surgery, the conditions under which the surgery is conducted, and the nature and severity of any concurrent disease. The importance of good surgical preparation cannot be over emphasised.[85,86,88-101]
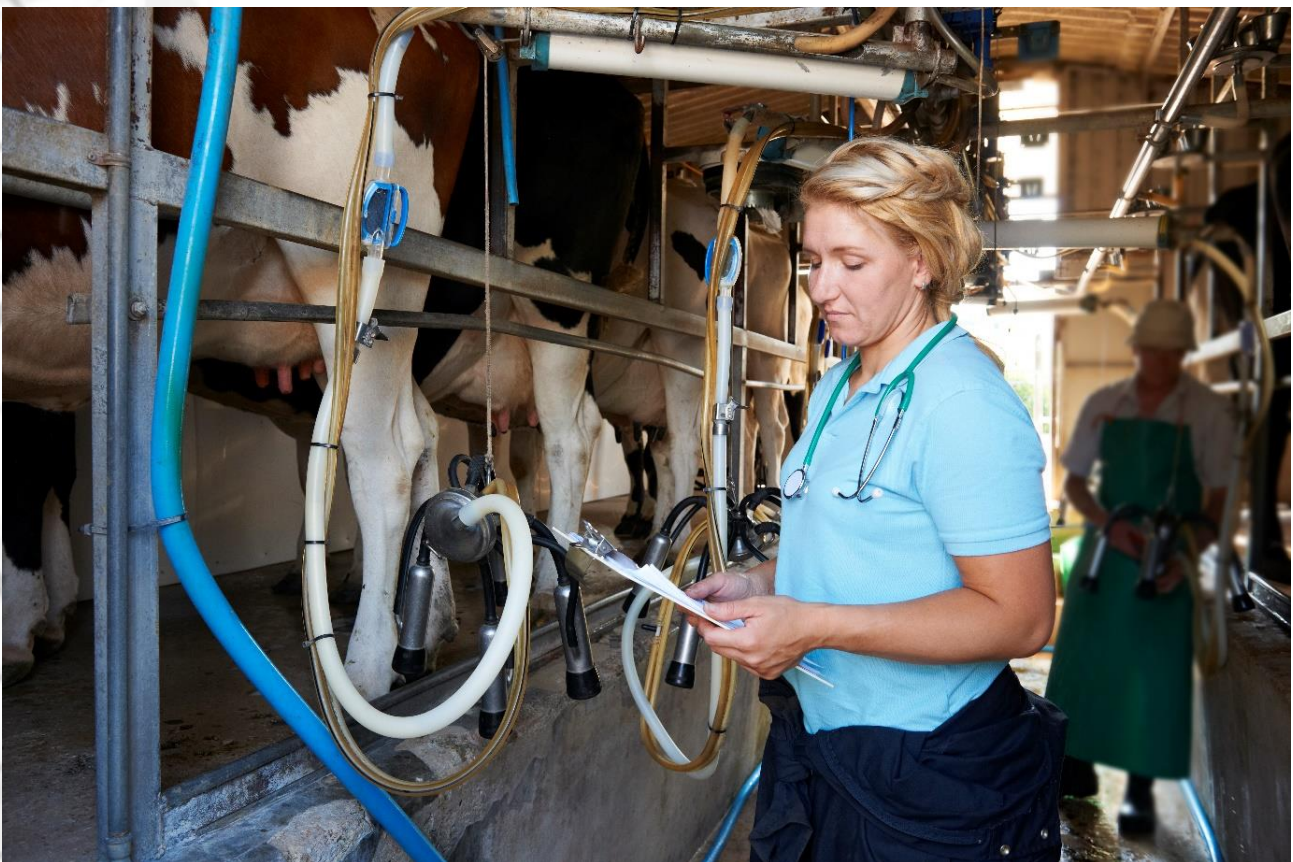
Mastitis

Body system/syndrome

Mammary gland. Mastitis may be subclinical (elevated somatic cell count, no visible signs) or clinical. Clinical mastitis is classified according to duration (acute vs chronic) and severity. Severity classifications include mild (changes in milk with normal gland and cow), moderate (changes in milk and gland, normal cow) and severe (changes in milk, gland and cow).

