INTRODUCTION

Emergencies resulting from autoimmune processes or connective tissue diseases (CTDs) are relatively uncommon in critical care medicine (CCM); nonetheless, if present, they can be life-threatening. The term autoimmune describes a number of disorders whose basic underlying pathophysiology is a derangement of the immune system’s ability to recognize “self.” Virtually any organ system may be subject to an inflammatory assault by one’s own immune system. Such disease processes may range from relatively mild and indolent, to fulminant and life-threatening. The following are scenarios that may be encountered by the critical care provider:

- A patient may be admitted to the intensive care unit (ICU) because of CTD complications or the complications of drug therapy;
- Clinical manifestations of CTD can affect every major organ.
- Clinical presentations vary and may include stridor, acute or progressive respiratory failure, life-threatening hemoptysis, acute renal failure, paralysis, cerebritis, mesenteric ischemia, or unstable spine. Septic shock due to an infected joint may occur.
- Placing an arterial line or obtaining a reliable pulse oximetric signal in a patient with systemic sclerosis (SSc) or severe vasculitis may be a problem.
- Some of the drugs used to treat these diseases may cause acute or chronic respiratory failure as well as mimic infection.
- Most of the drugs used to treat these diseases suppress the patient’s immune system, resulting in exposure to severe and uncommon infections.
- Presentation with acute, severe organ failure may be the first presentation of autoimmune disease (AD).
- Placing central venous line in a patient with unstable or motion-limited spine may be a problem.
- Minor trauma can cause disastrous consequences to a patient with ankylosing spondylitis.

Even though the exact causes and pathophysiology of many CTDs remain unclear, our understanding of the immunologic alteration and its manipulation by drugs has improved significantly in the last decade. New immune modulators have caused new complications as well.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA), a systemic debilitating AD affecting 1% to 2% of the population worldwide with women affected two to three times more than man is characterized by chronic progressive bilateral, inflammatory arthritis, and synovitis with other systemic manifestations. The involvement of extra-articular systems like the pulmonary, cardiovascular, renal, nervous systems, the skin, and the eye, with the tendency for infections and adverse effects of immunosuppressive drugs, expose the patient to multisystem disease which can lead to a life-threatening situation. RA—together with systemic lupus erythematosus (SLE)—is one of the leading diagnoses in patients with AD who are admitted to the ICU (1,3). It is likely that the interaction of genotype, environmental factors—like exposure to smoking and certain infections (EBV, CMV, *Escherichia coli* and Proteus)—and endogenous antigenic stimuli are the keys to the development of the disease (2). Molecular mimicry of a shared epitope by microbial proteins, epitope on T-cells containing human leukocyte antigen (HLA) molecules, and a potential proinflammatory signaling function that is unrelated to the role of the shared epitope in antigen recognition, lead to the destructive process.

The synovium in RA contains abundant myeloid cells and plasmacytoid dendritic cells that express cytokines (interleukin [IL]-12, -15, -18, and -23), HLA class II molecules, and stimulatory molecules that are necessary for T-cell activation and antigen presentation. Cytokines imported into the inflamed organ include tumor necrosis factor-α (TNF-α), IL-1, -2, -6, and lymphotoxin-β (2). A variety of innate effector cells—macrophages, mast cells, and natural killer cells—are found in the synovial membrane (2). The disease may involve many other mediators and cytokines in complex interactions and intracellular signaling pathways. Proteolytic enzymes have the ability to degrade components of the extracellular matrix and damage joints.

The role of antibodies against citrullinated peptides (ACPA) and extra-articular manifestations has been investigated over the last decade. Citrullination is a process in which arginine is converted to citrulline and as such its immunogenicity increases. In RA, a range of synovial proteins can become citrullinated and incite an antibody response (3). The American Rheumatology Association has established criteria for the diagnosis of RA that include joint involvement, serology (RF and ACPA), acute-phase reactants (ESR and CRP), and duration of symptoms (more or less 6 weeks) (4). Generalized fatigue, weakness, and involvement of other organs are common in patients with positive RF. Extra-articular manifestations of RA are common, but variable; they appear to be immune mediated and can shorten survival. The systemic manifestations of RA and their management present a unique challenge to the intensivist.

Pulmonary Manifestations of Rheumatoid Arthritis

The pulmonary complications of RA include all parts of the respiratory system—pleura, upper and lower airways,
parenchymal diseases, vascular, and musculoskeletal. The complications may be caused either by the disease itself, secondary to the treatment drugs or by other comorbidities like pulmonary embolism and lung cancer. The pulmonary complications in RA include manifestations such as pleural disease, rheumatoid nodules, Caplan syndrome, bronchiectasis (BE), and, in particular, interstitial lung disease (ILD) (9). All contribute to overall mortality.

**Pleural Involvement**

The involvement of the pleura is common (70% on autopsy studies) but with less clinical importance (only 3% to 5% are symptomatic) (3,7). Pleural disease is more frequent in males, patients over the age of 35 years and those with rheumatoid nodules. Most effusions are unilateral and symptoms of fever and pleuritic chest pain are common. A comorbid presentation of pericardial effusion is possible. Pneumothorax, although occurring, is rare (5,6). The mechanisms that have been suggested for the generation of pleural effusion in RA patients are impaired fluid reabsorption in inflamed pleura, necrosis of subpleural rheumatoid nodules, and capillary leak due to local production of cytokines and immune complexes (5). A thoracentesis should be done to make the diagnosis. The typical rheumatoid effusion is a turbid, straw-colored fluid (2). The white blood cell (WBC) count differential may be variable, ranging from primarily neutrophils in acute pleural effusion to mainly lymphocytes in fluid of 7 days of age and more; in 15% of cases, the predominant WBC type will be eosinophils (8). Infection must always be ruled out. Long-standing inflamed pleura can result in “pleural cast,” a situation in which evacuation of the pleural effusion does not result in re-expansion of the lung. In video-assisted thoracoscopy, the pleura appears thick and granular (7); peeling of the fibrous pleura might help in re-expanding the lung. Most cases of rheumatoid pleuritis improve with treatment of the underlying RA. Effusions that are small and asymptomatic do not require specific intervention and most of them will resolve within 3 years, with an average of 14 months (7).

