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Review

Bacterial osteomyelitis in veterinary orthopaedics: Pathophysiology, clinical presentation and advances in treatment across multiple species

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ABSTRACT

Bacterial osteomyelitis in veterinary patients can be challenging to diagnose and treat, given limited therapeutic options and reported success rates. Osteomyelitis is frequently associated with surgical implant devices, including those required to optimise stability and healing of fractures. However, management of osteomyelitis sometimes necessitates the removal of these surgical implant devices in order to eradicate infection or limit implant-related osteolysis. The goal of this article is to provide a general and species-specific review of bacterial osteomyelitis in a selection of domestic veterinary species, including cats, dogs, horses, cattle and camelids, with a focus on classification, clinical presentation, aetiologic agents, and common therapeutic interventions reported in the literature. New treatment options emerging from research and human medicine will be also discussed, as they also apply to current or future care of veterinary patients with osteomyelitis.

Introduction

Osteomyelitis, the inflammation of bone and bone marrow, is a challenging condition across all animal species, and is often caused by prior or persistent infection with pyogenic organisms (Weisbrode, 2009). The condition commonly results from iatrogenic or spontaneous inoculation of infectious agents into traumatic or surgical wounds (Johnson, 1994; Goodrich, 2006). It can also develop following haematogenous inoculation of bone, and occurs relatively more frequently in juveniles than in adults, especially in those with predisposing conditions including failure of passive transfer of maternal immunity or concurrent infection such as septicaemia or septic omphalitis (Weisbrode, 2009; Clegg, 2011). Due to anatomic differences in the macro- and microcirculation, haematogenous osteomyelitis most commonly occurs in the metaphysis and epiphysis of developing bones, and the diaphysis of long bones in adults (Baxter, 1996; Dernell, 1999). Osteomyelitis can also occur within vertebral bodies (Sutton et al., 2010; Crabtree and Jorgensen, 2012), or in any bone receiving an implant device such as a prosthetic joint or fracture fixation devices (Pacchiana et al., 2003).

A wide range of microorganisms are implicated in osteomyelitis with bacterial infections being the most frequently reported. Therefore, although other forms of osteomyelitis exist (e.g. fungal, atrophic) these will not be further discussed, and hereinafter osteomyelitis will refer to inflammation of the bone and bone marrow with an underlying bacterial aetiopathogenesis.

Post-traumatic osteomyelitis results from direct contamination of the bone, either at the time of trauma or at the time of surgery. Due to the nature of traumatic bone injury, and that of surgical bone injury (e.g. as a result of an elective orthopaedic procedure), there is often a degree of damage to the blood supply of the bone and the surrounding soft tissue. Reduce local blood flow interferes with the ability of host immune cells to infiltrate the affected tissue, and contributes to the development of additional necrotic tissue and dead space, all of which increase the risk of infection (Sayegh et al., 2001). In humans, the incidence of post-traumatic, implant-related osteomyelitis in open fractures can exceed 30% (Trampuz and Zimmerli, 2006). Whilst in elective joint replacement, incidence of implant-related osteomyelitis ranges from 0.3% to 1.6% (Pulido et al., 2008). In veterinary patients, the incidence of osteomyelitis has not been closely tracked, but has been reported as high as 31% of canine fracture repairs (Hunt et al., 1980) and 28% of equine fracture repairs (Ahern et al., 2010), for both open and closed fractures.

As mentioned above, haematogenous osteomyelitis results from the spread of bacteria to bone via the blood supply. Juvenile animals are thought to be predisposed to haematogenous osteomyelitis due to the presence of metaphyseal vascular anastomoses that form end arterial 'hair-pin' loops with very

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low velocity blood flow, and thus provide an ideal environment for bacterial seeding of that tissue (Firth, 1992; Baxter, 1996; Lew and Waldvogel, 2004; Gutierrez, 2005). Haematogenous osteomyelitis occurs more frequently in foals and calves compared to juvenile dogs and cats (Weisbrode, 2009; Clegg, 2011). Although generally rare in adult animals (Swinebroad et al., 2003), haematogenous osteomyelitis has been documented in the adult dog (Rabillard et al., 2011).

In addition to route of infection and type of infection, osteomyelitis can be classified as acute or chronic. Acute osteomyelitis is defined by a rapid onset of clinical signs, usually developing over a number of days. The definition of chronic osteomyelitis in animals is not clearly defined with respect to duration, but has usually been present for several weeks or more and is characterised by persistent infection with the presence of radiographic signs of alterations in bone architecture, bone sequestra, and sinus tracts (Johnson, 1994; Baxter, 1996; Lew and Waldvogel, 2004). In addition to bone sequestra, these deep-seated infections can involve antibiotic-resistant pathogens or those that produce biofilms. Chronic osteomyelitis complicated by avascular necrotic bone typically requires radical debridement, since antibiotic therapy alone is considered unlikely to resolve the infection (Dernell, 1999; Orsini et al., 2004). When the infection is associated with an implant device, such as those used in operative fracture fixation or elective joint-replacement surgery, management of osteomyelitis can be further complicated due to the presence of the device itself. Bacterial biofilm, associated with the surface of the implant device (further discussed below), reduces the effectiveness of antibiotic therapy against bacteria within the biofilms (Gristina and Costerton, 1984). Removal of the implant or a staged exchange protocol might be desirable, and is considered essential in human medicine; however, in veterinary medicine implant removal is not always possible, depending on the stage of healing and the species involved. This is particularly true in veterinary patients that cannot feasibly have their movement restricted. Successful treatment of osteomyelitis sometimes requires prolonged hospital stays, extended duration of antibiotic therapy, and potentially several revision surgeries (RSx) to debride necrotic and infected bone. In addition to the significant medical care costs, there can be significant functional defects, bone loss and protracted healing times, with a high risk of infection recurrence. This can be particularly challenging in athletic species, such as horses and dogs, reducing the ability to pursue active work, which in itself can lead to early retirement or euthanasia. In horses, an extended duration of non-weight bearing lameness can also lead to life-threatening sequelae such as laminitis in the contralateral limb (Baxter and Morrison, 2008).

