





INTERNAL MEDICINE

Canine Immune-Mediated Polyarthrititis: Meeting the Diagnostic and Therapeutic Challenges

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Immune-mediated polyarthrititis (IMPA) is an important condition to recognize in dogs. Treatment of IMPA is significantly different than treatment of many other conditions that may present with similar clinical signs, and protocols may vary between patients. Therefore, making an accurate diagnosis is critical. This article identifies some of the key considerations for establishing the diagnosis and making appropriate treatment plans for dogs with IMPA.

CLINICAL PRESENTATION

One challenge in recognizing IMPA is the variety of possible clinical presentations. The most obvious clinical findings include reluctance to walk, altered gait or lameness, and multiple swollen, painful joints.¹⁻⁵ Dogs often have a stilted gait or appear to be “walking on eggshells,” and lameness may be present in different limbs at different times. Spinal pain due to inflammation of articular facet joints or concurrent meningitis may also be present.³

METHODICAL APPROACH

There are multiple types of IMPA. Consider the benefits and risks of the diagnostic and treatment options for each differential diagnosis for a successful outcome.

Other clinical signs associated with IMPA (e.g., fever, lethargy, inappetence, vomiting, or diarrhea) may be less helpful in localizing the problem to the joints. These signs are sometimes the only ones observed in patients with IMPA.⁴⁻⁶ For example, in studies of dogs presented for further investigation related to fever of unknown origin, 8% to 40% were diagnosed with IMPA and many had no apparent joint pain or swelling.⁶⁻⁸ In another study of dogs with IMPA, most had stiffness or difficulty walking (80%), but only 40% had joint pain detected.⁴ Although some breeds are overrepresented in studies, IMPA can affect dogs of any breed, sex, age, or size.³⁻⁶

Therefore, it is important to consider IMPA as a primary diagnostic differential not only in cases with obvious joint disease, but also in cases with a general decline in mobility or chronic fever.

DEFINITIONS

IMPA is typically defined by a synovial accumulation of immune complexes (type III hypersensitivity), which starts a cascade reaction that draws neutrophils into the joint.⁹ Some



BOX 1 Differential Diagnoses for Canine Polyarthropathies

Non-immune-mediated causes

- Degenerative joint disease/osteoarthritis
- Hemorrhage
- Trauma
- Neoplasia
- Crystals (gout, pseudogout; rare in dogs)
- Infections
 - Bacterial
 - Aerobic cocci, rods
 - *Rickettsia*
 - Spirochetes
 - *Mycoplasma*
 - L-forms
 - *Bartonella*
 - Fungal
 - Protozoal (*Leishmania*)
 - Viral

Immune-mediated polyarthritis

- Primary
 - Nonerosive
 - Idiopathic (type I)
 - Systemic lupus erythematosus
 - Breed-associated (Shar-pei, Akita)
 - Polyarthritis-polymyositis
 - Steroid-responsive meningitis-arteritis
 - Polyarteritis nodosa
 - Sjögren's syndrome
 - Juvenile cellulitis
 - Erosive
 - Rheumatoid arthritis
 - Breed-associated (greyhound)
 - Idiopathic
- Secondary/reactive
 - Systemic or non-joint infection (type II)
 - Gastrointestinal disease (type III)
 - Non-joint neoplasia (type IV)
 - Systemic or non-joint inflammatory disease
 - Medication related
 - Vaccine induced

erosive forms of IMPA may also include a T cell-mediated response (type IV hypersensitivity) directed against articular cartilage.⁹

Historically, canine IMPA has often been classified into 4 types: idiopathic (type I), secondary to a non-joint infection (type II), secondary to gastrointestinal disease

(type III), and secondary to neoplasia (type IV).¹ A more simplified approach is to divide IMPA into primary and secondary disease. Primary IMPA describes idiopathic cases; secondary, or reactive, IMPA describes any situation in which the immune complex formation can be attributed to an identified underlying problem outside of the joints. Regardless of the classification system used, distinguishing the type of IMPA may help clinicians carefully consider possible underlying causative conditions and generate appropriate diagnostic plans.

DIAGNOSIS

When a dog presents with abnormal gait or lameness, the first steps involve trying to determine whether the underlying problem involves the muscles, nervous system, other soft tissues, long bones, or joints. Even when the joints are clearly painful, other diagnostic differentials should be considered. Some of the most common causes of polyarthropathy are listed in **BOX 1**. Characteristics of the IMPA subset of polyarthropathies include joint inflammation, lack of infection or neoplasia directly involving the joints, and a positive response to immunosuppressive therapy.