**Interstitial Lung Disease**

ILD is the most common pulmonary manifestation of RA lung disease and, while the rate of some extra-articular manifestations of RA have decreased with improvements in therapy, the incidence of ILD has remained fairly stable (10). The prevalence of ILD was noted in 34% of autopsies in patients with RA although, clinically, only 10% will develop symptoms (9). This might be explained partially by masking of the symptoms of ILD by poor functional status from joint disease until the ILD has significantly advanced. Although RA is more common in females, RA-associated ILD occurs twice more frequently in males. Onset of lung disease typically occurs in the fifth to sixth decades of life. Aside from age, high levels of ACPA and a history of tobacco use are risk factors as well, with one study finding an odds ratio of 3.8 for those who smoked greater than 25 pack-years (7,11). The mechanism and pathogenesis of ILD and fibrosis is not completely understood, but the autoanti-bodies RF and ACPA play major roles. There is a theory that high titers of RF and ACPA can be detected in lungs of patients much before the clinical appearance of the joint inflammation (13). Symptoms of dyspnea with minimal activity or at rest in a patient diagnosed with RA, and in the absence of clinical suspicion for infection or other respiratory complications, should raise suspicion for the diagnosis of ILD (7). Other symptoms include dry cough, pleuritic chest pain, fever, hemoptysis, and tachypnea. Râles (9) at both bases on chest examination are the most frequent finding. Pulmonary function tests (PFTs) demonstrate a restrictive defect with impairment of forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) (7); this is associated with statistically significant poorer prognosis (14,15). Airflow obstruction may coexist and be seen in patients manifesting airway involvement, i.e., bronchiolitis obliterans. High-resolution CT (HRCT) may show variable findings—subpleural, basal predominant, reticular abnormalities with honeycombing, traction BE with or without ground-glass opacities. Less common findings are interstitial pneumonia, including organizing pneumonia, diffuse alveolar damage (DAD), lymphocytic interstitial pneumonia, and desquamative interstitial pneumonia, fibrosis, and emphysema (7). The gold standard for diagnosis is lung biopsy, although sometimes it is not mandatory and diagnosis can be made according to the history, clinical, and radiologic findings (7). The common pathologic findings are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). Rarer findings are organizing pneumonia and acute interstitial pneumonia with DAD (3). Treatment with high-dose corticosteroids is the mainstay of therapy, particularly for cases of NSIP or organizing pneumonia where they may lead to regression of consolidation on imaging and potential clinical improvement (15). Cyclophosphamide (CYC) and azathioprine (AZA) have been used with success as adjuvant therapy with steroids (15). There are some old case reports of ILD regression following cyclosporine treatment (7). Recently, treatment with mycophenolate mofetil (MMF) has demonstrated improvement in pulmonary functional tests—FRC, symptoms and imaging in patients with non-UIP patterns of ILD, and led to stabilization among those with UIP (16).

Cases of efficacy in RA–ILD have been reported with methotrexate (MTX) use, although the agent is known to be associated with drug-induced pneumonitis (15). Biologic agents, specifically rituximab (RTX), have been used with some studies reporting improvement (17) and other studies noting worsening of ILD and mortality within weeks after initiating the drug in a subgroup of older patients (18). Risks and benefits of disease modifying antirheumatic drugs must therefore be weighed carefully, but in patients with significant pulmonary disease, potential benefits often outweigh risks of drug toxicity (7).

In some cases, respiratory symptoms may precede articular symptoms (9). Once the ILD is established, it is associated with a poor prognosis and 5-year survival approximating 50%. RA–ILD is a significant cause of mortality, with a median survival of 2.6 versus 9.9 years in RA patients without ILD. The increased mortality in RA–ILD is mainly due to ILD progression to respiratory failure. The literature shows that ILD contributes approximately 6% to 13% of the excess mortality of RA patients when compared to the general population, being one of the most significant causes of death, together with
cardiovascular complications (10), in this patient population. ILD is second only to cardiac disease as a cause of mortality in RA. Additional risk factors for mortality include advanced age, male gender, UIP pattern and extent of fibrosis on imaging or histopathology, low DLCO, and dynamic decline in FRC (14,19).

Airway Disease in Rheumatoid Arthritis

Upper Airway Problems and Obstruction. The clinical presentation of upper airway disease occurs more frequently in females with long-standing or severe disease. The pathologic process can be divided into three categories—rheumatoid nodules which appear on the vocal cords, vasculitis affecting the recurrent laryngeal or vagus nerves leading to vocal cord paralysis, and arthritis of the cricoarytenoid joint. The prevalence of findings on HRCT varies between 54% and 72%, but symptomatic disease occurs in only 26% of patients with RA (20). Symptoms of odynophagia, hoarseness, throat soreness, and cough occur early; mild obstruction may progress to exertional dyspnea and stridor. Erythema, vocal cord edema, or stridor may occur secondary to local infection or previous intubation. It is essential to suspect and diagnose these conditions early to avoid an emergent situation; laryngoscopy and HRCT have both been used to diagnose RA of the larynx. Findings on HRCT include synovial thickening, excess of synovial fluid, erosion and subluxation of the cricoarytenoid joint, and abnormal position of the true vocal cord (TVC) (21). On laryngoscopy, focal vocal cord lesions, changes in aryttenoid symmetry, bowing of the TVC, or decreased mobility of the TVC can be seen (20). Mild symptoms may be managed with nonsteroidal anti-inflammatory drugs (NSAIDs); local, topical, or systemic steroids; or RA-directed therapy. For more severe obstruction, surgical intervention may be required in addition to immediate airway management. Tracheal deviation due to severe cervical spine disease or laryngeal abnormality can make oral intubation difficult or impossible in some patients; it is advisable to use a small-caliber tube when intubating patients with laryngeal disease. The inhalation of a helium–oxygen mixture (e.g., 75% He and 25% O2) may help in patients with stridor and dyspnea. In others, emergent tracheostomy may be necessary to establish an airway. In states of vocal cords in the adducted position, a unilateral aryttenoideectomy and suturing of the ipsilateral cord in abduction can be performed. As airway obstruction can occur following extubation; this should be performed when neuromuscular blockade is fully reversed and the patient is awake. Close observation following extubation is required and equipment should be readily available to manage the airway (22).

Lower Airway Problems

Hyperresponsiveness. The estimation of the prevalence of obstructive airway disease in RA patients is often confounded by smoking or the presence of other RA–ILD (7). It seems that there is perhaps a slightly higher rate of chronic obstructive pulmonary disease (COPD) in patients with RA compared to those without (23). Treatment of hyperresponsiveness with β-agonists, inhaled anticholinergics, and steroids is similar to the management of asthma or COPD in patients without RA.

