Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder that poses a challenge to the emergency physician with its protean and occasionally dangerous manifestations. Morbidity for SLE patients is typically mediated through organ inflammation and destruction or the consequences of therapeutic immunosuppression. Further complicating lupus is the frequent association with the antiphospholipid syndrome (APS) and its corresponding venous and arterial thromboses. The diagnostic criteria reflective of its complexity and immunologic basis were first described in 1971. Today, the emergency department (ED) is a common venue for the evaluation and treatment of patients suffering from SLE.

Epidemiology
SLE is present in 20 to 70 per 100,000 of the general population. Although great variation in incidence exists worldwide, it is clear that two groups have consistently higher incidences: women, representing 90% of cases; and African Americans. Dramatic rises in incidence of SLE have been described during the past several decades, but it is suspected that this may be due to the implementation of more sensitive diagnostic criteria.

Principles of Disease
The exact etiology of SLE is not understood. It is likely to be related to multiple factors; genetics, environmental factors, race, hormones, medications, and immunology have all been implicated to varying degrees.

With women representing 90% of SLE cases, a strong role for estrogen in disease development has been well supported in large cohort studies. The disease also has a strong genetic link, with high rates of monozygotic twin concordance and tremendous genetic overlap at the human leukocyte antigen (HLA) alleles.

Anatomy and Physiology
SLE may cause disease in nearly any organ system in the body through inappropriate immune response to self and is often described as the prototype of all systemic, autoimmune disorders. Like its cause, its exact pathophysiologic mechanism is not completely elucidated. When a cell cycle ends (apoptosis), intracellular contents, including DNA-rich nucleosomes, are released into the bloodstream. For patients with SLE, this cellular debris may be regarded as nonself (i.e., an antigen) by the immune system. After exposure to these self antigens, the familiar immunologic cascade of antigen-presenting cells, T cells, and ultimately B cells and their plasma cell progeny is exacted, and patients form autoantibodies against their own cellular contents. These autoantibodies (which include anti–double-stranded DNA antibody, a commonly ordered rheumatologic assay in evaluation for SLE) may then mediate organ-specific disease and inflammation. This may occur through either direct attack and injury to parenchymal tissue or other mechanisms, such as formation of immune complexes that are deposited in tissue. On the basis of this immunologic understanding of the pathogenesis of SLE, the rationale for immunosuppression as both chronic and acute therapy for SLE can be appreciated.

The pathophysiologic mechanism of SLE may be different for each organ system. Indeed, the organ systems involved in any given patient’s disease may be different and may relate to the underlying presence or absence of antigens that resemble tissue from that organ system.

Clinical Features
In general, there are four broad presentations for a patient with SLE: symptoms related to SLE that is not yet diagnosed (e.g., idiopathic pericarditis, new rash); progression or acute deterioration due to known SLE (e.g., progressive nephritis, lupus enteritis); complications of immunosuppression from treatment of SLE (e.g., opportunistic infection); and complaints or disease unrelated to SLE (e.g., trauma, pregnancy).

The Patient with Undiagnosed or Suspected SLE
Although some elements, such as the malar rash, that form the diagnosis of SLE are nearly pathognomonic for SLE, a confident initial diagnosis in the ED may otherwise be rare or difficult. The literature is replete with ED-based case reports of extreme initial presentations with conditions such as Guillain-Barré, cardiac tamponade, and fulminant renal failure that subsequently were confirmed as complications of unrecognized SLE; however, in all cases the diagnosis of SLE was applied retrospectively. Because the workup for SLE is commonly conducted in a series of outpatient visits and relies on laboratory investigations that are uncommonly carried out in the ED, establishment of a new diagnosis of SLE in the ED is difficult. If a new diagnosis of SLE is suspected in an otherwise well patient, referral for an expedited workup is reasonable in most circumstances. The American College of Rheumatology classification criteria for SLE are presented in Table 118-1.
Table 118-1

<table>
<thead>
<tr>
<th>CONDITION*</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>Butterfly-shaped, red rash on the face that spares the nasolabial folds</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging (atrophic scarring may occur in older lesions)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by a physician</td>
</tr>
<tr>
<td>Nonerosive arthritis</td>
<td>Two or more peripheral joints, characterized by tenderness, swelling, or effusion</td>
</tr>
<tr>
<td>Serositis</td>
<td>History or clinical evidence of either pericarditis or pleuritis; includes otherwise unexplained pericardial or pleural effusions</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria (&gt;0.5 g/day) or cellular casts (red cell, hemoglobin, granular, tubular, or mixed)</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Otherwise unexplained seizures or psychosis</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Any of: hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Positive serology for any of: anti-DNA antibody, anti-Sm antibody, or antiphospholipid antibody (including antiphospholipid antibodies, lupus anticoagulant, or false-positive serology for syphilis)</td>
</tr>
<tr>
<td>Positive antinuclear antibody</td>
<td>Abnormal antinuclear antibody titer at any time in the absence of medications that may cause drug-induced lupus</td>
</tr>
</tbody>
</table>

*Patients exhibiting at least 4 of the 11 conditions listed here at any point in time meet the criteria for diagnosis of SLE.

Acute Presentations in the Patient with Known SLE

Emergency physicians are commonly faced with evaluating the acute complaints of patients with an established diagnosis of SLE. The workup of SLE-related complications is based on use of a disease-specific differential diagnosis.

SLE Exacerbation

Even with good medication compliance, SLE patients are prone to exacerbations of their disease, typified by worsening physical symptoms from increased organ inflammation and destruction. These exacerbations may involve organs already affected by SLE or new conditions manifested in previously unaffected organ systems. As a systemic disease, worsening symptoms in one organ system should reasonably prompt evaluation for progressive disease activity in other organs. True to the broad scope of SLE, the most accepted scoring system to grade SLE exacerbations accounts for 20 different markers of disease activity across 9 organ systems. Although such scoring systems have little role in the ED, it is important to identify when overall disease activity is increased as it typically signals the need to initiate or to escalate systemic therapy. In many cases, patients themselves are able to provide direction about the predictable course of their exacerbations and can be helpful in decision-making for therapy and disposition.

Specific Symptoms and Presentations

Fever. Improving survival for patients with SLE during the past several decades has been achieved with the use of improved immunosuppressive regimens. As a result, patients with SLE remain commonly affected by infections mediated by both typical and opportunistic organisms, suffering higher than average death rates from these infections. In one case series, infection was the leading reason for SLE patients to be admitted to the intensive care unit, superseding both renal failure and cardiovascular disease. Whereas absence of fever is insufficient in many cases to rule out infection, the presence of a fever is grounds for concern. Fever may also be due to increased overall disease activity. Given the heightened risk for SLE patients with infection, determination that a fever is due strictly to disease exacerbation should be made cautiously. The majority of infections in SLE are due to skin, lung, or urinary sources and are caused by typical organisms. However, largely because of the immunomodulating therapies that form the cornerstone of SLE management, opportunistic diseases are possible; Pneumocystis (carinii) jiroveci pneumonia, cryptococcal meningitis, Listeria infection, and herpes zoster have all been described.

Neuropsychiatric Presentations. According to the American College of Rheumatology, there are 19 different clinical manifestations of neuropsychiatric SLE, some of which are included in the diagnostic criteria (see Table 118-1). These 19 different presentations range vastly and include seizures, confusion, cranial neuropathies, demyelinating syndromes, myasthenia gravis, depression, psychosis, and anxiety. It may not be possible in the ED to determine whether such manifestations are due to neuropsychiatric SLE or to other, independent pathologic processes.

Headache. In general, headaches in a patient with SLE may be evaluated in a fashion similar to that for headaches in the general population. In one prospective cohort study, for instance, it was found that primary headache disorders, such as migraine and tension headaches, occur with the same frequency in SLE patients as in the general population. This was further supported by an extensive meta-analysis examining the implications of headache in SLE patients. In this study, the authors found no relationship between headache and SLE disease activity. Thus, despite recommendations to consider headache as suggestive of neuropsychiatric SLE or so-called lupus cerebritis, isolated headaches in the context of lupus may be treated in a fashion typical of other primary headache disorders. When a more malignant cause of headache is suspected, as suggested by meningismus, fever, or focal neurologic findings, an aggressive workup is warranted. When concern exists for an infectious cause of headache, consideration for opportunistic infections, such as cryptococcal meningitis, should be made in an immunosuppressed SLE patient. Further, because of common comorbid APS, consider sinus thrombosis in the SLE patient with new-onset focal central nervous system findings and headache.

