Canine Immune-Mediated Polyarthritis

PART 2: DIAGNOSIS AND TREATMENT

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--- **ABSTRACT** ---

Canine immune-mediated polyarthritis (IMPA) is a diagnosis of exclusion based predominantly on clinical signs, characteristic joint fluid analysis, and elimination of potential joint infection. Ultimately, an appropriate and sustained response to immunosuppressive therapy may become the final diagnostic criterion used. Identifying associated disease processes, including breed-specific syndromes, remote infection, inflammation, drug exposure, vaccine exposure, or neoplasia, as well as initial response to therapy, is often an important contributor to prognosis. This review article is the second of a two part series and focuses on the diagnosis and treatment of immune-mediated polyarthritis. The first article in this series, published in the January/February 2012 issue, concentrated on the pathophysiology of IMPA. (*J Am Anim Hosp Assoc* 2012; 48:71–82. DOI 10.5326/JAAHA-MS-5756)

Introduction

Immune-medicated polyarthritis (IMPA) is an important disease process in the dog. Inflammation in multiple joints can lead to intense pain and may profoundly affect quality of life. This review article is the second of a two part series. It's aim is to concentrate on the diagnosis and treatment of immune-medicated polyarthritis.

Epidemiology

Most retrospective studies of dogs with nonerosive immune-mediated polyarthritis report no sex predilection for the condition and report that young to middle-aged, medium- to large-breed dogs are most commonly affected.[1–4] Retrievers, spaniels, and German Shepherd dogs are strongly represented.[1–6] Although one study looking specifically at type I IMPA diagnosed a high incidence of affected German Shepherd dogs and Labrador retrievers, statistical analysis revealed that neither breed had an increased risk compared with the general hospital population.[2] Another retrospective study of 40 dogs with nonerosive polyarthritis reported the cocker spaniel to be at increased risk and found that small- to medium-breed female dogs were over-represented.[5] Finally, a recent study describing IMPA in a population of dogs from western Canada, where tick-borne disease is uncommon, found that middle-aged to older dogs weighing <10 kg were most commonly affected, suggesting that American Eskimos and Labrador retrievers may be predisposed to idiopathic IMPA.[6] These varied findings from different case series reinforce the fact that clinicians should consider IMPA to be a reasonable diagnostic possibility in dogs of any sex, age, breed, or size.

Major Presenting Complaints and Clinical Signs

IMPA can cause nonspecific systemic signs such as weight loss, inappetence, lethargy, and reluctance to move. Owners may or may not report more specific clinical signs such as swollen joints, altered

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gait, or lameness. Vomiting and diarrhea may also be mentioned in the recent history.[4,6]

Various retrospective studies of dogs with IMPA have found a range of clinical signs, although most reported fever, lethargy, weakness, reluctance to walk, a stiff or stilted gait, lameness, swelling of multiple joints (often in a bilaterally symmetrical pattern), and pain on palpation of the joints.[2–6] Neck and back pain may also be present either if vertebral articular facets are involved or if meningitis is present.[3]

Clinicians should be aware that dogs with IMPA commonly present with no obvious joint swelling or localizable pain. In one study of 40 dogs with polyarthritis, only 35% demonstrated lameness and only 40% demonstrated joint swelling.[5] In addition, IMPA has been reported as one of the most common causes of fever of unknown origin in dogs.[7]

Diagnostics and Differential Diagnoses

Ultimately, IMPA is diagnosed by arthrocentesis and synovial fluid analysis. Further diagnostic testing is necessary to determine whether an underlying disease is causing a reactive polyarthritis. In addition, other causes of joint disease, including septic arthritis, degenerative joint disease, neoplastic arthropathy, trauma, and hemophilic arthropathy, should be ruled out. Most of these listed conditions, however, are more likely to affect a single joint rather than the multiple joints typically affected in dogs with IMPA.[1]

When evaluating a dog with suspected polyarthritis, a recommended minimum database should include a complete blood count (CBC), serum chemistry panel, urinalysis, and urine culture.[1] Common CBC and blood chemistry findings noted in dogs with IMPA include leukocytosis, mild nonregenerative anemia, and mild hypoalbuminemia. A mild to moderate elevation in serum alkaline phosphatase (of an as yet undetermined cause) is also common.[2–6] A positive urine culture can help identify a urinary or blood-borne bacterial infection.

A thorough search for evidence of underlying infection, inflammatory disease, or neoplasia should be undertaken, including thoracic and abdominal radiographs and abdominal ultrasonography. If back or neck pain is detected, radiographs of the spine are indicated. In addition, radiographs of multiple joints should be considered to look for evidence of synovial effusion, soft tissue swelling, and signs of joint erosion and destruction, and to rule out other possible causes of joint disease. The hocks, carpi, and stifles are the most commonly affected joints in dogs with IMPA, whereas the more proximal and larger joints are more likely to be involved in patients with infectious arthritis.[1]

Many infectious and inflammatory diseases can be associated with the presence of rheumatoid factor in the serum, including infectious arthritis and osteoarthritis.[8] Rheumatoid factor is an autoantibody with specificity for the constant region (Fc) portion of an immunoglobulin molecule. Testing for rheumatoid factor is indicated if bilateral, symmetrical, and erosive changes are present on joint radiographs, especially if the distal joints are affected.[8,9] A positive test supports a diagnosis of rheumatoid arthritis in a dog in which erosion of articular cartilage is present but extra-articular manifestations of immune disease are absent, especially if joint cultures are negative.[8,9]

Systemic infectious diseases can lead to reactive IMPA. If the patient has lived in or visited areas in which certain infectious diseases are endemic, appropriate testing should be performed. Such diseases include Lyme disease, bartonellosis, ehrlichiosis, anaplasmosis, and Rocky Mountain spotted fever. Paired antibody titers, polymerase chain reaction testing, and specific *Bartonella* spp. culture techniques are some of the tests that may be considered.