Bronchiolitis—Follicular, Obliterans, and Obliterans with Organizing Pneumonia. Bronchiolitis refers to a pathologic process involving the bronchial wall. In follicular bronchiolitis, the pathologic process is bronchial dilation and wall thickening due to hyperplastic lymphoid follicles with germinal centers adjacent to airways. PFTs can demonstrate a restrictive or obstructive pattern. Treatment is directed at the underlying RA although severe or symptomatic disease might need corticosteroids and macrolide antibiotics (7). Obliterative bronchiolitis (also referred to as constrictive bronchiolitis) and obliteratorans with organizing pneumonia (BOOP) are more severe and often fatal conditions. The pathologic process is characterized by the presence of concentric fibrosis of the bronchial wall, with severe narrowing of the bronchiolar lumen with or without BE. Inflammatory infiltrates (predominantly lymphocytic) are present within the wall of bronchioles and centrilobular emphysema, adjacent to bronchiolar changes, could be present (24). It is more common in females and those with positive rheumatoid factor and long-standing untreated disease, and may also occur in the setting of certain medications including gold, penicillamine, sulfasalazine, and 5-fluorouracil, as well as postviral or Mycoplasma pneumoniae infections. In contrast to other rheumatoid lung manifestations, obliteratorans bronchiolitis presents with rapidly progressive dyspnea on exertion, cough, and bronchorrhea (24,25). HRCT findings are bronchial wall thickening, BE, mosaic pattern, centrilobular emphysema, and ground-glass opacities. PFTs show fixed airflow obstruction with a normal DLCO (24). Treatment includes discontinuation of the offending agent, which will occasionally result in the regression of symptoms; however, the overall prognosis is poor. High-dose corticosteroids and immunosuppression drugs like AZA and CYC have been used, although it is unclear whether these agents have any efficacy (24); a few case reports have described some improvement with anti-TNF therapy (26) and macrolide antibiotics may also be effective (25). In severe cases, lung transplant may be necessary.

Bronchiectasis. BE has been demonstrated on HRCT in approximately 30% of cases of RA, although it may be clinically silent (28); BE may precede or follow the development of RA (28). Patients with concomitant RA and BE have worse obstructive airways disease, increased susceptibility to recurrent pulmonary infections, faster lung function decline, and higher mortality rates compared to subjects with either condition alone (27). The use of immunosuppressive medications, particularly anti-TNF agents, increases the risk of pulmonary infections. Therapy is the same as for either condition alone, with bronchodilators, antibiotic, physiotherapy, and bronchial toilet.

Rheumatoid Lung Nodules

Rheumatoid nodules can occur in the lungs, particularly in patients with long-standing disease and with subcutaneous nodules. They are typically located along the interlobular septa or in subpleural regions. Nodules may be single or multiple, ranging in size from a few millimeters to several centimeters. Pathologic examination shows central fibrinoid necrosis with palisading mononuclear cells and associated vasculitis (7). Generally, the nodules are benign, cause no major symptoms, and are simply followed by periodic chest radiographs. Sometimes, however, nodules cavitate or rupture, and can cause hemoptysis, pneumothorax, pleural effusion, infection, or pyopneumothorax; confirmation to exclude coincidental
malignancy is very important. FDG-PET is a noninvasive imaging technique, which acts as a metabolic biopsy and can help in avoiding the morbidity and cost of invasive tissue sampling, but considering the lack of an established standard range of rheumatoid nodule metabolic activity, close monitoring, with or without the use of invasive diagnostic methods such as needle biopsy or VATS, is prudent in the management of lung nodules in RA (29,30). Caplan syndrome is a rare form of rheumatoid pulmonary nodules occurring with pneumoconiosis related to occupational exposure to coal, silica, or asbestos dust. The pathology is comparable to other rheumatic nodules in addition to pigmented cells seen due to pneumoconiosis. While the patients are most often asymptomatic with an overall good prognosis, sometime the nodules may become complicated with cavitation, infection, or rupture into the pleural space.

**Drug-Induced Lung Disease**

Most patients with diagnosed RA are on disease-modifying or immunosuppressant therapy; the lungs are commonly affected by these agents and, if the patient’s current drug therapy causes lung toxicity, withdrawal of the agent is necessary. Further, immunosuppressive therapy can predispose patients to systemic complications including infection; treatment with disease-modifying antirheumatic drugs (DMARDs) is associated with a high incidence of sepsis and malignancies. MTX, one of the most common first-line agents used to treat RA and hypersensitivity pneumonitis, has been well described in the literature. Incidence of MTX-induced lung disease is estimated 0.3% to 8% in 88 studies in which there were 3,463 RA patients treated with this agent (31). The clinical presentation of toxicity is not specific; dyspnea and nonproductive cough with or without systemic symptoms may predominate. HRCT demonstrates diffuse pulmonary opacities or patchy consolidation. BAL and lung biopsy are more helpful in ruling out alternative causes (i.e., infection) than in establishing the diagnosis of MTX-induced lung injury, although the presence of poorly formed nonnecrotizing granulomata and scattered eosinophils may suggest MTX-induced hypersensitivity pneumonitis, as these are not typical findings in RA–ILD (7). The diagnosis must be made after exclusion of other causes of pulmonary diseases. Treatment consists of drug cessation and, sometimes, corticosteroid therapy for patients who remain symptomatic after MTX withdrawal. Estimated mortality due to respiratory disease is 13% (31).

Leflunomide (LEF), a second-line therapy for RA used in place of MTX, has been associated with the development and exacerbation of ILD, potentially secondary to an active metabolite that may induce transition of lung epithelial cells to myofibroblasts, a process known as the epithelial–mesenchymal transition (7). LEF-induced ILD usually presents within the first 20 weeks of therapy initiation (33). Some risk factors noted are previous treatment with MTX, previous ILD, exposure to loading doses of LEF, and poor physical performance (32,33); LEF-induced ILD is a lethal complication with mortality rate of 19% (33). The main findings on CT scan are ground-glass opacities and honeycombing; the main histologic finding is DAD, which is a prognostic factor suggesting a poor outcome.

TNF-α inhibitors and RTX have been hypothesized to increase the risk of ILD, but clear causality has been difficult to prove. A randomized controlled trial evaluating the efficacy and safety of RTX in 465 patients with RA did not note any correlation with ILD (34). In fact, small case series have suggested a beneficial effect of RTX on CTD-associated ILD, with one retrospective review reporting improvement or stabilization of PFTs in 28 out of 33 patients (85%) with severe ILD (17). Another cohort study among 8,417 AD patients demonstrated that anti-TNF-α therapy, compared with nonbiologic therapies, did not increase the occurrence of ILD among patients with ADs (35). Another possible complication of anti-rheumatic drug therapy is noncardiogenic pulmonary edema (NCPE). This may be seen in patients taking high-dose aspirin, NSAIDs, MTX, and CYC, or in the setting of colchicine overdose. NCPE must be included in the differential diagnosis of any patient presenting with respiratory failure and a history of taking these drugs. Other complications of treatment with AZA include increased risk of lymphoma and malignant disorders (7).