While the clinical diagnosis of IMPA is generally established by arthrocentesis with synovial fluid analysis to identify the neutrophilic reaction, the overall diagnostic approach must also ensure that (1) appropriate alternative diagnoses such as noninflammatory or septic arthritis are considered and (2) the patient is appropriately evaluated for possible underlying causes of secondary IMPA. **FIGURE 1** provides a summarized general diagnostic approach when IMPA is suspected. The plan for any individual patient may vary significantly from this approach depending on the clinical presentation.

A thorough medical history and physical examination are important in all cases. Particular considerations related to the history are a full categorization of clinical signs, note of geographically relevant potential infectious disease exposures, recently administered medications or vaccines, and whether the patient has been receiving flea and tick preventives. The physical examination can be extremely helpful in localizing the source of problems for animals with lameness or abnormal gait. It is also critical for identifying clues about potential underlying diseases that could cause secondary IMPA and might help direct additional testing.

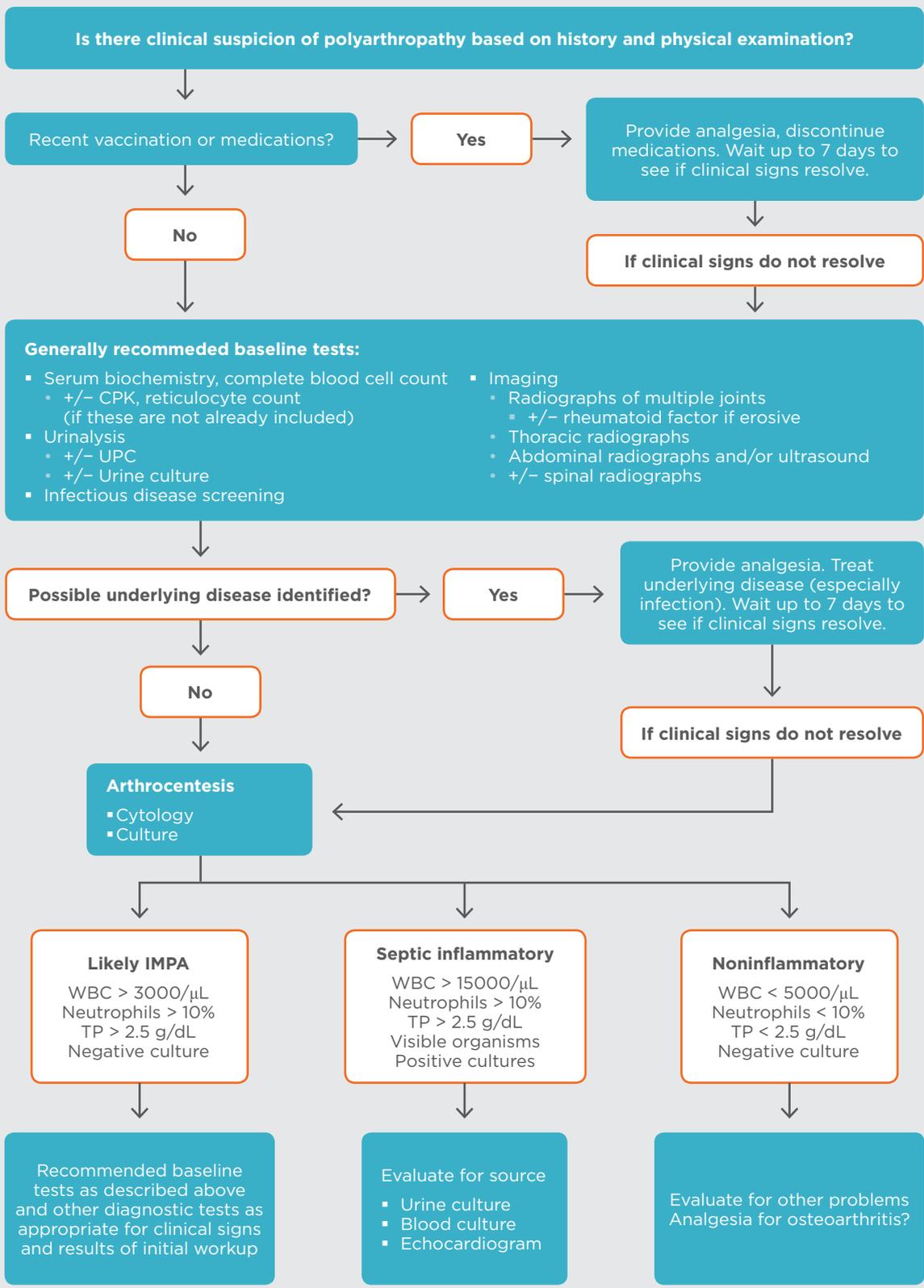


FIGURE 1. General diagnostic algorithm for cases of suspected polyarthropathy*

*It is always appropriate to consider the baseline tests and arthrocentesis to help establish the diagnosis.
 CPK = creatine phosphokinase, TP = total protein, UPC = urine protein-to-creatinine ratio, WBC = white blood count.



