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Orthopaedic Case Challenges Mini Series

Session 3: Inflammatory Arthritis

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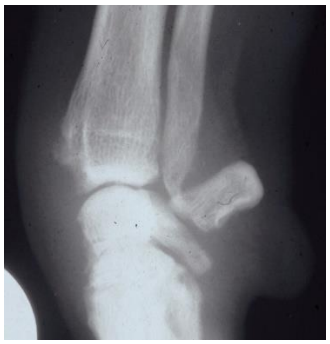

Inflammatory Joint Diseases

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IMMUNE-MEDIATED POLYARTHRITIS (IMPA)

Introduction

The classification of immune-mediated polyarthritis (IMPA) is summarised in Figure 4. The categorisation of various types of IMPA is driven by the presence or absence of extra-articular disease in addition to polyarthritis, the presence or absence of radiographically-observed erosive changes in the affected joints, and the presence or absence of any identifiable primary initiating disease process (e.g. remote infection or neoplasia). Although the classification system can help with case management and prognosis, it can often be difficult to accurately classify an individual case, particularly in the initial stages. In addition, the literature on canine IMPA is confused by alternative classification systems and case definitions between different studies. The clinician should remain focussed on tests that will influence clinical decision-making rather than merely an academic exercise in categorisation. IMPA appears to be an uncommon clinical condition but robust epidemiological data are sparse.

Aetiopathogenesis

The etiopathogenesis of IMPA remains unclear. However, data suggest that the disease involves abnormal B cell-T cell interaction, with presentation of antigens by B cells to T cells via HLA-DR eliciting T cell help and subsequent production of RF and ACPA. Inflammation is then driven either by B cell or T cell products stimulating release of TNF and other cytokines from synovial macrophages. It is possible that immunoglobulin or T cell receptor gene recombination and mutation may initiate the disease process. There is little doubt that both B and T cells are essential to the disease process but there is good evidence for neither cell being necessary at the site of inflammation. This tends to favour immune complexes as the initiators, even if not the sole perpetuators, of inflammation.

The early changes within the synovium are consistent with a normal immune response to an antigen. The formation and phagocytosis of immune complexes in response to a chronic antigenic stimulus is thought to be the key to the development of chronic IMPA. Persistence of the antigenic stimulus may be due to either recurrence or persistence of the inciting antigen(s) or from a derangement of normal down-regulation of the immune system following successful elimination of the inciting antigen(s).

It has long been suspected that certain infections could be triggers for IMPA. The "mistaken identity" theory suggests that an infection triggers an immune response, leaving behind antibodies that should be specific to that organism. However, the antibodies are not sufficiently specific and set off an immune attack against part of the host; this phenomenon is called *molecular mimicry*. It is also postulated that enzymatic or oxidative modification of cellular macromolecules results in the presence of neo-antigens to which autologous T-cells are not tolerant.

Occasionally, IMPA may appear in the period after vaccination and this has led to speculation that vaccination may initiate IMPA. Certainly, in kittens, this has been associated with the calicivirus component of a vaccine [1] although this appears to be of historic interest now, presumably due to reformulation of vaccines. One study of type I IMPA in dogs found no association between the time of vaccination and the onset of disease (Clements et al 2004). Thus, at present, there appears to be a lack of evidence to implicate vaccination with the onset of IMPA and robust epidemiological studies are required to answer this question.

In some forms of IMPA the inciting antigen can be identified. For example, IMPA associated with infection distant from the joints (akin to so-called reactive arthritis in humans) or in drug-induced IMPA. However, most cases of IMPA remain idiopathic.
In erosive forms of IMPA (e.g. canine RA), there is proliferation of granulation tissue ("pannus") which invades the margins of articular cartilage and subchondral bone. The release of proteolytic enzymes from pannus tissue is associated with destruction of extracellular matrix.

Extra-articular manifestations of disease are important in many IMPA cases and these are often a consequence of either immune complex deposition (e.g. immune-complex glomerulonephritis) or auto-antibody formation (e.g. anti-platelet antibodies giving rise to immune-mediated thrombocytopenia).