The role of biofilm in osteomyelitis

As briefly mentioned above, implant-related osteomyelitis is known to involve bacterial biofilm formation (Costerton, 2005; Brady et al., 2008). Bacterial biofilms are defined as communities of bacteria, encased within an extracellular polymeric substance produced by the bacteria themselves (McConoughey et al., 2014). Biofilm formation has been documented in patients with implant-related (Stoodley et al., 2008) and non-implant-related osteomyelitis (Marrie and Costerton, 1985). Fig. 1 shows a biofilm formed by *Staphylococcus aureus* in a mouse model of implant-related osteomyelitis (Sabate Bresco et al., 2017). Formation of a biofilm imparts significant antibiotic tolerance upon the bacteria within, leading to an increase in minimum inhibitory concentration (MIC) of up to 100-fold in most cases (Molina-Manso et al., 2013; Marques et al., 2015; Olsen, 2015). This antibiotic tolerance is due to a combination of factors including the limited diffusion of certain antibiotics into the biofilm matrix, an induced stress response to low concentrations of antibiotics, a hypoxic and low metabolic state deep within the biofilm rendering antibiotics that rely on metabolic activity ineffective, and the presence of bacterial persistor cells that are in a dormant state (Olsen, 2015). The biofilm also protects bacteria from host defences, including phagocytosis by cells of the immune system, and can limit the induction of proinflammatory immune responses when compared to non-biofilm associated bacteria (Thurlow et al., 2011). This tolerance to antibiotic therapy, and resistance to host defences, contribute to the high rate of treatment failure in osteomyelitis (Neil et al., 2010). Staphylococci are the most commonly isolated bacteria in clinical cases of osteomyelitis, and are known to readily form biofilm. The

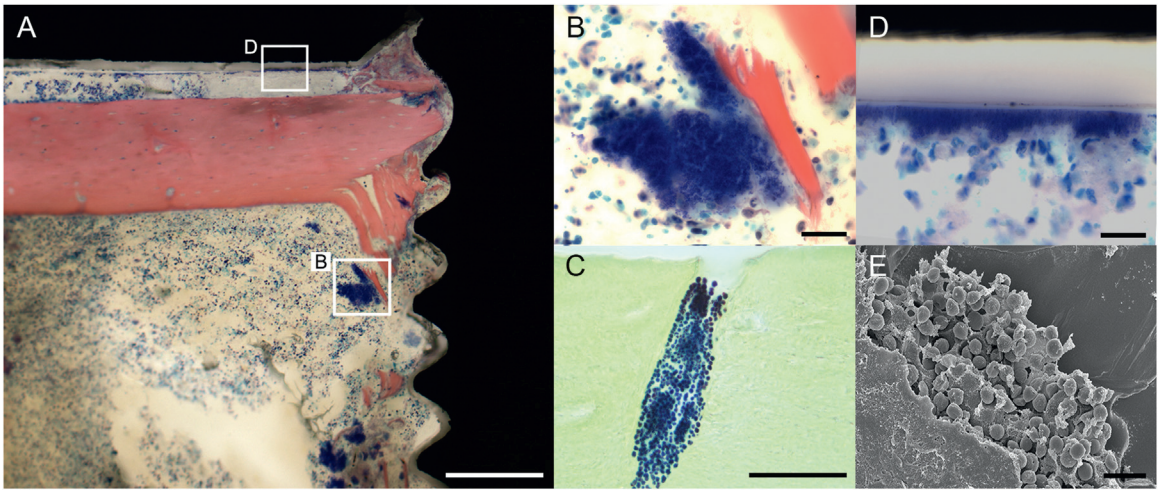

Fig. 1. Histological observation of bacteria in a mouse model of implant-related osteomyelitis (Rochford et al., 2016; Sabate Bresco et al., 2017). In this model, mice received a transverse osteotomy of the femur, which was fixed with a fracture fixation plate (horizontal black-coloured area at top of A and D) and four angular stable screws (vertical black area in A). *Staphylococcus aureus* was introduced on the surface of the plate prior to placement. (A) Overview photomicrograph of a Giemsa-eosin stained histological section showing a part of the femur, a screw, and the plate. A bacterial microcolony (deep blue staining material) can be seen on a necrotic bone fragment within the lower white box in A (scale bar: 200 μm) and magnified in B (scale bar: 20 μm). Bacteria were also observed infiltrating blood vessels in the bone (C; image taken from adjacent tissue section and is not visible in A, scale bar: 20 μm). Bacteria are also seen forming biofilm on the underside of the plate (upper white box in A, and magnified image in D (scale bar: 20 μm)). Note the gap between the plate and biofilm is an artefact of the fixation process. Finally, a scanning electron microscope image of bacterial biofilm on the surface of the explanted fracture fixation plate of a plate removed from a separate animal (E; scale bar: 20 μm).

only antibiotic with activity against staphylococcal biofilm is rifampicin, and as such is a cornerstone of the treatment of implant-related osteomyelitis, at least in human patients (Zimmerli and Sendi, 2017). For biofilms involving Gram-negative pathogens, ciprofloxacin is the antibiotic of choice in human patients (Aboltins et al., 2011). In veterinary patients, the use of these antibiotics is sometimes restricted for regulatory reasons, and few reports are available describing their efficacy.

Clinical presentation of osteomyelitis

Clinical signs

Clinical signs associated with osteomyelitis are consistent across different animal species and include lameness, swelling, heat, pain upon palpation, draining tracts (Fig. 2A), and localised erythema. Systemic signs such as pyrexia, leucocytosis, or elevation of other inflammatory markers such as serum amyloid A or fibrinogen are not consistent findings (Johnson, 1994; Mader et al., 1997; Goodrich, 2006). In the case of a haematogenous osteomyelitis additional systemic clinical signs such as pyrexia, tachycardia, tachypnoea, hypotension or other signs of sepsis attributable to the inciting bacteraemia or initial source of infection might not always be present (Johnson, 1994; Mader et al., 1997; Goodrich, 2006).

Diagnosis

A strong clinical suspicion of osteomyelitis is usually based upon a combination of clinical observations and diagnostic imaging. Commonly used diagnostic imaging modalities include radiography, ultrasonography, with CT and MRI sometimes used in small animals and horses. Typical radiological signs of osteomyelitis (Figs. 2 and 3) include regional osteopenia, periosteal reaction, focal bony lysis, endosteal scalloping, loss of bony trabecular architecture, new bone apposition and peripheral sclerosis (Gold et al., 1991; Goodrich, 2006). In chronic or untreated osteomyelitis, sequestra (Fig. 4) might be also identified (Pineda et al., 2009).

Ultrasonography can be particularly helpful in detecting accumulations of fluid around implants or irregularity of the bone surface (Carek et al., 2001).

MRI is able to identify both soft-tissue and joint complications (Gold et al., 1991) and can detect signs of infection, such as bone oedema, before radiological alterations are visible (Gold et al., 1991; Goodrich, 2006). The value of MRI and CT is markedly limited when metallic implant devices are in place (Gupta et al., 2015). Nuclear scintigraphy has also been used in veterinary patients (Goodrich, 2006), as a highly sensitive if not particularly specific modality for the investigation of possible osteomyelitis (Schauwecker, 1992). Positron emission tomography–computed tomography (PET-CT), which has been used in human medicine to detect low-grade osteomyelitis or loosening of joint prostheses in humans (Pineda et al., 2006), has also been described for veterinary patients (Randall, 2016).

