Immune-mediated polyarthritis (IMPA) is a common disease process in the dog. The immune-mediated polyarthropathies are divided into two major categories: erosive (or deforming) and non-erosive (or non-deforming).

Pathophysiology

Immune-mediated non-erosive polyarthritis is believed to be driven by a type III hypersensitivity reaction, where immune complexes comprised of antigen bound to antibody accumulate in the joint space. Implicated antigens are typically found in the systemic circulation, but can originate from within the joint space itself. Systemic immune complexes can arise from a variety of chronic antigenic stimuli, including but not limited to viruses such as distemper virus, other microbial agents, neoplasia, drug haptens or even dietary elements. In addition, antibodies directed against self-antigens, such as heat shock proteins, immunoglobulins (rheumatoid factors) and nuclear elements (anti-nuclear antibodies) can also form complexes that accumulate in the joint space. The presence of immune complexes in the joint space activates complement along the synovial membrane and within the synovial fluid. Complement fixation results in tissue damage and release of cytokines, some of which attract neutrophils. These neutrophils also release cytokines and lysosomal enzymes that cause further tissue damage.

In canine rheumatoid arthritis, a disease characterized by erosive joint damage, antibody directed against type II collagen has been found along the joint surface as well as rheumatoid factors within the joint fluid. In addition, chronic persistent synovitis exists that is characterized by perivascular accumulation of mononuclear cells, indicating a possible type IV hypersensitivity component to this destructive disease. T lymphocytes, macrophages and fibroblasts release matrix-degrading enzymes such as metalloproteinases, which cause cartilage degeneration and further inflammation.

Erosive Polyarthritis

The erosive forms of immune-mediated polyarthritis are very rare compared to the non-erosive forms, and represent only about 1% of all canine polyarthritis cases. These forms are characterized by the presence of radiographic changes consistent with subchondral bone destruction. Radiographic changes may include irregular joint surfaces, a narrowing or widening of the joint space, and punched out lesions along the joint surface. It is important to note that radiographic changes can take up to 6 months to appear. Therefore, dogs with apparently non-erosive forms of polyarthritis in which clinical signs persist should be periodically re-evaluated for erosive changes.

Rheumatoid arthritis is the most notable form of immune-mediated erosive polyarthritis, but Felty’s syndrome and erosive polyarthritis of Greyhounds have also been described. Felty’s syndrome is a disease triad characterized by rheumatoid arthritis, neutropenia and splenomegaly.
described in humans and several dogs. Erosive polyarthritis of greyhounds has been reported most frequently in Australia and England. *Mycoplasma spumae* has been isolated from at least one affected Greyhound.

Rheumatoid arthritis is typically diagnosed in small, middle aged dogs. Diagnostic criteria for rheumatoid arthritis in the dog are adapted from those defined for humans. The presence of 5 criteria is suggestive of rheumatoid arthritis, and the presence of at least 7 out of 10 criteria is considered supportive of a definitive diagnosis of canine rheumatoid arthritis.

**Diagnostic Criteria for Rheumatoid Arthritis in the Dog**

1. Stiffness
2. Pain on manipulation of at least one joint
3. Signs of arthritis for at least 3 months
4. Periarticular soft tissue swelling
5. Typical radiographic changes such as subchondral bone destruction, indicated by irregularity of articular surface or ‘punched out’ erosions and loss of mineralization of epiphysis, calcification of soft tissue around joint, changes in joint space (increased or decreased width) or extensive bone destruction with gross joint deformity
6. Inflammatory synovial fluid
7. Characteristic, symmetrical deformations of distal joints
8. Detection of rheumatoid factors (anti-globulins) in serum
9. Three of the following histopathologic changes in synovial membrane: marked villous hypertrophy, synovial cell proliferation, fibrin deposits, foci of necrosis and lymphocytic-plasmacytic infiltration
10. Extra-articular symptoms such as lymphadenopathy

The stifle and carpal joints in dogs with rheumatoid arthritis are commonly affected, and also occasionally the digital joints. Antibodies directed against IgM, IgG and IgA (rheumatoid factors) have been identified in the joint fluid and blood of dogs diagnosed with rheumatoid arthritis. Establishing a definitive diagnosis of rheumatoid arthritis is important since this disease has a more guarded prognosis compared to most of the more common non-erosive polyarthropathies.