Septic arthritis should also be ruled out before considering treatment with immunosuppressive drugs. Culturing the blood, urine and synovial fluid may help identify a possible local or systemic bacterial infection. In one study, all cases of bacterial infective arthritis with no history of a surgical procedure or penetrating wound at the affected joint had evidence of pre-existing osteoarthritis. Most bacteria cultured were skin commensals, including *Staphylococcus* spp. and *Streptococcus* spp. The elbow was the most common joint affected, followed by the hip, stifle, and hock joints.[10] Other bacteria that have been reported to cause septic arthritis that may require special culture techniques to diagnose include *Mycoplasma* spp. and L-form bacteria.[10,11] Evaluation of the heart valves via echocardiography may also be necessary to screen for endocarditis, particularly if a new or progressive murmur is auscultated. Endocarditis can lead to either a sterile reactive immune polyarthritis or a true infective arthritis via hematologic spread of organisms to one or more joints.[12,13] In a retrospective study of 71 dogs with infective endocarditis, those infected with *Streptococcus* spp. were more likely to have neutrophilic polyarthritis than dogs infected with other organisms.[12,13] It is important to realize that culturing bacteria from blood can be insensitive. Further testing for organisms such as *Bartonella* spp., *Aspergillus* spp., and *Mycobacterium* should be considered if infective endocarditis is suspected, despite negative bacterial blood cultures.[12,13] Uncommonly, cytology of synovial fluid may also help confirm septic arthritis by revealing the presence of infectious agents such as *Mycoplasma* spp., *Borrelia burgdorferi* spirochetes, *Ehrlichia ewingii*, and *Anaplasma phagocytophilum* morulae in neutrophils, *Leishmania* amastigotes within macrophages, or fungal hyphae.[14,15]

Nonimmune joint diseases diagnosed by synovial fluid analysis include synovial neoplasia and hemophilic arthropathies. Further

confirmatory testing will often be needed, such as a surgical biopsy if neoplasia is suspected or a complete coagulation profile if hemophilic arthropathy is suspected. Synovial cell sarcoma is one of the more common joint neoplasms and is most likely to affect a single joint in a large-breed dog, particularly the stifle or elbow joint.[16]

Further diagnostic testing depends on history, clinical signs, and suspected underlying diseases. Cerebrospinal fluid analysis, including immunoglobulin A levels, should be considered if neck pain is noted and steroid responsive meningitis-arteritis (SRMA) is suspected. If muscle pain is present, serum creatine kinase is elevated, and/or polyarthritis/polymyositis is suspected, muscle biopsies should be obtained. Last, if immune-mediated disease is demonstrated in multiple organs, screening for systemic lupus erythematosus (SLE) should be considered.

A definitive diagnosis of SLE can be made either if two major signs (described in part 1 of this review series) and a positive antinuclear antibody (ANA) titer are identified or if two minor signs and one major sign are identified along with a positive ANA titer. A probable diagnosis of SLE can be made if two major signs are present with a negative ANA titer.[17] Positive ANA titers represent detection of serum antibodies directed against nuclear material such as DNA, RNA, nucleoproteins, and histone proteins. More than 90% of SLE cases have a positive ANA titer.[17] Although an ANA titer of >1:40 is considered positive, a titer of >1:256 is more suggestive of SLE.[17] Positive ANA titers can also be detected with infectious, inflammatory, or neoplastic disorders. Therefore, clinicians should only run ANA titers when a multisystemic immune disorder is strongly suspected.[17,18] The lupus erythematosus cell preparation test, which identifies opsonized nuclear material within neutrophils and macrophages, is much less sensitive than the ANA test, but is more specific for SLE.[17–20]

Documenting the presence of other major signs besides polyarthritis may lead to looking for antiplatelet antibodies if thrombocytopenia is present, performing a urine protein-creatinine ratio if glomerulonephritis is suspected, performing a slide agglutination or Coombs test if anemia is present, or performing a skin biopsy if characteristic lesions such as erythema, scaling, crusting, depigmentation, or alopecia are found on the skin, at mucocutaneous junctions, or within the oral cavity.[19]

Arthrocentesis and Synovial Fluid Analysis

The diagnosis of IMPA is confirmed by demonstrating neutrophilic inflammation in the synovial fluid of multiple joints. IMPA is classically considered to be a "polyarthropathy," suggesting that five or more joints are involved. However, many cases of canine IMPA may involve fewer than five joints and could therefore be more strictly defined as an "oligoarthritis," which involves two,

three, or four joints.[21–25] Rarely, IMPA involving only one joint has been reported.[14]

The carpal and hock joints are the most common joints affected by immune-mediated inflammatory joint disease in the dog and should be aspirated when attempting to confirm a diagnosis of IMPA.[1–6,21–25] Aspiration of at least one larger and more proximal joint, such as the stifle joint, is also recommended. If attention is paid to aseptic technique, collection of joint fluid is associated with little risk of introducing infection or causing significant trauma to the joint.[14] Furthermore, shaving hair over the joint(s) or taking radiographs of the joint(s) in question can help identify more subtle expansion of the joint capsule if the presence of joint effusion is unclear.