Genetic predispositions
In humans, and more recently in dogs, significant genetic predispositions to IMPA syndromes have been documented.

*In humans, HLA-B*27 genes are well-recognised to be associated with certain types of polyarthritis. HLA B*27 (subtypes B*2701-2724) is a class I surface antigen encoded by the B locus in the MHC and presents microbial antigens to T-cells. HLA-B27 is strongly associated with a certain set of autoimmune diseases referred to as the "seronegative spondyloarthropathies". Associations have also been shown between allelic polymorphisms of the MHC in the HLA-DR region and the occurrence of human RA. It is estimated that MHC genes confer 30-50 % of the genetic component of susceptibility to human RA. Furthermore, there are additional correlations between the presence of allelic polymorphisms and the severity of disease, including the tendency to show seropositivity for rheumatoid factor, joint erosions and extra-articular disease. Interestingly, in dogs, similar Dog Leukocyte Antigen (DLA) haplotypes appear to predispose to canine IMPA. The DLA-DRB1, the dog homologue of the human HLA-DRB1 gene, has been characterized, and 100 DLA-DRB1 alleles have been defined so far [2-4]. Great variation in the distribution of DLA-DRB1 phenotype frequencies exists between different dog breeds. Dog and human DRB1 sequences show an average 86% nucleotide homology, with three 'hypervariable repeats' (HVR) defined at the same codons in both species. Interestingly, a conserved human HLA-DRB1 3HVR motif such as QRRAA is present in some dog DLA-DRB1 alleles and that this "shared epitope" is associated with polyarthritis in both species [5].*

Diagnosis of IMPA

This section will deal with generic issues associated with a diagnosis of IMPA. Generic treatment options are discussed in the following section and further details on the etiology, clinical features and prognosis for individual categories of IMPA are described in the final section on IMPA.

History and clinical signs
IMPA should be considered as a differential diagnosis for any dog or cat with signs of multiple joint pain or swelling, generalised stiffness, shifting lameness, or pyrexia of unknown origin [6]. IMPA can present in any age, breed or sex of dog or cat and with an onset that is acute or chronic. The clinical severity of IMPA can be very variable with presentations ranging from complete inability to stand with multiple and obvious joint effusions. to low-grade, insidious-onset stiffness or even lameness in a single limb at the opposite end of the spectrum.

Moderate pyrexia is common in cases of IMPA. IMPA is the most common diagnosis in dogs presenting with pyrexia of unknown origin (PUO). In one study of PUO, IMPA accounted for 20% of all cases and the authors suggested that IMPA should always be excluded before less common causes of PUO are considered [6].

Multiple and symmetrical joint pain and swelling is typical of IMPA, although some cases are asymmetric. Very occasionally, IMPA will affect only a single joint but this is an unusual scenario. However, even if only one joint appears clinically inflamed and swollen, the clinician is

advised to obtain samples from other joints and utilise the opportunity to distinguish between inflammation of a single joint and that of multiple; in some cases, this can help the clinician distinguish between IMPA and infective arthritis. Although some cases present with only a few joints (pauciarticular [<4 joints]) apparently affected, additional joints may succumb to disease as time progresses. With disease progression, secondary OA changes may also appear in affected joints with joint enlargement and fibrosis. In advanced cases with erosive disease joint deformities may develop along with joint instability and crepitus. It is important to note that obvious joint swelling and pain are not always palpable in IMPA cases and cytological evaluation of multiple joint fluid samples is mandatory to demonstrate multi-joint inflammation if IMPA is suspected.

Notable inactivity stiffness is a common clinical sign in cases of IMPA and this may persist for several minutes after rising, in contrast to OA where stiffness typically lasts for a few seconds after rising.

Diagnostic tests for IMPA

Synovial fluid analysis
The diagnosis of IMPA requires evidence of articular inflammation in several joints and this depends on cytology from a minimum of three synovial fluid samples from three different joints. It is recommended to sample at least four joints and to continue sampling until a minimum of three acceptable samples are obtained. It is easier to get sufficient volumes from effused joints, or the larger joints such as the shoulder, stifle, elbow and hip. However, IMPA often preferentially targets the smaller joints, particularly the carpus and tarsus.