Seizure. Because of incompletely understood mechanisms, seizures may occur as result of SLE disease activity. In one large series, seizures were observed in 11% of SLE patients, and in the majority of cases, either stroke or comorbid APS was present. Because of the high incidence of seizures, nonconvulsive status epilepticus is a consideration in SLE patients with an acute onset of altered mental status. The workup and management of seizures do not differ between patients with SLE and the general population.

Focal Neurologic Findings. On occasion, the patient with SLE may present with focal motor weakness. In those with SLE who also have APS, there is a significantly increased risk of stroke related to spontaneous arterial thrombosis. Demyelinating disease, such Guillain-Barré and cranial neuropathies, have also been occasionally attributed to SLE from unclear mechanisms.
Psoriatic Symptoms. Mood disorders, psychosis, and anxiety are considered potential manifestations of neuropsychiatric SLE. Distinguishing SLE-related from functional causes of psychiatric presentations poses a challenge and may not be possible in the ED. Although psychiatric presentations of SLE in the ED have not been directly studied, in the absence of concern for an organic cause of altered mental status, patients with SLE are approached in the same manner as patients without SLE. Corroboration with the patient’s rheumatologist may provide insight to history of similar events or guidance for treatment.

Cardiorespiratory Presentations and Diseases. Chest pain, in the form of either pleuritis or pericarditis, is among the diagnostic criteria for SLE (see Table 118-1). In addition to pericarditis and pleuritis, coronary artery disease (CAD), pulmonary embolism, and musculoskeletal causes are also common. Other forms of cardiac disease that occur without chest pain, such as verrucous (Libman-Sacks) endocarditis and various arrhythmias, may also be present.

Coronary Artery Disease. There is a dramatically increased risk of CAD in the context of SLE. This was demonstrated in a compelling retrospective cohort study of 500 women with lupus compared with age-matched controls from the original Framingham data. In this study, a 52-fold increased risk of myocardial infarction was determined in women between the ages of 35 and 44 years. These findings of increased risk of CAD have been supported by a number of other prospective trials. In one series, patients with SLE were found to have five times as likely to have CAD (based on coronary artery calcium scoring) as patients without SLE. In another series that profiled an even younger subset, it was found that among otherwise low- to moderate-risk women aged 22 to 45 years with complaints of chest pain, dyspnea, or decreased exercise capacity, there was an alarming 82% prevalence of CAD as determined by nuclear imaging. There was a similarly concerning prevalence of 43% of CAD in the asymptomatic “control” group who also had SLE. Further, traditional cardiac risk factors are found less often in patients with SLE who suffer consequences of CAD, suggesting that CAD in patients with SLE cannot be explained by the higher incidence of hypertension or hypercholesterolemia that these patients often exhibit. Thus, whereas there are many considerations for the cause of chest pain in patients with SLE (Table 118-2), CAD must be considered highly, and in fact more highly in patients who would otherwise be deemed to be low risk (young, reproductive age women). It is therefore appropriate to have a low threshold to initiate a workup with electrocardiography, cardiac biomarkers, and stress testing to rule out acute coronary syndromes in patients with chest pain and SLE.

In addition to being at risk for development of CAD, patients with SLE who are treated with percutaneous coronary intervention appear to fare poorly. In one retrospective analysis of 28 patients with SLE receiving percutaneous coronary intervention, reintervention, death, and recurrent myocardial infarction were significantly more likely compared with a similar cohort without SLE. Pericardial Disease. Pericardial effusion and pericarditis occur commonly in patients with SLE. It is estimated that symptomatic pericarditis occurs in 25% of patients with SLE during the course of their lives and that pericardial effusion occurs even more often, frequently in a silent fashion, in up to 50%. In clinically evident SLE-related pericarditis, dyspnea or pleuritic chest pain is common. Typical electrocardiographic findings (Fig. 118-1) have been shown to be present in less than half of cases, however. Given the increased risk of CAD in patients with SLE, ST elevation of any kind found on an electrocardiogram warrants very careful consideration. When diagnostic uncertainty exists, echocardiography, cardiac enzymes, or cardiac catheterization may be complementary. Treatment of pericarditis includes nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, as discussed later.

Pericardial tamponade, because of its dramatic nature, continues to receive attention as an initial presentation of SLE; however, large case series have shown that this life-threatening presentation occurs in less than 1% of patients with lupus. In large effusions without tamponade, medical management with high-dose glucocorticoids (1-2 mg/kg of methylprednisone) has shown favorable outcomes in averting the need for pericardiocentesis.

Pulmonary Embolism. Pulmonary embolism and deep venous thrombosis occur with increased incidence in patients with SLE. This is especially true for patients with SLE who also carry antiphospholipid (aPL) antibodies. These patients have an estimated 20- to 30-fold increased risk for thrombosis compared with the general population. Patients with SLE who do not have aPL antibodies still have a sixfold greater likelihood for development of pulmonary embolism and deep venous thrombosis compared with patients without SLE. Thus, all patients with SLE, regardless of their aPL antibody status, which is often unknown on presentation, should be considered at increased risk for venous thromboembolism.

Pleuritis. Pleuritis, due to autoantibodies acting against the pleura itself, is the most common respiratory condition occurring in SLE. Characterized by pleuritic chest pain with or without a pleural effusion or pleural rub, it has symptoms that overlap with those of other more serious conditions (see Table 118-2). If a pleural effusion is present, analysis of pleural fluid for antinuclear antibodies may be the most accurate method to confirm diagnosis but may be impractical in the ED. A diagnosis of pleuritis should be arrived at only after other causes of pleuritic chest pain in these thrombophilic, immunosuppressed patients have been ruled out.

<table>
<thead>
<tr>
<th>Table 118-2 Chest Pain and SLE in the Emergency Department: Common Causes, Workup, and Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONDITION</td>
</tr>
<tr>
<td>Pleuritis</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Pericarditis</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
</tbody>
</table>

APS, antiphospholipid syndrome; CK-MB, creatine kinase MB fraction; ED, emergency department; NSAIDs, nonsteroidal anti-inflammatory drugs.
Part III - Medicine and Surgery / Section Nine - Immunologic and Inflammatory

Immunologic and Inflammatory Dyspnea. Both anemia of chronic disease and hemolytic anemia are common; hemolytic anemia is more typical in those also carrying aPL antibodies. In cases of severe anemia recognized in the ED, a Coombs test can be diagnostic for immunologic hemolytic anemia. Other less common but noteworthy causes of shortness of breath in a patient with SLE include interstitial lung disease, lupus pneumonitis, diaphragmatic disease (so-called shrinking lung syndrome), and pulmonary hypertension.

Musculoskeletal Presentations. Arthritis commonly afflicts those with SLE, and increasing severity of joint pain may be a marker of increasing disease activity or an SLE flare. Arthritis or arthralgias are typically symmetrical and nonerosive (unlike rheumatoid arthritis) and may involve multiple joints. Arthritis is most commonly present in the hands, wrists, and knees but may be manifested in any joint. Aside from mild tenderness, the joints are often normal to physical examination and rarely experience deformity. Uncommonly, septic arthritis may complicate SLE. In one large retrospective analysis of SLE-related hospitalizations, only 0.3% of admissions were for septic arthritis. Possibly because of immunsuppressant use, including corticosteroids, Salmonella is an unusually frequent culprit organism that was isolated in 59% of cases in one study and most commonly found in the hip. An

Musculoskeletal Chest Pain. Musculoskeletal chest pain, related to underlying pectoral, intercostal muscle, or costochondral joint inflammation, may also occur in SLE. Similar to pleuritis, the threat of a more malicious underlying cause of pain should prompt the clinician first to seek other causes before arriving at this more benign cause. Treatment with NSAIDs or acetaminophen is generally appropriate.

Pneumonia. Pneumonia is the third most common infection in patients with lupus, after skin and urinary tract infections. Choice of antimicrobial coverage is determined by the severity of the infection and the degree of immunosuppression. For patients receiving long-term glucocorticoids or cyclophosphamide, coverage for organisms such as Pseudomonas and Legionella generally requires the use of a carbapenem or a fourth-generation cephalosporin in addition to either a respiratory fluoroquinolone or macrolide. There is no evidence to support the routine coverage for P. jiroveci in these patients.

