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## Recognizing and treating immune-mediated polyarthritis in dogs

This inflammatory joint condition presents in many forms, often causing systemic illness and sometimes causing cartilage and bone destruction. Learn to distinguish these forms and what treatments induce remission and alleviate pain.



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VETERINARY MEDICINE

Classification of Immune-mediated Polyarthritis in Dogs*	
<b>Nonerosive IMPA</b>	
<b>Idiopathic</b>	<ul style="list-style-type: none"> <li>Type I: No association with other disease process</li> <li>Type II: Associated with infection or chronic inflammation that is remote from the joints</li> <li>Type III: Associated with gastrointestinal or hepatic disease</li> <li>Type IV: Associated with neoplasia remote from the joints</li> </ul>
<b>Systemic lupus erythematosus/polyarthritis</b>	
<b>Polyarthritis-steroid responsive</b>	
<b>Drug-induced polyarthritis</b>	
<b>Neutrophil-associated polyarthritis</b>	
<b>Small-vessel polyarthritis</b>	
<b>Polychaetis in situ</b>	
<b>Idiopathic</b>	
<b>Erosive IMPA</b>	
<b>Idiopathic erosive arthritis</b>	
<b>Polyarthritis in golden retrievers</b>	

Immune-mediated polyarthritis (IMPA) represents a group of diseases that cause marked joint pathology and systemic illness. IMPA is defined as an inflammatory process that affects the synovium of two or more joints, has no identifiable infectious component, and is responsive to immunosuppressive therapy.<sup>1-3</sup> Early recognition, diagnosis, and treatment are essential in reducing morbidity and mortality associated with the disease. Classifying IMPA will help you determine treatment and prognosis and is based on clinical, radiographic, pathologic, and serologic findings (*Table 1*).<sup>1,4,5</sup>

Table 1

### CLASSIFICATION

IMPA is categorized as erosive or nonerosive (*Table 1*). Nonerosive IMPA demonstrates no radiographic signs of bone or cartilage destruction.<sup>1,4,5</sup> Erosive IMPA demonstrates radiographic evidence of cartilage and subchondral bone destruction in one or more joints.<sup>1,4,5</sup> Erosive forms are rare and account for less than 1% of all reported IMPA cases.<sup>5-7</sup> (See boxed text "The pathophysiology of IMPA".)

### OVERVIEW OF THE NONEROSIVE FORMS

Although several retrospective studies have suggested the susceptibility of certain breeds and sizes of dogs to nonerosive IMPA, inconsistencies among reports exist.<sup>7-9</sup> Thus, nonerosive IMPA may occur in any breed or size of dog. It occurs at a mean age of 4 to 6 years with no definite sex predilection.<sup>1,2,4,5,7-9</sup>

Most dogs present with a stiff, stilted, or "walking on eggs" gait; lameness; reluctance or inability to stand; and joint pain and effusion.<sup>1,2,4,5,7-9</sup> Commonly affected joints include the carpus, tarsus, stifle, and elbow; bilaterally symmetric joint involvement is frequent.<sup>5,7-9</sup> Spinal pain may also occur because of intervertebral joint inflammation.<sup>10</sup>

Systemic signs include anorexia, weight loss, fever, lethargy, and lymphadenopathy.<sup>1,2,4,5,7-9</sup> Up to 25% of dogs present with subtle or no signs of gait abnormality, lameness, joint effusion, or joint pain but have systemic signs of illness.<sup>5,11-13</sup> IMPA should be considered as an underlying cause of fever of unknown origin; it accounted for 20% of dogs presenting with a fever of unknown



### The pathophysiology of IMPA

origin in one study population.<sup>14</sup>

### Idiopathic

Idiopathic nonerosive polyarthritis is the most common form of IMPA and represents 58% to 83% of all reported cases of IMPA.<sup>1,5,8,9</sup> Idiopathic nonerosive polyarthritis has been classified into four subtypes depending on the presence of distant infection, gastrointestinal disease, or neoplasia (*Table 1*). The relevance of associated disease in canine IMPA is unknown, but similar associations are recognized in people and are thought to have pathogenic significance by acting as a trigger for IMPA.<sup>15</sup> Idiopathic types II, III, and IV are also referred to as *reactive IMPA* by some authors.<sup>2,8</sup>

Idiopathic type I IMPA is not associated with distant disease and accounts for most idiopathic nonerosive IMPA cases reported in dogs.<sup>5,7,8,15</sup> Idiopathic type II IMPA is associated with infectious or chronic inflammatory disease and has been reported with pyoderma, urinary tract infection, pneumonia, endocarditis, mastitis, dirofilariasis, fungal infection, pleuritis, and severe periodontal disease.<sup>1,5,8,15</sup> Idiopathic type III IMPA is associated with chronic gastrointestinal disease and has been reported with inflammatory bowel disease, intestinal malabsorption, bacterial overgrowth, and ulcerative colitis.<sup>1,5,8,15</sup> Idiopathic type IV IMPA is associated with distant neoplasia and has been reported with squamous cell carcinoma, mammary adenocarcinoma, leiomyoma, heart base tumor, and seminoma.<sup>1,5,8,15</sup>