Background/nature of infection/organisms involved

Mastitis is inflammation of the udder and is frequently caused by a bacterial infection. It is the most common disease of dairy cattle. The bacterial pathogens most commonly associated with mastitis in Australia include *Streptococcus uberis* (54.3%), *Staphylococcus aureus* (14.8%), *Escherichia coli* (11.7%) and *Streptococcus dysgalactiae* (8.9%)[102]. "No growth", or failure to isolate a pathogen from milk, is seen in approximately 20 – 25 % of cases. Non-invasive pathogens, such as *Streptococcus agalactiae*, *S. dysgalactiae*, and coagulase-negative *Staphylococcus* spp., colonise the epithelial lining of the ducts and alveoli of the mammary gland. *S. uberis* colonises the ducts and, to a limited extent, the mammary parenchyma. *S. aureus* is more invasive, causing fibrosis and microabscessation in the mammary parenchyma. Severe intra-mammary infections, where bacterial pathogens release endo- or exotoxins that induce acute local and systemic inflammatory responses, may be caused by coliforms, *S. aureus*, *Pseudomonas aeruginosa* and *Bacillus cereus.* Bacteraemia is a common feature of coliform mastitis and is detected in 4.3%, 9.1% and 42% of cows with mild, moderate and severe clinical signs, respectively.[103] Antimicrobial therapy to treat and control mastitis accounts for more than two thirds of all antimicrobial courses supplied to dairy farmers by veterinarians in Australia.[104] Costs associated with mastitis include, but are not limited to, reduced milk yield, loss of milk quality premiums, culling, mortality, medications, labour, reduced reproductive performance, discarded milk and transmission of disease to young stock.[105,106] While disease prevention strategies should always be the emphasis of herd management, disease events are inevitable, requiring contingencies for therapeutic intervention to promote cow health and welfare.

Key issues

- Mastitis is caused by a diverse range of environmental and contagious bacterial pathogens.
- There are a diverse range of diagnostic options available for the detection of mastitis pathogens.
- There is little evidence to broadly support antimicrobial susceptibility testing to guide antimicrobial treatment of mastitis.
- The indications for treatment are variable across pathogens.
- Prognosis is influenced by pathogen and cow factors (particularly prior mastitis history).

Tests for diagnosis

Most mastitis is diagnosed by dairy producers at milking time. Clinical mastitis may manifest as heat, swelling or pain in the udder and/or changes in the milk (wateriness or clots). Abnormal milk that persists for more than three squirts is used as an indication of mastitis.[107] Flakes of milk that do not persist for more than three squirts reflect teat canal infections that warrant monitoring but not antimicrobial treatment.[108,109]

At the time of writing, laboratory diagnosis of clinical mastitis is usually reserved for herd level milk quality problems and/or disease investigations. The use of rapid culture systems to facilitate mastitis treatment decisions is an emerging trend.[110-113] It has been reported that treatment of mild or moderate clinical mastitis cases can be postponed for one day with minimal adverse effects while producers wait for test results.[114]

Laboratory diagnosis is traditionally based on milk culture. The diagnostic laboratory should be advised when mycoplasmosis is suspected, as it requires a specific culture medium and longer incubation. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry has recently become available in several Australian veterinary laboratories, expediting identification of mastitis pathogens. PCR and/or LAMP assays have also been developed to detect the more common mastitis pathogens. These

assays are typically applied to bulk tank surveillance for *Mycoplasma* spp. and *Streptococcus agalactiae*. The *Mycoplasma bovis* PCR is also useful for rapid identification of clinical cases.

