Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is an immune-mediated, multisystemic disorder that has been reported occasionally in dogs, humans, rats, mice, and rarely cats. The disease has been studied in dogs as the animal model for SLE in humans. It has been considered “the great imitator” of many different diseases, involving multiple organ systems and presenting in a variety of ways with diverse clinical signs. This can make the disease a great diagnostic challenge. The pathogenesis of SLE is unknown, although a few theories have been implicated in the loss of self-tolerance and abnormal immune activation. These theories include hyperactivity of the B lymphocyte immune system resulting in abnormalities of T lymphocyte regulation; T suppressor lymphocyte hyporeactivity; complement pathway dysregulation; antigen-complement-antibody clearance dysregulation; genetic differences in the human leukocyte antigen (HLA) region (major histocompatibility complex-type proteins of the cell surface) of the genome; congenital complement deficiencies; and drug induction. The underlying pathologic condition of SLE is related to the presence of either excessive circulating antigen–antibody complexes (type III hypersensitivity; immunoglobulin [Ig] A, IgM, or C3) or antibodies directed toward self-antigen (type II hypersensitivity). Type IV hypersensitivity, in which cell-mediated activity is directed against self-antigen, may also be involved.

Triggers are considered multifactorial and include environmental (ultraviolet light), genetic, infectious (leishmaniasis, bartonellosis, ehrlichiosis, anaplasmosis, FeLV, FIV, FIP, etc.) and drug-related (propylthiouracil, hydralazine, procarcinamide, quinidine, heparin sulfate, to name a few) factors. The lesions caused by the circulating complexes are not organ specific and lead to the deposition of complexes on the basement membrane of vessels and organs, leading to inflammation of various regions of the body; examples include vasculitis, glomerulonephritis, synovitis, myositis, serositis, and dermatitis. The immune complexes can diffuse into the endothelial lining and cause a complement-mediated perivascular inflammatory reaction, inciting inflammatory mediators and resulting in chemotaxis, increased vascular permeability, and diapedesis. Lupus can be fulminant or exhibit an insidious pattern in which acute flare-ups and remissions occur. The presence of antinuclear antibodies (ANA) directed against nuclear material (DNA, RNA, nucleoproteins, and histone proteins) is the most common feature of this disease; in dogs, 61% to 74% of detectable ANA titers are positive to the histone proteins. The 1982 revised American College of Rheumatology diagnostic criteria for humans were adapted for the basis of a definitive diagnosis in small animal patients. Controversy remains regarding the definition and criteria for a diagnosis of SLE. Immunosuppression is vital to controlling this abnormal immune response, and several therapies have been implemented.

Diagnostic Criteria

Historical Information

Gender Predisposition: No sex predilection has been reported in animals; in humans, SLE occurs more often in women.

Age Predisposition
• Dogs: Young adults.
• Cats: Generally younger than 5 years (range, 1–11 years).

Breed Predisposition
• Dogs: German shepherds, Shetland sheepdogs, old English sheepdogs, Irish setters, beagles, collies, poodles, Afghan hounds, cocker spaniels, and mixed-breed dogs are overrepresented.
• Cats: Persians, Siamese, and Himalayans are overrepresented.

Owner Observations
• Fever.
• Shifting-limb lameness.
• Mucocutaneous skin lesions, crusting, alopecia, erythema, scaling, seborrhea, vesicular ulcerative dermatosis (bullous SLE).
• Polyuria, polydipsia.
• Cyclic relapse and remission.
Nonspecific complaints (e.g., lethargy, anorexia, weakness).

Neurologic signs.

Icterus.

Other Historical Considerations/Predispositions:

- Drug administration (see box, above).
- Infection: Leishmaniasis, bartonellosis, ehrlichiosis, FeLV, FIV, FIP.
- SLE-affected owners.
- Cholangitis, cholangiohepatitis.
- Genetic (human).