Synovial fluid analysis should include an assessment of the gross appearance of the fluid from each joint noting volume, viscosity, colour and transparency. Cytological examination should include a total and differential cell count as well as a careful assessment of cell morphology; a subjective assessment of a freshly stained smear can guide the clinician but should not be relied upon to distinguish between IMPA and infective arthritis [7]. If there is any suspicion of infective arthritis, the clinician should also submit synovial fluid in a blood culture bottle for culture and sensitivity testing.

In some cases it may not be possible to obtain sufficient synovial fluid for cytology. This may be the case in small dogs and cats, particularly if the disease is low-grade with minimal effusion and if the smaller distal limb joints are primarily affected. Synovial biopsy may be utilised is such instances and this may help to confirm the presence of infiltration of synovium with B and T lymphocytes, macrophages and neutrophils.

Once the presence of polyarthritis has been confirmed, the clinician should work to categorise the type of IMPA. Classification provides a definitive diagnosis that improves the accuracy of the prognosis and allows an appropriate therapeutic plan to be made. This process is primarily targeted at trying to identify an initiating cause (e.g. focus of infection remote from the joints, neoplasia, drug-induced IMPA). Thus the priority is evaluation of other body systems and a careful and thorough clinical examination, including an ophthalmological examination, is mandatory. Furthermore, a full blood count and serum biochemistry are recommended along with imaging of the thorax, abdomen and heart. Since endocarditis is one possible initiating factor for IMPA, careful auscultation of the heart is essential, but echocardiography is recommended for its increased sensitivity for detection of valvular lesions [8].

Articular imaging

Imaging of joints is typically recommended in cases of IMPA [9] but in most cases, at least at the time of initial diagnosis, the results are usually uninformative. Typically, early in disease, radiographs of joints will show effusion or joint swelling and little else; certainly the results are typically only in line with clinical findings and unlikely to change the clinician's actions; this brings in to question the value of such imaging at this stage. Overall, the author suggests that early in disease, imaging of joints is considered carefully and targeted selectively for individual cases.

As disease progresses and a patient is monitored on therapy, there can be a need to revisit the imaging room and obtain radiographs of affected joints to monitor for erosions, periosteal reactions, subluxations and deformities. Erosions are seen radiographically when there is destruction of subchondral bone. Osteophytes are uncommon in non-erosive disease, but marked periosteal proliferative bone formation may be seen in some specific forms of erosive IMPA (see Figure 1). Radiographic features of IMPA often show bilateral symmetry and there is a tendency for the distal limb joints to be affected to a greater degree.

Haematology, serum biochemistry and urinalysis

Haematological tests may typically reveal anaemia (auto-immune or 'anaemia of chronic disease'), leucocytosis or leucopenia, neutrophilia with a left shift, and thrombocytopenia [10,11]. Thrombocytopenia and leucopenia are especially seen in cases with systemic lupus erythematosus (SLE)[12]. Serum biochemistry tests may show urea, creatinine, alkaline phoshatase, alanine transferase, and aspartate transferase concentrations to be elevated [11,12]. Raised serum creatine kinase and aldolase concentrations may be seen in cases complicated by myositis [13]. Protein losing nephropathy or enteropathy may occasionally be encountered due to immune complex deposition; this may lead to decreased serum albumin concentrations. Globulins may be increased due to auto-antibody production. Urinalysis may demonstrate proteinuria may be detected as a result of (glomerulo)nephropathy.

Other tests

Some cases of IMPA are complicated by extra-articular disease and there may be an indication for additional investigations, such as electromyography and muscle biopsy when polymyositis is suspected [13] or cerebrospinal fluid analysis when aseptic meningitis is suspected because of concurrent spinal pain [14]. However, the clinician should carefully consider the risk-benefit of additional tests, particularly if they carry some risk to the patient. If the outcome of the test will not change the management of the case, the value of the test becomes debatable. Thus it can be argued that CSF analysis is unnecessary even if there is spinal pain because the treatment may be the same regardless of the test result.