Undifferentiated Dyspnea. Mitral valve insufficiency due to noninfectious vegetations, known as Libman-Sacks lesions, may cause a patient to experience dyspnea on exertion or, in rare severe cases, pulmonary edema (Fig. 118-2). Anemia, present in up to 50% of patients with SLE, may lead to a chief complaint of dyspnea. Both anemia of chronic disease and hemolytic anemia are common; hemolytic anemia is more typical in those also carrying aPL antibodies. In cases of severe anemia recognized in the ED, a Coombs test can be diagnostic for immunologic hemolytic anemia. Other less common but noteworthy causes of shortness of breath in a patient with SLE include interstitial lung disease, lupus pneumonitis, diaphragmatic disease (so-called shrinking lung syndrome), and pulmonary hypertension.
isolated swollen joint is not typical of SLE and prompts consideration for infectious arthritis. If septic arthritis is suspected, diagnostic arthrocentesis is recommended. Empirical treatment with 1 g of vancomycin and 1 g of ceftriaxone will cover likely organisms, including Salmonella. Myalgias are common in SLE and may be an early marker of increasing disease activity for some patients. Generalized muscle pain is typical, but muscle weakness is uncharacteristic. If muscle weakness is present, an underlying myositis or myopathy secondary to steroid use is considered.

Gastrointestinal Presentations. The most common gastrointestinal manifestation of SLE is oral ulceration, which occurs in nearly a third of patients with SLE. Treatment includes local symptom management (chlorhexidine mouthwashes, viscous lidocaine) combined with systemic therapy (hydroxychloroquine) in more severe or refractory cases. Abdominal pain commonly complicates SLE. The causes of abdominal pain, with the exception of lupus enteritis, are largely similar to those in patients without SLE, such as pancreatitis, gastroenteritis, and peptic ulcer disease. Lupus enteritis (also known as mesenteric vasculitis) typically results in diffuse abdominal pain and is the most common cause of acute abdominal pain in SLE. The abdominal pain itself may also be associated with nausea, vomiting, and nonbloody diarrhea. Laboratory investigations, such as white blood cell count, hemoglobin level, platelet count, and erythrocyte sedimentation rate (ESR), are not helpful as they do not differ significantly between those with enteritis and those with abdominal pain due to other causes. Although no “gold standard” for the diagnosis of lupus enteritis has been established, computed tomography (CT) is the most useful test to assess for this condition. Several CT scan findings are supportive, including bowel wall thickening (Fig. 118-3), engorgement of mesenteric vessels, and increased attenuation of mesenteric fat.

When lupus enteritis is suspected, early pulse steroids, at a dose of 1 to 2 mg/kg of methylprednisolone per day, should be administered. Surgical consultation should be obtained in severe cases or when bowel necrosis has occurred. With aggressive medical therapy, which may also include cyclophosphamide, the need for surgical management is uncommon. Other, less common gastrointestinal illnesses to which SLE patients are predisposed include protein-losing enteropathy and intestinal pseudo-obstruction. Last, in assessing abdomen pain in patients with SLE, clinicians should be mindful of the effects of chronic steroid use and increased risk for both hollow viscus perforation and peptic ulcers, which may occur in the absence of traditional symptoms.

Dermatologic Presentations. The most characteristic cutaneous manifestation of SLE is the malar rash. The rash has a “butterfly” distribution of raised erythema over the bridge of the nose and malar eminences while sparing nose and nasal-labial folds (Fig. 118-4). The other most common skin lesion found in SLE is the discoid rash. Discoid lesions are circular and raised, scaly lesions that may be commonly found on the face, scalp, and ears, often in association with pigment change, alopecia, and severe scarring (Fig. 118-5). Cutaneous lupus may exist in isolation without systemic involvement. Mild cases of worsening cutaneous lupus are treated topically with 1% hydrocortisone cream. Moderate to severe cases are treated with topical calcineurin inhibitors or even systemic therapy (e.g., hydroxychloroquine) in consultation with the patient’s internist or rheumatologist. In nearly all cases of SLE, avoidance of sun exposure is advisable and will help minimize cutaneous disease.

Renal Disease. Renal disease develops in approximately a third of SLE patients. Given a high prevalence and morbidity of renal disease as well as its tendency to carry few if any symptoms, screening urinalysis and assessment of renal function are prudent in nearly all but the most straightforward presentations of SLE to the ED. Lupus nephritis may cause a nephrotic-type disease, primarily characterized by proteinuria (>2 g/day) or a more nephritic...
Complications due to Medications

The remarkable improvements in life expectancy and disease control in SLE carry a cost. Chronic steroid use is associated with a well-known host of consequences, such as increased risk of CAD, osteoporosis, avascular necrosis, psychosis, hyperglycemia, and weight gain, among many others. More potent chemotherapeutic medications, such as cyclophosphamide, methotrexate, and azathioprine, may profoundly influence the patient’s immune response and cause increased vulnerability to conventional and opportunistic infections. Chronic NSAID use for the musculoskeletal consequences of SLE may contribute to peptic ulcer disease, especially if they are coadministered with glucocorticoids. Therapy with antimalarials, such as hydroxychloroquine, is common and generally well tolerated; however, retinopathy and both QT interval prolongation and refractory ventricular arrhythmias have been associated with prolonged use.60

Diagnostic Strategies

Diagnostic tests will depend on the patient’s presentation and whether a diagnosis of SLE is already established or being suspected for the first time.

Laboratory

In all but the most trivial presentations, order a serum creatinine concentration, urinalysis, and complete blood count because renal dysfunction, proteinuria, anemia, or thrombocytopenia may silently complicate SLE and be an important marker of increased disease activity. Leukocytosis, already a nonspecific finding, may be even less contributory in SLE patients taking glucocorticoids. Therapy with antimalarials, such as hydroxychloroquine, is common and generally well tolerated; however, retinopathy and both QT interval prolongation and refractory ventricular arrhythmias have been associated with prolonged use.60

Radiology

Radiography. In SLE, a chest radiograph may point to diagnoses such as pleuritis (pleural effusion); pericardial disease (enlarged cardiac silhouette); pneumonia, including atypical and opportunistic infections (airspace disease); and pulmonary embolism (normal).

Computed Tomography. CT scanning may be of particular value in identifying lupus enteritis in the patient with abdominal pain, and CT pulmonary angiography has become the preferred imaging modality for pulmonary embolism. In both cases, attention to the presence or absence of lupus nephritis must be made to guide the appropriate and safe use of intravenous contrast material.

Special Tests

Bedside echocardiography may be carried out to evaluate the presence of pericardial fluid when pericarditis is suspected on the basis of clinical or electrocardiographic findings. A number of studies have documented the safety and accuracy of emergency physicians’ identifying pericardial effusions with point-of-care ultrasound examination.53

Nuclear imaging may be helpful to assess for pulmonary embolism in patients with chronic kidney disease due to lupus nephritis.

Differential Diagnosis

In keeping with its highly varied presentations and permutations of disease activity, a number of other diseases may be confused with early SLE before its proper diagnosis. These include undifferentiated connective tissue disease, primary Sjögren’s syndrome, primary APS, fibromyalgia with positive antinuclear antibody, idiopathic thrombocytopenic purpura, drug-induced lupus, and early rheumatoid arthritis.64 For those with an established diagnosis of SLE, chief complaint–driven considerations for acute presentations are listed in Table 118-3.

Management

Nearly all noninfectious consequences of SLE are managed with introduction or escalation of immunomodulatory therapy. In the majority of disease states, a pulse dose of methylprednisolone at 1 to 2 mg/kg is appropriate. See Table 118-4 for additional therapeutic options for escalating disease severity.

For SLE patients presenting with infection who are receiving chronic steroid therapy, consider stress dose glucocorticoids, hydrocortisone 50 to 100 mg intravenously every 8 hours, in addition to appropriate antimicrobial coverage.