The use of rapid diagnostic systems (e.g. Acumast, Check-UP, Mastaplex, Petrifilm, biplates) to guide strategic treatment of clinical mastitis has the potential to reduce antimicrobial use. The effect of rapid culture systems on antimicrobial use will be influenced by the farm pathogen profile. Most of these systems focus on differentiating "no growth", Gram-negative and Gram-positive infections. The underlying logic of on-farm diagnostics is that treatment is not necessary for "no growth" or *E. coli* infections. On-farm diagnostics that identify *S. aureus* may also help with culling decisions. A New Zealand study found that the use of on-farm culture systems with selective antimicrobial therapy resulted in a 25% reduction in antibiotic usage with no increase in cows retreated for clinical mastitis.[115]

Antimicrobial susceptibility

There are numerous studies reporting the antimicrobial susceptibility of mastitis pathogens. Although antimicrobial susceptibility plays a role in response to therapy, there is little evidence of a correlation between *in vitro* susceptibility testing and treatment outcomes in the cow.[116,117] The clinical predictive value of antimicrobial susceptibility is limited by incomplete pharmacokinetic/pharmacodynamic data for commercial intra-mammary products and inadequate field studies validating susceptibility breakpoints.[118,119] There are no antimicrobial MIC breakpoints established for any of the intra-mammary products available in Australia that have been established based on antimicrobial concentrations achieved in the bovine mammary gland. Establishing antibiogram profiles of bacterial isolates from bulk tank milk samples has been proposed as an option for predicting the antimicrobial susceptibility of bacterial isolates from clinical cases on the same farm. There is currently no peer reviewed evidence validating this method or to indicate this treatment selection criterion influences treatment outcomes.

There are a limited number of studies validating the capacity of antimicrobial susceptibility testing to predict clinical outcomes.

Antimicrobial susceptibility testing is most relevant to herds that have a high prevalence of *S. aureus* due to the contagious nature of the organism and the likelihood that future infections may be caused by bacteria with similar antimicrobial susceptibility. Conversely, in herds where mastitis is predominantly associated with environmental organisms, antimicrobial susceptibility testing is unlikely to be informative because of the diversity of infecting strains, the time delay between infection and assessment of susceptibility and the poor correlation between susceptibility testing and clinical outcome.[116,117,120] Emergence of increasing beta lactam resistance has recently been reported in *S. uberis* mastitis isolates in New Zealand.[121] Cases associated with resistant isolates tended to have a lower cure rate following treatment.[121] *S. uberis* may behave either as an environmental or contagious pathogen.[122] At this time, no data are available to indicate whether antimicrobial susceptibility guided treatment decisions improves treatment outcomes for these beta lactam resistant *S. uberis* isolates.

Treatment

From a prudent antimicrobial drug use perspective administering antimicrobials via the intra-mammary route is recommended to achieve concentrations 100 to 1,000 fold higher than those obtained by parenteral administration using less antimicrobial.[123-125] Intra-mammary therapy is usually effective for treatment of mild to moderate mastitis. Intra-mammary treatment of the more invasive pathogens, such as *S. aureus* and *S. uberis*, is generally less effective, in part reflecting the difficulty of delivering antimicrobials to the site of infection.

Systemic antimicrobial therapy has been shown to improve clinical outcomes in cows with severe coliform mastitis, as opposed to mild and moderate cases where antimicrobial therapy has not improved outcomes.[126,127] Systemic treatment of cows with severe coliform mastitis is believed to provide benefit by helping the cow manage bacteraemia, which is a common feature of severe coliform mastitis. Improved clinical outcomes were observed in cows treated with trimethoprim/sulfadiazine (TMS) when the infecting organisms were susceptible to TMS. Systemic treatment with ceftiofur has also been demonstrated to reduce mortality and culling rates in cows with severe coliform mastitis.[127] Products containing ceftiofur carry a label restraint that they must not be used for the treatment of mastitis.

Some antimicrobial products are widely distributed within the mammary gland and others are not. Lipid soluble drugs, such as macrolides (erythromycin, tylosin), oxytetracycline, penethamate hydriodide and trimethoprim/sulphonamide are potentially suitable for systemic treatment of bacterial infections in the

udder.[128] Polar, water-soluble products distribute poorly to the mammary gland (e.g. beta-lactams), but these products may be suitable for intra-mammary delivery.