Serology

The appearance of auto-antibodies are well-established phenomena in human and canine IMPA. Rheumatoid factors (RF) are anti-immunoglobulin antibodies of IgM and IgA classes against the F_c portion of IgG [15,16]. RF and IgG can form immune complexes which contribute to the disease process. However, the appearance of RF in serum is not specific for canine RA and they can be a feature of other chronic inflammatory conditions. As such, assays for RF are only useful in helping to categorize a case of IMPA. These tests should not be used as a diagnostic test for canine IMPA or canine RA. About 80% of human RA patients are positive for RF and the remainder are said to be "seronegative", so the appearance of RF is not essential for a diagnosis of RA in human beings.

Anti-nuclear antibodies (ANA) are auto-antibodies directed at epitopes within the cell nucleus. In humans, a high ANA titer is indicative, but not specific for, systemic lupus erthyematosus (SLE) with 80-90% of SLE patients having raised ANA titers. However, raised ANA titers are also noted in a variety of chronic inflammatory diseases in humans such as RA, type I diabetes, autoimmune haemolytic anaemia, and Sjögren's syndrome. In dogs, the authors of a recent study suggest that measurement of ANA titer was not a useful diagnostic test in dogs without any major clinical or clinicopathologic abnormalities suggestive of SLE. In contrast, there was a good chance that results of the ANA assay would be positive and that the dog would be found to have SLE if at least two major signs were present. Findings suggest that it would be reasonable to limit the use of the ANA assay to those dogs that have at least one major sign (see SLE section for major signs) compatible with a diagnosis of SLE [17]. In that study, all 18 dogs in which SLE was diagnosed (from a pool of 120 dogs where ANA was measured) had ANA titers ≥ 160.

Classifying a case of IMPA

Once a diagnosis of IMPA has been made, further evidence can be gathered to classify the condition in more detail. Criteria have been established to standardise the diagnosis of the immune-mediated arthritides [9]. These are derived from similar criteria for the diagnosis of comparable conditions in humans, but have been adapted for use in dogs and cats because of species differences. A definitive diagnosis is made when the criteria for a given condition are satisfied and other causes of IMPA have been excluded. This can sometimes be difficult because there is a great deal of overlap between the different syndromes, reflecting common pathways in the pathogenesis. In addition, the classification of a case may change over time, for example as erosive changes become apparent on radiographs, a case may be moved from non-erosive to the erosive category.

Infective arthritis

Introduction

Infective (septic) arthritis in dogs and cats appears to be an uncommon condition involving microbial infection of the synovium followed by the synovial space. The usual etiology of infective arthritis is bacterial but mycoplasmal, protozoal, Rickettsial, and mycobacterial occur occasionally (Figure 4). The condition occurs in both dogs and cats.

Bacterial infective arthritis

Bacterial invasion of joints may arise from haematogenous localisation, direct penetration (surgical or traumatic), or local spread from adjacent tissues. In dogs, bacterial infective arthritis is usually a monoarthropathy, resulting in pain, swelling and lameness, which may be acute or chronic in onset [18]. Several different bacteria, most commonly *Staphylococcus intermedius*, *Staphylococcus aureus* and betahaemolytic *Streptococci spp*., have been implicated in bacterial infective arthritis in dogs [18-20]. In cats, the commonly isolated bacteria are *Pasteurella multocida* and *Bacteroides spp.*, reflecting the oral flora of the feline mouth and the frequency of penetrating cat bites as the route of infection for feline bacterial infective arthritis.