<table>
<thead>
<tr>
<th>CHIEF COMPLAINT</th>
<th>CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleuritic chest pain</td>
<td>Pericarditis, pleuritis, pulmonary embolism, pneumonia, musculoskeletal chest wall pain</td>
</tr>
<tr>
<td>Delirium</td>
<td>Neuropsychiatric lupus, steroid psychosis</td>
</tr>
<tr>
<td>Leg swelling</td>
<td>Deep venous thrombosis, renal failure, right-sided heart failure (pulmonary embolism, pulmonary hypertension), protein-losing enteropathy</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Pneumonia, anemia, pericarditis or pericardial effusion, pleuritis or pleural effusion, interstitial lung disease, shrinking lung syndrome</td>
</tr>
<tr>
<td>Pruritic or painful rash</td>
<td>Discoid SLE, drug reaction, sun exposure</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Lupus enteritis, peptic ulcer disease, pancreatitis, pseudo-obstruction</td>
</tr>
<tr>
<td>Fever</td>
<td>Infection, increased disease activity</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Arthralgias (lupus flare), osteoarthritis, septic arthritis, unrelated (gout, fibromyalgia)</td>
</tr>
</tbody>
</table>
NSAIDs

Much of the pain and morbidity associated with SLE is related to inflammation that is amenable to treatment with NSAIDs. Ibuprofen 400 to 600 mg orally four times a day or naproxen 500 mg orally twice daily is useful for conditions such as pericarditis, pleuritis, arthralgias, myalgias, and fever. Use of NSAIDs in patients with chronic kidney disease due to lupus nephritis or a history of peptic ulcer disease is discouraged. In such patients, acetaminophen is used for mild to moderate pain, and narcotics are recommended for severe pain.

Dermatologic Treatment

In cases of isolated cutaneous findings, topical treatment with corticosteroids is preferable to systemic therapy. Topical therapy may be initiated with 1% hydrocortisone cream to the affected area. In cases in which higher potency topical steroids are necessary, a preparation of 0.05% betamethasone applied once daily to the affected area for 2 weeks is appropriate.

Special Considerations

Antiphospholipid Syndrome

Present in nearly 40% of SLE patients, the antiphospholipid syndrome (APS) is considered when patients both have a clinical history of thrombosis and are carriers of one of a particular set of aPL antibodies directed against three specific serum proteins. These antibodies include the antiphospholipid antibody, the misleadingly named lupus anticoagulant, and the anti-β2-glycoprotein I antibody. The most thrombogenic of the antibodies is the lupus anticoagulant, with an odds ratio as high as 16 for the presence of the lupus anticoagulant, with an odds ratio as high as 16 for the presence of the aPL antibody. The most thrombogenic of the antibodies is the lupus anticoagulant, with an odds ratio as high as 16 for the presence of the aPL antibody.

Clinical Features. APS may present with any number of clinical features (Box 118-1), typically related to thrombosis or thromboembolism. A small subset of those with APS may present with multiple thrombotic sites and organ failures simultaneously. This condition is known as catastrophic APS.

Diagnostic Strategies. Assays to detect and to measure the presence of aPL antibodies are not generally available in a timely fashion and are impractical for use in the ED setting. However, there are two laboratory findings supportive of APS that may be useful or accidentally discovered during an ED workup:

1. A spuriously elevated PTT in the setting of a normal PT/INR may reflect APS. This in vitro finding, which contradicts the actual in vivo hypercoagulable state of the APS patient, is due to interference of the coagulation study by aPL antibodies. Confirmation of the presence of the interfering antibody is done by carrying out a mixing study. A mixing study requires repeating the PTT with a mixture of the patient’s blood and a 50% contribution from normal, control serum. In the presence of an inhibiting antibody, the PTT will remain elevated. If, however, the PTT was elevated for other reasons (most commonly heparin), the addition of normal clotting factors from the control serum will restore the PTT to normal.

2. The VDRL assay to test for syphilis contains cardiolipin and thus will commonly be falsely positive in patients with antiphospholipid antibodies or APS.

Drug-Induced Lupus

Drug-induced lupus is an SLE-like self-resolving illness characterized by arthralgias, myalgias, rash, and serositis; it may be brought on by as many as 80 different medications. Notably, the malar rash and major organ involvement are rare in this condition. In drug-induced lupus, antibodies against the body’s own histone proteins are common and purported to be a major mechanism of disease. Although the list of potentially implicated medications is long, those agents with most evidence for causing drug-induced lupus are summarized in Box 118-2. The diagnosis is typically clinical and confirmed by resolution of symptoms with the withdrawal of the offending medication. In addition to cessation of the culprit drug, NSAIDs or steroids for symptom control are indicated.

Disposition

Dispositions for the patient with SLE will vary significantly by clinical presentations. For patients with non–life-threatening presentations, such as increased musculoskeletal symptom burden, simple headache, or cutaneous reactions, discharge with appropriate follow-up is usually appropriate. However, patients with poor insight into their disease, significant comorbidities, or weak social or home supports may require admission.

With disorders characteristic of SLE flares (e.g., progressive lupus nephritis, lupus enteritis), new thrombotic events, and
infectious complications due to immunosuppression, the patient may need admission for initiation of systemic therapy (e.g., glucocorticoids, anticoagulation, antibiotics) and evaluation of response or deterioration. Admission to the intensive care unit is considered for those who, despite initial resuscitation, suffer progressive circulatory or respiratory derangement. Because of the high incidence of CAD in patients with SLE, patients with undifferentiated chest pain who have acute coronary syndrome ruled out in the ED should receive an expedited evaluation with provocative testing (e.g., exercise stress test) in a chest pain unit or on an outpatient basis. If an outpatient workup is pursued, prescribe daily aspirin therapy. The complexity of SLE often challenges physicians not specialized in its many nuances and intricate pathophysiologic changes. Reasons for rheumatologic referral of patients with SLE are presented in Box 118-3.75

VASCULITIDES

Perspective

The vasculitides are a heterogeneous group of disorders characterized by inflammatory damage of blood vessels. Arteries and veins of all sizes and their tributaries can be affected to varying degrees. Presentations can range from benign and self-limited to serious and life-threatening. Diagnosis can be challenging as early vasculitis syndromes are nonspecific and can mimic other infectious, inflammatory, or neoplastic conditions. Approximately 1 in 2000 adults are affected by some form of vasculitis, with a higher incidence in adults 65 to 74 years of age.76 In the United States, the most common vasculitis syndromes are giant cell arteritis, Wegener’s granulomatosis, and microscopic polyangiitis.77

Principles of Disease

The cause of most vasculitis syndromes is unknown. Most cases are believed to result from immune complex deposition in blood vessel walls, prompting a complement-mediated inflammatory reaction. This results in vessel wall damage and necrosis, leading to stenosis, occlusion, and subsequent end-organ ischemia. The clinical manifestations are determined predominantly by the size and distribution of blood vessels involved along with the histologic subtype of inflammation.

The most recognized system for classification of the primary vasculitis is by the size of blood vessel involved (Table 118-5). Large-vessel vasculitis involves the aorta and its immediate branches and in some cases the corresponding vessels in the venous system. Medium-vessel disease involves the macrovascular downstream from the main aortic branches. Small-vessel vasculitis involves capillaries, venules, arterioles, and glomeruli.

Clinical Features

Virtually all vasculitides involve some degree of constitutional symptoms, including fever, malaise, weight loss, and arthralgias. There is substantial overlap in the signs and symptoms associated with the large-, medium-, or small-vessel disorders. Practically, it is more useful to classify the vasculitides according to the pattern of organ system involvement or exposure most evident on presentation: vasculitis presenting with large-vessel occlusive symptoms, vasculitis typified by pulmonary-renal manifestations, vasculitis with characteristic cutaneous manifestations, and syndromes associated with environmental or foreign antigen exposure. This approach assists in refining the differential diagnosis for a given constellation of symptoms and directing initial therapy while awaiting the results of confirmatory tests or tissue biopsy, which are in most cases not readily available in the ED.

Table 118-5 Primary and Secondary Vasculitis: Classification and Associated Features

<table>
<thead>
<tr>
<th>Predominantly Large Vessel</th>
<th>Predominantly Medium Vessel</th>
<th>Predominantly Small Vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EXAMPLES</strong></td>
<td><strong>COMMON FEATURES</strong></td>
<td><strong>EXAMPLES</strong></td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Asymmetrical blood pressures</td>
<td>Cutaneous nodules</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>Claudication</td>
<td>Ulcers</td>
</tr>
<tr>
<td></td>
<td>Aortic disease</td>
<td>Mononeuritis multiplex</td>
</tr>
<tr>
<td></td>
<td>Renovascular hypertension</td>
<td>Digital gangrene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microangiurms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renovascular hypertension</td>
</tr>
</tbody>
</table>

Secondary Forms of Vasculitis

Connective tissue disorders (rheumatoid vasculitis, lupus erythematosus, Sjögren’s syndrome, others)
Infection (hepatitis B or C virus, human immunodeficiency virus)
Inflammatory bowel disease
Hypersensitivity (drug induced, others)
Vasculitis Presenting with Large-Vessel Occlusive Symptoms

Giant Cell Arteritis. Giant cell arteritis (GCA), also known as temporal arteritis, is a systemic vasculitis that affects medium-sized and large vessels. The most recognized symptoms are caused by occlusion of the superficial branches of the carotid artery, although systemic medium- and large-vessel disease involving the carotid, subclavian, aortic, vertebral, and iliac vessels may also be present. The most feared complication of GCA is irreversible visual loss, occurring in up to one third of patients. Early treatment can help prevent this complication, and thus the diagnosis is an important consideration in patients older than 50 years presenting with any combination of constitutional symptoms, headache, visual changes, and jaw claudication.