Local bone biopsy and positive bacteriological culture provide a definitive aetiological diagnosis for osteomyelitis (Goodrich and Nixon, 2004). Osteomyelitis might still be suspected in culture-negative biopsy, when histopathology or clinical signs of infection support the presence of infection independently. There is a risk of false positive culture result and misidentification of causative organism when swabs are taken rather than biopsies, or when superficial samples are taken from sinus tracts. Furthermore, there is an increased risk of false negative results if antibiotic therapy has recently been used, or when microbiological culture conditions are limited (e.g. lack of anaerobic culture, or short duration of incubation; Barer and Harwood, 1999; Nystrom, 2003). Similarly, biofilm formation can increase the likelihood of a false negative culture (Ehrlich et al., 2012). A positive culture of the underlying aetiological agent and resultant antibiotic susceptibility test to guide selection of antimicrobial therapy is critical to the successful

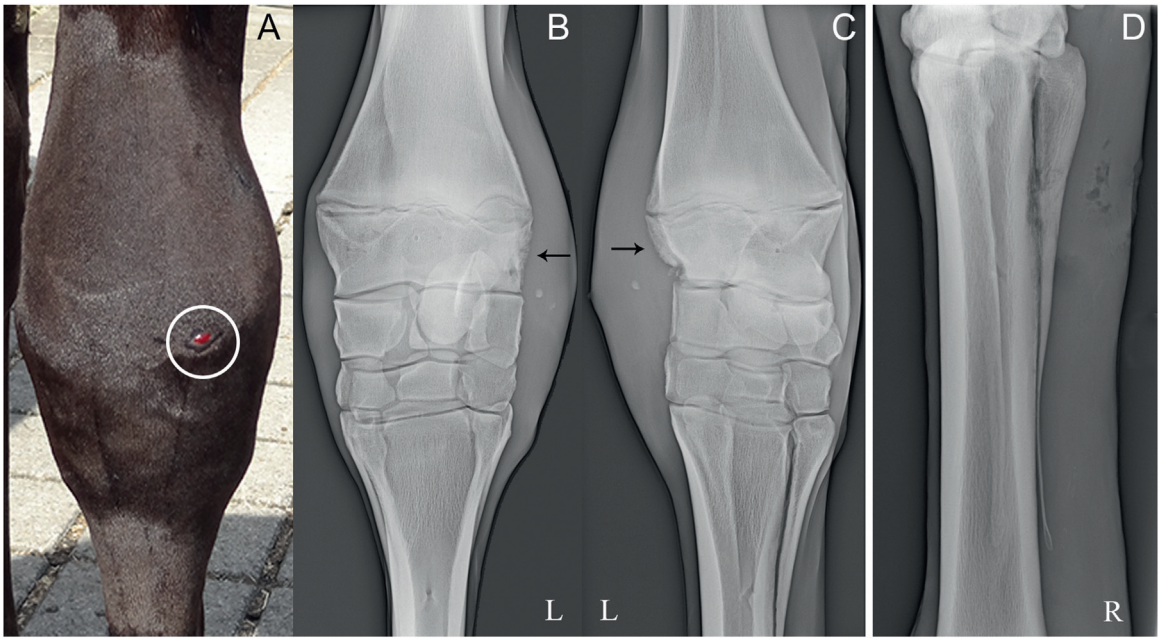

Fig. 2. Clinical (A) and radiographic images (B–D) corresponding to post-traumatic osteomyelitis in two horses. Photograph of the dorsal aspect (A), and dorso-palmar (B) and dorso 45° medial-palmarolateral oblique (C) radiographic images of the left carpus of a skeletally immature horse 19 days after a perforating trauma to the dorsal carpus. Clinical signs included lameness, localised swelling, heat, pain upon palpation, and a draining tract (circle). Subcutaneous swelling and intraarticular effusion with displaced radiopaque fragments of bone are associated with irregular bone contour and mottled radiolucency of the dorsolateral aspect of the distal radial epiphysis, compatible with osteomyelitis. Dorsolateral-palmaromedial radiograph (D) demonstrating focal osteomyelitis affecting the lateropalmar cortex of the proximal 3rd metacarpal diaphysis resulting from a perforating trauma in an adult horse. A linear skin defect overlying the palmarolateral proximal metacarpus corresponding to an irregular expanded region of increased soft tissue opacity (cellulitis) with subcutaneous radiolucencies (emphysema) are superimposed over a region of mottled, radiolucent (lytic) cortical bone.