Risk factors for bacterial infective arthritis appear to be previous surgery [20]to the joint or pre-existing joint disease (e.g. OA) [19]. The stifle, elbow and carpus appear to be the most frequently affected joints in the published reports [18-20]. Post-operative infections following articular surgery probably represent the most frequent cause of infective arthritis in dogs and cats. Infection rates in dogs between 0 and 2.7% were reported for the major joints of the dog in one study with no significant differences between joints [19]. In that study, the tarsus had the highest infection rate although the stifle joint was the most frequently affected due to the large number of stifle surgeries performed. The type of surgery may also influence the risk of infective arthritis. In a study comparing 496 lateral suture stabilisation (LSS) surgeries for canine cruciate ligament rupture and 406 TPLO surgeries, infection developed in 55 of 902 (6.1%) surgeries within 6 months after surgery. There was a significant difference in infection rate after the LSS surgeries (21/496 [4.2%]), compared with rate after the TPLO surgeries (34/406 [8.4%]). Factors associated with a significantly lower rate of infection included the use of suture material other than stainless-steel staples for skin closure, and postoperative oral administration of antimicrobials. Bacterial infection rates following total joint arthroplasty in dogs appear to be relatively low at approximately 1% [21-23] although revision total hip replacements carry a higher infection rate. Early postoperative infections (termed 'type I') commonly involve complications of wound healing, including purulent discharge, and the patient can have signs of systemic infection. Late chronic infections (termed 'type II') also originate at the time of surgery but have a delayed presentation (6 - 24 months) because of a small inoculum or low bacterial virulence. Type II infections appear to be most common in dogs with total hip replacement [21,24]. Staphylococcus species are the most commonly cultured bacteria from intra-operative swabs during total hip prosthetic implantation [25] and from cemented total hip prostheses of infected dogs [26]. However, positive intra-operative swab cultures to not associate with the subsequent development of an infected prosthesis. Infection after THR can occur as a result of intraoperative contamination, local extension of wound infection, or hematogenous infection

A blinded, randomized, controlled trial of dogs undergoing elective orthopaedic surgery at a US veterinary teaching hospital found that infection rate for control dogs (receiving saline injection only) was significantly higher than the rate for dogs treated with antimicrobials (penicillin or cefazolin) [27]. However, in a study of humans undergoing arthroscopic surgery there appears to be no benefit from prophylactic antibiotic therapy in preventing post-operative joint sepsis [28]. Of course, species and procedure differences are likely to be major factors for the opposing findings in these studies.

Infective arthritis secondary to extension from an adjacent soft tissue infection or osteomyelitis is uncommon. In one retrospective series, only 2 of 58 cases were as a result of extension of osteomyelitis [18].

Haematogenous spread of bacteria to a synovial joint appears to be the second most common route of infection in dogs although not all case series support this statement, and some authors suggest hematogenous spread is the most common form of infective arthritis [18,29]. In a minority

of dogs with infective arthritis due to suspected hematogenous spread there may be a septic focus elsewhere [19] but this is not usual. However, it is usual for affected joints to have pre-existing pathology such as OA [19]. This is also the case in human patients where a pre-existing pathology can be identified in 73% of non-immunocompromised adult patients with bacterial infective arthritis [30]. It is hypothesised that increased vasculature and blood flow to arthritic joints contributes to the increased frequency of bacterial invasion.

The vast majority of cases of bacterial infective arthritis present as a monarthropathy. Rarely, bacteria may simultaneously infect more than one joint in the same patient and this is most likely in an immature patient or an immunocompromised patient. Bacterial polyarthritis in puppies and kittens is typically secondary to omphalophlebitis, streptococcal pharyngitis or uterine/mammary infections in the bitch or queen. *Staphylococcus canis* is the most commonly incriminated organism in bacterial arthritis resulting from congenital or neonatal exposure [31]. In the adult, polyarthritis may be encountered secondary to septicaemia such as that which accompanies bacterial endocarditis.

The degree of articular cartilage damage caused by bacterial infection is variable and depends on the number, type and virulence of the organism present, the extent to which the organisms multiply, and the local and general immunity of the patient. Initially, infection causes inflammation of the synovium. This is reflected in the synovial fluid which becomes hypercellular with high numbers of polymorphonuclear leukocytes. The hypercellular joint fluid is a potent source of lysosomal enzymes. Proteolytic enzymes such as matrix metalloproeinases (MMPs) are also released from the lysosomal granules of synovial cells which may also result in synovial, cartilage and bone catabolism. Macrophages in the synovium are activated by bacterial antigens such as lipopolysaccharide and release inflammatory cytokines such as tumour necrosis factor-alpha and interleukin-1. Such cytokines induce a catabolic response from synovium and cartilage resulting in proetolysis.