**Acute Respiratory Infections in Rheumatoid Arthritis**

Serious infections are a major concern in patients with RA and contribute to an increased overall mortality. Acute respiratory failure (ARF) can occur either due to direct infection of the lung—i.e., pneumonia—or as systemic reaction to infection like acute respiratory distress syndrome (ARDS). Patients with RA have elevated susceptibility to serious infections due to features of the disease itself, comorbidities, and immune modulating agents (IMAs). Patients with RA treated with IMAs are in risk for opportunistic lung infections. TNF-α is involved in the host defense against invasion of viruses and bacteria, and glucocorticoids are immunosuppressive agents. Of note, mycobacterial disease has been highly associated with anti-TNF therapy (7). Activation of dormant tuberculosis, lung infections with *Pneumocystis jiroveci*, and a high incidence of influenza are only some of the opportunistic infections in RA patients; prophylactic therapy recommendations for patients starting IMAs have been promulgated (7,40). RA patients manifesting new ground-glass changes superimposed on their baseline underlying ILD is always a concern; in the appropriate clinical setting, patients must be evaluated with appropriate diagnostic interventions (7).

**Neurologic Complications and Cervical Spine Involvement in RA**

In general, neurologic symptoms and deficits are more common in RA patients than in normal controls (42). Cervical spine disease in RA may cause atlantoaxial subluxation, cord compression, and neurologic deficits. Patients with long-standing disease or/and early and extensive erosive peripheral joints are the most vulnerable to these pathologies. MRI, followed by surgery for decompression and fusion, should be considered in severe cases. Peripheral nerve involvement includes entrapment neuropathies like in carpal tunnel syndrome and mononeuritis multiplex that may be associated with muscle wasting and functional impairment. EMG and nerve conduction studies may be necessary for diagnosis. Treatment is mainly supportive, including modification of activities and splints, corticosteroid injections in appropriate sites (e.g., the carpal tunnel), treatment of the underlying disease, and surgery in cases where medical
management has failed. Other wide-spectrum conditions that occur in RA are attributed to vasculitis causing neuropathy, encephalopathy, and stroke (41,45). As intensivists, the clinical presentation of atlantoaxial subluxation with instability of the cervical spine is a critical problem. Therapy for cervical spine instability may be as simple as a cervical collar to maintain spinal stability, halo traction, or surgery. Neck positioning required for intubation can be fatal in patients with unrecognized C1–C2 disease.

**Airway Management and Anesthetic Implications of RA**

Airway management in a patient with upper airway, cervical spine, or laryngeal disease is both a concern and a challenge for the anesthesiologist and intensivist. Preoperatively, a thorough history of the RA, including duration of the disease, severity, drugs treatment, and systemic complications, is obtained. Physical examination, including the range of movement of all joints—and especially mouth opening—temporomandibular joint (TMJ) function, neck flexion and extension, and mandibular protrusion are evaluated. Pain assessment and a meticulous neurologic examination should be documented. Patients taking more than 10 mg of prednisone per day should be given an appropriate perioperative steroid cover; if MTX is being used, it should be continued (43). Perioperative discontinuation of other immunosuppressants and biologic therapy, for elective surgery remains controversial (44).

Airway problems may result from various causes, as discussed earlier. There are no published evidence-based guidelines nor a general consensus on the need to obtain cervical spine radiographs before surgery in asymptomatic patients. However, it may be reasonable to obtain such films in patients with longstanding and severe disease (44). The issue in RA patients is the increased prevalence of difficult airways; therefore, it is wise to assess, preinduction, potential difficulties in placement of an endotracheal tube in these patients. Neck positioning in direct laryngoscopic technique may be very difficult or potentially dangerous in some of these patients; hoarseness raises the suspicion of criocarotid involvement. Consideration will have to be given to avoiding endotracheal intubation in favor of a supraglottic airway device versus the use of an awake fiberoptic nasopharyngoscopy or glidescope (44); in severe cases, a preoperative tracheostomy may be required. On extubation, one may consider the use of an airway exchange device and observe the patient in a high dependency area for some time post extubation (44). In the postoperative period, careful observation of the airway and breathing pattern is required; pain should be adequately controlled to permit early mobilization, early DVT prophylaxis should be considered and, in case of infections, DMARDs should be suspended temporarily and appropriate antimicrobials started (44).

**Cardiovascular Manifestations of Rheumatoid Arthritis**

Cardiovascular disease is one of the leading causes of death among RA patients. Cardiovascular features in RA are common and can involve every part in the cardiovascular system. Pericarditis, cardiomyopathy/myocarditis, cardiac amyloidosis, coronary vasculitis, dysrhythmias, valvarl disease, and congestive heart failure (CHF) and ischemic heart disease are found more frequently and are associated with an increased mortality as compared with the general population (36).

**Pericardial Disease**

The most common cardiac involvement in RA is pericarditis. Although it occurs in 30% to 50% of patients—predominantly in males with severe disease—clinical evidence of pericarditis is present in less than 10%. Pericarditis may precede the diagnosis of RA in some patients, and diagnosis and early treatment can improve outcome. Treatment with NSAIDs, corticosteroids, and/or other immunosuppressive drugs seems appropriate in the majority of patients with a definite diagnosis of RA-associated pericarditis, and in severe cases, pericardectomy is warranted (36).

**Cardiomyopathy**

Histologic diagnoses of cardiomyopathy in postmortem studies are as high as 3% to 30%. The RA-associated cardiomyopathy may be the result of focal nonspecific, diffuse necrotizing, or granulomatous myocarditis. Some drugs used in the treatment of RA have also been associated with cardiomyopathy, for instance, corticosteroids and antimalarials (36). Cardiac amyloidosis is one of the causes of restrictive cardiomyopathy, and the infiltration with fibrillar proteins can cause a loss of compliance, impairing diastolic, as well as systolic, function. Immunosuppressive treatment should be considered if an RA patient is diagnosed with amyloidosis.

**Coronary Artery Disease**

Vasculitis of the coronary arteries has been observed in up to 20% of RA patients in postmortem studies. Differentiation between atherosclerosis and diffuse cardiac vasculitis may be made by the detection of coronary artery calcification on coronary CT for atherosclerosis. RA patients with life-threatening vasculitis should be treated promptly with immunosuppressive drugs (36).

**Rheumatoid nodules**—also called rheumatoid granuloma—may occur in all organs and also in the epicardial fat, epicardium, myocardium, interventricular septum, chordae tendineae, aorta, and valves. If functional impairment occurs resultant from these nodules, surgical treatment should be considered (36).