Treating idiopathic type I IMPA involves administering immunosuppressive, immunomodulating, and disease-modifying agents, while treating idiopathic types II, III, and IV focuses on resolving the underlying disease process. The prognosis of idiopathic type I IMPA is good to guarded, while idiopathic types II through IV have a variable prognosis depending on the treatability of concurrent disease.<sup>1,5,7,8,15</sup>

### SLE polyarthritis

Systemic lupus erythematosus (SLE) is a progressive multiorgan autoimmune disease in which polyarthritis is one of the most frequently observed clinical findings. SLE preferentially afflicts male German shepherds and other medium- and large-breed dogs; it is diagnosed at a mean age of 5 years.<sup>1,6,11-13,16,17</sup> Clinical signs of SLE can be intermittent and include polyarthritis, hemolytic anemia, thrombocytopenia, glomerulonephritis, polymyositis, skin lesions, fever of unknown origin, oral ulceration, and lymphadenopathy (*Table 2*).

Table 2 Criteria for Diagnosing Systemic Lupus Erythematosus*		
*Definite SLE: Two or more major signs with positive serologic test results; both serologic and major signs and two or more minor signs with positive serologic test results		
*Probable SLE: One major sign with positive serologic test results; two major signs with negative serologic test results		
Major Signs	Minor Signs	Serologic Tests
Glomerulonephritis	Central nervous system signs	Anti-dsDNA antibody (titer)
Neuropsychiatric	Fever of unknown origin	Anti-cardiolipin antibody
Leukopenia	Complex serositis	Lower titer antinuclear self-precipitation
Polyarthralgia	Oral ulceration	
Polymyositis	Pericarditis	
Low titer**	Rheinitis	
Disseminated purpura		

Table 2

Because of its variable presentation and progressive nature, SLE is often difficult to diagnose early in its course. Later in the disease process when other clinical manifestations appear, SLE may be more readily diagnosed. SLE is definitively diagnosed when two major signs and positive serologic test results are present or one major and two minor signs and positive serologic test results are present (*Table 2*).<sup>13</sup> A

probable diagnosis is made with one major sign and positive serologic test results or two major signs and negative serologic test results (*Table 2*).<sup>13</sup> SLE polyarthritis has a similar presentation to other nonerosive forms of IMPA and reportedly accounts for 8% to 20% of canine IMPA cases.<sup>2,5,8,17,18</sup>

The treatment of SLE polyarthritis is similar to the treatment of idiopathic forms and requires administering immunosuppressive and immunomodulating medications. If other organ systems are involved, treatment must also address other clinical signs. Remission is attainable with treatment and may also occur spontaneously.<sup>6,13</sup> The prognosis of SLE is variable, and concurrent organ dysfunction is often responsible for death or euthanasia.

### Polyarthritis-meningitis syndrome

A syndrome in which steroid-responsive meningitis arteritis (SRMA) occurs with polyarthritis has been described.<sup>1,6,10,16</sup> It was first seen in Bernese Mountain dogs, Weimaraners, and German shorthaired pointers but has since been documented in many breeds.<sup>10</sup> In one study, 29% of dogs with IMPA had associated spinal pain,

and, of those, nearly 50% were confirmed to have concurrent SRMA by cerebrospinal fluid (CSF) analysis.<sup>10</sup>

Dogs with polyarthritis-meningitis syndrome are suspected to have spinal pain due to a combination of meningeal and intervertebral joint inflammation.<sup>10</sup> Polyarthritis-meningitis syndrome occurs in young, male, medium- to large-breed dogs, and clinical signs include lethargy, reluctance to walk, and cervical pain, particularly on flexion and extension of the neck.<sup>1,6,10</sup> Effusion involving appendicular joints may not be obvious.<sup>6</sup>

The treatment of SRMA and IMPA is similar, but the syndrome is important to recognize since recurrence or neurologic damage may occur if it is treated inappropriately.<sup>10,19</sup> Most dogs with SRMA respond to immunosuppressive therapy with a good to guarded prognosis. It is not known whether dogs with both IMPA and SRMA have a different prognosis than dogs with SRMA alone.<sup>10</sup>