BOX 2 Getting the Most Out of Arthrocentesis

- Sample at least 3 joints, including the carpus or tarsus, as these are most commonly affected.^{3,5,11} Sampling multiple joints increases the chances of finding significant inflammation in a joint. Finding inflammation in multiple joints reduces the likelihood of septic arthritis.
- Make slides at the time of fluid collection. Synovial fluid samples can undergo rapid cellular degradation in tubes.
- Avoid making smears too thick. Use the tiniest drop possible to make the slides. If a large drop is used, the cells may be too crowded. If the fluid is very viscous, holding the spreader slide at a lower angle may help spread the sample more thinly.¹⁰
- If sample volume is >0.5 mL, submit synovial fluid in a micro-EDTA tube for fluid analysis in addition to making slides. Fluid analysis allows for more accurate cell counts than slide estimates.
- Avoid “greedy” sample collection that may result in blood contamination. The amount of fluid that can be collected varies based on many factors (e.g., patient size, severity of effusion), but there is little benefit to collecting more fluid than necessary for slides, fluid analysis, and culture.
- If a small amount of blood enters the hub of the syringe, release the plunger to ensure that there is no negative pressure and withdraw the needle from the joint. Take the needle off and make slides directly from the syringe, or use a second needle and syringe to suction the uncontaminated portion of the sample from the original syringe to make slides.
- Interpret results in light of the complete blood count. If there is blood contamination in the sample, keep in mind that a peripheral leukocytosis may result in falsely elevated synovial fluid cell counts.
- Submit a sample from at least 1 joint for culture.
- A negative joint culture result does not rule out septic arthritis. Only 40% to 50% of suspected septic arthritis cases have a positive joint culture result.¹⁰⁻¹⁴ Particularly in cases with only 1 obviously abnormal joint, septic arthritis should remain in the differential diagnosis.

Arthrocentesis may be performed early in the workup or after baseline tests as listed in **FIGURE 1**. Sedation or anesthesia is typically used to avoid patient discomfort and to aid joint immobilization, which can help prevent blood contamination. Several sources provide excellent information about the techniques for aspiration of fluid from different joints.^{10,11} Some tips to get the most useful information from a joint fluid analysis are included in **BOX 2**. One key is to collect fluid from multiple joints, since they may not all be affected to the same degree.

Normal synovial fluid should contain <3000 white blood cells per microliter with a predominance of mononuclear cells and <2.5 g/dL of protein.¹⁵ Most IMPA cases have significantly higher white blood cell counts with a predominance of neutrophils and higher protein concentrations. Typical cell count, cell population, and protein concentration characteristics of joint fluid for several conditions are included in **TABLE 1**. However, it can be difficult to characterize the specific disease process with only these parameters because there may be significant overlap between different diseases and there are exceptions to every expectation.

It is also generally recommended to culture a sample from at least 1 joint. The best samples for culture are the most grossly abnormal, such as those that are discolored or have markedly reduced viscosity, or those with the most fluid obtained. Unfortunately, some potential infectious organisms are not identified by routine culture methods, and a high rate of false-negative culture results has been reported even for cases with septic arthritis.^{10,12-15} Improved detection of infection was documented in 1 study by inoculating a pediatric blood culture bottle and incubating for 24 hours before plating for culture; however, this finding was not repeatable in another study.^{13,14}

Unless there is a specific finding from the history or physical examination, the search for possible underlying non-joint inflammatory, infectious, or neoplastic disease can involve a wide range of tests and be quite expensive. Baseline tests include a serum biochemistry panel, a complete blood cell count, and urinalysis, with plans to follow up on any identified abnormalities. Many patients with IMPA have results consistent with systemic inflammation on these tests, such as leukocytosis, mild nonregenerative anemia, and hypoalbuminemia.³⁻⁵ A mild increase in serum alkaline phosphatase of unknown cause is also seen in many cases.³⁻⁵

Infectious disease screening should be considered based on individual exposure risks, including the geographic areas in which the animal has lived or traveled, exposure to other animals and potential disease vectors, and preventive medicine history. If initial lab work does not identify localized abnormalities, imaging tests—including thoracic radiography, abdominal radiography and/or ultrasonography, and radiography of multiple joints—should be considered, with follow-up of identified abnormalities.