In most dogs, arthrocentesis can be performed using standard sedative protocols without the need for general anesthesia. In preparation for collecting joint fluid, the skin over each joint should be shaved and cleansed using sterile technique. Some commonly used landmarks for arthrocentesis are demonstrated in **Figures 1–3**.[26] A 25- or 22-gauge needle of sufficient length to enter the joint cavity should be used: a needle as short as 0.5-inch will suffice for smaller joints such as the carpus or hock; a 1.5-inch needle is typically sufficient for the stifle, elbow, and shoulder; and a 2-inch needle may be needed to access the hip joint in larger dogs. A 3 mL syringe will provide adequate negative pressure to draw out the joint fluid. The needle is attached to the syringe before attempting arthrocentesis. Most joints are in a more open configuration when in moderate flexion. When in the ideal position, palpation helps to further identify the best route to enter the joint capsule. The clinician should minimize blood contamination by avoiding superficial vessels. Once the joint space is entered, the syringe plunger should be gently drawn back and the needle hub carefully observed. Since viscous joint
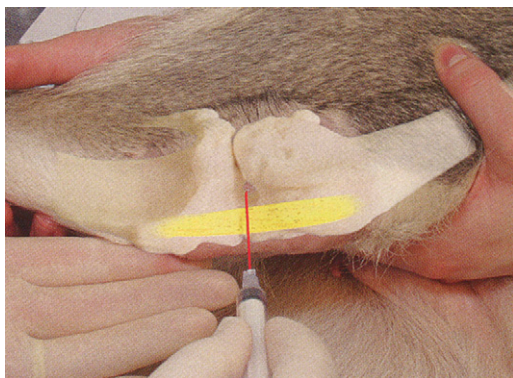

FIGURE 1 *Digitally modified photograph showing arthrocentesis of the carpus and anatomic landmarks. The needle is inserted at the anteromedial aspect of the radiocarpal space.*
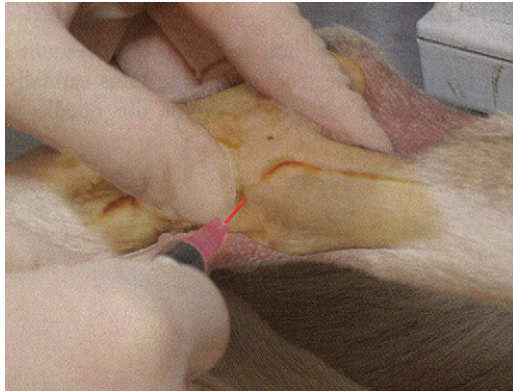
FIGURE 2 *Digitally modified photograph showing anterior approach to the hock joint and anatomic landmarks.*

fluid can take time to enter the syringe, patient observation of the hub of the needle is required before making the decision to re-direct and try again if no fluid appears. In the smaller joints of normal dogs <0.25 mL of joint fluid is obtained during arthrocentesis. If >0.5 mL is collected, the joint is considered likely to be diseased.[14,15] If the needle contacts the joint surface, the plunger of the syringe should be released, the needle backed out slightly, and suction reapplied. After fluid collection, the plunger should be slowly released before exiting the joint capsule to minimize blood contamination.

The color of the joint fluid that initially enters the needle hub can help determine whether blood contamination is iatrogenic. If the fluid is initially clear but later appears reddish, iatrogenic contamination is likely. If the sample is initially red-tinged, joint inflammation most likely led to pathologic hemorrhage. Regardless, samples with significant blood contamination should be placed in an ethylenediaminetetraacetic acid (EDTA, lavender top) tube to avoid

FIGURE 3 *Digitally modified photograph showing arthrocentesis of the stifle joint and anatomic landmarks. Enter just lateral to the midpoint of the patellar tendon then direct the needle medial and caudal toward the center of the joint.*

clot formation and submitted with a current CBC. Comparing peripheral blood and joint fluid cell counts may enable the clinical pathologist to distinguish nucleated cells present due to inflammation from those introduced by blood contamination.[14]

HA is responsible for maintaining the viscosity of joint fluid and coating the synovium.[14] The presence of inflammatory cells or bacteria in the joint can lead to degradation of HA by leukocyte proteases or bacterial hyaluronidases. HA can also be diluted by an influx of plasma if the joint vasculature is more permeable than normal due to inflammation.[14,15] To evaluate the viscosity of joint fluid, clinicians can use the subjective "string test" or the laboratory mucin clot test.[14,15] Care should be taken to avoid direct contact with joint fluid that may contain infectious organisms. For the string test, a drop of fluid is placed between two gloved fingers. The string of normal synovial fluid should only break when the fingers are parted by more than ∼2.5 cm. Alternatively, a drop of synovial fluid can be allowed to fall freely from the end of the aspiration needle. The synovial fluid should create a ∼2.5 cm long string before breaking. Although a decrease in fluid viscosity is typically expected in inflamed or infected joint fluid, one study reported only ∼50% of all joint samples taken from 40 dogs diagnosed with IMPA appeared to have a gross reduction in viscosity.[5]

Ideally, a sufficient amount of joint fluid will be collected to make several direct smears with enough volume fluid remaining to place in a standard lavender (EDTA) top tube for fluid analysis, including protein concentration, total nucleated cell count, and differential cell count. In many cases, only a small quantity of fluid is obtained. If so, one drop of fluid should be placed on a glass slide, smeared using standard methods, and allowed to air dry. If blood contamination of the fluid is suspected, a current CBC should also be submitted. One study comparing results obtained from a hematology analyzer (Coulter counter) versus assessment of direct smears of synovial fluid found that estimates of total WBCs obtained from smear evaluation alone were often falsely elevated and that there was considerable variation in estimated cell counts between clinicians.[27] A synovial fluid smear can, however, be used to estimate the total nucleated cell count into broad categories of normal, increased, or markedly increased.[14]

Normal canine synovial fluid contains <3,000 cells/mL.[14] Greater than 90% of these cells are mononuclear and <5% are mature, nondegenerate neutrophils.[15] The majority of mono-nuclear cells are nonreactive macrophages with few vacuoles. Small lymphocytes are also present in lower numbers and, on occasion, a synoviocyte may be seen.[15] In canine IMPA, synovial fluid volume is often increased. Fluid obtained may be turbid and/or discolored, and it typically has a decreased viscosity. The protein and nucleated cell content are usually increased, with cell

counts often >5000/μL. Fluid from abnormal joints is more likely to clot. The percentage of neutrophils is usually increased to 10–95% of total nucleated cells, and they are typically nondegenerate neutrophils. Although the results of synovial fluid analysis in dogs with IMPA almost always support the diagnosis, on rare occasions, a synovial membrane biopsy is required.[14,15]