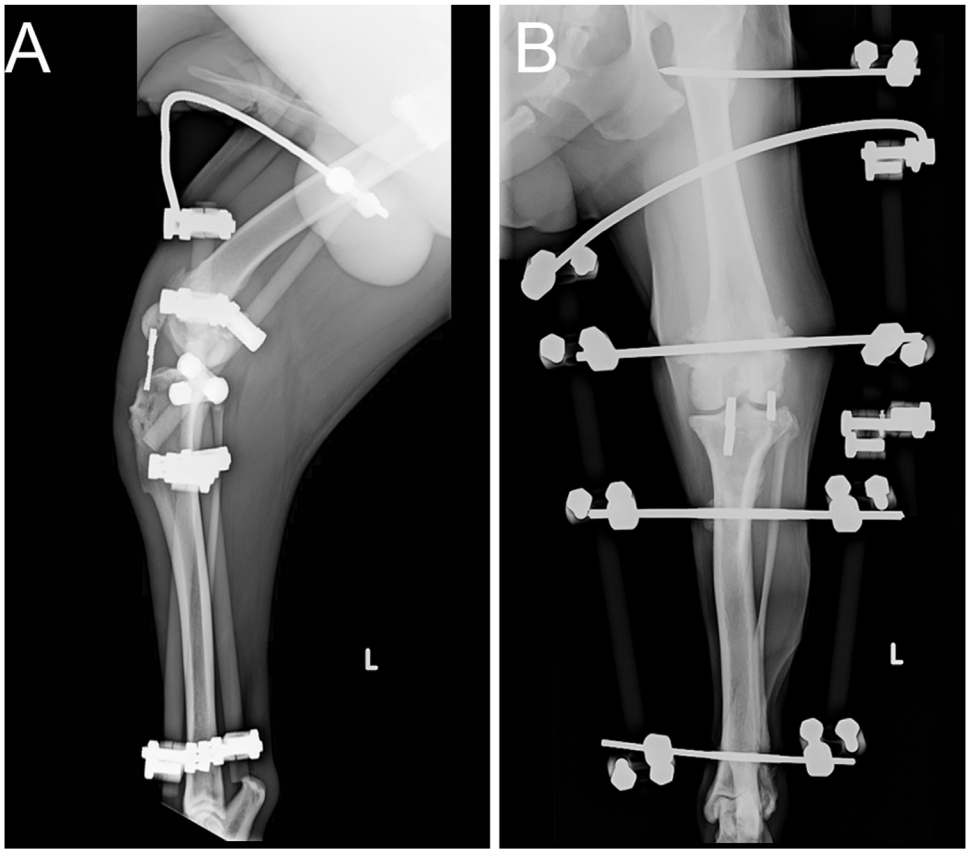

Fig. 3. Implant-related osteomyelitis of the left stifle of a dog 6 weeks after surgical management of patellar ligament rupture: Medio-lateral (A) and cranio-caudal (B) radiographic projections show the presence of moderate permeative lysis within the tibial tuberosity and around the drill hole within the patella. There is moderate, rough and solid periosteal new bone formation at the cranial margin of the tibial tuberosity, and the irregularly outlined radiolucent halos surrounding the femoral and proximal pins with associated palisading periosteal new bone formation. These changes are also visible in a mild form at the distal tibial pin.

treatment of osteomyelitis (Johnson, 1994). Table 1 summarises the common aetiological agents and incidence rates for various types of osteomyelitis across veterinary species.

Treatment and prognosis

Acute haematogenous osteomyelitis can generally be managed medically provided that antibiotic therapy is appropriate and commences promptly following the onset of clinical signs (Giguère et al., 2013). In contrast, chronic osteomyelitis usually requires surgical debridement (Lew and Waldvogel, 2004), including removal of sequestra and necrotic bone or soft tissue (Baxter, 1996; Dernell, 1999). In the case of post-traumatic osteomyelitis, delayed use of implants, temporary fixation with an external fixator, or even implant removal, might be necessary to eliminate the risk or complication of biofilm associated with the device (Buckley et al., 2017). Strategies to increase the concentration of antibiotics within the local bone environment include the placement of antibiotic-loaded materials such as bone cement, polymethyl methacrylate (PMMA) beads, calcium phosphate, or collagen (Schneider et al., 1995; Tobias et al., 1996; Holcombe et al., 1997), and, in large animals, regional limb perfusion (Whitehair et al., 1992; Murphey et al., 1999; Kelmer, 2016). Antibiotic treatment should be based on an antimicrobial susceptibility test whenever possible. However, until culture and antibiotic susceptibility test results are available, broad-spectrum antibiotics should be administered. Recommended antibiotics for the treatment of osteomyelitis in different species, as described in the literature, are summarised in Table 2. There are comparatively more data for companion animals and horses, whilst the data for ruminants and camelids are scarcer. No specific recommendations are available for the antibiotic treatment of osteomyelitis in cattle, although some guidelines are available for septic arthritis (Constable et al., 2008).

Although a highly undesirable outcome, as a last resort for small companion animals, amputation is an option where the osteomyelitis is limited to a single limb.

The prognosis of osteomyelitis depends on the time of presentation, the degree of alteration in bone architecture, and response to treatment, which can be expensive, especially in large animals (Trostle, 2004; Richardson and Ahern, 2012).

Species-specific features of osteomyelitis

Dogs and cats

The first characterisation of osteomyelitis in companion animals, was published in the mid 1970's and early 80's (Vaughan, 1975; Hirsh and Smith, 1978; Griffiths and Bellenger, 1979; Hunt et al., 1980). The most common causes in those studies were trauma and surgical site infections that extended to the bone. The trauma typically related to fight injuries or collision with a motor vehicle, both of which can result in direct contamination of the bone via penetrating injuries or open wounds and damage to the surrounding vasculature. Motor vehicle trauma (78%) and dog bite injuries (17%) were specifically listed as the reasons for osteomyelitis in long bones of dogs (n = 52) in a more recent study (Siqueira et al., 2014). Bacterial culture was positive in 88% of these cases, with *Staphylococcus* spp. being the most commonly isolated organisms. In a retrospective study of osteomyelitis in dogs and