### **Polyarthritis-polymyositis syndrome**

Polymyositis has been described as a manifestation of canine SLE, but a non-lupoid syndrome of polyarthritis and polymyositis has been described.<sup>1,4,16,20</sup> The syndrome occurs most commonly in young to middle-aged spaniel breeds.<sup>4</sup> Dogs present with waxing and waning stiffness, joint effusion, myalgia, muscle contracture, and progressive bilaterally symmetric muscle atrophy.<sup>1,4,16,20</sup> Treatment is similar to that of idiopathic IMPA, but the presence of concurrent muscle involvement worsens the prognosis, and response to treatment is variable.<sup>16,20</sup>

### **Drug-induced polyarthritis**

IMPA has been associated with the administration of a variety of medications, including sulfonamides, lincomycin, erythromycin, cephalosporins, phenobarbital, and penicillins.<sup>1,2,4</sup> Sulfonamides, including sulfadiazine, sulfamethoxazole, and sulfadimethoxine, are most commonly implicated.<sup>21-24</sup> Polyarthritis induced by sulfonamides is most notable in Doberman pinschers and other large breeds and occurs at recommended drug dosages.

Signs of polyarthritis occur, on average, five to 20 days after drug exposure.<sup>21-24</sup> With previous exposure, signs may occur more rapidly.<sup>21-24</sup> Clinical signs are typical of IMPA (e.g. lameness, swollen and painful joints, fever, and lymphadenopathy) and may occur with concurrent hypersensitivity reactions including thrombocytopenia, hepatopathy, neutropenia, keratoconjunctivitis sicca, hemolysis, uveitis, or skin and mucosal lesions.<sup>21-24</sup>

Treatment involves discontinuing the drug; improvement in polyarthritis generally occurs within 24 hours.<sup>21-24</sup> Complete recovery generally occurs within two to five days of drug withdrawal. Some cases require immunosuppressive therapy for quicker and more complete resolution of clinical signs. The reported prognosis is generally good.

### **Vaccine-associated polyarthritis**

Vaccines have been implicated as an inciting event for IMPA but such cases are poorly documented within the veterinary literature.<sup>1,4,5,15,25</sup> In reported cases, IMPA caused by vaccines occurred within 30 days of vaccination. A true cause-and-effect relationship is difficult to prove, and little is known about a potential pathophysiologic mechanism. Canine distemper antigens have been found in immune complexes from joints of dogs with erosive IMHA and may suggest vaccine involvement.<sup>16</sup> Most vaccine-associated IMPA cases are self-limiting and may require a short course of immunosuppressive treatment.

### **Breed-specific polyarthritis**

Breed-specific cases of nonerosive IMPA include syndromes observed in Akitas and Chinese Shar-Peis.

A rare, nonerosive polyarthritis affects adolescent Akitas and may occur concurrently with meningitis or other organ involvement.<sup>16,26</sup> Affected dogs are treated with immunosuppressive agents, but response is generally poor.

Shar-Peis can experience a polyarthritis syndrome known as *Shar-Pei fever* or *swollen hock syndrome*.<sup>1,2,16</sup> It is an autosomal recessive disease associated with elevated interleukin-6 production.<sup>1</sup> The age of onset is variable, and the syndrome typically presents as cyclical episodes of fever and joint swelling of one or both hocks.<sup>1,2</sup> Joint swelling may be due to effusion or periarticular swelling, and enthesopathies (abnormalities involving the tendon or ligament attachments to bone) may be present.<sup>1,2</sup> Amyloidosis can be a component of the disease and occurs independent of fever and joint swelling.<sup>1,2</sup>

These cyclical episodes may require palliative treatment but can spontaneously resolve. Treatment of amyloidosis has been attempted with colchicine, but no studies have proved its efficacy.<sup>1,2</sup> Prognosis is variable depending on the degree of amyloidosis, and renal or liver failure is often the cause of death.<sup>1,2</sup>

## OVERVIEW OF THE EROSIIVE FORMS

As stated previously, two main erosive forms of IMPA exist—idiopathic and a polyarthritis that affects greyhounds.

### Idiopathic

Idiopathic erosive IMHA occurs in all dog breeds but is most frequent in smaller breeds, with an average age of onset of 2 to 6 years and no sex predilection.<sup>6,16,27-30</sup> Early in its course, dogs present with stiffness (especially after rest), intermittent lameness, and swelling of single or multiple joints.<sup>27-30</sup> The carpal, tarsal, and phalangeal joints are most often affected, and bilaterally symmetric joint involvement is common.<sup>27-30</sup> Clinical signs wax and wane over time, and lameness and stiffness may be accompanied by fever, lethargy, inappetence, and lymphadenopathy. The disease is progressive, but the rate of progression varies.<sup>27-30</sup> Chronic disease results in connective tissue degeneration, including the joint capsule and intra-articular ligaments, which leads to further joint instability, causing subluxations and luxations.<sup>27-30</sup>

The treatment of erosive IMPA involves administering immunosuppressive, disease-modifying, or anti-inflammatory medications. Overall, lifelong therapy is needed, and response to treatment and long-term prognosis are poor.