Joint sepsis and immune-mediated arthritis can produce very similar changes in total joint fluid nucleated and differential cell counts. Although degenerate neutrophils are suggestive of bacterial or possibly a fungal joint infection, neutrophils from infected joints are often not significantly degenerate. Consequently, further testing of joint fluid may be needed to distinguish infected from noninfected joints. If only small amounts of joint fluid are obtained, a drop of fluid can be added to culture medium. Alternatively, traces of synovial fluid can be washed from the syringe and needle by aspirating sterile saline or enrichment broth. Direct culture of joint fluid on blood agar, however, produces false negative results in 50–70% of patients with septic arthritis.[14] One canine study demonstrated that inoculating a pediatric blood culture bottle with synovial fluid, incubating for at least 24 hr, and then streaking the blood culture medium on appropriate plate media significantly reduced false negative culture results. This approach was also more successful than synovial membrane biopsy cultures.[28] Joint fluid collected in EDTA should not be cultured because the anticoagulant can inhibit bacterial growth. More recently, real-time broad-based polymerase chain reaction assays have been described that rapidly identify bacteria in synovial fluid. These methodologies may eventually replace joint fluid culture as a means of identifying joint infection in dogs.[29–31]

Infectious agents are occasionally identified by direct cytologic examination of joint fluid. For example, rickettsial morulae have been found in neutrophils in the synovial fluid of up to 1% of affected patients.[15] Other organisms that may be seen include bacteria within neutrophils, *B. burgdorferi* spirochetes, *Mycoplasma* spp., *Leishmania* amastigotes within macrophages, and either fungal hyphae or yeast bodies.[14,15,32]

Treatment

Treatment of polyarthritis should target the underlying cause (if applicable) and concurrently address pain and inflammation. The overall goals of therapy are to achieve long-term remission with the lowest possible dose of medication and to prevent recurrence of joint inflammation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be administered to treat both pain and inflammation and may be the only medication needed for mild, transient cases of polyarthritis, such as those induced by vaccination. NSAIDs should be used with extreme caution in dogs with impaired renal or hepatic function and in dogs that are dehydrated.[33] If steroids are indicated for further treatment, NSAIDs should be discontinued for at least 48 hr before glucocorticoids are administered. A longer washout period may be needed depending on the NSAID or in older or more debilitated dogs. The prostaglandin analog misoprostol can be added to either help avoid or treat gastric ulceration induced by NSAIDs alone or by overlapping NSAIDs and glucocorticoids. Misoprostol should not be handled by pregnant women. Although less effective than misoprostol for NSAID-associated gastric ulceration, the proton pump inhibitor omeprazole can also be prescribed.[33]

In areas where tick-borne disorders such as Lyme disease and rickettsial infection are prevalent, initial therapy for polyarthritis should be limited to analgesics and empirical treatment with doxycycline. A recent American College of Veterinary Internal Medicine consensus statement on Lyme disease in dogs recommended treating with 10 mg/kg doxycycline *q* 24 hr for 1 mo.[34] The same doxycycline dose should be effective for most common tick-borne diseases. Dogs with polyarthritis induced by tick-borne disease typically demonstrate clinical improvement within the first 7 days of doxycycline administration.[34]

Immunosuppressive therapy, primarily with glucocorticoids, is the cornerstone of therapy in most dogs with IMPA. It can, however, be dangerous in patients with bacterial arthritis, especially if it is related to a systemic bacterial infection. Since IMPA is almost never immediately life threatening, it is preferable to withhold immunosuppressive therapy until bacterial arthritis has been reasonably excluded. In patients where bacterial arthritis is suspected, treatment should be initiated with a broad spectrum β-lactamase-resistant bactericidal antibiotic until culture and sensitivity results return or until diagnostic test results suggest that a bacterial infection is not present.[10]

Specific treatment protocols have been described for the various manifestations of polyarthritis described in the first part of this series. Treatment of drug-induced polyarthritis, for example, requires discontinuation of the inciting drug and possibly a short, tapering course of glucocorticoids.[35] Dogs diagnosed with polyarthritis/polymyositis have been treated with a combination of cyclophosphamide and a tapering dose of prednisone with varying success.[36] Dogs diagnosed with SRMA have been successfully treated with either prednisone alone or a combination of prednisone and azathioprine.[37,38] Juvenile-onset polyarthritis in Akitas has also been treated with multidrug protocols, including a combination of prednisone and azathioprine, but with a less reliable positive outcome.[39] In dogs with type II–IV idiopathic polyarthritis, joint inflammation will usually resolve when the underlying disease process is successfully

identified and either treated or removed. Occasionally, additional treatment with analgesics and possibly glucocorticoids will be required.[21–23] Again, in many cases of type II (reactive) polyarthritis triggered by infection, immunosuppressive doses of steroids will be contraindicated.[40] Tick-borne diseases, however, may benefit from concurrent treatment with doxycycline and a tapering dose of glucocorticoids.[41–44] Sulfasalazine has been used to treat cases of type III (enteropathic) arthritis and rheumatoid arthritis associated with gastrointestinal disease and provides a combination of anti-bacterial, anti-inflammatory, and immunosuppressive properties.[40]

Side effects of this medication are uncommon but can be severe as described in **Table 1**.