The success of mastitis treatment can be measured by clinical resolution and microbial cure. Clinical resolution is the standard measure on farm. It is based on observation of the disappearance of clinical signs indicative of mastitis. However, it is not a definitive indication of pathogen elimination, as the infection may regress to subclinical mastitis. Return to 'normal milk' and regression of clinical signs usually takes 2-6 days. Premature estimation of clinical cure may result in an erroneous judgement that treatment of a case failed. There is no consistent definition of clinical cure in the veterinary literature,[129] so an anecdotal recommendation is to make an assessment at the end of the withholding period. Other parameters used to evaluate treatment success include cow side tests (e.g. rapid mastitis test; RMT), somatic cell counts, recurrence of clinical mastitis and milk production.[116] Using a RMT or Somatic Cell Count (SCC) to define success is confounded by the lag between microbiological cure and resolution of the inflammation within the gland, may result in an erroneous judgement that treatment of a case failed. Therefore, the use of RMT to determine treatment success or failure (and hence the need for re-treatment or some other action) is not recommended. The time to resolution of the inflammatory response is influenced by the inciting pathogen. For example, in one study 42% of mastitic quarters returned to a RMT score of "trace" within 36 days of microbiological cure, with a range from 29% for *Klebsiella* spp. to 78% for *E. coli*.[130] When evaluating on-farm treatment protocols it is necessary to have a pre-determined definition of success and failure to provide a consistent outcome assessment. In the absence of culture data, it is difficult to distinguish treatment failure from a new infection. The time interval from treatment to re-emergence of clinical signs is used as a proxy for distinguishing treatment failure from new infection. The cut off is somewhat arbitrary, with periods of time ranging from 7 to 14 days commonly applied.[130]

The success of mastitis therapy is not limited to the appropriate choice of antibiotic for the causative organism. Host factors that influence the likelihood of treatment success include parity, days in milk, number of quarters affected, conformation and duration of infection.

Intra-mammary antimicrobial therapy

Intra-mammary infusion carries a risk of iatrogenic infection associated with poor infusion technique. This was illustrated by a Victorian study in which 13% of cows developed a new infection with a different organism following intra-mammary therapy.[131] Attention to detail in hygienic teat preparation is important to minimise the risk of iatrogenic infection. Tissues lining the teat duct are very susceptible to damage from rough cannula insertion. The risk of damage is reduced by partial insertion of the cannula. Partial insertion has been demonstrated to improve the efficacy of dry-cow therapy compared to full insertion.[132]

Commercially available intrammary products in Australia use 10 different antimicrobial compounds either alone or in combination (amoxicillin/clavulanic acid, ampicillin, cephalonium, cefuroxime, cloxacillin (including sodium and benzathine salts), dihydrostreptomycin, neomycin, novobiocin, oleandomycin and oxytetracycline).

Comparative treatment trials conducted in Australia and New Zealand reported similar outcomes from the commercial products evaluated.[133-137] For mastitis caused by Gram positive pathogens there is no evidence to suggest broad-spectrum products (generally products containing a combination of antimicrobials) outperform narrow spectrum products. Mastitis caused by *E. coli*, which is the most common cause of coliform mastitis, has a high rate of spontaneous resolution. *Klebsiella* spp., the second most common cause of coliform mastitis, has a propensity to cause persistent infections. A clinical trial in the USA reported improved clinical and bacteriological cure of *Klebsiella* spp. mastitis following treatment with a broad-spectrum product that is not available in Australia.[138] *Klebsiella* spp. are not a common cause of mastitis in Australia.