**Non-Erosive Polyarthritis**

Non-erosive forms of immune-mediated polyarthritis that lead to neutrophilic inflammation in multiple joints include idiopathic polyarthritis, vaccine- and drug-induced polyarthritis,
polyarthritis/polymyositis syndrome, steroid-responsive meningitis-arteritis, and breed specific polyarthropathies such as juvenile-onset polyarthritis of Akitas and familial Chinese Shar-pei fever. Systemic lupus erythematosus (SLE) also commonly involves the joints but less than 20% of canine cases of polyarthritis can be attributed to SLE. Idiopathic polyarthritis is by far the most common form of non-erosive immune-mediated polyarthritis in the dog. 

**Idiopathic Polyarthritis**

Idiopathic polyarthritis refers to all cases of immune-mediated arthropathy that cannot be classified into the other groups previously mentioned. Sporting dogs and large breed dogs are over-represented, and the majority of affected patients are young adults with ages ranging from about 2 to 5 years. Breeds that are commonly diagnosed include the Labrador Retriever, Golden Retriever, German Shepherd, Cocker Spaniels and American Eskimo.

Idiopathic polyarthritis has been categorized into four sub-types: Type I - no underlying disease, Type II - reactive, Type III - enteropathic and Type IV - neoplasia-related. Types II to IV are often grouped together and referred to as the reactive polyarthritides. It should be noted that regardless of subtype, the pathophysiologic change that occurs in the joint space is the same. These subtypes merely point to the presence or absence of a concurrent disease process.

In *Type I* (uncomplicated) polyarthritis, the cause is unknown, and no underlying disease can be detected. This is the most common form of the idiopathic polyarthritides, accounting for approximately 50%-65% of all idiopathic polyarthritis cases.

In *Type II* (reactive) polyarthritis, an infectious or inflammatory disease distant from the joints is the underlying cause of the polyarthritis. These diseases produce antigens that combine with antibodies to form immune complexes that accumulate in the joints, activating complement and leading to inflammation. Type II polyarthritis accounts for approximately 10-25% of all idiopathic polyarthritis cases. The underlying infection can be bacterial, fungal, protozoal or viral, and can be located anywhere in the body including the heart valves, vertebral bodies or disc spaces, uterus, kidneys or lower urinary tract including prostate, respiratory tract including tonsils, oral cavity, skin, or even ears. Non-infectious inflammatory diseases such as pancreatitis have also been reported in association with immune-mediated arthritis.

*Type III* (enteropathic) arthritis is associated with the presence of gastrointestinal or hepatic disease. Only about 5% of all idiopathic polyarthritides cases are in this category. It has been theorized that disease of the gut leads to an increase in intestinal permeability to potential antigens, which then stimulate the production of immune complexes.

*Type IV* arthritis is associated with neoplasia that exists outside the joints. This is an uncommon manifestation of idiopathic polyarthritis, occurring in only about 2% of dogs with polyarthritis. It has been reported to occur in dogs with neoplasms such as pancreatic adenocarcinoma, renal carcinoma, tonsillar carcinoma, squamous cell carcinoma, mammary carcinoma, leiomyosarcoma, and lymphoma. Neoplasia may act as an antigenic stimulus against which antibodies are formed, leading to circulating immune complexes that deposit in the joint spaces.
**Vaccine-Induced Polyarthritis**

Vaccine-induced polyarthritis can occur after a first vaccination or after a booster vaccine. Clinical signs are evident within 30 days of receiving the vaccine. Vaccine-induced polyarthritis is usually transient, resolving within several days. However, some breeds such as the Akita appear to be predisposed to this condition, and suffer a longer course of vaccine-associated polyarthritis. Reports in Akitas describe profound joint pain and cyclic fevers lasting 24-48 hours, with initial signs occurring 3 to 30 days following vaccination. Prognosis is guarded in affected Akitas, who often do not respond to immunosuppressive therapy.