Dysrhythmia is an important cause of mortality in RA and may be secondary to ischemia, conduction abnormalities due to rheumatoid nodules, amyloidosis, or CHF. It seems that RA patients may have an increased sympathetic activity, which could play a role in the development of ventricular tachydysrhythmias.

**Valvular Disease**

The most prevalent valve disease in RA is mitral insufficiency, followed by aortic insufficiency. CHF contributes to the excess mortality primarily through the increased incidence of CHF in RA, rather than increased mortality associated with CHF in patients as compared with non-RA patients (37). Left ventricular systolic dysfunction has been found to be three times more common than in the general population, and is associated with abnormal electrocardiography, suggesting that echocardiographic screening of RA patients with abnormal...
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Electrocardiography may be worthwhile. Additionally, right and left ventricular diastolic dysfunctions are found more frequently in RA patients without evident cardiovascular disease (38). Recurrence of cardiac events appears to be higher among RA patients as compared with matched controls. Cardiovascular death seems to be associated with markers of systemic inflammation in RA, i.e., increased sedimentation rate, RA vasculitis, and RA lung disease (39). The use of corticosteroids and MTX is associated with a reduced cardiovascular mortality and morbidity (36).

Vasculitis and Skin Involvement

Patients with active extra-articular disease and high rheumatoid factor titer can develop vasculitis, which may then manifest as muscle pain or weakness, infarcts of the nail beds, and gangrene of the fingertips due to distal arteritis, cutaneous ulcerations, sensory neuropathy, or mononeuritis multiplex. Arteritis of visceral vessels may manifest as abdominal pain; the lung, heart, and spleen may also be involved (45). Skin manifestations are frequently associated with episcleritis, as well as pleural and pericardial effusions. Rheumatoid nodules are the most frequent skin manifestation in RA. The pathologic process is vasculitis of small vessel with central fibrinoid necrosis surrounded by fibroblasts. Subcutaneous nodules commonly appear on extensor surfaces subject to external pressure, for example, the upper forearm and elbow. Pyoderma gangrenosum is a rare disease associated with RA. It is characterized by chronic, recurrent ulceration of noninfective origin; it is a circumscribed necrotizing vasculitis of unknown etiology. Although these lesions typically affect the lower limbs, they can also affect the entire body (45).

Muscle Involvement

Muscle weakness in a patient with RA is common and multifactorial; it may be due to synovitis and joint disease, deformed joints, myositis, or polymyositis and, occasionally, it is resultant from drug-induced myopathy. Corticosteroids, HMG-CoA inhibitors, and antimalarial drugs can also cause muscle weakness or myopathy.

Osteoporosis, Osteopenia, and Skin Involvement

Osteoporosis and osteopenia of the hip or lumbar spine are common in patients with RA, usually resulting in stress fractures of long bones and vertebral compression deformities. Skin changes include atrophy and ecchymosis due to steroid use, and ulceration due to chronic stasis, arterial insufficiency, or neutrophilic dermatoses.

Renal Involvement

Renal involvement in RA is rare. Absent vasculitis, glomerulonephritis, and interstitial nephritis are uncommonly seen (45). Secondary amyloidosis is the most common finding among patients with nephritic syndrome. Frequently, however, renal abnormalities are iatrogenic and caused by medications used to treat RA, especially NSAIDs, gold, cyclosporine, and penicillamine.

Hematologic Involvement

Hematologic manifestations in RA can be broadly categorized into areas of anemia, neutropenia, thrombocytopenia, thrombocytosis, eosinophilia, and hematologic malignancies (45). Anemia of chronic disease, a normocytic hypochromic pattern, is the most common extra-articular symptom of active disease. The degree of anemia correlates with disease activity, degree of articular inflammation, and the erythrocyte sedimentation rate (ESR). Felty syndrome is a clinical condition characterized by an enlarged spleen, anemia, and thrombocytopenia. These patients may come to the ICU postsplenectomy. Pseudo-Felty syndrome, or “large granular lymphocyte (LGL) syndrome,” is characterized by splenomegaly, circulating LGLs, and neutropenia; these patients are prone to repeated infections. Lymphoproliferative disease can occur in patients with RA and, in some, may be due to therapeutic interventions—especially MTX and the newer biologic DMARDs.

Central Nervous System Involvement

The central nervous system (CNS) is usually not affected in RA, although small-vessel vasculitis of the vasovasorum of nerves can cause mononeuritis multiplex and peripheral neuropathy (45). Cervical myelopathy, caused by atlantoaxial subluxation or pannus formation, occurs frequently in RA patients with severe and long-standing disease.

Eye and Oral Involvement

The most frequent ocular manifestation of RA is keratoconjunctivitis sicca, affecting at least 10% of patients. It is frequently observed together with xerostomia in a secondary Sjögren syndrome (SS) (45). Episcleritis, inflammation of the layer superficial to the sclera, occurs in less than 1% of patients with RA and is generally a self-limiting condition. Scleritis is a more aggressive process, characterized by an intensely painful inflammation of the sclera itself. Peripheral ulcerative keratitis develops as an extension of scleral inflammation with involvement of the peripheral cornea and can lead to corneal melting (45).

Treatment of Rheumatoid Arthritis

The therapy of RA has evolved significantly in the past few years. The proper management of RA requires the identification of the stage, activity, and severity of disease. Early aggressive therapy is given to minimize the severe disability commonly seen in patients with advanced RA, but the goal of complete remission remains elusive (7). While a clear, optimal drug treatment algorithm is lacking, in general, the drugs can be divided into three classes: (a) NSAIDs; (b) glucocorticoids; and (c) DMARDs, both traditional and biologic. In general, NSAIDs and corticosteroids have a short onset of action while DMARDs can take several weeks or months to demonstrate a clinical effect. Traditional treatment is started with NSAIDs for symptomatic relief of stiffness and pain. Because cartilage
damage and bony erosions frequently occur within the first two years of disease, rheumatologists now move aggressively to a DMARD agent early in the course of disease, usually as soon as a diagnosis is confirmed. DMARDs have a slower effect upon RA than NSAIDs and corticosteroids, but DMARD agents alter the disease course of RA and improve radiographic outcomes.

DMARDs should be started as soon as RA is diagnosed; analgesic drugs are also sometimes helpful in decreasing pain until DMARDs take effect. Corticosteroids are used for flare-ups, although, like the DMARDs, their side-effect profile is significant. Aggressive biologic therapy targets specific components of the immune response, such as inhibition of TNF by monoclonal antibodies, inhibition of IL-1, inhibition of T-cell activation, and B-cell depletion. The first-line therapy is MTX alone or in combination with sulfasalazine and hydroxychloroquine, termed “triple therapy.” The currently available drugs are summarized in Table 141.1.