Table 3. Intra-mammary lactating antimicrobial active ingredients available in Australia

Action	Drug	Distribution in Gland	Antimicrobial Activity in Milk[118,139,140]	Treatment interval (h)
Beta lactams	Ampicillin	Good	Similar	12
	Cefuroxime	?	Similar	24
	Cloxacillin	Limited	Similar	24 - 48
Protein synthesis inhibitors	Neomycin	Poor	Markedly Reduced	24 - 48
	Dihydrostreptomycin	Poor	Reduced	24 - 48
	Lincomycin	Good	?	12 - 24
	Novobiocin	Good	Reduced	24 - 48
	Oleandomycin	?	?	24
	Oxytetracycline	Limited	Reduced	24

Source: House JK Humphris M, Petrovski KR . Development, monitoring and evaluation of clinical mastitis protocols. 2015 Dairy Australia Countdown 2020 Symposia, Melbourne.

Currently there is insufficient evidence available to determine the relative efficacy of the different mastitis therapies[141]. If we accept this, treatment choices should be guided by the good antimicrobial stewardship principles of using a narrow spectrum drug and an intra-mammary route in preference to systemic and on-label dosing.[142]

Extended Therapy Beyond Label Directions

Lactating cow therapies are designed to provide a therapeutic antimicrobial drug concentration for a short duration and consequently yield a short milk withholding period. Inadequate duration of therapy has been proposed as a potential cause of treatment failure,[143] prompting research into extended therapy.

The risk of iatrogenic infection is an important consideration prior to implementing extended therapy. When attention to detail is poor, the risk of introducing a new infection with repeated intra-mammary infusions may be greater than the benefit of any treatment effect.[131]

A number of studies have been conducted evaluating the effect of increasing the duration of therapy on clinical outcomes for cows with chronic subclinical or recurrent clinical intra-mammary infections caused by S. aureus, S. uberis and coliforms.[138,143-148] [149] These trials have generally achieved higher cure rates than standard treatment regimens, but the results have differed between the causative pathogens and the magnitude of the improvement is sometimes limited.[150,151] The trials have also involved intra-mammary products that are not available in Australia. No trials have been conducted to compare outcomes for short and long antimicrobial courses using products available in Australia.

Indiscriminate use of extended mastitis treatment hoping for a better cure is not economically logical, recommended, or consistent with prudent antimicrobial use, and there is a considerably higher risk of milk residue violations. In a study involving cefquinome it was found that approximately 5 to 10 cows would need to undergo extended therapy (compared to standard therapy) to achieve one additional cure.[151] Extended therapy is an off-label drug use in all but one of the commercial intramammary products. The period of time that antimicrobial residues persist in the milk of a cow will be prolonged and withholding guidelines are not available, increasing the risk that there will be detectable antimicrobial residues in bulk milk.

Parenteral Therapy

Although higher concentrations of antimicrobial drugs are achieved in mammary tissue using intramammary products, there are limited studies comparing the efficacies of intramammary and parenteral therapy in the treatment of clinical mastitis.[134] [152] The results of these studies suggest the

efficacy of systemic and intramammary antimicrobial therapy are likely to be similar. Intramammary therapy is considered preferable from a prudent drug use perspective, as less antimicrobial is used and distributed into other body systems, such as the gastrointestinal tract, and the environment. Consequently, fewer bacteria are exposed to the antimicrobial than when parenteral treatment is used.

Parenteral therapy may have clinical advantages over intra-mammary infusion when multiple quarters of a cow are infected concurrently , in the face of a *Mycoplasma bovis* outbreak (to decrease pathogen spread at the time of treatment), when treating large numbers of cows in a 'blitz therapy', or when animal behaviour poses a safety risk to operators trying to infuse intramammary antimicrobials.[135]

Parenteral Antimicrobial Options

Trimethoprim-sulphonamide combinations

Trimethoprim has a short plasma half-life in adult cattle (approximately 40 minutes) and is poorly absorbed from extravascular injection sites. At lower doses, similar to the recommended label doses in Australia, trimethoprim has been reported to fail to reach therapeutic concentrations in the mammary glands of adult ruminants.[153-155] An improved clinical outcome for cows with coliform mastitis was achieved by treatment with TMS using a significantly higher dose than the label dose for Australian products. Cows were administered an intramuscular loading dose of 8 mg trimethoprim/kg and 40 mg sulfadiazine/kg, followed by three daily doses of 4 mg trimethoprim/kg and 20 mg sulfadiazine/kg.[126]