Once no underlying cause of polyarthritis has been identified, infection has been reasonably excluded, and a provisional diagnoses of type I (uncomplicated) idiopathic polyarthritis has been established, a tapering dose of a glucocorticoid is indicated if symptoms persist after more conservative treatment protocols have failed. Immunosuppressive doses of prednisone, prednisolone, or meth-ylprednisone (2–3 mg/kg/day *q* 24 hr or divided) can be started initially. This dose is administered until there is no cytologic

TABLE 1

Cytotoxic Drugs and Immune Modulators

	Mechanism of action / *Indications for use*	Dose	Monitoring/side effects
Sulfasalazine	Immunosuppressive, anti-inflammatory, antibacterial *IMPA type II, rheumatoid arthritis*[40]	25 mg/kg PO *q* 12 hr for 2–3 wk, taper to least effective dose[40]	Perform a baseline Schirmer tear test. Periodically monitor for keratoconjunctivitis sicca. Can cause GI side effects, cholestasis, dermatitis, neutropenia, and immune-mediated diseases[33]
Azathioprine	Purine antagonist, Immunosuppressant *IMPA, IBD*[33]	2 mg/kg *q* 24 hr for 2 wk or until remission then taper to *q* 48 hr	Monitor for bone marrow suppression, hepatotoxicity, pancreatitis, and GI side effects[33]
Cyclophosphamide	Alkylating agent. Antineoplastic and immunosuppressive *IMPA, rheumatoid arthritis, polymyositis*[33]	1.5 mg/kg if > 30 kg, 2 mg/kg if 15–30 kg, 2.5 mg/kg if <15 kg. Give the dose on 4 consecutive days once weekly[40]	Tablets cannot be split. Avoid treating for >4 mo. Monitor CBC for marrow suppression and urine for sterile hemorrhagic cystitis. GI signs and alopecia also possible[33]
Leflunomide	Inhibits T cell proliferation and B cell antibody production *Rheumatoid arthritis, IMPA*[69]	3–4 mg/kg PO *q* 24hr. Allow 6 wk before dose adjustment or adjust dose to maintain a plasma trough level of 20 µg/mL.[45]	Monitor for vomiting, lymphopenia, and anemia. Teratogenic[33,69]
Mycophenolate mofetil	Inhibits T and B cell proliferation during S phase *Rheumatoid arthritis*[69]	10 mg/kg PO *q* 8hr or 10 mg/kg PO *q* 12 hr. Taper dose by 50% after 2–3 wk or if hemorrhagic GI signs are noted[69,70]	Monitor for hemorrhagic GI side effects, weight loss, decreased activity, lymphopenia, and infection.[33] Mycophenolate mofetil capsules may produces less side effects than sodium salt enteric-coated tablets[33]
Levamisole	Anthelmintic with immunomodulatory action *Systemic lupus erythematosus*[40]	Combine 0.5–1.0 mg/kg prednisone *q* 12 hr PO with 2–5 mg/kg levamisole PO q 48 hr (maximum dose is 150 mg/patient). Taper prednisone over 1–2 mo. Continue levamisole ≥4 mo if relapse occurs[47,50]	Monitor for neurotoxicity, immune-mediated skin eruptions, anemia, lethargy, dyspnea, and pulmonary edema[33]
Aurothiomalate	Gold preparation. Anti-inflammatory, increases lysosomal membrane stability, and inhibits function of phagocytes and T-cells *Rheumatoid arthritis*[40]	0.5 mg/kg IM *q* 7 days for 6–8 wk. Repeat cycle every 2–3 mo if needed	Injection may be painful. Can use local anesthetic before administration. Give small test dose before starting therapy to screen for overt side effects. Monitor for renal insufficiency, dermatitis, stomatitis, hepatic necrosis, leucopenia, thrombocytopenia, corneal ulcers, and proteinuria[33,40]
Auranofin	Gold preparation *As above*	0.05–2 mg/kg PO *q* 12 hr	Considered less toxic and less potent than aurothiomalate. Diarrhea is common[40]
Methotrexate	Antimetabolite. S phase-specific. Inhibits folic acid, antineoplastic *Rheumatoid arthritis*[69]	2.5 mg/m^2 PO 2–3 times/wk or 0.3–0.8 mg/m^2 IV *q* 7 days	GI side effects are most common. High doses can also lead to listlessness, marrow toxicity, hepatopathy, renal tubular necrosis, alopecia, depigmentation, and pulmonary infiltrates/fibrosis[33,69]

CBC, complete blood count; GI, gastrointestinal; IM intramuscular(ly); PO, *per os*.

evidence of joint inflammation or the clinical signs of arthritis are no longer present. The dose can then be tapered every 2–3 wk by 25–30% until the approximate physiologic dose of 0.2–0.3 mg/kg/day is reached. Tapering glucocorticoids too quickly can lead to relapses that may be less responsive to treatment than the original manifestation of the disease.[21–23,40] The addition of supplementary immunosuppressive agents should be considered if remission is not attained or if relapse occurs during treatment with steroids alone. Immunosuppressive drugs that have been used in dogs with IMPA, as well as proper dosages, monitoring, and associated side effects, are listed in Table 1. If side effects with glucocorticoids or other immunosuppressive agents are intolerable, monotherapy with leflunomide can also be considered. Leflunomide is an immuno-modulating agent that inhibits T and B lymphocyte proliferation, suppresses immunoglobulin production, and interferes with leukocyte adhesion and diapedesis.[45] In a recent prospective study, 14 dogs received leflunomide as the primary treatment of IMPA. Other medications given concurrently in some dogs in that study included NSAIDs, tramadol, and doxycycline. Of the 14 dogs, 1 dog did not respond, 5 dogs had a partial response, and 8 dogs returned to a normal quality of life based on subjective assessment of clinical signs.[45] Leflunomide side effects were minimal and most dogs were treated for 4–6 wk before a dose reduction was attempted.[45]

When treating with a combination protocol, once remission of clinic signs is achieved, the drug causing the most concerning side effects (or, if no major side effects are seen, the most expensive drug) is typically tapered first. There are no controlled studies in dogs that show that one immunosuppressive agent is better than another for treatment of IMPA, and efficacy seems to depend on the individual patient.[2,4,23] Therefore, if one immunosuppressive agent does not appear to be working, it can be replaced by another. In some patients, all drug therapy can gradually be tapered then discontinued without relapse. In other patients, an ongoing, low dose of a glucocorticoid is required in conjunction with an immunosuppressive agent. In these cases, the lowest possible doses that maintain clinical remission should be administered.[40] Controlling pain is also an important part of restoring quality of life and allowing for tapering of immunosuppressive medications. Oral analgesics that may be combined with either NSAIDs or corticosteroids to control pain include tramadol, gabapentin, amantadine, and acetaminophen.[45,46] **Table 2** lists indications, dosing suggestions, and side effects of these medications and other noncytotoxic remedies used in IMPA.