As in other forms of cartilage catabolism, in experimental bacterial arthritis, glycosaminoglycans (GAG) such as aggrecan are degraded in cartilage before collagen. The loss of GAG allows degradation of the collagen network and irreversible change. Experimentally, antibiotic therapy begun within 24 hours of infection will decrease collagen loss but does not prevent GAG loss from the cartilage matrix [32]. Synovial fluid is usually free of all the factors of the blood clotting system but in septic arthritis fibrin deposits form. The deposition of fibrin on the cartilage surface limits the normal exchange of cartilage metabolites and nutrients with the synovial fluid and this may a further contributor to cartilage damage.

Diagnosis of bacterial infective arthritis

Bacterial infective arthritis can affect any breed of dog or cat and at any age. Clinical signs typically include moderate-severe lameness, which is often acute in onset, single joint swelling with pain on manipulation and palpable warmth, and local lymphadenopathy. Pyrexia is detected in the minority of cases and the absence of pyrexia should not preclude a differential diagnosis of infective arthritis [33]. A small minority of affected animals may show systemic signs and appear to be depressed or may be recumbent.

Suspicion of infective arthritis should prompt the clinician to perform immediate arthrocentesis. Typically the fluid if of increased volume and appears turbid and possibly accompanied by haemarthrosis. Synovial fluid should be submitted for cytological examination including total and differential nucleated cell counts. Bacterial infective arthritis should be a working diagnosis (‘probable’ bacterial infective arthritis) if clinical signs and analysis of the affected synovial fluid suggest bacterial infective arthritis. Such synovial fluid has a highly cellular appearance,

observed subjectively on direct smear examination, with a predominantly neutrophil population of cells. On close inspection of the smear, neutrophils may show degenerative and toxic changes such as pyknotic nuclei, degranulation and cell rupture. Careful examination of the synovial fluid smear may identify intracellular bacteria and such a feature is pathogonomic for bacterial infection but is only seen in a minority of cases. An automated cell count of more than $5{\cdot}0 \times 10^9$ cells/L and greater than 40% neutrophils should raise suspicion of bacterial infective arthritis. In acute cases, cell counts are usually very high and between 100-250 x 10^9/L with 98% neutrophils. However, in chronic cases cell counts may be lower and in the region of 40-100 x 10^9/L.

The result of bacteriological culture of synovial fluid should ***not*** be used as a diagnostic criterion because a significant minority of such samples will be negative on this test [19]. Despite this finding, culture of synovial fluid should be attempted in all suspect cases of bacterial infective arthritis. It is highly recommended that a blood culture medium is used for culture of synovial fluid to increase the likelihood of a positive result [34,35]. In addition, an initial incubation in this medium can increase the sensitivity of the test.

It has been suggested that, in the absence of positive synovial fluid culture, synovial biopsy is more likely to yield a positive culture result [9]. This may be justified if there is a pressing clinical need to obtain a positive culture (e.g. failure to of a case to respond to broad spectrum antibiotic therapy or doubt regarding the diagnosis and a need for synovial histology). However, a study in horses suggested that culture from synovium was no more likely to yield a positive result compared to synovial fluid culture [36] and data in the dog support that finding [35].

Polymerase chain reaction (PCR) for bacterial DNA may be used to identify bacteria in synovial fluids. However, a study of human beings with septic arthritis failed to demonstrate that bacterial PCR offered any advantage over standard culture methods [37]. In addition, studies in human beings with IMPA have also identified a variety of bacteria using PCR of synovial fluids from affected patients and the authors concluded that bacteria may track in low numbers to joints that are already inflamed [38,39]. PCR may be difficult to interpret because only one copy of genomic DNA from a bacterium is required for a positive result. Thus it is also likely in dogs that PCR for bacterial DNA will lead to 'false positive' results for bacterial infective arthritis. This may provide an explanation for the high frequency of positive bacterial PCR results from synovial fluids in cases of canine cruciate ligament rupture [40] that are not obviously associated with a cytological response typical of infective arthritis. Of course, it should also be considered that low copy numbers of bacterial DNA and peptidoglycans may *contribute* to the overall inflammation in diseases other than infective arthritis.