Penethamate hydriodide

The efficacy of systemically administered penethamate hydriodide has been compared with different intra-mammary therapies. In a New Zealand trial, the overall bacteriological cure rate of clinical mastitis of 76.4% was lower than that achieved with intra-mammary therapy with a combination of procaine penicillin and dihydrostreptomycin (84.9%).[134] The difference was explained by a significantly better efficacy of the intra-mammary treatment against clinical infections caused by coagulase-negative staphylococci. However, systemic treatment with penethamate did cure subclinical infections in quarters adjacent to the clinically affected quarter. A bacteriological cure rate of 54.3% seen in a US study was not significantly different from the cure rate of 45.9% obtained by intra-mammary treatment with a combination of cloxacillin and ampicillin.[152] This study also reported collateral reduction in the SCC in the systemically treated cows. Penethamate has a Gram-positive spectrum of activity and thus is not appropriate for systemic treatment of severe coliform mastitis.

Erythromycin

Erythromycin comes in an oily base and is administered by deep intramuscular injection. Tissue reaction and pain at the site of injection are often observed and may limit repeated drug administration. Good susceptibility (MIC $\leq$ 0.5 μg/mL) is observed with gram positive aerobes and facultative anaerobes (*Bacillus* spp., *Corynebacterium* spp., coagulase negative staphylococci and streptococci). *Enterobacteriaceae* and *Mycoplasma bovis* are generally resistant (MIC $\geq$ 8 μg/mL). Erythromycin reaches levels in milk four or five times higher than those present in plasma (in healthy mammary glands). There are a number of studies that refer to the treatment of mastitis with erythromycin.[131] However, there is a paucity of controlled studies that provide a comparative evaluation of treatment efficacy compared to alternative therapeutic options or untreated controls.

There is insufficient evidence to recommend routine use of parenteral administration of erythromycin for treatment of mastitis.

Tylosin

Tylosin is a macrolide antibiotic with similar pharmacokinetics and a similar spectrum of activity to erythromycin, but it is generally less active against Gram negative bacteria and more active against *Mycoplasma bovis*. In a clinical trial in which the predominant pathogen was *S. uberis*, similar results were achieved treating cows with tylosin base (5 g injected 3 times at 24-h intervals) compared to treating cows with penethamate hydriodide (5 g injected 3 times at 24-h intervals).[135] There was also no difference between the treatments in the proportion of cases with a bacteriological cure (81.2% for penethamate hydriodide and 83.8% for tylosin) or in the average somatic cell counts.[135]

Oxytetracycline

Intramuscular injection of oxytetracycline hydrochloride at label dose rates (4 mg/kg) results in poor distribution to the milk.[156] Additionally, its activity in milk is decreased; MICs are two to five times higher than those seen in broth cultures.[156,157] However, following intravenous injection, oxytetracycline distributes into milk at similar concentrations to serum and has been recommended as a parenteral treatment for use in conjunction with intra-mammary therapy.[158] In a field trial evaluating oxytetracycline hydrochloride (10 mg/kg) for treatment of severe coliform mastitis, clinical outcomes were better when the infecting organism was susceptible (MIC < 8 µg/mL) to oxytetracycline.[159]

Recommendations for parenteral therapy

Parenteral therapy for mastitis is generally not recommended as a primary treatment option for mastitis.

Exceptions to this recommendation include:

Severe coliform mastitis or multiple quarter infections with gram negative pathogens

- o Trimethoprim (8 mg/kg) and sulphonamide (40 mg/kg) IM followed by trimethoprim (4 mg/kg) and sulphonamide (40 mg/kg) IM every 24h for 3 days (note this is an off-label dosage regimen); or
- o Oxytetracycline hydrochloride at 11 mg/kg IV every 24 h for 3 days (note this is an off-label dosage regimen).

In the face of a mycoplasma outbreak where intramammary therapy carries risk of disease transmission.