TREATMENT

Most IMPA cases are treated with immunosuppressive medications. However, these medications may be contraindicated for several diseases that present with similar signs, such as septic arthritis, or be unnecessary for some causes of secondary IMPA, such as those related to vaccines or common vector-borne diseases. The authors generally wait 24 to 48 hours for preliminary joint fluid culture results before starting immunosuppressive therapy. Because vector-borne diseases are relatively uncommon in our area, we typically do not wait for results of external laboratory tests before starting immunosuppression if point-of-care testing is negative.

Analgesia

For patients that present with joint pain, analgesic medications are indicated while awaiting test results to confirm the diagnosis. Although nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most effective medications for many disorders associated with joint pain, they should mostly be avoided in cases for which IMPA is considered a likely differential diagnosis. If NSAIDs are used, a washout period of at least 48 hours should be observed before the administration of steroid medications, which may end up delaying effective treatment. Nonetheless, NSAIDs may be appropriate in cases in which the use of steroids is not anticipated, or when definitive treatment is delayed while awaiting test results or completing a course of antibiotics for a non-joint infection. Other options for analgesia in outpatient cases might include opioids (such as tramadol or fentanyl patches), gabapentin, or amantadine.

Doxycycline Trial

In many cases of polyarthritis secondary to vector-borne disease, such as Lyme disease or rickettsial infections, a positive response to doxycycline (10 mg/kg PO q24h) is expected within the first week of treatment.¹⁶ Therefore, if these conditions are diagnosed or highly suspected, the initial approach may consist of a therapeutic trial limited to analgesics and doxycycline.^{10,16} If dramatic improvement is noted within a week, treatment should be continued for 28 days.¹⁶ If there is no improvement after a week, additional diagnostic testing or immunosuppressive therapy should be considered.

Underlying Disease

Control of the causative disease process is an important part of successfully treating many secondary IMPA cases. This may include discontinuing medications if a drug reaction is suspected, treating a non-joint infection with antibiotics, controlling concurrent gastrointestinal problems, or removing or treating neoplastic lesions. Some cases of secondary IMPA may resolve when the underlying immune trigger has resolved. Specifically, IMPA related to recent vaccination or sulfonamide administration has been reported to resolve in as little as 3 days without immunosuppressive therapy.^{17,18} It is also important to recognize that, as in many other immune-mediated diseases, an untreated underlying immune trigger may limit the effectiveness of immunosuppressive therapy in cases of IMPA.

Immunosuppressive Medications

Primary (idiopathic) IMPA is treated with

TABLE 1 Characteristics of Synovial Fluid in Dogs With Common Joint Disease Conditions¹⁵

CONDITION	TOTAL PROTEIN (G/DL)	TOTAL NUCLEATED CELL COUNT (CELLS/ μ L)	CELL POPULATIONS
Normal	<2.5	\leq 3000	>90% mononuclear cells <5%–10% neutrophils
Noninflammatory (i.e., degenerative joint disease, trauma)	<2.5	\leq 5000	>90% mononuclear cells \leq 10% neutrophils
Septic inflammatory (rod/cocci bacteria)	>2.5	>15,000 (often >50,000–100,000)	>75% neutrophils
Other infectious inflammatory (e.g., Lyme, Ehrlichia)	>2.5	>3000 (often >10,000)	>60% neutrophils
IMPA	>2.5	>3000 (often >10,000–50,000)	>10% neutrophils (typically >90% neutrophils)



immunosuppressive medications. Similarly, immunosuppression is warranted for cases of secondary IMPA when control of the underlying condition is not possible or clinical signs persist despite control of the underlying problem. Glucocorticoids are the most commonly used medications, and clinical improvement is typically rapid. A typical protocol starts with an immunosuppressive dose of prednisone or prednisolone at 2 to 3 mg/kg/day. However, this may represent a relative overdose for large dogs. Based in part on the results of a recent study, the authors typically start with a dose of 2 mg/kg/day for dogs <20 kg and 40 mg/m²/day for dogs >20 kg.¹⁹