**Drug-Induced Polyarthritis**

Drug-induced polyarthritis has been reported with multiple different drugs in many different breeds, although the most widely reported manifestation occurs secondary to sulfonamide administration, particularly in Doberman Pinchers. Other drugs that have been implicated include phenobarbital, erythropoietin, penicillins, lincomycin, erythromycin and cephalosporins. Typically, the affected animal has either received the inciting drug in the past or has been on the medication long-term. Clinical signs usually resolve within 2-7 days of discontinuing the drug. Reactions associated with sulfonamide in dogs occur an average of 2 week after drug initiation or 1 hour to 10 days after drug re-exposure.

**Polyarthritis/Polymyositis Syndrome**

Polyarthritis/polymyositis syndrome is characterized by polyarthritis initially accompanied with focal or generalized muscle pain and swelling followed by eventual muscle atrophy and fibrosis. Most recorded cases of polyarthritis/polymyositis syndrome have been identified in spaniels. Animals present with fever and painful joints and muscles. Muscle enzymes including creatine kinase are often elevated, and diagnosis is based on the combination of electromyography, muscle biopsies and joint taps.

**Steroid-Responsive Meningitis-Arteritis**

Steroid responsive meningitis-arteritis (SRMA) is currently the most widely accepted term describing a disease syndrome that causes meningitis in medium and large breed dogs less than two years of age. The syndrome was first recognized in young laboratory Beagles, and was referred to as ‘Beagle pain syndrome’. Canine pain syndrome, canine juvenile polyarteritis syndrome, canine meningeal polyarteritis, aseptic suppurative meningitis, and necrotizing vasculitis are also terms that have been used to describe essentially the same disease condition. Other breeds that are predisposed to SRMA include the Boxer, Bernese Mountain Dog, Akita and German Short Haired Pointer. Typically, affected animals present with an acute onset of neck pain, fever and lethargy.

Cerebrospinal fluid analysis reveals inflammation and an increase in protein. More specifically, a high level of immunoglobulin A is found both systemically and intrathecally. Paired measurements of IgA in the serum and CSF have proven useful for diagnosing SRMA. Histopathology of affected dogs shows migration of inflammatory cells into the meninges and inflammation of the meningeal arteries causing stenosis of these vessels. Wide spread arteritis in dogs with SRMA, however, can affect any organ system. The coronary arteries are often
involved in the Beagle, and affected dogs commonly have a combination of myositis, meningitis and polyarthritis.

The combination of immune-mediated polyarthritis and apparent SMRA is more common than suspected. Up to one in three dogs with IMPA also has spinal pain, which may often be due to SMRA. Spinal pain was most commonly demonstrated in the cervical region when the head was flexed or extended. It is recommended that a CSF tap be performed on all dogs suspected IMPA that have concurrent joint and spinal pain.

*Juvenile-Onset Polyarthritis of Akitas*

Juvenile-onset polyarthritis occurs in affected Akitas between 9 weeks and 9 months of age. Affected dogs experience cycles of fever and severely painful and swollen joints that result in a reluctance to stand or walk. Neck and back pain can also be present, as well as mild to moderate lymphadenopathy. Episodes last about 24-48 hours before spontaneously resolving. Joint fluid analysis reveals neutrophilic inflammation. Occasionally, sterile suppurative meningitis is revealed via CSF analysis. Significant laboratory findings may include mild to moderate non-regenerative anemia, neutrophilic leukocytosis, mild hypoalbuminemia and mild hyperglobulinemia. Pedigree analysis in affected Akitas suggests that the disease is inherited. Akitas that exhibit characteristic clinical signs should therefore not be breed. Some clinicians believe that the development of this disease and its close association with immunization suggests that juvenile-onset polyarthritis in Akitas may be an immune-mediated response triggered by viral antigens or other components of vaccines. Others believe the apparent association with vaccination is coincidental, and that the disease naturally arises during the age when multiple booster vaccines are required.