In this scenario therapy is targing gram positive pathogens where it is most likely to be therapeutic. The treatment in this case is not targeting mycoplasma as there is no registered product with efficacy against mycoplasma.

- o Penethamate hydriodide at 5g IM every 24 h for 3 days; or
- o Tylosin at 10mg/kg IM every 24 h for 3 days

In situations where there is risk of injury to farm personell or cows (eg blitz treatment of *Streptococcus agalactiae*, or treatment of a fractious heifer) and where multiple quarters are infected with gram positive pathogens

In this situation therapy is targeted at gram positive pathogens where it is most likely to be therapeutic.

- o Penethamate hydriodide at 5g IM every 24 h for 3 days; or
- o Tylosin at 10mg/kg IM every 24 h for 3 days

On farms that report a better response to parenteral verses intra-mammary therapy and a reluctance to utilise intra-mammary therapy there is likely to be an underlying problem with intra-mammary infusion technique. "Poor responses to therapy" reflecting iatrogenic infections induced by contaminated or traumatic infusion technique.

Dry Cow Therapy

High concentrations of long acting antimicrobials are administered at drying off to cure existing and reduce the risk of new intramammary infections. Dry cow therapy reduces the incidence of clinical mastitis and high somatic cell counts in early lactation. Dry cow therapy has been found to be more effective in preventing new infections with Gram-positive mastitis pathogens than coliforms. This may reflect the fact that most dry cow preparations target Gram-positive pathogens, which are more frequently associated with persistent infections. Similar efficacy has been reported for broad and narrow spectrum dry cow formulations.[160] Broad spectrum dry cow formulations may reduce the risk of clinical coliform mastitis during early lactation,[161] but a similar reduction may be achieved using a narrow spectrum product combined with an internal teat sealant.[162]

There is no evidence to support the use of dry cow formulations to treat refractory cases of mastitis in lactating cows. Long acting intramammary preparations should not be used for the treatment of clinical mastitis during lactation. Long acting preparations are formulated to release the antimicrobial agent over an extended period in the low volume udder of the dry cow, so appropriate antimicrobial concentrations

are not achieved in the short inter-milking period during lactation. The use of dry cow products during lactation also introduces a significant risk of antimicrobial residue violation, as drug excretion data have not been established for this application. Dry cow formulations should not be used for the treatment of mastitis in lactating cows.

Internal Teat Sealant

Internal teat sealants composed of bismuth subnitrate offer an alternative option for reducing the risk of new intramammary infections during the dry period. The inert paste forms a physical barrier, reducing the risk of pathogens infecting the mammary gland. When administered appropriately, teat sealants reduce new infections over the dry period and reduce the SCC and the risk of clinical mastitis in early lactation.[163] [164] [52] Administration of internal teat sealants is commonly combined with dry cow intramammary products. Attention to detail with aseptic administration of internal teat sealants is very important, especially when they are being used without dry cow intramammary preparations. Unhygienic administration of internal teat sealants can be very costly, leading to dry cow mastitis and mortality.[165]

Selective Dry Cow Therapy

Blanket dry cow therapy, or treatment of all quarters of all cows irrespective of infection status, has been effective in reducing the prevalence of the contagious pathogens *S. agalactiae* and *S. aureus*. When the prevalence of subclinical mastitis is low, most quarters treated with blanket dry cow therapy are not infected and therefore do not require antimicrobial therapy. With selective dry cow therapy where antimicrobial use is focused on treating existing intramammary infections, internal teat sealants are typically administered to cows not treated with antimicrobials to prevent new infections. Several strategies can be used to select the quarters of cows to receive antimicrobial dry cow therapy. The two most common screening strategies include milk culture or algorithms based on individual cow SCC and health records. For herds that perform routine individual cow SCC, a single test in late lactation was as predictive of intramammary infection at drying off as multiple tests throughout lactation.[166] The use of a single herd test is an economic and effective option for the identification of animals that require dry cow antimicrobial treatment. The ideal selective dry cow therapy programme delivers equivalent udder health to blanket dry cow therapy with significantly less antimicrobial use. If improperly implemented, selective dry cow therapy has the potential to increase the incidence of clinical and subclinical mastitis in the subsequent lactation. A useful fact sheet has been prepared by Dairy Australia called "Guide to choosing an appropriate dry cow treatment strategy" that provides a decision tree for dry cow treatment choices.