### Erosive polyarthritis in greyhounds

Erosive polyarthritis in greyhounds is a sporadic disease first reported in Australia in the 1970s.<sup>6,16,30,31</sup> It has subsequently been recognized in the United Kingdom and United States. This disease affects young greyhounds between the ages of 3 to 30 months and has no sex predilection.<sup>6,16,30,31</sup> Its clinical presentation is similar to that associated with idiopathic erosive polyarthritis in which distal joints are affected, but it appears to be a more slowly progressive disease, causes a nonsuppurative synovitis, and has less severe subchondral erosions than idiopathic erosive polyarthritis.<sup>6,16,30,31</sup> Treatment is similar to idiopathic erosive IMPA, and response is variable.

## DIAGNOSIS OF IMPA

The key in the diagnosis of IMPA is synovial fluid analysis; however, a comprehensive diagnostic evaluation should be performed to rule out infectious causes and identify associated disease. Diagnostics should include a complete blood count (CBC), serum chemistry profile, urinalysis, urine culture, rickettsial titers, thoracic and abdominal radiography, joint radiography, and synovial fluid analysis with bacterial culture. Other diagnostics to consider on a case-by-case basis include an abdominal ultrasonographic examination, an antinuclear antibody (ANA) test, a muscle biopsy, a synovial biopsy, or CSF analysis.



1. Placing a drop of synovial fluid between fingers is one way to assess synovial fluid viscosity.

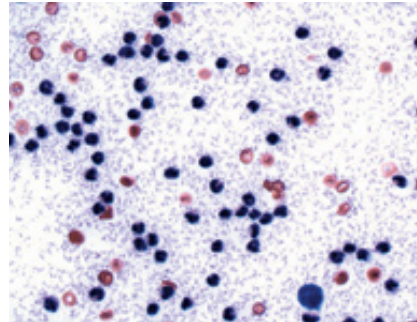
### Synovial fluid analysis with bacterial culture



2. Collect joint fluid in a purple top (EDTA) tube for cytologic analysis and a red top tube for culture and sensitivity.

Clinical suspicion of polyarthritis, even in the absence of obvious joint effusion, should prompt you to perform arthrocentesis.<sup>1,2,6,16,18,30</sup> Normal synovial fluid is relatively clear and viscous and does not clot on exposure to air (*Figures 1 & 2*). The volume of fluid collected from normal joints is < 0.1 to 0.25 ml.<sup>32</sup> Normal synovial fluid is relatively acellular, with a protein concentration < 2.5 g/dl and a nucleated cell count < 3,000 cells/ $\mu$ l.<sup>32</sup> Mononuclear cells predominate.

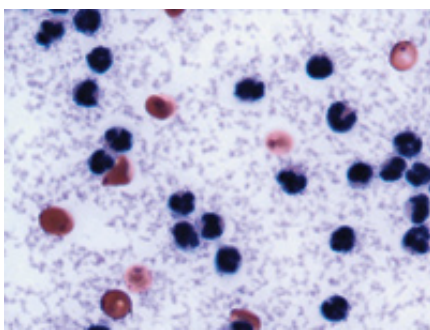
In cases of erosive or nonerosive IMPA, joint fluid may be thin, turbid, and increased in volume. The protein concentration is usually > 2.5 g/dl, and nucleated cell counts are > 3,000 cells/ $\mu$ l, ranging from 4,000 to 300,000 cells/ $\mu$ l.<sup>32</sup> Nondegenerate neutrophils typically account for most cells, but synovial fluid with greater than 12% nondegenerate neutrophils is still consistent with IMPA (*Figures 3 & 4*).<sup>5,11-13</sup> Recent studies have shown that pleomorphic inflammation can be present with IMPA in which mononuclear cells account for 50% or more of the synovial cell count.<sup>12,13</sup> This appears particularly true if a dog has been receiving immunosuppressive medications or has a waxing and waning form of disease.<sup>2</sup>



3. Cytologic examination of synovial fluid from a dog with IMPA demonstrating large numbers of nondegenerate neutrophils. Greater than 2 cells per high power field is elevated (500X, high power field).

The amount of synovial fluid collected from arthrocentesis is often small. If quantity limits analysis, determining cell counts and types is most important. This can be accomplished with a microscopic evaluation of one drop of synovial fluid on a slide. Greater than 2 cells/hpf is abnormal,<sup>5,7,8,32</sup> and an estimate of cell count and type is enough to aid in diagnosis.