*Familial Chinese Shar-Pei Fever*

Familial Chinese Shar-Pei fever is an inherited autoinflammatory disease characterized by unexplained, recurring attacks of inflammation that seem to be triggered by stress. Symptoms consist of waxing and waning 24-36 hour episodes of high fever usually starting before 18 months of age, although adult onset attacks are not uncommon. Of those affected Shar-Peis that experience fever, approximately half have concurrent ‘swollen hock syndrome’. Swollen hock syndrome is characterized by periarticular swelling due to cellulitis with or without inflammation in the joint itself. Although several joints can be affected, most cases involve the tibio-tarsal joint. Occasionally, the muzzles of affected dogs may be warm, swollen and painful. Other physical symptoms may include mild vomiting or diarrhea, abdominal pain and signs of back, joint or pleural pain. Complete blood count and blood chemistry results may reveal leukocytosis with a left shift and an elevation of alkaline phosphatase.

Dogs affected with familial Shar-Pei fever have abnormally high resting levels of interleukin-6. Interleukin-6 is a pro-inflammatory cytokine that stimulates the liver to make acute phase proteins and the hypothalamus to increase the body’s core temperature. Many Shar-Peis that have intermittent fever episodes eventually develop amyloidosis, although amyloid accumulation can occur without clinical evidence of fever, and fever can occur without the development of clinically significant amyloidosis. Dogs that develop amyloidosis often die of protein-losing nephropathy or renal failure at a mean age of 4 years. Since it has been demonstrated that
familial Shar-Pei fever is compatible with autosomal recessive inheritance, Shar-Peis with cyclic fever should not be breed.

Persistent overwhelming levels of acute phase proteins or an inability to metabolize these proteins leads to accumulation of amyloid in several body organs. In the Shar-Pei, the specific protein that accumulates is amyloid AA, a breakdown product of serum amyloid A. Amyloid AA accumulates primarily in the kidneys, but other organs can be affected, most notably the liver. Diagnosis of amyloidosis is usually based on renal biopsy, although fine needle aspirates of the liver containing amyloid have also been described. Microscopic examination of renal parenchyma tissue stained with Congo Red reveals accumulation of beta pleated sheets of amyloid AA, mostly in the renal medulla. Detecting early renal disease in affected Shar-Peis by monitoring both specific gravity and urine protein concentration is therefore imperative.

**Systemic Lupus Erythematosus**

Systemic lupus erythematosus is a multisystemic immune-mediated disease reported infrequently in the dog. Predisposition to SLE is thought to be inherited. Mixed breed dogs as well as German Shepherds, Shetland Sheepdogs, Beagles, Afghan Hounds, Irish Setters, Old English Sheepdogs, Cocker Spaniels, Collies and Poodles are over represented. Onset of disease typically occurs between 2 to 4 years of age, although older dogs can be affected. Multiple concurrent immunologic reactions can be present in SLE patients, including type III (antigen-antibody complex mediated), type II (antibody directed against cellular self antigens including nuclear material, red blood cells, white blood cells and platelets) and, to a lesser degree, type IV (cell mediated activity against self antigen) hypersensitivities.

Clinical findings can be separated in two main categories (major signs and minor signs) based on their importance in contributing to the diagnosis of SLE. **Major signs** include polyarthritis, glomerulonephritis, hemolytic anemia, leukopenia, thrombocytopenia, characteristic skin lesions and polymyositis. **Minor signs** include fever, central nervous signs, oral ulcerations, lymphadenopathy, pericarditis and pleuritis. Non-erosive polyarthritis is the most frequent primary sign of SLE in dogs, and about 80% of canine SLE patients have polyarthritis. Consequently, the resultant shifting leg lameness is the most common finding on physical examination of dogs diagnosed with SLE.

**Major Presenting Complaints and Clinical Signs**

Immune-mediated polyarthritis can cause non-specific systemic signs such as weight loss, inappetance, lethargy and reluctance to move. Owners may or may not report more specific clinical signs such as swollen joints, altered gait or lameness. Vomiting and diarrhea may also be mentioned in the recent history. 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 these joints. Neck and back pain may also be present if vertebral articular facets are involved or if meningitis is present. Clinicians should be aware that dogs with IMPA commonly present with no obvious joint swelling or localizable pain. IMPA has been reported as one of the most common causes of fever of unknown origin in dogs.
**Diagnostics and Differential Diagnoses**

Ultimately, immune-mediated polyarthritis is diagnosed by arthrocentesis and synovial fluid analysis. Further diagnostic testing is necessary, however, to determine if 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, however, are more likely to affect a single joint versus the multiple joints typically affected in dogs with IMPA.