Alternative or adjunctive immunosuppressive agents may be used in patients with glucocorticoid intolerance or comorbidities that suggest unacceptable risks for steroid use (e.g., congestive heart failure, hyperadrenocorticism), or in patients that do not experience clinical improvement on steroids alone. Immunosuppressive agents commonly used in the treatment of IMPA are listed in **TABLE 2**. These drugs may be used concurrently with glucocorticoids to speed up the tapering process or to improve disease control in refractory cases. Leflunomide and cyclosporine have been shown to be effective single-agent alternatives to steroids for treatment of primary IMPA in dogs, with complete responses seen in approximately 60% to 70% of cases.^{20,21}

Regardless of the medications used, immunosuppressive doses are generally continued at the initial dose until at least 2 weeks after resolution of clinical signs (fever, lameness, joint effusion). Ideally, repeat joint taps are performed to confirm resolution of the inflammation, since clinical signs sometimes abate before joint inflammation, but this is not always feasible because of cost or client perception related to the invasiveness of the procedure. Some data suggest that C-reactive protein levels help in differentiating IMPA from osteoarthritis and monitoring response to therapy.²²⁻²⁴ Measurement of serial C-reactive protein levels may help in detecting some cases of poorly controlled IMPA, but this method has a low sensitivity compared to repeat arthrocentesis, and the authors do not use C-reactive protein measurement in these cases.²⁴

Following clinical remission, the steroid dose is reduced gradually (20% to 30%) every 3 to 4 weeks, with careful monitoring for signs of relapse. Tapering medications too quickly has been proposed to increase the risk of relapse.¹⁰ If more than one immunosuppressive agent is used, only one should be tapered at a time. The decision of which medication to taper first is generally based on the reason for using multiple medications, but most often it is the steroid. In particular, if the patient is having clinically significant side effects related to the steroid or has another condition that may

TABLE 2 Alternative or Adjunctive Immunosuppressive Medications for Treatment of IMPA in Dogs

MEDICATION	INITIAL DOSE	POSSIBLE SIDE EFFECTS	OTHER CONSIDERATIONS
Cyclosporine	5 mg/kg PO q12h	Gastrointestinal signs (may be reduced by freezing tablets without loss of efficacy), secondary infections, ^{11,20} gingival hyperplasia, papillomatosis, hypertrichosis, neoplastic disease	<ul style="list-style-type: none"> Complete remission in 70% of IMPA cases when used as sole agent²⁰ Use with caution if diabetes mellitus or renal dysfunction Many potential drug interactions Expensive
Leflunomide	2-4 mg/kg PO q24h	Diarrhea, lethargy, increased liver enzymes, secondary infections, thrombocytopenia, unexplained hemorrhage	<ul style="list-style-type: none"> Complete remission in 58% and partial remission in 36% of IMPA cases when used as sole agent²¹ Use with caution if hepatic or renal dysfunction Can be expensive
Mycophenolate mofetil	10 mg/kg PO q12h	Severe gastrointestinal upset, dose-dependent diarrhea, weight loss, lymphopenia, leukopenia, papillomatosis, dermal infections	<ul style="list-style-type: none"> Not studied as sole agent therapy for IMPA May need to use dose reduction if significant renal dysfunction Generic form is relatively inexpensive
Azathioprine	2 mg/kg PO q24h for 7-14 days, then either decrease frequency to q48h or decrease dose to 1 mg/kg	Gastrointestinal signs, bone marrow suppression, pancreatitis, hepatotoxicity, secondary infections, neoplastic disease	<ul style="list-style-type: none"> Not studied as single-agent therapy for IMPA, but anecdotal reports of use as an adjunct to steroids Use with caution if hepatic or renal dysfunction Relatively inexpensive



be adversely affected by steroid administration, the steroid should be tapered first. In most cases, the authors wait at least 3 to 4 weeks after the steroid has been completely stopped before considering a decrease in the dose of another immunosuppressive medication. The authors typically do not try to wean patients completely off of immunosuppressive therapy for at least 4 to 6 months from the start of the treatment. If there is a relapse, the medication protocol should be changed back to the most recent effective dose or combination, although some patients require even higher doses to regain control of the disease. Some patients may require very long-term or lifelong immunosuppressive therapy; if this is the case, the goal is to find the lowest effective dose.

CONCLUSION

Clinical presentations of canine IMPA—and therefore diagnostic and therapeutic strategies—vary greatly. One important clinical tip is to consider IMPA as a diagnostic differential in cases without obviously swollen or painful joints. Even when IMPA is strongly suspected, deciding which tests are appropriate to evaluate for possible underlying disease and how to start immunosuppressive medications is often difficult. By thinking carefully about the differential diagnosis and the relative benefits and risks of the different diagnostic and treatment options, successful outcomes are possible for many dogs. **TVP**

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