The author would suggest that it is useful to use a criteria-based system for the diagnosis of bacterial infective arthritis.

Table 2: Criteria for the diagnosis of bacterial infective arthritis

1	Typical history and clinical signs
2	Synovial fluid cytology consistent with bacterial infective arthritis
3	Positive bacteriological culture

A diagnosis of 'definite' bacterial infective arthritis is based on the presence of all three criteria. A diagnosis of 'probable' bacterial infective arthritis is based on the presence of criteria 1 and 2. It should be noted that, in rare cases, there is crossover between 'probable' bacterial infective arthritis and IMPA because there are a small number of cases of IMPA that present as monoarthropathy and the synovial fluid cytology may be very similar to an infected joint with a high percentage of polymorphonuclear neutrophils. Such cases are best treated initially as 'probable' bacterial infective arthritis and the response to therapy noted. If there is no response to a minimum of three broad spectrum antibiotics, as assessed by no change in synovial fluid cell counts, it is reasonable to adopt a diagnosis of 'probable' monarthritic IMPA and treat appropriately.

Although diagnostic imaging is not required for the diagnosis of bacterial infective arthritis, is can be useful as a means to stage the disorder and document any secondary changes that have occurred. Plain radiography is most often employed. Non-specific changes include soft tissue swelling centred on the joint line, joint effusion and, with time, osteophytosis. Joint effusion may be easily assessed in joints such as the stifle where the infrapatellar fat-pad allows delineation of the joint cavity. However, in other joints (e.g. shoulder or hip), the clinician may need to carefully assess the joint space width compared to the contralateral joint to gain any possible information regarding increased synovial fluid volume [41]. In some cases where the bacteria initiate catabolic processes within tissues, there can be erosive changes in the subchondral bone. Such changes can appear within 10-14 days in uncontrolled infection and they signal significant damage to articular structures and a reduced prognosis for full recovery.

Treatment of bacterial infective arthritis

Treatment of bacterial infective arthritis can involve several approaches: joint aspiration (an inherent part of synovial fluid sampling), joint irrigation, arthroscopic synovectomy, systemic antibiotics and local antibiotic delivery systems. The evidence base for the correct approach to canine and feline patients with bacterial infective arthritis is currently small and consists of retrospective case series. Similarly, clear guidelines do not exist for the management of human beings with septic arthritis [42,43].

Systemic antibiotics are a standard feature of all treatment regimens and in the first instance they are often used intravenously to rapidly gain effective tissue concentrations. In the absence of confirmatory culture and sensitivity information, broad spectrum antibiotics are used. In one series, the most common protocols were clavulanate-potentiated amoxicillin, cefalexin, clavulanate-potentiated amoxicillin combined with metronidazole, or cefalexin combined with metronidazole [19]. Once the results of bacterial culture and sensitivity testing are received, the clinician can decide to continue with the initial drug(s) or opt to change to an alternative protocol in the light of the sensitivity tests. The median duration of treatment in the study by Clements and colleagues [19], was 28 days (range 21-112 days). The author would recommend a minimum of 28 days of therapy with repeat arthrocentesis and synovial fluid analysis at the end of that

period. If the cell count has not returned to normal and the neutrophil percentage is still above 3%, it is recommended that antibiotic therapy is continued until synovial fluid cytology is within the normal range (or one consistent with OA if that is present).