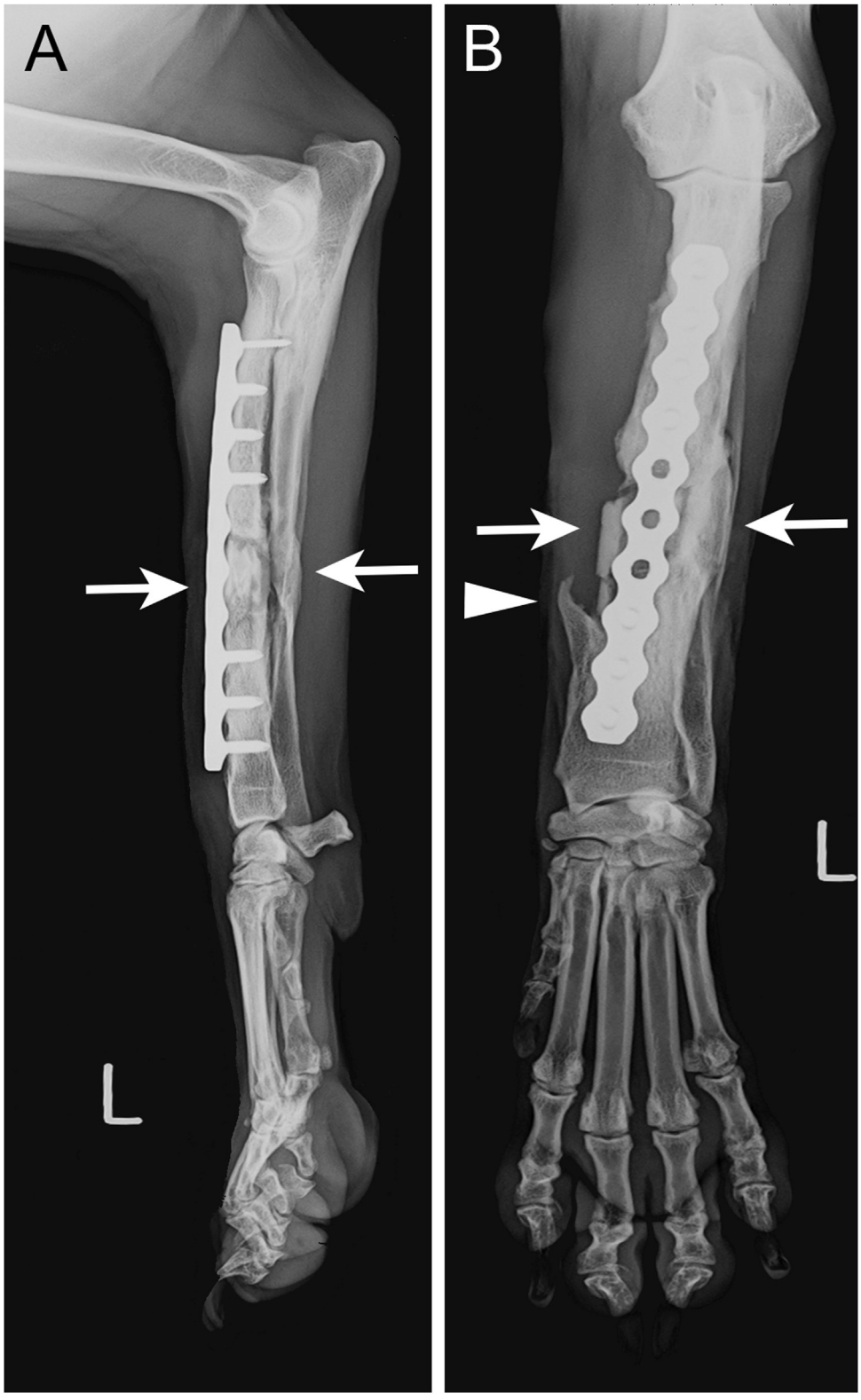

Fig. 4. Medio-lateral (A) and cranio-caudal (B) radiographs of the left radius and ulna of a dog taken 4 months after internal fixation of open, comminuted, mid-diaphyseal radius and ulna fractures following vehicular trauma. The culture revealed a streptococcal infection.
Despite four months of oral antibiotic therapy, started after fracture repair, with cefalexin and enrofloxacin at appropriate doses the dog developed a delayed union of the fractures with persistent soft tissue swelling, osteomyelitis and sequestrum in the mid radial diaphysis. Note the presence of callus, which is bridging the former fragments and the square shaped bone fragment of approx. 2 cm length (arrows), which is surrounded by a radiolucent halo consistent with the involucrum (arrowhead). There is moderate intramedullary sclerosis of the proximal and distal radial and ulna diaphysis noticed. The fracture healed after a revision surgery comprising removal of the sequestrum, debridement and autologous bone graft.

Table 1
Overview of common aetiologic agents and incidences for various types of osteomyelitis across veterinary species.

Species (Reference)	n[a]	Type of osteomyelitis	Recovered organisms	Time period
Dogs (Rabillard et al., 2011)	3	Haematogenous	*Staphylococcus* sp., *Streptococcus* sp., *Klebsiella* sp., *Clostridium* sp.	Not reported
Dogs (Pacchiana et al., 2003)	7/397	Post-operative (post-TPLO surgery)	*S. aureus, S. intermedius*	1998–2001
Dogs (Ireifej et al., 2012)	1/100	Post-operative (post-total hip replacement surgery)	Not reported	2007–2010
Dogs (Hunt et al., 1980)	31/100	Post-traumatic (post-fracture repair)	*Staphylococcus pyogenes*	1973-1978
Dogs (Pozzi et al., 2013)	2/30	Post-traumatic (post-fracture repair of radius and ulna)	Not reported	2006–2011
Dogs (Siqueira et al., 2014)	52	Post-traumatic	Beta-haemolytic *Staphylococcus* and *Escherichia coli*	2000–2013
Dogs, cats (Griffiths and Bellenger, 1979)	39/502	Post-traumatic (post-fracture repair)	*Staphylococcus*, *Streptococcus*, Gram negative bacteria	1974–1978
Dogs, cats (Fournet et al., 2018)	3/41	Post-traumatic (post-fracture repair)	Not reported	2008–2016
Foals (Neil et al., 2010)	108	Haematogenous	Enterobacteriaceae, *Streptococcus* sp., *Staphylococcus* sp.	1995–2001
Horses (Snyder et al., 1987)	60	Post-traumatic (post-fracture repair)	Multi-organism (Enterobacteriaceae, *Streptococcus* sp., *Staphylococcus* sp., *Pseudomonas* sp., *Actinobacillus* sp.)	1974–1985
Horses (Moore et al., 1992)	233	Post-traumatic	Enterobacteriaceae, *Streptococcus* sp., *Staphylococcus* sp.	1979–1989
Horses (Ahern et al., 2010)	53/192	Post-traumatic	Enterobacteriaceae, *Staphylococcus* sp., mixed populations	1990–2006
Cattle (Firth et al., 1987)	70	Haematogenous	*Trueperella pyogenes, Salmonella* sp.	1964–1981
Cattle (Verschooten et al., 2000)	445/4462	Haematogenous and post-traumatic	*Trueperella pyogenes,* others	1981-1993
Camelids (Semevolos et al., 2008)	4/24	Post-traumatic (post-fracture repair)	Not reported	2000–2006
Camelids (Rousseau et al., 2013)	36	Haematogenous and post-traumatic	Not reported	1999–2010
Camelids (Knafo et al., 2012)	3/28	Post-traumatic (post-fracture repair)	Not reported	1998–2008

[a] Number of animals is either total number of cases with osteomyelitis, or a ratio of infected/non-infected animals as reported by the authors.

Table 2
Recommended antibiotics for the treatment of osteomyelitis as reported in the clinical literature.

Species (Reference)	Recommended antibiotics	Treatment duration and route of administration (ROA)
All (Giguère et al., 2013)	Cephalosporins, clindamycin or ampicillin-sulbactam	Acute: parenteral high doses for at least 3 weeks; Chronic: 2 weeks parenterally further 4–6 weeks orally
Companion animals (FECAVA, 2014)[a]	Clindamycin (pending culture and antimicrobial susceptibility results)	Not reported
Companion animals (SvHKS, 2013)[b]	Not reported	Treatment should continue for 1–2 weeks beyond resolution of clinical signs; ROA not reported
Dogs and cats (Guardabassi et al., 2008)	1st choice: clindamycin, amoxicillin-clavulanate or cephalosporins 2nd choice: based on antimicrobial susceptibility testing For local therapy (PMMA): gentamicin	Chronic: 3–8 weeks or more orally
Horses (Weese et al., 2008)	1st choice: penicillin with aminoglycoside 2nd choice: ceftiofur with aminoglycoside 3rd choice: enrofloxacin	Treatment duration not reported; ROA: parenterally
Horses (Wilson, 2001)	1st choice: cefazolin or cephalothin + amikacin Alternate choices: cefazolin or cephalothin + gentamicin; oxacillin + gentamicin or amikacin; rifampin + amikacin; enrofloxacin For regional limb perfusion: amikacin or gentamicin	Not reported
Horses (Goodrich, 2006)	Cephalosporin + amikacin or penicillin + gentamicin (pending culture and antimicrobial susceptibility results)	Parenteral 7–10 days, further 1 month or longer oral
Horses (Baxter, 1996)	Cephalosporin + amikacin (pending culture and antimicrobial susceptibility results)	Parenteral 7–10 days, further 1 month or longer oral
Horses (Werner et al., 2003)	For regional limb perfusion: gentamicin	Not reported