Physical Examination Findings

- Polyarthropathy: Shifting-limb lameness is the most common clinical sign (more than two swollen or painful joints).
- Skin lesions: Mucocutaneous; symmetric, nonpruritic, multifocal crusting; alopecia; erythema; scaling; seborrhea; oozing of the face, pinnae, ears, neck, ventrum, distal limbs, footpads; vesicles; bullae; erosions.
- Persistent or recurring fever.
- Ocular lesions: Uveitis, chorioretinitis.
- Icterus: Secondary to an immune-mediated hemolytic anemia or hepatic dysfunction.
- Lingual, palatine, oral ulcerations.
- Lymphadenopathy, splenomegaly.
- Possibly myalgia in patients with polymyositis.

Laboratory Findings

Laboratory findings in animals with SLE are highly variable; some patients present with many abnormalities, while other have minimal abnormal results.

- Complete blood count: Anemia (regenerative or nonregenerative), thrombocytopenia, leukopenia, spherocytosis.
- Serum biochemical profile: Renal or prerenal azotemia (glomerulonephritis may be present even if no azotemia is identified), hypoalbuminemia (vasculitis, proteinuria), hyperglobulinemia (polyclonal gammopathy; possibly hyperbilarubinemia in patients with hemolytic anemia or hepatobiliary disease); elevated creatine kinase and aspartate aminotransferase levels (myositis of the masticatory muscles, myocarditis, polymyositis).
- ANA: Immunofluorescent assay (IgG) positive (>1:40; more suggestive if >1:256) in more than 90% of SLE cases.
- Urinalysis: Proteinuria, isosthenuria; casts may be seen if renal azotemia or an underlying urinary tract infection is present.
- Urine protein:creatinine ratio: >0.5 (often >3.0) mg/dl in patients with glomerulonephritis.
- Coombs’ test: Positive result if associated with immune-mediated hemolytic anemia.
- Coagulation panel: Elevated activated partial thromboplastin time and prothrombin time have been reported (rare).

Other Diagnostic Findings

- Joint radiography: Usually nonerosive effusion in one or multiple joints.
- Lupus erythematosus (LE) cell preparation: Highly specific for SLE; time consuming and less sensitive than ANA test.
- Identifies opsonized nuclear material within neutrophils and macrophages.
- Thoracic radiography: Pericardial effusion or pleural effusion (rare); used to rule out neoplasia as a cause for secondary immune-mediated disease.
- Skin biopsy: Histopathology: Orthokeratotic hyperkeratosis in the epidermis and perivascular lymphoplasmacytic infiltration of the superficial dermis; interface dermatitis and folliculitis with infiltration of lymphocytes, plasma cells, and neutrophils; pigmentary incontinence; peridermal basal cell vacuolation with occasional necrosis.
- Immunohistochemistry: IgM deposition at dermal–epidermal junction; IgM and C3 deposition can be found in both lesional and normal skin.
### Diagnostic Differentials

- **Rheumatoid arthritis**: Confirmed with joint radiographs ± rheumatoid factor assay.
- **FeLV, FIV, FIP, Bartonella vinsonii subsp. berkhoii, Ehrlichia canis, Leishmania infantum, Anaplasma phagocytophila**: Diagnosed via serologic evaluation.
- **Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia**: Diagnosed via a Coombs’ test, presence of autoagglutination, and bone marrow aspiration.
- **Primary bone marrow disease**: Diagnosed via bone marrow aspiration and/or biopsy.
- **Bacterial endocarditis**: Diagnosed via blood cultures and echocardiographic evidence of a vegetative valvular lesion. This can be an occult cause for other immune-mediated diseases.
- **Immune-mediated polyarthritis, steroid-responsive meningitis, artetitis, polymyositis**: Diagnosed via joint taps, joint radiography, cerebrospinal fluid tap, muscle biopsies.
- **Idiopathic megaesophagus** (dogs): Diagnosed by exclusion; rule out hypoadrenocorticism, myasthenia gravis, lead toxicity.
- **Cholangitis, cholangiohepatitis** (cats): Diagnosed via liver biopsy.
- **Septic arthritis**: Diagnosed via joint culture ± cytologic evaluation.
- **Protein-losing nephropathy, including amyloidosis or glomerulonephritis** (idiopathic or secondary to...)