The incidence of GCA has been increasing steadily during the past 20 to 40 years. The syndrome is tightly coupled to age, with a mean age at onset of 70 years and a range of 50 to 90 years. The incidence increases sharply after the age of 50 years, with an estimated incidence of 33 per 100,000 patients. The disease is twice as common in women than in men, and smoking increases the risk of GCA sixfold in women.

GCA is frequently associated with a spectrum of nonspecific symptoms, such as fever, weight loss, and fatigue. Common presenting complaints include headache, visual symptoms, jaw claudication, and myalgias and associated polymyalgia rheumatica. Headache, the most common presenting symptom, occurs in three quarters of patients with GCA. Although it is classically located in the temporal area and in association with tenderness along the superficial temporal artery, no specific pattern of headache location or severity is predictive of the temporal arteritis, and in untreated patients the headache may improve or disappear, even though active disease is still present. The presence of tenderness, prominence, or beading of the superficial temporal artery on physical examination is associated with GCA, whereas the absence of any temporal artery abnormality is associated with a modest decrease in the likelihood of disease. Changes in visual acuity occur as a result of occlusive arteritis of the posterior ciliary artery or less common retinal artery occlusion. Visual loss may occur in one or both eyes and at times be painless; interruptions in acuity may be partial or complete, transient or permanent. The visual deficit is often profound, with 80% of patients unable to appreciate hand waving. Funduscopic findings in patients with acute visual loss include optic disk pallor and edema, in keeping with ischemic optic neuritis. Complete visual loss that is present for more than a few hours is usually irreversible. Diplopia may also occur as a result of ischemic ophthalmoplegia; oculomotor nerve lesions typically spare the pupil.

Thoracic aortic aneurysms are 17 times more likely to occur in patients with GCA compared with age-matched controls. The vertebral-basilar arteries are affected in 75 to 100% of patients, leading to signs of verteobasilar insufficiency, including gait disturbance, dizziness or vertigo, and vomiting. The diagnosis of GCA should be considered in elders with signs of verteobasilar insufficiency in conjunction with constitutional symptoms and an elevated ESR.

In the presence of symptoms consistent with occlusion of superficial branches of the carotid artery, the diagnosis is usually straightforward. The American College of Rheumatology has developed a scoring system that lends equal weight to each of five diagnostic criteria (Box 118-4). Patients with a score of ≥2 require temporal artery biopsy for the diagnosis to be confirmed; in patients with a score of ≥3, a biopsy adds little information beyond clinical and laboratory appraisal. An ESR of ≥80 mm/hr is common, although approximately 20% of patients with an ESR of <50 mm/hr will go on to have biopsy-proven temporal arteritis. An elevated C-reactive protein level has improved sensitivity over ESR and may actually be the preferred diagnostic test, with a reported sensitivity for GCA of 97.5%. The gold standard for diagnosis remains temporal artery biopsy, with established sensitivity of 90 to 95%. Bilateral biopsies should be considered in patients for whom clinical suspicion is high and initial findings on biopsy are normal. The role of color duplex ultrasonography in the diagnosis of temporal arteritis remains controversial; one study showed no benefit in establishing the diagnosis when it was added to a carefully performed physical examination. High-resolution magnetic resonance imaging may be used alone or as a diagnostic adjunct to biopsy in atypical or challenging cases.

Given the high stakes and morbidity associated with missed or delayed diagnosis, initiate treatment for temporal arteritis as soon as the diagnosis is considered to prevent permanent visual loss. The mainstay of treatment remains high-dose corticosteroids, initiated in the ED and continued until the diagnosis can be confirmed or excluded on subsequent biopsy. A typical initial regimen is oral prednisone 60 to 100 mg daily (or 1 mg/kg) with a temporal biopsy scheduled within 1 week of presentation. More than half of patients treated within 24 hours of presentation will achieve some recovery, compared with only 6% when treatment is delayed beyond this interval. Oral corticosteroids do not alter the sensitivity of temporal artery biopsy when it is performed within 2 weeks of initiation of therapy. Some authors recommend switching to intravenous corticosteroid treatment for 3 days should vision continue to deteriorate despite timely initiation of oral prednisone. Acetylsalicylic acid may be useful as an adjunct to decrease ischemic complications.

Takayasu’s Arteritis. Takayasu’s arteritis, also known as pulseless disease or occlusive thromboaoartopathy, is a systemic large-vessel vasculitis of unknown etiology that primarily affects young women of Japanese and Southeast Asian descent. It is characterized by granulomatous inflammation of the aorta and its branches, leading to massive intramural fibrosis and symptoms of large-vessel stenosis, thrombosis, and aneurysm.

Takayasu’s arteritis is a rare disorder worldwide, with a reported incidence of 0.2 to 2.6 cases per million in western Europe and North America, although this number is much higher in Japan. The disease is eight times more common in women than in men; symptoms are first manifested between the ages of 15 and 25 years. The diagnosis should be considered in women younger than 40 years who present with signs and symptoms of large-vessel occlusion, including upper limb claudication, decreased or asymmetrical pulses, and unexplained hypertension accompanied by constitutional symptoms such as fever and weight loss.

The most common presenting symptoms related to vascular occlusion are claudication (most commonly of the upper extremity, 35%), reduced or absent pulse (25%), hypertension (most often associated with renal artery stenosis, 20%), carotidynia (20%), lightheadedness (20%), and asymmetrical arm blood pressures (15%). Cerebrovascular ischemia, stroke, aortic insufficiency, and visual symptoms are present in 10% of patients. Approximately 80% of patients will have an identifiable bruit on physical examination, and 50% will go on to have asymmetrical
blood pressures.\(^9\) One third of patients will have cardiac complications, including aortic insufficiency and regurgitation, myocarditis, congestive heart failure, and cardiac ischemia from coronary artery aneurysm.\(^9\) Patients presenting after the age of 40 years or without signs of vascular occlusion pose a diagnostic challenge; only nonspecific constitutional symptoms or fever of unknown origin may initially be manifested, leading to diagnostic and therapeutic delays.

Although an elevated ESR (>80 mm/hr) is suggestive of Takayasu’s arteritis, the majority of laboratory investigations are nonspecific, and the diagnosis is almost always secured on the basis of clinical assessment and diagnostic imaging. Patients younger than 40 years who present with symptoms of large-vessel occlusive disease (bruit, absent pulse, claudication) are candidates for axial imaging of the aorta and its major branches; options include CT angiography and magnetic resonance angiography, both of which have largely replaced digital subtraction angiography as the imaging method of choice.\(^10\) Once a diagnosis of Takayasu’s arteritis is made, oral corticosteroids (e.g., 0.5 to 1 mg/kg prednisone daily) are indicated and continued for 4 to 12 weeks, followed by a gradual taper. It is a self-limited disorder in 20% of patients; the remainder will go on to have a relapsing-remitting or chronic progressive course requiring long-term corticosteroids.\(^10\) Steroid-sparing agents such as azathioprine, cyclophosphamide, and tumor necrosis factor inhibitors may be added in patients who relapse. Patients should be observed closely by a rheumatologist and vascular surgeon; those who do not respond to corticosteroids may benefit from surgical reperfusion, including bypass grafting and percutaneous transluminal angioplasty. Indications for admission include signs and symptoms of acute end-organ ischemia, aortic insufficiency, myocarditis, and decompensated congestive heart failure. The most common causes of death are congestive heart failure, renal failure, and infectious complications.\(^10\)

Vasculitis Typified by Pulmonary-Renal Manifestations

Vasculitis syndromes in this category are characterized by a predominance of pulmonary and renal manifestations, including dyspnea, cough, pulmonary infiltrates, and renal insufficiency secondary to glomerulonephritis, in addition to a variety of systemic symptoms. Wegener’s granulomatosis, microscopic polyangiitis, and Churg–Strauss syndrome share a strong association with the presence of antineutrophil cytoplasmic antibodies (ANCA) of various subtypes, including cytoplasmic staining (c-ANCA) and perinuclear staining (p-ANCA), measured in the blood by enzyme-linked immunosorbent assay or direct immunofluorescence.\(^10\) Whether ANCA are involved in pathogenesis or are simply markers of disease is unclear. The absence of ANCA does not rule out an ANCA-associated vasculitis syndrome because between 20 and 50% will have negative assays.\(^10\)

A comparison of the common presenting features of Wegener’s granulomatosis, microscopic polyangiitis, Goodpasture’s syndrome, and Churg–Strauss syndrome is shown in Table 118-6.