Varying amounts of synovial fluid and inflammation will be present in different joints, so sample multiple joints. Most commonly, arthrocentesis of the carpal, tarsal, and stifle joints is recommended.<sup>5,7,8,18</sup> One study obtained a diagnosis of IMPA most readily from arthrocentesis of bilaterally symmetrical tarsal joints.<sup>8</sup>



4. Synovial fluid from an IMPA patient demonstrating nondegenerate neutrophils (1000X, oil immersion).

Bacterial infections should also be ruled out through aerobic and anaerobic bacterial culture of synovial fluid. Polyarticular joint infections are rare and occur through hematogenous spread of organisms and have been described with omphalophlebitis in neonates and bacterial endocarditis in mature animals.<sup>1,2,7</sup>

Degenerate neutrophils and bacteria in synovial fluid are diagnostic for a bacterial infection. However, synovial fluid from infected joints can also have a predominance of nondegenerate neutrophils and no obvious bacteria.<sup>32</sup> A critical assessment of bacterial culture results with other clinical, physical,

and diagnostic findings is essential, as only 50% to 70% of bacterial joint infections will have positive bacterial culture results.<sup>32</sup>

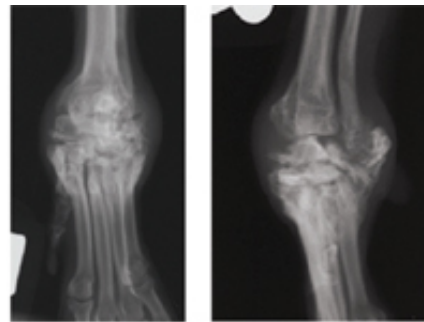
### CBC, serum chemistry profile, and urinalysis

CBC findings in patients with IMPA include a neutrophilic leukocytosis (24% to 69% of patients), leukopenia (8% to 24% of patients), mild nonregenerative anemia (15% to 35% of patients), and mild thrombocytopenia (8% to 27% of patients).<sup>5,6,8,9,15</sup> Other findings in patients with IMPA include an elevated alkaline phosphatase activity (10% to 60% of patients), hypoalbuminemia (7% to 27% of patients), and an

elevated urine protein:creatinine ratio (7% to 30% of patients).<sup>5,6,8,9,15</sup> Findings from a CBC such as a neutrophilic left shift, severe anemia, severe thrombocytopenia, evidence of hemolysis, or serum chemistry results consistent with renal or hepatic disease should prompt your suspicion of other infectious or multiorgan disease processes.

### ANA test

Perform an ANA test in dogs with multiorgan disturbances. Most dogs with IMPA have negative ANA results,<sup>16</sup> but a positive result should increase your suspicion of SLE.<sup>33</sup> To help confirm a diagnosis of SLE, a lupus erythematosus cell preparation can be performed, but an ANA test is preferred because of increased sensitivity and availability through reference laboratories.<sup>13</sup>



### Radiography



7 & 8. Lateral and dorsopalmar carpal radiographs in a dog with intracapsular swelling (effusion) typically seen with nonerosive IMPA.

Obtain joint

5 & 6. Dorsopalmar and lateral carpal radiographs demonstrating lesions typical of an advanced case of erosive IMPA in a dog. Note the intracapsular swelling, collapsed joint spaces, subchondral bone erosions, and periarticular osteophytosis.

radiographs to rule out other causes of lameness and joint pathology and to characterize IMPA as erosive or nonerosive (Figures 5-8). Radiographs typically demonstrate joint effusion and periarticular soft tissue swelling with IMPA.<sup>1,2,6,15</sup> On occasion, joint effusion is not detected.<sup>5</sup> In

advanced cases of erosive IMPA, subchondral bone erosions, subluxations, luxations, or ankylosis is present.<sup>29,30</sup> If you suspect erosive disease, obtain stressed medial, lateral, flexed, and extended radiographic views of the carpus and tarsus as they are useful in detecting joint instability. Early in the disease process, radiographs of both erosive and nonerosive IMPA may appear similar with no obvious erosion.<sup>30</sup> Thus, later in the disease process, you may need to repeat radiographs to determine the true form of disease.

### Antigen and antibody tests

Vector-borne infectious polyarthritis, particularly in disease-endemic areas, should be ruled out with appropriate antibody titers (initial and convalescent) and antigen detection methods (PCR, immunohistochemistry). Rickettsial organisms, including *Borrelia burgdorferi*, *Rickettsia rickettsii*, *Ehrlichia canis*, and *Anaplasma phagocytophilum*, and other vector-borne agents such as *Leishmania* species cause a polyarthritis that can be difficult to differentiate from IMPA.<sup>1,32</sup> A recent study demonstrated a significantly greater percentage of dogs with IMPA were seropositive for *B. burgdorferi* than dogs in the general hospital population and suggested that some cases of IMPA were due to Lyme disease.<sup>5</sup> Because of difficulty in completely ruling out some vector-borne diseases, assessing response to an antibiotic trial may be warranted before initiating immunosuppressive therapy.