#### Summary of Diagnostic Criteria

- **Polyarthropathy; sterile suppurative inflammation**.
- **Glomerulonephritis (proteinuria ± renal azotemia)**.
- **Positive ANA titer (>1:40)**.
- **Dermatitis**: Alopecia, erythema, scaling, and crusting.
- **Immune-mediated anemia, leukopenia, thrombocytopenia**.
- A diagnosis of SLE can be made based on a scheme of major and minor clinical signs (see box above) or the American College of Rheumatology scheme (see box on page 10).
  - **Definite SLE**: Positive serology in conjunction with two major signs or one major sign and two minor signs.
  - **Probable SLE**: One major sign with positive serology, two major signs with negative serology; three criteria from American College of Rheumatology scheme; or immune-mediated polyarthritis (IMPA) and a positive ANA test.

**ON THE NEWS FRONT**

- The relative risk ratio for SLE development among pet dogs owned by human patients with SLE was near infinity compared with pet dogs owned by non-SLE households. The prevalence of SLE among pet dogs of SLE human patients was estimated as 508 per 10,000. This raises the question of whether a common environmental factor or zoonotic agent may be involved in the development of human and canine SLE.
- Of dogs with positive antibody titers to *Bartonella vinsonii* subspec. *berkhoii* or *Ehrlichia canis*, 11.1% are ANA positive; of dogs with positive titers to *Leishmania infantum*, 20% are ANA positive.
infectious diseases), neoplasia, or other inflammatory diseases (e.g., inflammatory bowel disease, cutaneous pyoderma, chronic hepatitis).

**TREATMENT RECOMMENDATIONS**

**Patients Requiring Emergency Stabilization**

- Patients in shock: IV fluid crystalloid therapy (dogs, 90 ml/kg; cats, 50 ml/kg) given in one-quarter boluses over 20 to 30 minutes.
- Hypoproteinemia: Colloidal support (hetastarch, 20 ml/kg/d IV) should be considered.
- Hemolytic crisis:
  - Packed erythrocytes: 10–20 ml/kg given over 3 to 4 hours.
  - Hemoglobin-based oxygen-carrying products: 5–30 ml/kg; current recommendation is to start with 5–10 ml/kg given slowly and then to assess improvement. Caution should be taken to avoid fluid overload when administering to cats; 5 ml/kg total dose at a rate 5 ml/hr is recommended.
- Coagulopathy/disseminated intravascular coagulation: Fresh-frozen plasma, 10–20 ml/kg IV over 2 to 4 hours.
- Respiratory difficulty due to pleural effusion/acute respiratory distress syndrome: Supplemental oxygen support and evaluation of pleural fluid via thoracentesis (thrombocytopenic patients are at risk of hemorrhage if platelet count <30,000).
- Acute hypertensive crisis due to severe glomerulonephritis ± renal failure:
  - Amlodipine: Dogs, 0.2–0.4 mg/kg/day PO or per rectum; cats, 0.625 mg PO once daily.
  - Benazepril or enalapril: 0.25–0.5 mg/kg PO q12–24h. However, angiotensin-converting enzyme inhibitors are unlikely to lower blood pressure significantly.
  - Hydralazine: Dogs, 0.5–2 mg/kg PO bid–tid; cats, 2.5 mg PO bid.
  - Nitroprusside if systolic pressure exceeds 200 mm Hg:
    - Dogs: 1–2 µg/kg/min IV; dosage should be increased q3–5min until a predicted target blood pressure is obtained.
    - Cats: 0.5 µg/kg/min IV; dosage should be increased q3–5min until a predicted target blood pressure is obtained.
  - Ideally, the goal is to reduce blood pressure by 25% over a 4-hour period to allow re-adaptation of cerebral blood flow.
  - Direct arterial blood pressure is required for accurate assessment.
- Thromboembolic disease or tendency: Heparin therapy (high- or low-molecular-weight therapy) may be considered for patients at increased risk for embolic crisis but should be evaluated in light of patient’s systemic inflammation and corticosteroid therapy used.