The need for joint irrigation or surgical intervention at the time of initial presentation and in the absence of a penetrating wound or infected surgical implant is controversial. The literature is based on retrospective studies and, as such, there may be bias as to whether clinicians opted for purely medical therapy or a combination of antimicrobials plus surgical intervention. Nevertheless, there is not any convincing evidence that surgical intervention is necessary unless there is gross contamination of the joint [19,41]. Surgical interventions can involve:
Joint irrigation. This can be simply achieved by placement of two needles in to the joint at arthrocentesis sites and irrigation with copious quantities of sterile lactated Ringer's solution (or normal saline).

Arthroscopic inspection and lavage of the joint. This is recommended if there has been a penetrating wound and there may be gross contamination of the joint or foreign bodies within the joint. Arthroscopy facilitates removal of foreign material and directed lavage of joint recesses. In addition, synovial resection can also be performed manually or with a powered shaver if the clinician so chooses. However, such an approach is not supported by clinical evidence.

Open exploratory arthrotomy. This if not recommended but may be necessary in a minority of cases should arthroscopy not be available, or if a surgical implant requires removal because it is acting as a nidus, or potential nidus, for infection. Surgical intervention may not be justified in the first-line protocol for management of most cases of bacterial infective arthritis. However, if appropriate antibiotic therapy fails to bring the clinical signs under control, the author would recommend arthroscopic irrigation and inspection of the joint. In addition, if infected implants are present, removal is essential to resolve the infection.

Local antibiotic delivery systems may be employed in certain circumstances [44-47]. For example, in some instances the antibiotic of choice (based on culture and sensitivity) will have a toxicity profile that precludes long term systemic use. Should the use of such drugs prove necessary, local slow release preparations may be useful. Such systems employ an implantable carrier such as polymethylmethacylate (PMMA) or collagen from which the antibiotic is eluted over a period of weeks. Implantable carriers are used most frequently in the face of multi-resistant organisms such as methicillin-resistant *Staphylococcus aureus* [44].

Drug-delivery systems used for slow release may be divided into two groups: (1) non-biodegradable and (2) biodegradable carriers. The non-biodegradable option is poly(methyl methacrylate) (PMMA), which is used clinically as bone cement in orthopaedic surgery and is rigid after full polymerisation. For the treatment of bacterial infective arthritis, preformed antibiotic-impregnated PMMA beads threaded on a wire are available commercially and are implanted into joint recesses.

The biodegradable carriers have the advantage of being degraded, mainly by hydrolysis, to non-toxic end products. Such carriers may consist of inorganic salts (hydroxyapatite, tricalcium phosphate) or of polymeric biomaterials. Biodegradable polymeric carriers offer a broad range of characteristics, including degradability, permeability and certain mechanical properties. Natural polymers are large proteins, such as processed fibres of bovine collagen, gelatin and polysaccharides like hyaluronan. Collagen antibiotic carriers are commercially available and their use in dogs has been reported [44].

Patient monitoring and prognosis

Clinical response to successful treatment should be seen within 24-48 hours in acute cases. A reduction in pain and lameness should be apparent, along with resolution of pyrexia, and this provides the clinician with confidence that initial treatment has been effective. The author strongly recommends repeat synovial fluid analysis to monitor the efficacy of treatment and direct clinical decision-making. Repeat synovial fluid total and differential cell counts should be performed after 7-14 days of therapy and the results compared to the initial counts. The results of culture and sensitivity testing may indicate that a change in antibiotic therapy is justified on the basis of the resistance profile of the bacterium in question. Treatment should be continued continuously for a minimum of 28 days or when clinical signs have resolved, whichever is the longer. A repeat synovial fluid analysis should be performed prior to the withdrawal of antibiotic therapy and this is unlikely to be before 28 days. The author continues with antibiotic therapy until the cell count is within the normal/osteoarthritic range and the percentage of neutrophils is at or below 3%.

There is little information on the prognosis of dogs affected by bacterial infective arthritis. In one series, 17 of 32 joints recovered fully, 13 partially and two failed to recover [19]. Thus, in this series, infection was resolved in 94% of cases. Other reports document similar outcomes [41]. An important consideration influencing outcome assessment is that infected joints often have pre-existing pathology (e.g. OA) and so a full recovery is unrealistic.

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