### Muscle and synovial biopsy, CSF analysis, and rheumatoid factor test

Perform a muscle biopsy in cases of suspected polyarthritis-polymyositis syndrome.<sup>1,20</sup> With this syndrome, muscle biopsy samples demonstrate inflammatory infiltrates, often focal, with varying degrees of atrophied muscle fibers and areas of necrosis.<sup>20</sup> A synovial biopsy, while usually not indicated in patients with acute disease, can be useful in diagnosing erosive IMPA before radiographic changes are evident.<sup>29,30</sup> With erosive IMPA, synovial biopsy samples demonstrate villous hypertrophy of the synovial membrane and extensive infiltration of mononuclear cells into the synovium.<sup>28,30,34</sup> CSF analysis should be performed in cases of suspected polyarthritis-meningitis syndrome.<sup>10,19</sup> In these cases, typical

CSF findings are a normal to moderately elevated protein level and a neutrophilic or mixed leukocyte pleocytosis.<sup>10</sup> A rheumatoid factor test is not a specific or sensitive test for diagnosing idiopathic erosive IMPA in dogs.<sup>6</sup>

## TREATMENT

Medication	Dose
Corticosteroids	2.0 mg/kg PO once daily for 48 hours
Nonsteroidal anti-inflammatory drugs (NSAIDs)	See Table 1 for dosing
Cyclophosphamide	1.5 mg/kg (for dogs > 30 kg), 2 mg/kg (for dogs 15 to 30 kg), or 2.5 mg/kg (for dogs < 15 kg) for the first four consecutive days of each week and given concurrently with prednisone at an anti-inflammatory dose once daily
Azathioprine	2.2 mg/kg daily for two to four weeks and given concurrently with prednisone at an anti-inflammatory dose of 0.5 to 1 mg/kg every other day
Levamisole	1.5 mg/kg PO once daily for 48 hours
Immunomodulators	See Table 1 for dosing

Treatment of erosive and nonerosive IMPA involves treating joint inflammation and any identified, underlying immunologic trigger. Numerous treatment regimens have been proposed that involve single or multiple agents, including immunosuppressive drugs, immunomodulating drugs, or newer disease-modifying agents (defined by their ability to slow disease progression) (Table 3). A standard treatment of IMPA is difficult to identify, as controlled prospective clinical trials are unavailable.

Table 3

Regardless of the treatment regimen chosen, the goal is remission. If remission is not attained, the goals of treatment are to achieve the lowest possible level of joint inflammation, minimize joint damage, and enhance physical function and

quality of life while minimizing drug toxicity. Monitor the patient regularly to ensure that these goals are being met and, if not, determine if an alternative course of therapy is necessary.

### Nonerosive

Treatment of idiopathic types II through IV IMPA, drug-induced IMPA, and vaccine-associated IMPA relies on identifying and treating underlying causes. Failure to identify triggers will result in persistent or recurrent joint inflammation.<sup>1,2,4</sup> Once the cause is addressed, most cases resolve on their own. Some may require additional treatment as discussed below. Other treatments may be indicated for SLE and Shar-Pei fever, as previously discussed.

Other forms of IMPA, including idiopathic type I IMPA, SLE polyarthritis, polyarthritis-meningitis syndrome, polyarthritis-myositis syndrome, and polyarthritis in Akitas, require treatment with immunosuppressive, immunomodulating, and disease-modifying drugs.

**Immunosuppressants.** Corticosteroids are often the initial treatment of choice because of the low cost of treatment and rapid rate of action.<sup>1,2,4,6,18</sup> About 80% of dogs with idiopathic type I IMPA respond to immunosuppressive doses of prednisone,<sup>9,15</sup> but half of these dogs require long-term or combination drug therapy to maintain remission.<sup>15,18</sup> Prednisone is initially administered at immunosuppressive doses of 2 to 4 mg/kg/day until remission is achieved (see *Monitoring section below*). Once remission is achieved, prednisone is then gradually reduced over an extended period, usually two to four months.<sup>1,4,6,18</sup>

If clinical signs recur upon dose reduction or discontinuation, reinstitute prednisone at the initial dose or add another drug to therapy. If a patient needs to receive prednisone long-term to control clinical signs, use the lowest effective dose, preferably on an every-other-day dosing schedule. Side effects associated with long-term corticosteroid use include iatrogenic hyperadrenocorticism, diabetes mellitus, urinary tract infections, pyoderma, and breakdown of collagen in tendons and ligaments.<sup>35</sup>