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. Common CBC and blood chemistry findings noted in dogs with IMPA include leukocytosis, mild non-regenerative anemia and mild hypoalbuminemia. A mild to moderate elevation in serum alkaline phosphatase of as yet undetermined cause is also common. A positive urine culture can help to 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, or to rule out other possible causes of joint disease. The hocks, carpi and stifles are the most commonly affected joints in dogs with IMPA, while more proximal and larger joints are more likely to be involved in patients with infectious arthritis.

Rheumatoid factor is an autoantibody with specificity for the constant region (Fc) portion of an immunoglobulin molecule. Many infectious and inflammatory diseases can be associated with the presence of rheumatoid factor in the serum, including infectious arthritis and osteoarthritis. Testing for rheumatoid factor is indicated if bilateral symmetrical, erosive changes are present in joint radiographs, especially if distal joints are affected. A positive test would support 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.

Systemic infectious diseases can lead to reactive immune-mediated polyarthritis. If the patient has lived in or visited areas in which such diseases are endemic, appropriate testing should be performed. Such diseases would include Lyme disease, Bartonellosis, Ehrlichiosis, anaplasmosis and Rocky Mountain spotted fever. Paired antibody titers, polymerase chain reaction testing and specific *Bartonella* 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. Many cases of bacterial infective arthritis with no history of a surgical procedure or penetrating wound at the affected joint have evidence of pre-existing osteoarthritis. Most bacteria cultured from infected joints are skin commensals, including *Staphylococcus* and *Streptococcus* species. The elbow is the most common joint affected, followed by the hip, stifle and hock joints. Other bacteria that have been reported to cause septic
arthritis and may require special culture techniques include Mycoplasma species and L-form bacteria. 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. Culturing bacteria from blood can be insensitive. Further testing for organisms such as Bartonella, Aspergillus and Mycobacterium should be considered if infective endocarditis is suspected despite negative bacterial blood cultures. Uncommonly, cytology of synovial fluid may also help confirm septic arthritis by revealing the presence of infectious agents such as Mycoplasma species, Borrelia burgdorferi spirochetes, Ehrlichia ewingii and Anaplasma phagocytophilum morulae in neutrophils, Leishmania amastigotes within macrophages or fungal hyphae.

Non-immune joint diseases diagnosed by synovial fluid analysis include synovial neoplasia and hemophilic arthropathies. However, 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.

Further diagnostic testing depends on history, clinical signs and suspected underlying diseases. Cerebrospinal fluid analysis, including IgA levels, should be considered if neck pain is noted and steroid responsive meningitis-arteritis (SRMA) is suspected. If muscle pain is present or creatine kinase is elevated and polyarthritis/polymyositis is suspected, muscle biopsies should be obtained. Lastly, 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 if 2 major signs and a positive anti-nuclear antibody (ANA) titer are identified, or if 2 minor signs and 1 major sign are identified along with a positive ANA titer. A probable diagnosis of SLE can be made if 2 major signs are present with a negative ANA titer. 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. Positive ANA titers can also be detected with infectious, inflammatory or neoplastic disorders. Therefore, clinicians should only run ANA titers when a multi-systemic immune disorder is strongly suspected. The lupus erythematosus (LE) cell preparation test is much less specific for SLE. This test identifies opsonized nuclear material within neutrophils and macrophages. Documenting the presence of other major signs besides polyarthritis may lead to looking for anti-platelet 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.