[a] See: FECAVA, 2014. Poster Federation of European Companion Animal Veterinary Association (FECAVA) Recommendations for Appropriate Antimicrobial Therapy. http://www.fecava.org/sites/default/files/files/Hygiene%20poster.pdf. (Accessed 20 June 2019).
[b] See: SvHKS, 2013. Danish Small Animal Veterinary Association (SvHKS) - Antimicrobial Use Guidelines for Companion Animal Practice. www.fecava.org/sites/default/files/files/DSAVA_AntibioticGuidelines%20-%20v1-1_3(1).pdf. (Accessed 20 June 2019).

cats that included both non-surgical and surgical cases (n = 39), most non-surgical cases of osteomyelitis in cats developed from contiguous, infected soft tissue, whereas most cases of osteomyelitis in dogs followed reduction of closed fractures (Griffiths and Bellenger, 1979). Of the cases that had culture performed (n = 21), 48% had *Staphylococcus* spp. isolated and 14% had *Streptococcus* spp. isolated, over half had Gram-negative species cultured, over a third had mixed cultures, 10% cultured *Trueperella* (formerly *Actinomyces* or *Corynebacterium*) and 10% had negative culture.

In post-operative osteomyelitis, there are varying reports of complication rates and aetiologic agents depending on the procedure in question. In a 2002 study including 19 dogs, olecranon osteotomies to stabilise humeral fractures, resulted in osteomyelitis of the fracture repair in five cases (26%), of which

four of the dogs (21%) had concurrent osteomyelitis as a complication of the osteotomy (Halling et al., 2002). The prevalence of osteomyelitis associated with prosthetic joints in dogs has been reported at up to 11% (Dyce and Olmstead, 2002; Gemmill et al., 2011; Forster et al., 2012). In a study examining complications associated with tibial plateau levelling osteotomy (TPLO) for the management of cranial cruciate ligament rupture, 2% cases (n = 7 of 397) developed implant-related osteomyelitis and the most common aetiologic agents were *S. aureus* and *Staphylococcus intermedius* (Pacchiana et al., 2003). In addition, the economic impact of surgical site infection management should be considered: with mean cost incurred due to surgical site infection approaching 50% of the cost of the original TPLO surgery in dogs (Nicoll et al., 2014).

Haematogenous osteomyelitis is rare in adult dogs, and is characterised by lameness and/or abscess formation in the absence of a history of trauma (Rabillard et al., 2011). The most common causative micro-organisms include: *Staphylococcus* sp., *Streptococcus* sp., *Klebsiella pneumoniae,* and *Clostridium* sp. (Gilson SD, 1989; Emmerson and Pead, 1999). In a recent case series, several anaerobic species (*Propionibacterium acnes*, *Gemella morbillorum, Bacteroides* and *Fusobacterium* sp.) were described in two out of the three dogs included in the study (Rabillard et al., 2011).

Horses and foals

Horses are relatively commonly afflicted with osteomyelitis. Haematogenous osteomyelitis is more frequent in foals than in adults, especially in neonates due to bacteraemia secondary to causes such as omphalitis, or a failure of passive transfer of maternal immunity resulting in an inadequate response to bacteraemia (Glass and Watts, 2017). The orthopaedic site where infection tends to localise is often that part of the metaphysis or epiphysis that is close to the physis and/or the joint, resulting in septic epiphysitis, metaphysitis, physitis and/or septic arthritis respectively (Fig. 5; Hall et al., 2012). These infections are often caused by Gram-negative organisms such as *Actinobacillus* sp., *Escherichia coli, Klebsiella* sp., *Pseudomonas* sp., and *Salmonella* sp., although Gram-positive organisms such as *Streptococcus* sp. can be involved, particularly in older foals (Neil et al., 2007, 2010). In the largest single study documenting infecting pathogens in osteomyelitis in foals, Enterobacteriaceae (31%), *Streptococcus* sp. (26%), and 15% *Staphylococcus* sp. (15%) were the predominant species (Neil et al., 2010). *Rhodococcus equi* osteomyelitis or septic arthritis in foals has been infrequently described in the literature (Desjardins and Vachon, 1990; Firth et al., 1993; Kelmer and Hayes, 2009); however, this should be considered a potential aetiologic agent.

A similar profile of microorganisms is also reported in traumatic or post-operative osteomyelitis in horses. Polymicrobial osteomyelitis has been described in horses, which has not been so widely reported in dogs and cats. In one study of surgically-repaired fractures in horses (long or cuboidal bone fractures; arthrotomy/arthroscopy procedures for removal or internal fixation; splint bone fractures; and facial or mandibular fractures), 36 of the 60 cases (25 cases with implants out of the 60 cases) with positive cultures were polymicrobial infections (Snyder et al., 1987). Species isolated included Enterobacteriaceae (24%), *Streptococcus* sp. (23%), *Staphylococcus* sp. (18%), *Pseudomonas* sp. (11%) and *Actinobacillus* sp. (5%). In another study of musculoskeletal infection in horses (n = 233), with cases of osteomyelitis, septic arthritis and tenosynovitis, a total of 424 bacterial isolates were cultured (Moore et al., 1992). Yet again, the majority were Enterobacteriaceae (28.8%), *Streptococcus* sp. (22.4%), and *Staphylococcus* sp. (19.1%). Most recently, Ahern et al. (2010) described the features of post-operative infection following internal fixation of long bone fractures and arthrodesis in horses. Of 192 horses requiring internal fixation documented over a 16-year period at a tertiary referral centre, 53 had post-operative infection. Of these 53, only 42 had a positive culture: 17/53 (32%) were Gram-positive, 15 (28%) were Gram-negative and 21 (40%) were mixed Gram-negative and Gram-positive. Coagulase-negative *Staphylococcus* spp. (11/53, 21%) was the most commonly cultured Gram-positive and *Enterobacter cloacae* (13/53, 24.5%) the most common Gram-negative.