In cases of canine SLE, immunosuppressive doses of glucocorticoids are the cornerstone of treatment with additional cytotoxic agents if needed. Azathioprine, cyclosporine, cyclophosphamide, and chlorambucil have all been reportedly used by clinicians in refractory SLE patients (Table 1). The goal of treatment is to achieve complete remission with resolution of clinical signs and a negative ANA titer.[17,19,20,47] After complete remission is attained, medications are tapered gradually over at least 6 mo. In addition to more traditional immunosuppressive agents, levamisole may be considered in refractory SLE patients. Levamisole is an immunostimulatory drug that enhances T cell differentiation and activity.[48] It regulates cell-mediated immune reactions by restoring effector functions of peripheral T lymphocytes, including suppressor cells, which have been shown to be lacking in SLE patients.[49] One study of SLE dogs described a protocol that combined prednisone at 0.5–1.0 mg/kg *q* 12 hr with 2–5 mg/kg levamisole (maximum dose 150 mg/patient) *q* 48 hr. The prednisone was tapered over 1–2 mo and the levamisole was continued for 4 mo or longer if a relapse occurred. This protocol induced remission in 25/33 dogs with SLE.[47,50] Other more specific therapies depend on the organ system being attacked and may include avoiding exposure to ultraviolet light in dogs with skin lesions or treating glomerulonephritis with low-dose aspirin, omega-3 fatty acids, a low protein renal diet, and angiotensin-converting enzyme inhibitors.

Treatment of dogs with familial Chinese shar pei fever focuses on protecting high molecular weight hyaluronic acid (HA) molecules from oxidative degradation, relieving clinical signs of fever and inflammation, and preventing amyloidosis. A wide range of antioxidants and anti-inflammatory medications have been suggested for use in shar peis with clinical fevers including omega-3 fatty acids, methylsulfonylmethane, vitamin C, vitamin K2, vitamin E and selenium, curcumin with bioperine, α-lipoic acid, boswellia, resveratrol, and lecithin.[51,52] The use of NSAIDs, such as dipyrone or meloxicam, has been described to control fever in dogs with temperatures >40.6 °C.[51,52] Colchicine is administered to impair the release of serum amyloid A from the liver by binding to hepatocyte microtubules and preventing amyloid secretion. Chronic administration of colchicine should be paired with cobalamin supplementation (Table 2).[51,52]

Erosive arthritis in dogs is more refractory to treatment and may require life-long therapy.[53] Because *Mycoplasma* spp. have been found in the joints of some greyhounds with erosive arthritis, trial therapy using an antibiotic effective against these organisms (such as tylosin) may be warranted before considering immunosuppressive therapy.[40,53] There is little published data available regarding the treatment of rheumatoid arthritis in dogs. Treatment recommendations are therefore usually extrapolated from the human literature. In human patients with rheumatoid arthritis, glucocorticoids are used as the first line of defense and are frequently combined with additional medications referred to as disease-modifying antirheumatic drugs (DMARDs). Depending on