**Arthrocentesis and Synovial Fluid Analysis**

The diagnosis of IMPA is confirmed by demonstrating neutrophilic inflammation in the synovial fluid of multiple joints. Immune-mediated polyarthritis is classically considered to be a ‘polyarthropathy’, suggesting that 5 or more joints are involved. However, many cases of canine IMPA may involve fewer than 5 joints, and could therefore be more strictly defined as
‘oligoarthritis’ (involvement of 2-4 joints). Rarely, immune-mediated monoarthritis involving only one joint has been reported. 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.

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. Aspiration of at least one larger and more proximal joint, such as the stifle joint, is also recommended. Shaving hair over or taking radiographs of joints 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 a sterile technique. A 25 or 22 gauge needle of sufficient length to enter the joint cavity should be used: a needle as short as 1/2 inch will suffice for smaller joints such as the carpus or hock, a 1 to 1½ inch needle is typically sufficient for the stifle, elbow and shoulder, and a needle as long as 2 inches may be needed to access the hip joint in big dogs. A 3 cc 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. While in the ideal position, palpation helps to further identify the best route to take 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 fluid can take time to enter the syringe, patient observation of the hub of the needle is required before making the decision to redirect and try again if no fluid appears. In the smaller joints of normal dogs, less than 0.25 mls of joint fluid is obtained during arthrocentesis: if greater than 0.5 mls is collected, the joint is considered likely to be diseased.

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, whereas 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 EDTA tube to avoid 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.

Hyaluronic acid is responsible for maintaining the viscosity of joint fluid and coating the synovium. The presence of inflammatory cells or bacteria in the joint can lead to degradation of hyaluronic acid by leukocyte proteases or bacterial hyaluronidases. Hyaluronic acid can also be diluted by an influx of plasma if the joint vasculature is more permeable due to inflammation. To evaluate the viscosity of joint fluid, clinicians can use the subjective ‘string test’ or the laboratory mucin clot test. 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 approximately 1 inch. Alternatively, a drop of synovial fluid can be allowed to fall from the end of the aspiration needle, and should produce a string of similar length before
breaking. Although a decrease in fluid viscosity is typically expected in inflamed or infected joint fluid, only about one half of all joint samples taken from dogs diagnosed with IMPA has a gross reduction in viscosity.

Ideally, a sufficient amount of joint fluid will be collected to make several direct smears with enough volume left over to place in a standard purple 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 1 drop 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 CBC should also be submitted.

Normal canine synovial fluid contains less than 3,000 cells/ml. Greater than 90% of these cells are mononuclear and less than 5% are mature, non-degenerate neutrophils. The majority of mononuclear cells are non-reactive macrophages with few vacuoles. Small lymphocytes are also present in lower numbers and, on occasion, a synoviocyte may seen. In canine immune-mediated polyarthritis, synovial fluid volume is often increased. Fluid obtained may be turbid and/or discolored. It typically has a decreased viscosity, and the protein and nucleated cell content are usually increased, with cell counts often greater than 5000/µl. Fluid from abnormal joints is actually more likely to clot. The percentage of neutrophils is usually increased to 10-95% of total nucleated cells, and they are typically non-degenerate. 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.

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 degenerative. Consequently, further testing of joint fluid may be needed to distinguish infected from non-infected 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. One canine study demonstrated that inoculating a pediatric blood culture bottle with synovial fluid, incubating for at least 24 hours 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. More recently, real-time broad-based PCR assays have been described that rapidly identify bacteria in synovial fluid, and these methodologies may eventually replace joint fluid culture as a means of identifying joint infection in dogs.

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. Other organisms that may be seen include bacteria within neutrophils, *Borrelia burgdorferi* spirochetes, *Mycoplasma* species, *Leishmania* amastigotes within macrophages, and fungal hyphae or yeast bodies.
**Treatment**

Treatment for polyarthritis should target the underlying cause if applicable, and concurrently address pain and inflammation. The overall goal of therapy is to achieve long term remission with the lowest possible dose of medication, and to prevent recurrence of joint inflammation.

Non-steroidal anti-inflammatory drugs (NSAIDs) can be administered to treat 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. If steroids are indicated for further treatment, NSAIDS should be discontinued for at least 48 hours before glucocorticoids are administered. A longer washout period may be needed depending on the NSAID, or in older or more debilitated dogs. The prostaglandin analogue misoprostol can be added to 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 used as a substitute.