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<td>Nonsteroidal anti-inflammatory drugs (NSAIDs)</td>
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<tr>
<td>Corticosteroids</td>
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<tr>
<td>Tumor necrosis factor alpha (TNF) inhibitors</td>
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<tr>
<td>T-cell costimulatory blockade</td>
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<td>B-cell depletion</td>
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<tr>
<td>Interleukin-6 (IL-6)</td>
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<tr>
<td>Interleukin-1 (IL-1)</td>
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<tr>
<td>Other immunomodulatory and cytotoxic agents</td>
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**Diagnosis, Treatment, and Monitoring of Lung Disease in RA**

The treatment of lung disease in RA is empiric, based upon the underlying problem. Usually, the pulmonary manifestations of RA respond well to corticosteroids; other immunosuppressive drugs are often added when pulmonary disease progresses and/or steroid side effects appear. It is important to differentiate between the pulmonary effects of the underlying CTD and complications due to treatment, such as opportunistic infections, and toxic and idiosyncratic drug reactions. Unrelated primary pulmonary disease such as COPD may also be present.

Investigation can start with bronchoalveolar lavage (BAL) and, if further investigation is needed to establish or exclude a diagnosis of lung involvement, open-lung biopsy is the gold standard (7,48). As the natural history is variable, clear guidelines for monitoring lung disease do not exist. Obtaining
baseline PFTs, including spirometry, lung diffusion, and lung volumes, is important, and follow-up tests can be tailored based on the patient’s symptoms. Once abnormalities are detected, or a patient is on treatment, appropriate follow-up with PFTs and chest CT may be done. High-resolution chest CT appears more sensitive than PFTs for detecting small airway disease (7).

ICU, Postoperative Care, and Outcomes

Patients with RA may be admitted to the ICU due to non–RA-related medical or surgical diseases requiring ICU care (46–48). Medical complications from the drug treatment of RA can occur, including severe sepsis and shock, gastrointestinal (GI) bleeding, airway compromise due to sedative and narcotic use, respiratory failure from lung disease, or spinal cord compression and neurologic impairment. Careful administration of the drugs and close monitoring are essential. Respiratory failure due to restrictive or obstructive lung disease also makes these patients susceptible to pulmonary complications. Close neurologic monitoring of these patients is important.

Prospective studies evaluating ICU admission and outcome of patients with RA are limited (46) and most studies are retrospective in nature (47,48). All appear to show a mortality rate ranging between 21% and 50% and more than 50% of the patients have respiratory involvement (46). Such analyses are good for predicting outcome in a research setting, but are difficult to use in predicting the outcome of an individual patient. Short-term mortality correlates with a higher simplified acute physiologic score (SAPS) or SOFA score, poor health status, prior corticosteroid therapy, and infection. Acute infection, the main reason for ICU admission, is a negative predictor for survival.

Invasive Monitoring Catheter Placement

Placing a radial arterial catheter may be difficult in advanced cases of RA due to joint flexion deformities at the wrist; additionally, arteries may be small and calcified. Patients may have severe peripheral arterial disease, vasculitis, or carpal tunnel syndrome, and may be at risk of increased complications of the radial artery arterial line placed (12,13). It is better to avoid inserting a peripheral arterial catheter in a patient with Raynaud phenomenon (RP). If a patient needs continuous blood pressure (BP) monitoring, one should preferably insert a femoral arterial line. Central line placement in the neck may be a problem due to fusion or flexion deformities of the cervical spine.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is an inflammatory arthropathy that affects predominantly young adults, with an average onset of age between 20 and 30 years. The majority of patients with AS present HLA-B27, which is reported to contribute to the pathophysiologic manifestations of this disease. AS mainly involves the axial skeleton; it often begins in the sacroiliac joints and then ascends to involve the remaining spine (41). The main complication in AS is neurologic involvement due to axial disease with fusion of the bones in the spine, which causes loss of flexibility of the back and necks. Other manifestations are pulmonary, cardiovascular, GI, and renal, along with a possible involvement of the eyes (49–52).

Cardiac manifestations in patients with AS are found in 2% to 10% of patients (49). The pathologic process is inflammation coupled with platelet aggregation, leading to endarteritis around the aortic root and valve. This process stimulates fibroblast hyperactivity resulting in tissue thickening involving the aortic anulus, cusps, aortmitral junction along with the conduction system (49). This explains the high incidence of aortic (82%) and mitral disease, and arrhythmias in AS. Aortic regurgitation is most commonly seen in patients with AS; however, mitral regurgitation is also known to occur, although less commonly (49). Conduction and rhythm abnormalities are among the most commonly observed cardiac manifestations of patients with AS; these usually predate other cardiac manifestations such as valvular insufficiency. In addition, first-degree AV block has been found in HLA-B27 positive patients, even in those without rheumatologic manifestations of AS (49). Other abnormalities include sinus tachycardia and prolonged QT interval. These patients are more prone to autonomic dysfunction and orthostatic hypotension (49). The myocardium is involved, as well, with impairment of coronary microvascular function and LV diastolic function, and the severity of these impairments correlates well with high levels of CRP and TNF-α (49).

Pulmonary manifestations of AS include fibrosis of the upper lobes, ILD, and ventilatory impairment due to chest wall restriction, sleep apnea, asthma, and spontaneous pneumothorax (49–51). Subclinical abnormalities can be demonstrated in HRCT; the lung parenchymal abnormalities include emphysema, apical fibrosis, mycetoma, and nonspecific ILD (49). The abnormal lung parenchyma is a fertile bed for superinfection with a variety of organisms including atypical mycobacterium, Mycobacterium tuberculosis (TB), and Aspergillus. Restricted chest wall motion can lead to restrictive pulmonary function. Dorsal kyphosis from involvement of the thoracic spine, costovertebral, sternoclavicular, and sternomanubrial joints leads to impairment of chest wall expansion with breathing, with or without abnormal PFTs (49). Spontaneous pneumothorax is a very rare complication of AS and correlates with apical lung fibrotic changes. The incidence of obstructive sleep apnea (OSA) is three times higher than that seen in the general population. Possible mechanisms for the development of OSA in AS are restriction of the oropharyngeal airway by compression from cervical spine involvement or temporomandibular involvement, restrictive pulmonary disease, and cervical spine disease causing compression of the medullary respiratory centers (49). A formal sleep evaluation should be considered in patients complaining of severe fatigue. Treatment of OSA in AS is the same as for patients without AS and includes continuous positive airway pressure (CPAP), smoking cessation, and, if needed, weight loss to achieve a normal body mass index. Interestingly, treatment with anti-TNF-α agents improves AS patients’ assessment of sleep disturbances (49,50).