TABLE 2

Anti-Inflammatory, Analgesic, Antioxidant, and Miscellaneous Medications

	Mechanism of action *Indication(s) for use*	Dose *Monitoring/side effects*
Prednisone, prednisolone	Glucocorticoid steroid hormone with multiple immunosuppressive and metabolic effects	2–3 mg/kg PO *q* 24 hr or divided (immunosuppressive dose). Taper by 25–50% every 2–3 wk until physiologic dose or least effective dose is reached
	Many immune-mediated joint diseases	*Polyphagia, polydipsia/polyuria, behavior changes, GI ulceration, delayed wound healing, muscle weakness, hair loss*
Deracoxib	NSAID with anti-inflammatory, analgesic, and antipyretic activity via inhibition of cyclo-oxygenase enzymes and prostaglandin synthesis[33]	Chronic use: 1–2 mg/kg PO once daily[70]
	Control pain and inflammation in IMPA	*Vomiting, diarrhea, stomach and duodenal ulceration, renal injury[70]*
Carprofen	NSAID	2.2 mg/kg PO or SQ *q* 12 hr or 4.4 mg/kg PO or SC *q* 24 hr
	Control pain and inflammation in IMPA	*Vomiting, diarrhea, GI ulceration, renal injury, and (rarely) idiosyncratic acute hepatotoxicity[70]*
Firocoxib	NSAID	5 mg/kg PO *q* 24 hr[70]
	Control pain and inflammation in IMPA	*Vomiting, diarrhea, GI ulceration, and renal injury. Rarely, behavior changes[70]*
Etodolac	NSAID	10–15 mg/kg PO *q* 24 hr[70]
	Control pain and inflammation in IMPA	*Vomiting, diarrhea, GI ulceration, renal injury, soft stool, weight loss, keratoconjunctivitis sicca[70]*
Tepoxalin	NSAID that inhibits both cyclo-oxygenase to decrease synthesis of prostaglandins and lipoxygenase to decrease syntheses of inflammatory leukotrienes[70]	10–20 mg/kg PO *q* 24 hr[70]
	Control pain and inflammation in IMPA	*Vomiting, diarrhea, and GI ulceration. Use with caution in patients with renal insufficiency[70]*
Meloxicam	NSAID	0.2 mg/kg PO (first dose only) then reduce to 0.1 mg/kg PO *q* 24 hr[70]
	Control fever in familial Chinese char pei fever.[51] *Control pain and inflammation in IMPA*	*Vomiting, diarrhea, GI ulceration, renal injury[70]*
Dipyrone	NSAID, IL-1β inhibitor	0.5–1.0 mL/dog SC (of a 500 mg/mL solution)[52]
	Control fever in familial Chinese shar pei fever[51]	
Acetaminophen	Analgesic, antipyretic[33]	Up to 15 mg/kg PO *q* 8 hr[70]
	Control pain in IMPA	*Higher doses can cause liver toxicity*
Tramadol	Synthetic μ-receptor opiate agonist that also inhibits reuptake ofserotonin and norepinephrine[33]	2–5 mg/kg PO *q* 6–8 hrs[33]
	Control pain in IMPA	*CNS effects (i.e., excessive sedation, agitation, anxiety, tremor, dizziness) or GI effects (i.e., inappetence, vomiting, constipation to diarrhea)[33]*
Amantadine	NMDA receptor antagonist[70]	3–5 mg/kg PO *q* 24 hr[46]
	Chronic joint pain	More effective when used with other analgesics such as an opiate or NSAIDs[33,46]
		Rare anxiety and dry mouth[70]
Gabapentin	Anticonvulsant, analgesic	Start with 5–15 mg/kg PO *q* 12 hr and gradually increase as needed up to 40 mg/kg PO *q* 8–12 hr[70]
	Treat chronic neuropathic/joint pain not responding solely to NSAIDs or opiates[70]	*Sedation and ataxia[70]*
Colchicine	An anti-inflammatory/analgesic derived from the meadow saffron plant	Gradual increase dose up to 0.025–0.03 mg/kg PO *q* 12 hr
	Prevent amyloid secretionin familial Chinese shar pei fever[71]	*GI side effects.[71] Monitor CBC for bone marrow suppression and decreased cobalamin levels[71]*
Methylsulfonylmethane	Anti-inflammatory. Metabolite of dimethylsulfoxide	500–1,000 mg/dog *q* 24 hr[71]
	Familial Chinese shar pei fever[71]	*Decrease dose if diarrhea occurs*

CBC, complete blood count; CNS, central nervous system; GI, gastrointestinal; IL, interleukin; IMPA, immune-mediated polyarthritis; NMDA, *N*-methyl D-aspartate receptor; NSAID, nonsteroidal anti-inflammatory drug; PO, *per os*; SC, subcutaneous(ly).

the response of the individual patient to therapy, more than one DMARD may be used at the same time. DMARDs that are used in human medicine include hydroxycholoquine, sulfasalazine, methotrexate, D-penicillamine, gold salts, azathioprine, cyclophosphamide, cyclosporine, and leflunomide. Chrysotherapy using gold salts has also been recommended for refractory cases of canine rheumatoid arthritis.[23,40] Human patients who fail to respond to standard DMARDs may be prescribed tumor necrosis factor

(TNF)-α blocking or inhibiting agents such as infliximab, adalimumab, and etanercept.[54,55] High concentrations of the proinflammatory cytokine TNF-α are present in the synovial space of both humans with rheumatoid arthritis and dogs with polyarthropathies. Targeting this cytokine may help to control inflammation.[54,56,57] Although initially helpful, the use of biologic molecules such as TNF-α are limited by the development of an immunogenicity that may render them ineffective. Immunogenicity is reduced by the concurrent use of drugs that inhibit the immune system. All three TNF-α blocking agents used in combination with methotrexate have been shown to slow progression of disease, increase mobility, and decrease clinical signs in human patients with rheumatoid arthritis.[54,55] Alternatives to TNF-α blocking agents in human rheumatoid arthritis patients include the interleukin-1 receptor antagonist anakinra, the T cell costimulation modulator abatacept, and the B cell modulator rituximab.[54] The essential protein structure and properties of both TNF-α and interleukin-1 are highly conserved among mammals. It is therefore possible that dogs with rheumatoid arthritis and conceivably other forms of IMPA could eventually be shown to benefit from medications developed for use in humans that target these particular cytokines.[57] In addition to immunosuppressive drug therapy, splenectomy is the last resort treatment for Felty's syndrome (rheumatoid arthritis, neutropenia, and splenomegaly).[23,58] Splenectomy is based on the presumption that the spleen is the site of immune-mediated neutrophil destruction.[58]

Patients on immunosuppressive therapy should be monitored closely for infections. Urinary tract infections, often with minimal clinical signs and detectable only via culture, are commonly associated with chronic immunosuppressive therapy. Pneumonia is another possible infection that may go undiagnosed due to vague clinical signs such as lethargy and inappetence. Fungal infections are also more likely in animals that are immunosuppressed.