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 doxycycline at 10 mg/kg every 24 hours for 1 month. 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.

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 this 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, beta-lactamase-resistant bactericidal antibiotic until culture and sensitivity results return or until diagnostic test results suggest that a bacterial infection is not present.

Specific treatment protocols have been described for the various manifestations of polyarthritis described previously. Treatment for drug induced polyarthritis, for example, requires discontinuation of the inciting drug and possibly a short tapering course of glucocorticoids. Dogs diagnosed with polyarthritis/polymyositis have been treated with a combination of cyclophosphamide and a tapering dose of prednisone with varying success. Dogs diagnosed with SRMA have been successfully treated with prednisone alone or a combination of prednisone and azathioprine. Juvenile onset polyarthritis in Akita dogs has also been treated with multi-drug protocols including a combination of prednisone and azathioprine, but with a less reliable positive outcome. In dogs with Type II to Type IV idiopathic polyarthritis, joint inflammation will usually resolve when the underlying disease process is successfully identified and treated or removed. Occasionally, however, additional treatment with analgesics and possibly
glucocorticoids will be required. In many cases of Type II (reactive) polyarthritis triggered by infection, immunosuppressive doses of steroids will be contraindicated. Tick borne diseases, however, may benefit from concurrent treatment with doxycycline and a tapering dose of glucocorticoids. Sulfasalazine has been used to treat cases of Type III (enteropathic) arthritis and rheumatoid arthritis associated with gastrointestinal disease, and provides a combination of antibacterial, anti-inflammatory and immunosuppressive properties.

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 glucocorticoids is indicated if symptoms persist after more conservative treatment protocols have failed. Immunosuppressive doses of prednisone, prednisolone or methylprednisone (2-3 mg/kg/day once daily or divided) can be started initially. This dose is administered until there is no cytologic evidence of joint inflammation or the clinical signs of arthritis are no longer present. The dose can then be tapered every 2-3 weeks by 25-30% until the approximate physiologic dose of 0.2-0.3mg/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. 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 include azathioprine, cyclosporine, mycophenolate mofetil and leflunomide. If side effects with glucocorticoids or other immunosuppressive agents are intolerable, monotherapy with leflunomide can also be considered.

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. 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 glucocorticoid is required in conjunction with an immunosuppressive agent. In these cases, the lowest possible doses that maintain clinical remission should be administered. 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.

In cases of canine SLE, immunosuppressive doses of glucocorticoids are the cornerstone of treatment with additional cytotoxic agents added if needed: azathioprine, cyclosporine, cyclophosphamide, and chlorambucil have all been reportedly used by clinicians in refractory SLE patients. The goal of treatment is to achieve complete remission with resolution of clinical signs and a negative ANA titer. After complete remission is attained, medications are tapered gradually over at least 6 months. In addition to more traditional immunosuppressive agents, levamisole may be considered in refractory SLE patients. 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 ACE inhibitors.
Treatment for dogs with Shar-Pei fever focuses on prevention of amyloidosis, decreasing inflammation and relieving episodic clinical signs of fever. The mainstay of prevention of amyloidosis is colchicine. Colchicine impairs the release of serum amyloid A from the liver by binding to hepatocyte microtubules and preventing amyloid secretion. Although colchicine is unable to reverse renal disease that has already occurred, the drug has been shown to decrease proteinuria in dogs with renal amyloidosis, slow disease progression and decrease the number or fever episodes. Colchicine should be started in any Shar-Pei with cyclic fevers since up to 30% of these dogs may develop life threatening renal amyloidosis. A wide range of antioxidant, dietary supplements and anti-inflammatory medications have been suggested for use in Shar-Peis with clinical fevers including omega 3 fatty acids, methylsulfonylmethane (MSM), vitamin C, vitamin K2, vitamin E and selenium, curcumin with bioperine, alpha-lipoic acid, boswellia, resveratrol and lecithin. In addition to these supplements, a high quality, balanced, commercial dog food that contains an adequate level of Vitamin D3 that is low in simple carbohydrates and grains is recommended. Monitoring magnesium and cobalamin levels as well as careful attention to gastrointestinal, skin and thyroid health is also paramount. The use of NSAIDs such as dipyrone and meloxicam has been described to control fever in dogs with temperatures over 105°F. Protein-losing nephropathy in dogs with familial Shar-Pei fever is treated with angiotensin-converting enzyme (ACE) inhibitors, a renal diet and low-dose aspirin to help prevent thromboembolic disease.