Renal diseases associated with AS include renal dysfunction due to analgesic use or abuse—especially NSAIDs—IgA nephropathy, and secondary amyloidosis; end-stage renal disease may result, and the prognosis is poor (50).

GI manifestations consist of asymptomatic ileal and colonic mucosal ulcerations detected by endoscopic examination.
Endoscopically, lesions were found seven times more frequently in patients with spondyloarthopathy compared with patients with other inflammatory arthritides.

Eye involvement may also occur, including uveitis, cataracts, glaucoma, intraocular pressure, and macular edema.

**SYSTEMIC SCLEROSIS: SCLERODERMA**

SSc is a systemic AD characterized by endothelial dysfunction resulting in a small-vessel vasculopathy, fibroblast dysfunction with excessive collagen production and fibrosis, and immunologic abnormalities. The classification of SSc is subdivided based on the extent of skin involvement into diffuse cutaneous sclerosis (dcSSc), limited cutaneous sclerosis (lcSSc) or SSc sine scleroderma (53). In the diffuse type of scleroderma, any organ system may be involved in the disease process—musculoskeletal, kidney, lung, circulatory system, and the GI tract. Fibrotic and vascular pulmonary manifestations of SSc, including ILD and pulmonary arterial hypertension (PAH), are the leading causes of death (54). The lcSSc, characterized by CREST syndrome, consists of calcinosis cutis, RP, esophageal dysmotility, sclerodactyly, and telangiectasia.

RP is episodic, reversible arterial vasospasm in the digits, characterized by sequential color changes of pallor (“white”), acrocyanosis (“blue”), and reperfusion hyperemia (“red”). It is precipitated by changes in temperature or stress. Some patients with SSc can develop progressive structural changes in the small blood vessels, with permanently impaired flow, digital ulceration, or infarction. Vascular injury and subsequent chronic damage underlies other serious complications of SSc, including PAH, scleroderma renal crisis, and gastric antral vascular ectasia, and contributes to the pathogenesis of cardiac and GI complications.

The lungs are involved in almost 100% of the patients, whether with or without symptoms. The abnormalities are divided into direct pulmonary involvement—ILD with or without PAH, airways disease, and pleural involvement, or indirect pulmonary complications—aparation, infection, drug toxicity, malignancy, respiratory muscle weakness, restrictive lung disease from chest wall involvement, and lung disease secondary to cardiac involvement (54). Clinically, parenchymal lung involvement often appears early after the diagnosis of SSc, with 25% of the SSc patients developing progressive dyspnea, cough, and respiratory failure within 3 years (55). The pathologic process is presumed to be related to abnormal interactions between endothelial cells, lymphocytes/macrophages, and fibroblasts leading to an excess production of extracellular matrix by fibroblasts, increased levels of the pro-inflammatory cytokines IL-8, TNF-α, and macrophage inflammatory protein-1α, and autoimmune antibodies, in combination with genetic and epigenetic regulators (56,57). In up to 75% of patients, PFTs show a reduction in FVC; a reduction in DLCO is seen in almost all patients (54). HRCT may demonstrate NSIP, ground-glass opacities, and/or coarse reticulations or honeycomb cysts; definitive diagnosis may be made by lung biopsy (54).

Treatment for ILD should be given as early as possible since even the most efficient treatment cannot reverse a damaged lung. Treatment should be given as soon as PFTs demonstrate progression in reduction in FVC and DLCO. The initial therapy is CYC or MMF; the latter has same effectiveness as CYC according to recent studies (58). Glucocorticoids or RTX may be used for refractory disease, and lung transplantation for end-stage lung disease (59). There are some promising experimental studies that demonstrate an improvement of skin and pulmonary function after nonmyeloablative autologous hematopoietic stem cell transplantation; this is superior to treatment with CYC for up to 2 years, but still follow-up is needed (60).

Pulmonary vascular disease that leads to PAH is most common in SSc patients. PAH may occur in 10% to 33% of patients with progressive SSc. An autopsy study revealed changes compatible with PAH in 50% of patients with the CREST syndrome; while PAH in SSc patients is almost exclusively associated with ILD, it may be the sole pulmonary manifestation in patients with the CREST syndrome (61). The pathologic process of PAH in collagen vascular diseases is characterized by chronically impaired endothelial function, increased pulmonary vascular resistance due to remodeling, and occlusion of the pulmonary arterioles (62). Clinical findings of PAH are subtle in the beginning, including dyspnea on exertion, low exercise tolerance, palpitations, and the development of edema and ascites due to overt right heart failure (61). Echocardiography is the most important diagnostic tool in patients with suspected PAH and should be used as a screening tool in patients at high risk for the development of PAH (61). PAH associated with SSc is not responsive to calcium channel blockers or anti-inflammatory drugs like glucocorticoids and/or immunosuppressive therapy. Prostacyclin (e.g., epoprostenol) has potent pulmonary vasodilator, antiplatelet aggregating, and antiproliferative properties. Continuous intravenous epoprostenol improves exercise capacity and hemodynamics compared with conventional therapy; however, there has been no demonstrable effect on survival rate (62). Sildenafil, a phosphodiesterase type V inhibitor that reduces the catabolism of cGMP, thereby enhancing the cellular effects mediated by nitric oxide, has become a widely used and highly efficacious therapy for PAH; such as, silde-nafil is a first-line drug of choice for oral therapy for functional class (FC) II or III SSc PAH patients. The impact of long-term sildenafil therapy on survival in patients with SSc–PAH remains to be determined (62). Endothelin receptor antagonist (Bosentan) is effective in idiopathic PAH and in PAH related to CTD—particularly SSc—improving 6-minute walk distance, hemodynamic parameters, and time to clinical worsening (63). Moreover, Bosentan has a beneficial effect on the prevention of new digital ulcers (up to almost 50% less new digital ulcers). The treatment effect appears to be more pronounced in the most severe cases (patients with three or more digital ulcers at baseline) (63). PAH is progressive and often fatal within 5 years.

GI involvement is very common in patients with scleroderma, including esophageal hypomotility, gastroesophageal reflux, chronic esophagitis, and stricture formation, all of which may result in aspiration pneumonia, pseudo-obstruction, malabsorption, and fecal incontinence. Vascular ectasia in the stomach is not uncommon and may cause chronic GI bleeding and anemia.

Kidney disease is very common in SSc and may be asymptomatic. Autopsy data suggests that 60% to 80% of patients with the diffuse type of SSc have kidney damage; acute onset...
of renal failure with moderate or malignant hypertension may be noted. Microangiopathic hemolytic anemia, pulmonary edema, headache, blurred vision, hypertensive encephalopathy, or seizures may also occur. Treatment with angiotensin-converting enzyme inhibitors may be helpful in improving local blood flow. Sildenafil and Bosentan may be used for improvement of the peripheral and pulmonary circulation.