Some dogs with type I idiopathic polyarthritis and most dogs with rheumatoid arthritis will require long-term or life-long management. Although cage rest is recommended during acute episodes when affected dogs are still significantly painful, a gradual increase in activity should be allowed over time because long-term management should encourage a lean body condition through exercise and dietary restriction. Diets or dietary supplementations high in omega-3 fatty acids should also be considered in an effort to control inflammation.[40,59]

In dogs with apparently nonerosive IMPA that is refractory to therapy, periodic radiographs of multiple joints are warranted to look for progression to erosive arthritis. Permanent damage to joints in dogs with the erosive form of IMPA may cause collapse of the joint space. In these cases, surgical treatment of badly affected joints may be warranted, particularly if the underlying polyarthritis is in remission. Arthrodesis of collapsed joints may increase comfort, and synovectomy may help reduce local inflammation within that joint.[23,40] Intra-articular injection of glucocorticoids such as triamcinolone or methylprednisolone has also been suggested as a means of controlling local inflammation.[40]

Monitoring Response to Therapy

Swelling and pain associated with IMPA often respond to glucocorticoids or a combination of glucocorticoids and other immunosuppressive agents within 7 days of commencing therapy. Because significant joint inflammation may still be present despite resolution of clinical signs, the gold standard for monitoring response to therapy is to repeat arthrocentesis before the first tapering of medication to ensure that the patient is in true remission.[40,60] Documentation of a substantial decrease in total WBCs and neutrophils in synovial fluid on repeat joint taps is considered to be a good prognostic sign. If no significant improvement is observed in synovial fluid cytology, continuation of aggressive immunosuppression or commencement of alternative medications should be considered.[2,21,40] Repeated arthrocentesis appears to be a relatively benign procedure. A recent study demonstrated that arthrocentesis using 22-gauge needles to sample the stifle and 25-gauge needles to sample the carpi and tarsi four times each at 3 wk intervals did not induce synovial neutrophilic inflammation in nine healthy dogs.[60]

Measuring acute phase protein levels during the course of treatment of IMPA may offer a practical alternative to either repeat arthrocentesis or simple observation of clinical signs for monitoring response to therapy. C-reactive protein (CRP) is an acute phase protein produced by the liver in response to inflammation that is commonly used in human medicine to monitor several inflammatory disorders, including rheumatoid arthritis. The rapid production of CRP in response to inflammation and the subsequent short circulating half-life make this protein a good biologic marker of progression for many inflammatory diseases. Serum CRP is significantly elevated prior to treatment in dogs with IMPA and when the disease is active during relapse.[61,62] Elevations in CRP are more pronounced in dogs with IMPA compared with dogs diagnosed with degenerative joint disease or intervertebral disk disease. One case series that included 38 dogs diagnosed with various forms of idiopathic polyarthritis reported that patients in which CRP concentrations normalized immediately after starting glucocorticoids had a better disease course.[62] Another single case report that monitored CRP over the course of therapy in a dog with type II idiopathic polyarthritis reported that measurement of the protein provided clinically useful information that was

superior to either clinical observation or monitoring CBC counts.[63] Currently, a commercial enzyme-linked immunosorbent assay kit is available that is specific for canine CRP.[64]

Prognosis

Erosive arthritis in dogs is associated with a poor long-term prognosis. In most cases, multidrug protocols are required to keep the disease in remission. Permanent joint destruction often leads to an inferior quality of life, even if the underlying inflammatory process responds to medical therapy.[23,53]

In contrast, the prognosis for most forms of nonerosive polyarthritis in dogs is fair to good. The prognosis in dogs with idiopathic polyarthritis depends on the subtype. In dogs with types II–IV, the prognosis is good and relapse is unlikely if the underlying disease can be identified and resolved.[21–23] Outcomes in dogs with type I (uncomplicated) idiopathic polyarthritis are also generally favorable. One study of 39 cases of canine type I polyarthritis reported that most responded to therapy: 56% of affected dogs were cured, 13% relapsed but were subsequently treated successfully, 18% required life-long therapy to maintain remission, and only 15% were euthanized or died because of their disease.[2] Relapses occurred weeks to months after tapering or stopping medications.[2] Some of the dogs that relapsed required life-long therapy to remain in remission, whereas others were finally cured.[2] When clinical signs resolved, remission was confirmed via repeat synovial fluid analysis.[2] The prognosis for dogs with vaccine- and drug-induced IMPA is excellent. Recovery times are usually relatively short, and relapse is unlikely.[40,65] Akitas with vaccine-induced IMPA, however, are reported to require more intense initial therapy compared with most other dog breeds and are less likely to respond to treatment.[65,66] A case report describing spaniels with polyarthritis/polymyositis suggested that this condition can be challenging to treat. Only two of six dogs achieved complete remission during treatment with a combination of cyclophosphamide and prednisone. Of the remaining four dogs, two relapsed and two never responded to therapy.[36] Most dogs with SRMA respond to immunosuppressive therapy, although relapses are possible. Older SRMA patients with high cerebrospinal fluid immunoglobulin A levels tend to experience more frequent relapses and require a longer duration of therapy. In contrast, boxers tend to have an excellent clinical outcome.[37,38,67,68] Akitas with juvenile-onset polyarthritis have a guarded prognosis. Breakthrough symptoms are common, even on multidrug protocols combining prednisone and azathioprine. Some Akitas, however, recover after tapering immunosuppressive drugs and do not relapse.[39] Dogs with familial Chinese shar pei fever tend to have self-limiting episodes of fever, inflammation, and swollen hock syndrome. Theoretically, the frequency of these episodes can be controlled by protecting HA from degradation. The long-term prognosis for shar peis that have also developed significant amyloidosis is guarded because many die of kidney or liver failure at a median age of 4 yr.[52] Prognosis in dogs with SLE varies with 40% of patients being dead within 1 yr and >50% achieving long-term survival.[17] Prognosis is favorable in dogs that are treated early in the development of the disease and in those that respond to glucocorticoid therapy alone. Prognosis is less favorable if renal failure with proteinuria is present, if initial response to therapy is less evident, or if relapses occur frequently.[17,19,20,47]

Conclusion

Success in treating dogs with IMPA is dependent on recognizing and addressing all associated disease processes. From there, treating with immunosuppressive therapy may be required. Monitoring patients closely for signs of remission or relapse of IMPA is imperative as is tapering medications at appropriate intervals or adding/altering medications if indicated. Prognosis is dependent on the presence or absence of erosive joint damage as well as the clinician's ability to control factors that may be contributing to the development of immune-mediated inflammation in the joints. ∎

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