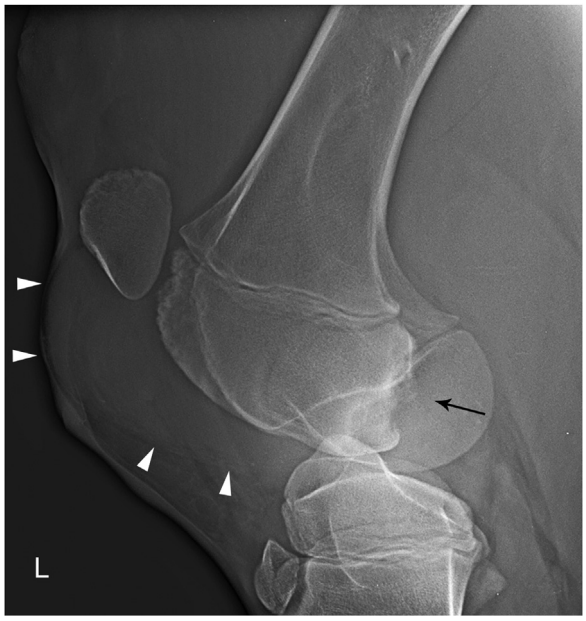

Fig. 5. Single caudal 60° lateral-craniomedial oblique radiograph of the left stifle of a skeletally immature horse with severe osteomyelitis of the distal femur: A large, irregularly outlined, lytic bone lesion partially effaces the caudodistal aspect of the medial femoral condyle (black arrow). There is moderate extracapsular soft tissue swelling of the stifle and severe femoropatellar and femorotibial joint effusion (white arrowheads) visible. The lucencies seen within the trochlear ridge and patella are normal in juvenile horses due to incomplete endochondral ossification.

Adult horses can be challenging due to their specific anatomy and temperament. They can be difficult to manage as they often do not tolerate prolonged periods of stall rest. They are also prone to developing laminitis in the contralateral limb (Baxter and Morrison, 2008), and although the best way to prevent support-limb laminitis is to reduce pain in the affected limb, often by intense analgesic therapy, such therapeutic interventions can create additional complications (Fackelman et al., 2000; Baxter and Morrison, 2008). For these reasons, osteomyelitis is a difficult disease to treat in this species and often results in euthanasia on welfare grounds (Peloso et al., 1996).

Other animal species

Cattle

In contrast to horses, it is of note that cattle commonly have osteomyelitis caused by *Trueperella pyogenes* (Firth et al., 1987; Verschooten et al., 2000). In addition to haematogenous spread in neonates, trauma associated with placement of dystocia chains around the distal limbs of calves during parturition has been associated with the development of osteomyelitis, either via local extension through traumatic wounds or by disruption of the vascular supply to the bone and surrounding soft tissue (Aksoy et al., 2009; Desrochers et al., 2014). Post-traumatic osteomyelitis in cows can develop from wounds e.g. a penetrating injury or decubitus ulcer on the distal limb (Greenough, 1997; Fubini and Ducharme, 2016). In a study of 4462 cows that were radiographed from 1981 to 1993, approximately 10% were diagnosed with

osteomyelitis in the appendicular skeleton based on clinical and/or radiograph examination, making this an important entity in cattle (Verschooten et al., 2000). Haematogenous osteomyelitis was approximately three times more frequent than post-traumatic osteomyelitis in this study with the carpus, metacarpus, tarsus and metatarsus most commonly affected. Since the use of internal fixation for fracture repair or arthrodesis is often not economically viable in cattle, little is known about the development of post-operative osteomyelitis. If osteomyelitis is located in the digit, amputation of the affected claw is a realistic option (Heppelmann et al., 2009).

Camelids

The majority of the reported cases of osteomyelitis in alpacas and llamas is either traumatic or post-operative. Alpacas and llamas are generally calm post-operatively and have a relatively small body size which makes them easier to handle than other large domestic mammals (Kaneps, 1996). Despite this, a report by Semevolos et al. (2008) found that 21 of 24 camelids that had undergone orthopaedic surgery of the appendicular skeleton had complications. Of those, seven had a delayed union or non-union with a confirmed infection at the fracture site in four cases (Semevolos et al., 2008). In a retrospective analysis of 28 camelids that had radiologically diagnosed long-bone fractures, 3 had osteomyelitis, of these three cases two had delayed, mal- or non-union including one with sequestrum formation (Knafo et al., 2012). Interestingly, a recent study of 36 cases of osseous sequestration in adult camelids found no history of trauma in the majority of cases, and the authors suggested that haematogenous osteomyelitis could occur in otherwise healthy adult camelids (Rousseau et al., 2013).

Emerging diagnostic and treatment options

The mainstay of osteomyelitis treatment remains debridement and long-term antibiotic therapy (Mader et al., 1993; Glass and Watts, 2017). A range of newer approaches to the prevention and treatment of osteomyelitis are routinely presented in the scientific literature; however, few new technologies have been introduced to clinical veterinary or human medicine. The research trends that seem to be emerging on to the market include antibiotic-coated implants (Metsemakers et al., 2015) and antibiotic-loaded bone void fillers or antibiotic-loaded bone osteoconductive materials (McNally et al., 2016). These technologies can increase the duration of high local concentrations of antibiotics and do not require repeat administration compared to systemic administration. However, in general, systemic antimicrobial therapy is still required. Currently, local delivery of antibiotics to large veterinary patients, especially horses and cattle, is more commonly achieved by regional limb perfusion, as mentioned above (Kelmer, 2016).

Other, as yet experimental, local delivery vehicles are also emerging in the literature. A thermo-responsive, gentamicin-loaded, hyaluronic acid-derived hydrogel has shown prophylactic efficacy in a rabbit humeral osteotomy model of internal fixation fracture repair contaminated with *S. aureus* (Ter Boo et al., 2016). The hydrogel offered equivalent protection to the closest current clinical standard, a gentamicin-loaded collagen gel. However, it might offer a greater versatility in terms of application, with a greater distribution throughout complex wounds (Ter Boo et al., 2016). Similar gels have been described in human patients recently (Romano et al., 2016), and could also be an interesting alternative in veterinary medicine in the future.

Basic research studies have also revealed further understanding of fracture-related infection. Studies have shown that the stability of fracture fixation both influence fracture healing (Rittmann and Perren, 1974), and influence infection (Sabate Bresco et al., 2017). Although no clinical studies have confirmed the importance of fracture stability, there are abundant experimental data supporting the principle that stability is crucial for optimal outcome of an infected osteosynthesis (Friedrich and Klaue, 1977; Merritt and Dowd, 1987; Worlock et al., 1994; Buckley et al., 2017; Kates and Borens, 2017; Sabate Bresco et al., 2017).