**Standard Treatment**

- Prednisone or prednisolone:
  - Dogs: 1.0–2.0 mg/kg PO bid for 14 days or longer until clinical improvement is seen; the dosage should then be slowly tapered over 6 months to 0.25–0.5 mg/kg every other day. Some patients will be able to be tapered off steroids completely.
  - Cats: 2–4 mg/kg PO bid for 14 days; the dosage should then be slowly tapered over 6 months to 0.5 mg/kg every other day or discontinued if possible.
  - If relapse occurs during the tapering phase, the dosage should be increased to an effective remission dosage and maintained there until clinical remission is achieved for 2 to 4 weeks. Tapering can then be reinitiated at a slower pace.

**AMERICAN COLLEGE OF RHEUMATOLOGY SCHEME (1982)**

Patient must meet four of 11 criteria to be diagnosed as having SLE:

- **Erythema:** Redness of skin (face most common)
- **Discoid rash:** Depigmentation, erythema, erosions, ulcerations, crusts, and scaling affecting the face
- **Photosensitivity:** Unusual reaction to sunlight
- **Oral ulceration:** Oral or nasopharyngeal ulcerations
- **Polyarthritis:** Nonerosive arthritis involving two or more joints, usually with associated pain, swelling, or effusion (usually not very marked)
- **Serositis:** Nonseptic inflammatory cavity effusion (pleuritis, pericarditis)
- **Renal disorders:** Persistent proteinuria (>0.5 mg/dl) or cellular casts (erythrocyte, hemoglobin, granular, tubular, or mixed)
- **Neurologic disorders:** Seizures or psychosis in the absence of offending drugs or known metabolic disorders (uremia, hepatic encephalopathy, ketoacidosis, electrolyte imbalances)
- **Hematologic disorders:** Hemolytic anemia (with reticulocytosis) or leukopenia, lymphopenia, or thrombocytopenia (<100,000/mm³)
- **Immunologic disorders:** Antihistone or anti–Sm nuclear antigen, anti-type 1 or T-cell subsets, or CD4:CD8 ration >4.0
- **ANAs:** By immunofluorescent assay

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  - If relapse occurs during the tapering phase, the dosage should be increased to an effective remission dosage and maintained there until clinical remission is achieved for 2 to 4 weeks. Tapering can then be reinitiated at a slower pace.
• If no clinical improvement is seen with prednisone in 7 to 10 days:
  — Azathioprine (2 mg/kg PO once daily for 14 days, then every other day for 28 days, and finally 1 mg/kg every other day) can be used in dogs (not recommended for use in cats because of bone marrow toxicity). Azathioprine also allows a lower dosage of prednisone to be used when side effects are unacceptable. $$
  — Chlorambucil (0.25–0.5 mg/kg PO q24–48h, although dosages vary throughout the literature). $$$

• If severe dehydration or fever occurs, IV fluid therapy (crystalloids if colloid oncotic pressure is normal) should be considered: 40–60 ml/kg/d IV (maintenance rate) plus enough to correct estimated percentage of dehydration and ongoing losses.

**Alternative/Optional Treatments/Therapy**

The following options should be considered when routine drug therapy is not effective, or well tolerated, in individual animals.