If prednisone monotherapy is ineffective, not tolerated, or not preferred, an additional cytotoxic drug is used adjunctively with prednisone. Azathioprine and cyclophosphamide are most commonly used with prednisone and have been shown to induce remission in patients with IMPA.<sup>15,18</sup> The superiority of one drug over the other is unknown. Azathioprine is initiated at a dose of 2.2 mg/kg daily for two to four weeks and given concurrently with prednisone at an anti-inflammatory dose of 0.5 to 1 mg/kg every other day.<sup>2,6</sup> After induction, azathioprine is then reduced to an every-other-day dose that alternates with prednisone.<sup>2,6</sup> Cyclophosphamide is initiated at a dose of 1.5 mg/kg (for dogs > 30 kg), 2 mg/kg (for dogs 15 to 30 kg), or 2.5 mg/kg (for dogs < 15 kg) for the first four consecutive days of each week and given concurrently with prednisone at an anti-inflammatory dose once daily.<sup>6</sup> Both treatment regimens are continued for two to four months, after which, if a patient is in remission, the azathioprine or cyclophosphamide is gradually withdrawn.<sup>6</sup>

Side effects of azathioprine include bone marrow suppression and hepatotoxicosis.<sup>35</sup> Side effects of cyclophosphamide include bone marrow suppression and hemorrhagic cystitis.<sup>35</sup> Because of the potential for hemorrhagic cystitis, cyclophosphamide should not be used for more than four months,<sup>1,6</sup> and azathioprine may have the advantage of being better tolerated for long-term use. If a patient cannot be weaned from cyclophosphamide, chlorambucil may be substituted for maintenance therapy with fewer side effects.<sup>6,29</sup> Chlorambucil has not been shown to be effective at inducing IMPA remission.

If a patient remains in remission once the cytotoxic agent is discontinued, a patient can be gradually weaned off prednisone. If remission is not attained with the addition of cyclophosphamide or azathioprine or is not maintained once the drugs are removed, levamisole, leflunomide, or cyclosporine may be added or substituted for the cytotoxic agent (*Table 3*).

**Immunomodulating drugs.** Levamisole, an anthelmintic with immunomodulating properties, has been shown to be effective in treating SLE polyarthritis<sup>36</sup> and in relapsing cases of IMPA.<sup>1,4</sup> In a study population of German shepherds affected with SLE and polyarthritis, levamisole induced remission in 76% of dogs.<sup>36</sup> It is administered at a range of dosages but most commonly at 2.2 mg/kg every other day or 0.5 to 2 mg/kg three times weekly.<sup>35</sup> To treat SLE, levamisole was administered at a dosage of 2 to 5 mg/kg (maximum of 150 mg/dog) every other day with a concurrent initial dosage of prednisone of 1 to 2 mg/kg/day.<sup>36</sup> Side effects may include lethargy, vomiting, diarrhea, agitation, hemolytic anemia, and cutaneous drug eruption; these signs appear to occur most commonly at higher dosages.<sup>35</sup>

**Disease-modifying agents.** Leflunomide has been recently evaluated for use in treating canine IMPA.<sup>3</sup> The drug was used as monotherapy in dogs not receiving previous medication for polyarthritis and in those that relapsed while receiving prednisone. Ninety-three percent of dogs had a complete or partial response with treatment, and, of those responding, 63% had to continue to receive the drug long-term to maintain remission.<sup>3</sup> Leflunomide was used at a dose of 3 to 4 mg/kg in this study and appeared to be safe and well-tolerated. Some authors recommend adjusting the leflunomide dose to a trough level of 20 µg/ml.<sup>6,35</sup> It has not been investigated for use in combination with corticosteroids. Side effects include mild anemia, decreased appetite, and lethargy.<sup>37</sup>

Cyclosporine has gained popularity for use in the treatment of a variety of immune-mediated conditions and may prove useful in treating IMPA. When used as a sole agent for treating IMPA, it was ineffective.<sup>9</sup> Further investigation may find it efficacious as adjunct therapy. Side effects include gingival hyperplasia, gastrointestinal upset, or recrudescence of infectious disease.<sup>35</sup>

## Erosive

The use of many drugs in the treatment of erosive IMPA has been extrapolated from data in human patients, and a variety of different therapeutic protocols and agents have been suggested. Within veterinary medicine, little evidence exists regarding the superiority of one protocol over another, and no treatment has proved consistently effective in halting the progression of erosive IMPA in dogs. For best efficacy, treatment needs to begin early in the disease process, before marked joint damage. Drugs used to treat erosive IMPA include immunosuppressive, disease-modifying, or palliative medications.