Erosive arthritis in dogs is more refractory to treatment and may require life long therapy. Since Mycoplasma has been found in the joints of some Greyhounds with erosive arthritis, a trial therapy using an antibiotic effective against this organism (such as tylosin) should be administered before considering immunosuppressive therapy. 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 only rheumatoid arthritis, glucocorticoids are used as the first line of defense, and are frequently combined with additional medications referred to as disease-modifying anti-rheumatic drugs (DMARDs). Depending on 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. In addition to immunosuppressive drug therapy, splenectomy is often the last resort treatment of Felty’s syndrome (characterized by rheumatoid arthritis, neutropenia and splenomegaly). Splenectomy is based on the presumption that the spleen is the site of immune-mediated neutrophil destruction.

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 since long-term management should encourage 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.

In dogs with apparently non-erosive 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. Intra-articular injection of glucocorticoids such as triamcinolone or methylprednisolone has also been suggested as a means of controlling local inflammation.

Monitoring Response to Therapy

Swelling and pain associated with immune-mediated polyarthritis often respond to glucocorticoids, or a combination of glucocorticoids and other immunosuppressive agents, within 7 days of commencing therapy. Since significant joint inflammation may still be present despite resolution of clinical signs, the gold standard for monitoring response to therapy would be to repeat arthrocentesis before the first tapering of medication to ensure that the patient is in true remission. Documentation of a substantial decrease in total white cell count 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.

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 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 C-reactive protein in response to inflammation, and subsequent short circulating half-life, make the protein a good biologic marker of progression for many inflammatory diseases. Serum C-reactive protein is significantly elevated prior to treatment in dogs with IMPA, and also when the disease is active during relapse. The prognosis for long term remission appears to be better in those dogs with various forms of idiopathic polyarthritis in which C-reactive protein concentrations normalize rapidly after starting glucocorticoids.

Prognosis

Erosive arthritis in dogs is associated with a poor long-term prognosis. In most cases, multi-drug 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.

In contrast, the prognosis for most forms of non-erosive polyarthritis in dogs is fair to good. The
prognosis in dogs with idiopathic polyarthritis depends on the sub-type. In dogs with types II to IV, the prognosis is good and relapse is unlikely if the underlying disease can be identified and resolved. Outcomes in dogs with Type I (uncomplicated) idiopathic polyarthritis are also generally favorable. The prognosis for dogs with vaccine- and drug-induced IMPA is also excellent. Recovery times are usually relatively short, and relapse is unlikely. Akitas with vaccine-induced IMPA, however, are reported to typically require more intense initial therapy compared to most other dog breeds and are less likely to respond to treatment. Polyarthritis/polymyositis can also be challenging to treat. Most dogs with steroid responsive meningitis arteritis respond to immunosuppressive therapy, although relapses are possible. Older SRMA patients with high CSF IgA levels tend to experience more frequent relapses and require a longer duration of therapy, whereas Boxers tend to have an excellent clinical outcome. Akitas that develop juvenile-onset polyarthritis have a guarded prognosis. Break-through symptoms are common, even on multi-drug protocols combining prednisone and azathioprine. However, some Akitas recover after tapering of immunosuppressive drugs, and do not relapse. Prognosis for dogs with familial Shar-Pei fever that have already developed significant amyloidosis is guarded. Many die from kidney or liver failure at a median age of 4 years. However, if amyloidosis is prevented or controlled, particularly with colchicine, dogs with Shar-Pei fever have anecdotally been reported to live for over 10 years. Prognosis in dogs with SLE varies, with 40% of patients being dead within one year and more than 50% achieving long-term survival. 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, initial response to therapy is less evident or relapses occur frequently.