**Wegener’s Granulomatosis.** Wegener’s granulomatosis is a c-ANCA–associated systemic necrotizing vasculitis of small and medium-sized blood vessels with a predilection for the upper and lower respiratory tracts and kidneys. The constellation of upper respiratory, pulmonary, and renal disease in patients with constitutional symptoms suggests Wegener’s granulomatosis. In the absence of pulmonary or renal symptoms, the diagnosis is extremely challenging and often missed. Wegener’s granulomatosis is more common in white individuals but otherwise shows no specific pattern of distribution for age, sex, or geography. The annual incidence is estimated to be 3 per 100,000 people.\(^10\)

Constitutional symptoms including fever, malaise, and weight loss are often evident on initial presentation. Upper airway disease is the most common presenting symptom of Wegener’s granulomatosis, with 90% of patients developing upper respiratory tract symptoms in some form.\(^10\) Upper airway manifestations include serous otitis media with or without suppurrative infection, hearing loss, sinusitis, nasal mucosal ulcerations and septal perforation, epistaxis, and laryngotracheal disease.\(^10\) Subglottic stenosis is the most common laryngotracheal lesion, present in about 16% of patients, the severity of which can range in presentation from mild dyspnea to acute airway obstruction and respiratory distress.\(^10\) Nearly 50% of pediatric and adolescent patients will have some degree of subglottic stenosis, with implications for airway management. Lower respiratory symptoms include cough, dyspnea, pleuritis, and hemoptysis. Radiographic studies may demonstrate pulmonary infiltrates and nodules, although the severity of radiographic findings does not always correlate well with symptom severity (Fig. 118-6). A minority of patients present with diffuse alveolar hemorrhage, which has an associated mortality of approximately 50%.\(^10\) Renal embarrassment tends to be a later finding, developing in a subset of patients with generalized disease. Once progressive renal failure has developed, it may evolve rapidly during days to weeks, leading to end-stage renal disease that, if left

### Table 118-6

<table>
<thead>
<tr>
<th>Feature</th>
<th>Wegener’s Granulomatosis</th>
<th>Microscopic Polyangiitis</th>
<th>Goodpasture’s Syndrome</th>
<th>Churg–Strauss Syndrome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary infiltrates or nodules</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>Asthma and eosinophilia in CSS</td>
</tr>
<tr>
<td>Alveolar hemorrhage</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>Progressive renal failure uncommon in CSS</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>Often a prominent feature of CSS</td>
</tr>
<tr>
<td>Upper airway disease</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>++</td>
<td>ENT disease favors WG</td>
</tr>
<tr>
<td>Purpura</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Peripheral nervous system involvement</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Central nervous system involvement</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>


*ANCA-associated syndromes.

CSS, Churg-Strauss syndrome; ENT, ear, nose, and throat; WG, Wegener’s granulomatosis.

---

**PART III • Medicine and Surgery / Section Nine • Immunologic and Inflammatory**
untreated, is associated with a mean survival of 5 months. 107 Chronic renal insufficiency can develop despite appropriate treatment, with a subset of patients requiring dialysis or renal transplantation. 106

The list of associated symptoms in Wegener’s granulomatosis is myriad and speaks to the systemic nature of the disease. Ophthalmologic (scleritis, episcleritis, uveitis), cutaneous (palpable purpura, subcutaneous nodules, ulcers), neurologic (mononeuropathy and polyneuropathy, cerebral vasculitis, cerebral hemorrhage, or thrombosis), and cardiac (pericarditis, myocarditis) disease may be present to varied degrees.

ED management is directed first toward life-threatening pulmonary hemorrhage and sequelae from acute or decompensated chronic renal insufficiency. The combination of diffuse alveolar hemorrhage and subglottic stenosis represents a “double hit” difficult airway, requiring extreme caution during endotracheal intubation. Although a large endotracheal tube is preferred for the management of massive hemoptysis, selection of a smaller tube size may be required to bypass a narrow subglottic corridor. Fiber-optic intubation through an intubating laryngeal mask airway has been advocated. 109 Combination therapy with corticosteroids and cyclophosphamide is considered the current standard of care for patients with acute flares and has dramatically changed the disease prognosis. Before the use of steroids, 1-year mortality approached 90%; combination therapy with corticosteroids and cyclophosphamide has improved the 5-year survival to nearly 90%, with the majority of patients achieving remission. 105,109,116 Methotrexate plus corticosteroids may be used instead of cyclophosphamide in less severe presentations involving systemic disease. 110 Patients presenting with new or suspected Wegener’s granulomatosis and those with severe disease require admission for high-dose intravenous dual-agent therapy. The diagnosis is typically confirmed by open lung biopsy. 105,111 Patients who present with new respiratory symptoms or infiltrates on the chest film should probably be hospitalized and treated for infection until it is proven otherwise, given the morbidity associated with pneumonia in an immunocompromised host.

Goodpasture’s Syndrome. Goodpasture’s syndrome describes the clinical triad of glomerulonephritis, pulmonary hemorrhage, and circulating anti–glomerular basement membrane (GBM) antibodies. The syndrome is distinct from Goodpasture’s disease, which consists of glomerulonephritis and anti-GBM antibodies without pulmonary hemorrhage. Goodpasture’s syndrome is not associated with ANCA; anti-GBM autoantibodies target type IV collagen found in the basement membranes of glomeruli and pulmonary alveoli, causing autoimmune damage through a type II hypersensitivity reaction. 112 The disease can affect people of all ages, with white individuals more commonly affected. 112 The incidence is bimodal; one peak occurs in 20- to 30-year-old men and a second in 50- to 70-year-olds of both sexes. The incidence is believed to be about 1 case per 2 million individuals. 113

There is substantial variation in the presentation of patients with anti-GBM disease. Pulmonary or renal symptoms may exist alone or in combination, although the two are most often present together. Fever, malaise, and weight loss are common early symptoms. Pulmonary symptoms range from dyspnea and cough to hypoxemia and frank pulmonary hemorrhage, which can be massive and life-threatening. Chest radiographic findings may be normal or demonstrate hilar pulmonary infiltrates sparing the apices and costophrenic angles. Renal failure can be insidious or be manifested as rapidly progressive glomerulonephritis with acute kidney injury and volume overload. Urinalysis shows characteristic signs of acute glomerulonephritis, including hematuria, proteinuria, and red cell casts. Definitive diagnosis is made by lung or renal biopsy demonstrating linear deposition of anti-GBM antibodies in the alveolar or glomerular basement membranes, respectively. 112

Initial management of patients with massive pulmonary hemorrhage is focused on securing a definitive airway and addressing hemodynamic instability. Bronchoscopy or chest radiography can be used to identify the source of hemorrhage, and selective intubation of the contralateral mainstem bronchus or use of a double-lumen endotracheal tube and ventilating with the affected lung in the dependent position may improve oxygenation. High-dose methylprednisolone (10–15 mg/kg) and cyclophosphamide are the mainstays of immune suppressive therapy. Therapeutic plasma exchange can be used to decrease the level of circulating anti-GBM antibodies during acute presentations. 114 Patients who have end-stage renal disease may be candidates for renal transplantation, assuming anti-GBM antibodies are undetectable with treatment, else the disease may recur in the transplanted graft. 115 The prognosis has improved in recent years owing in part to the more aggressive use of therapeutic plasma exchange.