**Immunosuppressants.** Immunosuppressive agents used to treat erosive IMPA in dogs include prednisone, azathioprine, cyclophosphamide, and chlorambucil. Using corticosteroids as monotherapy in dogs with erosive IMPA has a limited effect<sup>6,29</sup> and is not recommended as it may promote cartilage damage.<sup>38</sup> Administering prednisone in combination with azathioprine, cyclophosphamide, or chlorambucil has a variable benefit in slowing the progression of disease.<sup>2,6,29</sup> Protocols for these agents are similar to those described above for nonerosive IMPA except that prednisone is initiated at higher immunosuppressive doses for several weeks to allow time for other agents to reach efficacy.<sup>2</sup> Long-term therapy is generally required, and care must be taken to monitor for adverse effects.

**Disease-modifying agents.** Gold salts, hydroxychloroquine, penicillamine,



methotrexate, and leflunomide are disease-modifying agents that have been used in veterinary medicine to treat erosive IMPA.<sup>6,18,29</sup>

Gold salts, hydroxychloroquine, and penicillamine reportedly have had some therapeutic success in treating erosive IMHA but with variable efficacy. Objective data evaluating these drugs are limited, but the use of gold salts is reported most frequently.

Gold salts include an injectable formulation (sodium aurothiomalate) and an oral formulation (auranofin). They have been used most successfully in combination with anti-inflammatory doses of prednisone. Protocols vary, but sodium aurothiomalate is given at a dosage of 1 mg/kg intramuscularly once weekly for six weeks. Six week cycles are repeated every two to three months as a patient requires. Auranofin is given at a dosage of 0.05 to 0.2 mg/kg orally twice daily. Side effects of gold salts include blood dyscrasias, diarrhea, ulceration of mucous membranes, erythema multiforme, hepatotoxicosis, and renal disease<sup>35</sup> and may limit their use in some patients. Thus, close monitoring during therapy is critical.

Leflunomide and methotrexate have proven efficacious in treating a rheumatoid-like syndrome in cats.<sup>39</sup> Neither drug has been evaluated for erosive IMPA in dogs, but some authors recommend their use in refractory cases.<sup>1,2</sup>

**Palliative therapy.** Erosive IMPA is often diagnosed after severe joint disease has occurred and palliative therapy should be used to improve function and control pain. Palliative therapy includes administering NSAIDs and other pain medications such as opioids or tramadol. Additionally, physical therapy, surgical stabilization of joints, and the supplementation of glucosamine-chondroitin and omega-3 fatty acids may be beneficial.<sup>2,4,6,16,18,29,34</sup>

## MONITORING

Assess a patient's response to therapy through its clinical signs and repeated synovial fluid analysis.<sup>1,2,6,16,18</sup> Reducing or withdrawing drugs prematurely may result in exacerbating the clinical signs and make it more difficult to sustain a long-standing remission. Even in the absence of clinical signs, synovial inflammation may persist. Ideally, arthrocentesis should be performed before each anticipated reduction in drug dose but is especially important before the first drug reduction. Repeated arthrocentesis should be performed on previously documented inflamed joints.<sup>6</sup> No recommendation exists on the number of joints to reevaluate with synovial fluid analysis. Repeated arthrocentesis in a healthy dog does not appear to alter the type and numbers of cells in synovial fluid significantly.<sup>40</sup> However, sequential arthrocentesis in a patient receiving immunosuppressive therapy is still a concern, and strict aseptic technique should be used.

C-reactive protein may be useful for monitoring IMPA remission. C-reactive protein is an acute phase protein that rapidly increases in the serum of patients in response to infection, inflammation, and tissue destruction. Several studies have demonstrated a linear relationship between the amount of C-reactive protein in serum and the amount of inflammation in synovial fluid in patients with IMPA.<sup>41,42</sup> Because of these studies and the existence of reference values at major laboratories,<sup>43</sup> C-reactive protein values can be used to monitor the induction and maintenance of remission in IMPA patients.

Patients also need to be monitored for potential adverse effects of medications used to treat IMPA. This monitoring may include performing CBCs, serum chemistry profiles, urinalyses, and urine bacterial cultures. Monitoring should begin within one or two weeks after initiating the drug and be continued at appropriate intervals thereafter. If adverse effects are noted, appropriate dose reductions should be made or the drug should be discontinued.

## SUMMARY

Canine IMPA can be a challenging disease to diagnose and treat. Nonerosive IMPA predominates, with idiopathic type I accounting for most cases. Keys to diagnosis are recognizing the clinical signs, performing synovial fluid analysis, and ruling out other disease processes. The treatment of both nonerosive and erosive IMPA involves immunosuppressive, immunomodulating, and disease-modifying drugs. In dogs with nonerosive IMPA, the prognosis and response to treatment vary according to cause but is often guarded to good, with many patients responding to single agent or

combination drug therapy. In dogs with erosive IMPA, treatment needs to be aggressive and lifelong, and efficacy is limited by the presence of marked joint damage before the initiation of treatment.

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