• Cyclophosphamide: 50 mg/m² PO every other day or once daily 4 days/wk (use is controversial). $$
• Levamisole: 3–7 mg/kg PO every other day for 4 months (maximum dose, 150 mg/d). Best if used with prednisone at 0.5–1.0 mg/kg bid. $$$
• Splenectomy for refractory cases of immune-mediated hemolytic anemia and immune-mediated thrombocytopenia. $$$
• Plasmapheresis to remove IgG and immune complexes of IgG, IgM, and IgA from circulating plasma. $$$
• Gene therapy using a nonviral peptide vector (experimental). $$
• Chrysotherapy. $
• Other: Dapsone, colchicine, omega-3 or -6 fatty acids, cyclosporine, pentoxifylline. $
• Selective immunotherapy (currently being developed).

**Supportive Treatment**

• Glomerulonephritis: Angiotensin-converting enzyme inhibitors (enalapril or benazepril, 0.25–0.5 mg/kg once or twice daily), low-protein diet ± low-dose aspirin, omega-3 fatty acid therapy.
• Refractory thrombocytopenia: Vincristine (0.01–0.025 mg/kg IV once/wk as needed). Variable doses described in the literature; this is my (AB) recommendation.
• Associated organ failure should be treated.
• Bacterial infections should be avoided and identified infectious agents treated aggressively; because of their immune deficiency, dogs with SLE are prone to infection.

**CHECKPOINT**

Reported prognosis varies from 40% of patients being dead within 1 year to more than 50% of patients achieving long-term survival.

• Pain management.

**Patient Monitoring**

• Complete blood count, chemistry panel, and urinalysis should be conducted monthly until remission is achieved, then every 3 months for 1 year and every 6 months thereafter. Changes in packed-cell volume, platelet counts, hepatic enzyme activities, electrolyte status, and renal parameters are particularly important. Complete blood counts should be monitored more frequently if patient is on immunosuppressive therapy with the potential for bone marrow suppression (i.e., azathioprine, chlorambucil, cyclophosphamide, cyclosporine, colchicine, and levamisole).
• ANA should be evaluated monthly until negative, then every 3 months for 1 year and every 6 months thereafter.
• Urine protein:creatinine ratio should be checked at 2 weeks and then monthly until normal and every 3 to 6 months thereafter.
• Serial blood pressure evaluations are indicated for patients with evidence of glomerulonephritis: Weekly until normal, then every 2 weeks for 1 month and monthly thereafter.
• Joint taps should be used to confirm remission after clinical signs resolve.
• Patient should be monitored for resolution of skin lesions.

**Home Management**

• Exposure to ultraviolet light should be avoided in animals with skin lesions.
• Water should be freely available for animals with protein-losing nephropathies and those receiving prednisone/prednisolone therapy because of the common side effects of polyuria and polydipsia, as well as polyphagia, alopecia, calcinosis cutis, and the like.

**Milestones/Recovery Time Frames**

• Regression of ANA titers within 2 to 4 weeks; negative titers are often seen within the first 2 to 3 months of therapy.
• Serum complement activity measurement of regression within the first 4 weeks of therapy.
• Quick clinical recovery: Clinical improvement appreciated within 3 to 7 days of starting therapy.
**Treatment Contraindications**
- NSAIDs in association with steroid therapy. The combination of therapies can cause severe complications, such as gastroduodenal ulceration and renal papillary necrosis.
- Use of immunosuppressive drugs in the face of active infection may be contraindicated, necessitating the ruling out of infectious causes of the clinical signs before initiating therapy.

**PROGNOSIS**

**Favorable Criteria**
- Animals that respond to glucocorticoid therapy alone.
- Early diagnosis and commencement of therapy.
- Return of negative ANA titer.
- Resolution of clinical signs.
- Increase in the CD8:CD4 ratio.
- Cats usually respond to therapy better than dogs and may respond better to prednisolone than prednisone.

**Unfavorable Criteria**
- Renal failure or involvement; proteinuria.
- Poor response to therapy or frequent relapses during appropriate tapering of therapy.
- Bronchopneumonia.
- Septicemia.
- Organ failure with infection.

**RECOMMENDED READING**