Microscopic Polyangiitis. Microscopic polyangiitis was first recognized in a subset of polyarteritis nodosa patients who presented with segmental glomerulonephritis. 116 This systemic small-vessel vasculitis is the most common cause of the pulmonary-renal syndrome, leading to renal failure and pulmonary hemorrhage, the two most clinically relevant features of microscopic polyangiitis. The disease affects men and women equally and typically is manifested in the fourth or fifth decade of life, although it may occur at virtually any age. 117 The annual incidence in the United States is approximately 3.8 cases per 1 million population. The characteristic presentation of rapidly progressive renal failure in
ANCA-positive vasculitis syndromes and may preferentially affect the lower urinary tract and prostate gland, leading to obstructive uropathy. Cardiac manifestations, including restrictive pericarditis and cardiomyopathy leading to congestive heart failure, are more common in Churg-Strauss syndrome compared with Wegener’s granulomatosis and microscopic polyangiitis. Mononeuritis multiplex, asymmetrical neuropathy, and cranial neuropathies are the most frequently observed neurologic symptoms, seen in up to 80% of patients. Gastrointestinal symptoms include infarction, perforation, and hemorrhage secondary to infiltration of the small bowel or stomach.

Laboratory investigation demonstrates a persistently elevated eosinophil count (>1500 cells/mm³), although this does not correlate well with the presence of active disease. Myeloperoxidase-ANCA antibodies are seen in about 40% of cases. Pulmonary infiltrates are typically patchy and transient in nature (Löeffler’s syndrome). The diagnosis of Churg-Strauss syndrome is made by a combination of clinical and histologic features; evidence of necrotizing vasculitis or extravascular granulomas on skin or lung biopsy in conjunction with eosinophilia, asthma, and allergy is highly suggestive of the disease.

Corticosteroids are the mainstay of treatment, although immunomodulating agents such as cyclophosphamide may be added to achieve remission in cases complicated by cardiac, renal, or gastrointestinal involvement. The overall survival for patients with Churg-Strauss syndrome approaches 80%, with an increased relative risk of death predicted by the presence of renal and gastrointestinal symptoms.

### Vasculitis with Characteristic Cutaneous Manifestations

Cutaneous vasculitis involves inflammation of the blood vessels of the skin. The diseases listed here are associated with cutaneous manifestations that are often characteristic and an important element of disease recognition in the ED. Constitutional signs and symptoms of systemic multisystem disease may also be present.

**Erythema Nodosum.** Erythema nodosum, a vasculitis of the venules and veins of the skin, is characterized by tender, subcutaneous nodules on the tibial surfaces of the lower legs. Erythema nodosum is presumed to be a hypersensitivity response to systemic diseases or drug therapy, although no clear precipitant can be identified in 30 to 50% of cases. Peak incidence occurs in the spring or fall months among 18- to 34-year-olds, with a male-to-female ratio of approximately 1:4.

The prodromal stage of erythema nodosum consists of nonspecific constitutional symptoms, fever, malaise, and myalgias. The distribution of subcutaneous nodules favors the lower extremities, although lesions may be appreciated on the forearm, trunk, and thigh (Fig. 118-7). The nodules tend to be erythematous, well circumscribed, and exquisitely tender to touch and develop a blue hue as they resolve. Arthralgias may be present in conjunction with or before the cutaneous eruption.

Viral upper respiratory tract infections, streptococcal infection, tuberculosis, and sarcoidosis are common precipitants. Drugs associated with erythema nodosum include penicillins, sulfonamides, oral contraceptive medication, and phenytoin. Less common associations include autoimmune conditions, such as inflammatory bowel disease and SLE; histoplasmosis; *Yersinia*, *Salmonella*, and *Chlamydia* infections; coccidioidomycosis; and psittacosis.

Management of erythema nodosum is generally supportive and directed toward symptom control and treatment or elimination of the underlying cause. Cutaneous nodules secondary to infection resolve within 6 to 7 weeks; in contrast, 30% of idiopathic cases may persist beyond 6 months. NSAIDs may be useful for
Polyarteritis Nodosa.

Polyarteritis nodosa is a necrotizing vasculitis of unknown etiology affecting small and medium-sized blood vessels. The disease can involve multiple systems, most commonly the skin, nervous system, and gastrointestinal tract. Necrosis occurs preferentially at arterial bifurcations and branch sites, leading to microaneurysm formation, thrombosis, emboli, organ ischemia, and infarction. Polyarteritis nodosa affects men about twice as often as women, and onset occurs at any age, although the peak is typically the fourth to sixth decade of life. Annual incidence is between 2 and 9 cases per 1 million individuals. Whereas the initial presentation can be nonspecific, the combination of cutaneous lesions and adult-onset hypertension with evidence of systemic illness suggests polyarteritis nodosa.

Cutaneous manifestations occur in one third of patients. Palpable purpura with or without ulceration is recognized in the fingers, ankles, malleoli, and pretibial areas. Digital cyanosis may be seen secondary to ischemia. Splinter hemorrhages and livedo reticularis may also be observed. Renovascular arteritis can cause hypertension, which may at times be severe. Peripheral neuropathies in the form of mononeuritis multiplex or polyneuropathy are present in up to 50% of patients. Mesenteric vasculitis can produce abdominal angina and in rare cases lead to frank mesenteric ischemia, infarction, and perforation, often with devastating consequences.

Treatment generally begins with a corticosteroid (e.g., prednisone 1 mg/kg), and a second immunosuppressive agent is added for severe or extensive disease. Abdominal catastrophes may require surgical intervention; prognosis in these cases is poor. Polyarteritis nodosa is almost always fatal if it is left untreated, although the prognosis has been much improved with the use of control of arthralgias; corticosteroids and colchicine are reserved for the management of protracted or refractory disease.

Henoch-Schönlein Purpura.

Henoch-Schönlein purpura is a small-vessel vasculitis characterized by palpable purpura and gastrointestinal and renal manifestations associated with immunoglobulin A immune complex deposition in blood vessels. The 1990 American College of Rheumatology criteria for Henoch-Schönlein purpura include the presence of two or more of the following: age at onset younger than 20 years, palpable purpura, bowel angina, and vessel wall granulocytes on biopsy (sensitivity of 87.1%, specificity of 87.7%). Although the disease can affect adults, it is most commonly seen in children younger than 5 years.

Henoch-Schönlein purpura usually is manifested 1 to 2 weeks after a viral upper respiratory tract infection with a triad of palpable purpura, arthralgias, and abdominal pain. Purpuric lesions cluster in dependent regions with a predilection for the legs and buttocks (Fig. 118-8). Colicky abdominal pain and bloody stools can occur secondary to gastrointestinal vasculitis. A rare complication of Henoch-Schönlein purpura in children is enterointestinal intussusception (ileoileal, jejunojejunal, jejunoileal), which may be associated with severe abdominal pain, lethargy, bloody diarrhea, and signs of obstruction or perforation. Glomerulonephritis is typically mild and may be manifested as hematuria, red cell casts on urinalysis, and azotemia.

Management in mild disease is generally supportive, and symptoms can intermittently recur for several weeks. NSAIDs control arthralgias in most cases but are avoided if renal impairment is present. Glomerulonephritis is treated more aggressively, with a combination of corticosteroids and cyclophosphamide, azathioprine, or mycophenolate mofetil, and generally demonstrates full resolution with time. Enterointestinal intussusception can be difficult to diagnose with standard approaches (ultrasonography, air-contrast enema), and if the index of suspicion is high, patients should be assessed by a pediatric general surgeon.

Figure 118-7. Tender subcutaneous nodules associated with erythema nodosum. (From Kliegman R: Nelson Textbook of Pediatrics, 18th ed. Philadelphia, WB Saunders, 2007.)

Figure 118-8. Purpuric lesions associated with Henoch-Schönlein purpura, some of which have coalesced and undergone central necrosis. (From Habif TP: Clinical Dermatology, 5th ed. New York, Mosby, 2009.)
systemic corticosteroids. In a prospective study, the presence of two or more prognostic factors (azotemia, proteinuria, cardiomyopathy, gastrointestinal involvement, or neurologic signs) predicted a 5-year mortality of 46%; if none was present, the 5-year mortality was 12%.128

Behçet’s Disease. Behçet’s disease is a complex, chronic small-vessel vasculitis that may affect the mucocutaneous, ocular, cardiovascular, renal, gastrointestinal, pulmonary, urologic, musculoskeletal, and central nervous systems. Early descriptions of the disease date to the time of Hippocrates and the third book of endemic diseases.135 The disease is defined by the presence of aphthous oral ulcers plus two or more of the following: genital aphthae; cutaneous lesions; and neurologic, oral, or rheumatologic manifestations. The exact pathogenesis remains unknown. Behçet’s disease is found worldwide, with the highest prevalence in Turkey, Japan, the Middle East, and Mediterranean regions. The disease affects people of all ages, although patients often first present in the second or third decade of life.136 The male-to-female ratio varies somewhat according to geography; women are more commonly affected than men in northern Europe and the United States, with an estimated prevalence in these regions of about 1 in 150,000 individuals.137,138

The triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis in young adults is highly suggestive of Behçet’s disease. Oral aphthous ulcers are the defining characteristic of the disease (Fig. 118-9). The lesions are typically found on the tongue, lips, buccal mucosa, and gingiva; the tonsils, palate, and pharynx are less commonly affected. The ulcers are painful, have a yellow, necrotic base, and may appear alone or in crops of three to ten. Genital ulcers appear on the scrotum and penis in men and the vulva or vaginal mucosa in women. Skin lesions include erythema nodosum–like subcutaneous nodules, pyoderma gangrenosum, cutaneous thrombophlebitis, and pustular acne-like folliculitis.139 Ocular symptoms are common and constitute a major source of morbidity in Behçet’s disease. Findings may include uveitis, iritis, and optic neuritis. Hypopyon, once considered a characteristic feature of the disease, is uncommon. Visual symptoms may be bilateral or unilateral and can occasionally lead to permanent vision loss. Neurologic manifestations include brainstem and corticospinal tract syndromes (neuro-Behçet’s), aseptic meningoencephalitis, increased intracranial pressure, and cerebral sinus thrombosis complicated by optic nerve ischemia and atrophy.140 Gastrointestinal ulcers can cause obstruction or ileocecal perforation.141

Inflammatory oligoarthritis of the ankles, knees, elbows, and wrists is present in 40 to 60% of patients.137 The diagnosis of Behçet’s disease is made primarily on clinical grounds. The appearance of genital lesions can be ambiguous, and other causes of painful genital ulcers need to be ruled out. Oral and genital ulcerations are often managed successfully with a topical steroid. Management of severe mucocutaneous disease involves systemic corticosteroids (e.g., prednisone, 1 mg/kg), low-dose thalidomide, or methotrexate.142 Treatment of systemic disease may be accomplished with a corticosteroid alone or in combination with cyclophosphamide or azathioprine.137 Ocular manifestations, including uveitis, are usually managed with prednisone plus azathioprine and require a rapid referral to an ophthalmologist. The presence of cerebral venous sinus thrombosis is an indication for immediate heparinization. Behçet’s disease often has a complicated and protracted course, with morbidity related primarily to ophthalmologic complications. Death can occur from neurologic, cardiovascular, and gastrointestinal sequelae or from complications related to long-term immunosuppressive therapy.

Vasculitis Associated with Environmental or Foreign Antigen Exposure

Vasculitis Caused by Cocaine Adulterated with Levamisole. Levamisole is an immune-modulating agent that has been used to treat autoimmune disorders, various forms of cancer, and the nephrotic syndrome. The drug has been withdrawn from the U.S. market owing to the frequency and severity of side effects, including antibody-mediated agranulocytosis and autoimmune vasculitis. Since 2005, the incidence of cocaine cut with levamisole (added at the source of supply to add bulk and weight to the raw product) has been increasing, and some 70% of cocaine seized at U.S. borders contains levamisole to varying degrees.143 Levamisole is not detected by routine blood and urine toxicology testing, and specialized testing with gas chromatography or mass spectrometry is of limited clinical utility given the short half-life of the drug (5.6 hours); it is unlikely to be detected in the plasma or urine beyond 24 to 72 hours after the last exposure.143

The rash associated with levamisole involves tender palpable purpuric plaques with a predilection for the cheeks, nose, and earlobes (Fig. 118-10). Treatment is typically supportive; spontaneous resolution occurs with discontinuation of the offending agent. The agranulocytosis associated with levamisole is transient.
and fully reversible within a week to 10 days after discontinuation of the offending agent. Patients may present with asymptomatic agranulocytosis detected on routine blood work or with fever, sepsis, or signs of overwhelming infection. Febrile patients are treated aggressively with broad-spectrum antibiotics and a septic workup directed at the likely source of infection, similar to febrile neutropenia associated with chemotherapy. Afebrile patients are also often admitted for investigation and observation until their neutrophil count recovers.

**Cryoglobulinemic Vasculitis.** Cryoglobulins are immunoglobulins that precipitate from serum at cold temperatures.\(^{144}\) Damage to small and medium-sized blood vessels occurs when cryoglobulins bind to circulating antigens and deposit in vessel walls, prompting a complement-mediated inflammatory reaction and cryoglobulinemic vasculitis.

Three types of cryoglobulinemic vasculitis syndromes have been identified. Type I is associated with Waldenström’s macroglobulinemia and multiple myeloma and produces a syndrome of hyperviscosity with symptoms of presyncope, altered mental status, and stroke. Types II and III are known as the mixed cryoglobulinemias and represent 80% of recognized cryoglobulinemic syndromes. There is a strong association between these subtypes and hepatitis C, Sjögren’s syndrome, and SLE. The mixed cryoglobulinemias are manifested with a triad of purpura, arthralgias, and myalgias along with glomerulonephropathy and vasculitic peripheral neuropathy. Purpuric lesions are typically multiple and confluent and appear preferentially in dependent areas and the lower extremities in particular.\(^{144}\) Renal failure is the most serious consequence of cryoglobulinemia and is present in 20 to 60% of patients.\(^{145}\)

The diagnosis is based on the presence of serum cryoglobulins accompanied by typical clinical features; the most salient elements of the differential diagnosis include SLE and Henoch-Schönlein purpura. Skin biopsy can be helpful in confirming the diagnosis.

Management involves identification and treatment of associated diseases, such as hepatitis C and multiple myeloma. Low-dose corticosteroids are helpful when systemic symptoms are present but should be avoided while antiviral therapy is being initiated. Plasmapheresis may be useful in life-threatening cases related to cryoprecipitation or serum hyperviscosity. Features associated with Buerger’s disease, serum sickness, and hypersensitivity vasculitis are outlined in Table 118-7.

**Table 118-7  Summary of Buerger’s Disease (Thromboangiitis Obliterans), Serum Sickness, and Hypersensitivity Vasculitis**

<table>
<thead>
<tr>
<th><strong>BUERGER’S DISEASE</strong></th>
<th><strong>SERUM SICKNESS</strong></th>
<th><strong>HYPERSENSITIVITY VASculitis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>Small and medium-sized arteries and veins of the extremities</td>
<td>Immune complex deposition in blood vessel walls</td>
</tr>
<tr>
<td>Associated exposures</td>
<td>Heavy cigarette smoking Cold exposure</td>
<td>Foreign protein or serum Penicillin-based antimicrobials Sulfa drugs NSAIDs</td>
</tr>
<tr>
<td>Common symptoms</td>
<td>Pain, paresthesias Claudication Rest pain</td>
<td>Fever, arthralgias, and diffuse lymphadenopathy Pruritus, skin lesions</td>
</tr>
<tr>
<td>Physical examination findings</td>
<td>Poorly healing wounds, ulcerations Splinter hemorrhages Digital ischemia and necrosis Distal-to-proximal progression</td>
<td>Urticaria Purpuric skin lesions Scarlatiniform rash Erythema multiforme Azotemia, proteinuria Myocarditis, pericarditis</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Angiography: demonstrates “corkscrew” pattern of collateral vessels; rule out other causes of ischemia</td>
<td>Clinical</td>
</tr>
<tr>
<td>Management and outcome</td>
<td>Smoking cessation Meticulous wound care Protection from trauma and thermal injury</td>
<td>Supportive Systemic corticosteroids for severe disease Recovery generally within 4–6 weeks</td>
</tr>
<tr>
<td>Comments</td>
<td>Up to 50% of patients who continue to smoke will require amputation</td>
<td>Incidence has decreased with modern immunization programs and the use of products derived from human serum</td>
</tr>
</tbody>
</table>

*NSAIDs,* nonsteroidal anti-inflammatory drugs.
Consultation with a rheumatologist may be helpful in diagnostic, management, and disposition decisions for patients with SLE.

**Vasculitides**

- Vasculitis syndromes should be considered in the presence of systemic symptoms such as fever, malaise, and weight loss plus pulmonary, renal, or cutaneous manifestations.
- Massive hemoptysis and acute renal failure can occur in Wegener’s granulomatosis, Goodpasture’s disease, microscopic polyangiitis, and Churg-Strauss syndrome. Tracheal stenosis may be present in Wegener’s granulomatosis, further complicating airway management.
- Many patients with established vasculitis are receiving high-dose or combination immune suppressive therapy, making them vulnerable to opportunistic infections and overwhelming sepsis.
References