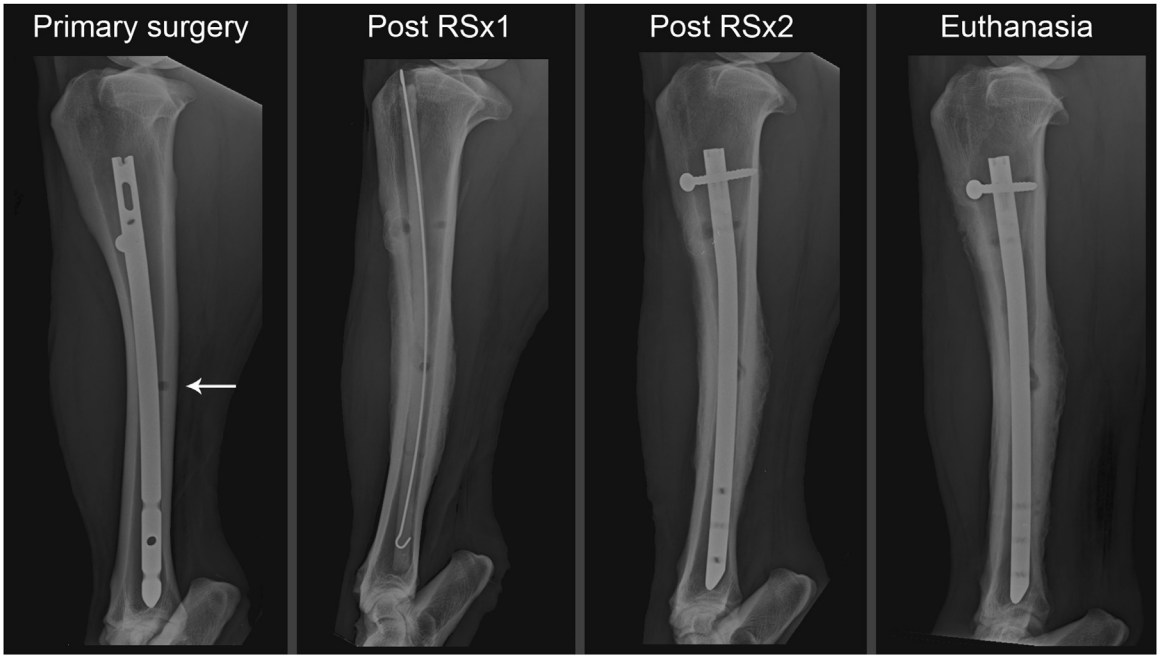

Fig. 6. Treatment stages for chronic implant-related osteomyelitis as performed in a sheep model: These representative mediolateral radiographs illustrate the progression from 'primary surgery' with placement of the intramedullary nail in the tibia and a localised inoculation with Methicillin-resistant *Staphylococcus aureus* (arrow), through revision surgery 1 after 8 weeks (Post RSx1: implant removal, temporary placement of an antibiotic-loaded cement K-wire combined with systemic antibiotics), the second revision surgery 2 weeks later (Post RSx2: debridement and implant exchange), and finally euthanasia 4 weeks after that. Note the progressive hyperostosis and irregular bone structure with lytic areas around the inoculation point (Moriarty et al., 2017).

As mentioned in the introduction, treatment of human prosthetic- or other implant-related infections involves staged exchanged protocols. Specific models have been developed to replicate the complex treatment protocols for humans with chronic implant-related osteomyelitis. A sheep tibia intramedullary nail model (Fig. 6) infected with methicillin-resistant *S. aureus* (MRSA) was established to investigate two-stage revision of implant-related osteomyelitis (Moriarty et al., 2017). In a first RSx performed after 8-weeks (Fig. 6, Post RSx 1), the implant was removed and a temporary antibiotic-loaded cement coated K-wire was inserted and animals received systemic antibiotic therapy. A second RSx (Fig. 6, Post RSx 2) was performed after a further 2-weeks, with debridement and implant exchange. This treatment works well for methicillin-sensitive *S. aureus*; however, infections caused by MRSA did not respond to this treatment regimen even though pathogen-adapted antibiotic therapy was used. This model can be used to assess novel interventions for the treatment of chronic implant-related infections, particularly for infections involving MRSA (Moriarty et al., 2017).

Non-resorbable materials such as PMMA have been shown to have clinical utility; however since they are non-resorbable, there might be a need for subsequent surgery to remove the material. In order to overcome this, certain degradable or absorbable materials have been developed. Absorbable orthopaedic implants are used in selected cases in both human (Bostman et al., 1989; Ibrahim et al., 2015) and veterinary medicine (Saikku-Bäckström et al., 2005; Mageed et al., 2018) because they can reduce the need for implant removal and thus the risk of an additional surgery and associated surgical site infections (Li et al., 2013). Although requirements for RSx could in theory be reduced, other complications such as foreign body reactions, formation of sterile sinus tracts or osteolysis have to be considered (Bostman et al., 1990; Stroud, 2002). For these reasons, the absorbable implants have not yet replaced conventional metal implants in clinical practice and further research and development is required in this area (Ciccone et al., 2001; Dziuba et al., 2013; Traverson et al., 2018).

Conclusions

Osteomyelitis remains a challenge in all animal species commonly encountered in veterinary medicine. Juvenile animals are relatively more frequently affected by haematogenous osteomyelitis, whilst post-traumatic or post-operative osteomyelitis is more common in adults. Definitive diagnosis of osteomyelitis requires consideration of the complete clinical picture: the clinical signs, clinical pathology, diagnostic imaging, and local biopsies for bacterial identification. Knowledge of species-specific infectious agents can also be helpful, e.g. infections in dogs and cats are frequently caused by *Staphylococcus* sp. and *Streptococcus* sp., those in adult cattle by *Trueperella pyogenes* infections and those in horses commonly involve polymicrobial infections. A positive culture and the corresponding antibiotic susceptibility test are helpful for an effective treatment. The key to treatment of osteomyelitis remains debridement and antibiotic therapy, ideally with implant removal whenever appropriate. Some new antimicrobial approaches are emerging from basic science and human medicine, but these are only slowly emerging in veterinary medicine. Although the prognosis for osteomyelitis can be poor in some cases, with continued advancements, improvements might be possible in the coming years. With these advancements, the goal is that osteomyelitis will become a much more readily treated condition, thus decreasing hospitalisation times, cost of treatment, pain and discomfort.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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