Ancillary Therapy for Mastitis

Ancillary mastitis treatments include NSAIDs, oxytocin and fluid therapy. Non-steroidal anti-inflammatory therapy may provide benefit by reducing inflammation and swelling, improving the distribution of antimicrobials within the affected quarter, and by blocking inflammatory mediators. Some studies have shown improved clinical and reproductive outcomes when NSAIDs are used concurrently with antibiotic therapy [167] [168]. In contrast to NSAID's studies evaluating the therapeutic benefit of oxytocin compared with no treatment have found no increase in self-cure rates[130,169-171] Concurrent administration of oxytocin with intra-mammary antimicrobial therapy has also been reported to lower the rate of bacteriological cure compared to intra-mammary antimicrobial therapy alone.[171] Fluid therapy is indicated for treatment of severe mastitis. Endotoxaemia is a common feature of severe mastitis, resulting in fever, tachycardia, forestomach hypomotility, weakness, and occasionally diarrhoea and dehydration.[172]

Treatment of subclinical mastitis

Treatment of subclinical mastitis is generally not recommended. The economic benefit may be equivocal because of the costs of treatment, milk discard, and low treatment efficacy[173,174]. Herds infected with *S. agalactiae* may be the exception, where a good response to treatment is likely and treatment of subclinical infections may reduce the risk of disease transmission.[117]

Prognosis

The probability of successful mastitis treatment is influenced by the host and the pathogen. Host factors that influence the likelihood of success include parity, days in milk, number of quarters affected, conformation and duration of infection. New Zealand's Livestock Improvement Corporation reported cure rates were 75% for the first treatment, 45% for the second treatment and 12% for the treatment.[175]

Pathogens that only colonise the milk ducts are more likely to be cleared than invasive pathogens such as *S. aureus*. The relationship between common mastitis pathogens and their response to treatment are shown in Table 4.

Table 4. Common mastitis pathogens and the expected response to treatment

Pathogen	Anticipated treatment response
Environmental	
Streptococcus uberis	82–91% clinical cure[134,176,177]
Streptococcus dysgalactiae	90–98% clinical cure[134,176,177]
Escherichia coli	High rate (85%) of spontaneous cure without treatment[117]
Klebsiella spp.	Low rate of spontaneous resolution (18 - 37%),[130,178 179] [138] bacteriological cure rate following intramammary treatment of 74 % [138,179]
Coagulase negative staphylococci	85% clinical cure[135,180]
Contagious	
Streptococcus agalactiae	Approaching 100%.
Staphylococcus aureus	Bacteriological cure rate of 20 – 60%. Probability of cure influenced by parity, stage of lactation, historic ICC, number of infected quarters, antimicrobial susceptibility of strain.[181]
Mycoplasma spp.	Treatment not recommended due to poor response. No cell wall - beta lactam antimicrobials ineffective. Cull.
Miscellaneous	
Corynebacterium bovis	There are limited reports about the response of *Corynebacterium bovis* to treatment. In one study 70% of cases resolved following treatment.[182] Milking procedure rather than antimicrobial treatment should be the focus of *Corynebacterium bovis* management. Effective application of post milking teat dip is fundamental to reducing prevalence in herds with a high incidence of *Corynebacterium bovis* associated mastitis.
Trueperella pyogenes	Poor/often associated with abscessed quarters.
Nocardia spp.	Poor (may be associated with contamination at infusion).
Yeasts/Moulds	Poor (no effective antimicrobials).
Pseudomonas spp.	Poor (may be associated with contamination of water sources in milking parlour).

Source: House JK Humphris MA, Petrovski KR . Development, monitoring and evaluation of clinical mastitis protocols. 2015 Dairy Australia Countdown 2020 Symposia, Melbourne.

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