A patient with SSc is a huge challenge to the intensive care physician. Pulmonary and cardiac insufficiency, renal crisis, skin lacerations, GI bleeding, and sepsis in immune compromised patient are only part of the difficulties these patients may have. Sometimes the admission to ICU is the first crisis in an undiagnosed SSc patient and one will need all the expertise to diagnose and treat this population. The outcome of SSc patients admitted to the ICU is extremely poor and depends on the severity of the underlying visceral organ involvement and the timing of admissions (64).

### SJÖGREN SYNDROME

SS is a chronic autoimmune inflammatory disorder characterized by diminished lacrimal and salivary gland function. SS can exist as a primary disorder or as a condition that is associated with another well-defined autoimmune process such as RA, SLE, scleroderma, or inflammatory myositis. The diminished exocrine gland function leads to the “sicca complex,” a combination of dry eyes and dry mouth (65). Extraglandular features may also occur, including vasculitis, pulmonary disease, peripheral and CNS abnormalities, cardiovascular manifestations, and the involvement of GI tract, renal and musculoskeletal systems (66); lymphoma may be noted several years after the diagnosis of SS.

Few reports have been published regarding the characteristics and outcome of SS patients in ICUs. One report evaluated the causes for hospitalization in SS primary SS patients, noting that 7 of them were admitted to the ICU (67). The main causes for hospitalization in these 55 patients were disease activity (33.3%) and infection (32.4%). Hepatic involvement, vasculitis, and increased disease damage were associated with higher risk for hospitalization in SS patients (67).

Lung involvement including airway manifestations such as bronchiolitis, interstitial pathologies—nonspecific interstitial pneumonitis, usual interstitial pneumonitis, and lymphocytic interstitial pneumonitis—and PAH may lead to ICU admission. In addition, CNS manifestations such as transverse myelitis and CNS vasculitis due to SS are possible causes for ICU admissions.

### IDIOPATHIC INFLAMMATORY MYOPATHIES

Idiopathic inflammatory myopathies, including dermatomyositis (DM) and polymyositis (PM), are usually associated with progressive, symmetrical muscle weakness over several months. However, an acute disease onset is occasionally seen and underlying muscle disease may be suspected and evaluated only later during the ICU stay. The most common indication for admission to the ICU and death in patients with DM is respiratory failure due to exacerbation of muscle weakness, ILD, or recurrent aspiration, pneumonia, and sepsis (68–71).

Cardiac complications of inflammatory myopathies including tachydysrhythmias, conduction abnormalities, or heart failure with a dilated cardiomyopathy may also require ICU admission. Inflammatory myopathies are associated with an increased mortality rate (72).

### SYSTEMIC LUPUS ERYTHEMATOSUS

#### General Considerations and Epidemiology of ICU Admissions

SLE is a chronic autoimmune inflammatory disease with a variety of presentations that may be organ or life-threatening. According to the American College of Rheumatology (ACR) classification criteria, the diagnosis of SLE is made when four or more of the criteria are met, either simultaneously or serially, as shown in Table 141.2 (73). Recently, the Systemic Lupus International Collaborating Clinics (SLICC) group revised and validated the ACR SLE classification criteria. According to the SLICC group (Table 141.3), the patient must satisfy at least four criteria, including at least one clinical criterion and one immunologic criterion, OR the patient must have biopsy-proven lupus nephritis (LN) in the presence of antinuclear antibodies or anti–double-stranded DNA antibodies (74).

SLE may be influenced by a variety of factors, including those genetic, hormonal, environmental, and immunologic. SLE affects adult women approximately 10 times more frequently than men, with a predilection for females in their 20s or 30s; the course of SLE may be indolent or explosive.

In the 1950s, only 50% of SLE patients survived past five years. However, this rate has increased to over 90% in the 2000s (75). The increase in five-year survival rate may be attributed to several factors, including recognition of milder forms of the disease, improved diagnostic techniques, and earlier therapeutic intervention. In addition, more efficacious use of therapeutic modalities such as immunosuppressive agents, antibiotics, antihypertensive drugs, hemodialysis, and transplantation may have improved the survival rate of SLE patients.

However, some SLE patients require hospitalization in an ICU due to (1) manifestations of the disease (e.g., an exacerbation, a new manifestation, or even the diagnosis of the disease); (2) infections; and (3) acute, nondisease-associated serious illnesses that may be aggravated by the underlying disease. Notably, an increasing number of reports regarding SLE in ICUs have been published in last 15 years. Review of published literature on ADs in ICUs revealed that since the year 2000, SLE has replaced RA as the most frequent AD found in ICUs (1), with a prevalence of 38% to 61% (76–78). These changes may be related to the intensive treatment of RA, which led to a significant decrease in the systemic complications of this disorder. Furthermore, systemic involvement in SLE may be responsible for the increased ICU admission rates. According to several early studies, 4% to 4.9% of hospitalized SLE patients required ICU admission (79–80). However, more recent study states that the proportion of ICU admission was higher and reached 13.8% from all the patients hospitalized due to SLE (81). In addition, a higher ICU mortality rate was found in SLE patients (28% to 79%) (82–90) in comparison with all other ADs patients (17% to 55%) (67).
Causes of ICU Admission

Infection

Infection and disease flare-up are the most common reasons for ICU admission of SLE patients. Several studies have shown that infections, mainly pneumonia (77,79), are the leading cause for ICU admission in patients with SLE (83,88,92).

One recent study regarding this issue found that 35.7% of the SLE patients hospitalized in an ICU between 2002 and 2010 suffered from infections (93). A comparison between SLE patients admitted to the ICU due to an infection and SLE patients admitted due to noninfectious causes did not demonstrate a correlation between increased risk for infection and any particular clinical features of SLE. However, SLE patients with infections had a higher APACHE II score, higher maximum temperature, higher minimum and maximum heart rate (HR), lower minimum and maximum systolic blood pressure (SBP), and longer ICU length of stay compared to SLE patients with noninfectious causes. No statistical differences in WBC (SBP), and longer ICU length of stay compared to SLE patients

TABLE 141.2 American College of Rheumatology Criteria for the Diagnosis of Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Malar rash</td>
<td>Fixed erythema over the malar eminences, tending to spare the nasolabial folds</td>
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<tr>
<td>Discoid rash</td>
<td>Erythematous raised scaly patches with follicular plugging; atrophic scarring may occur in older lesions</td>
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<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration, usually painless</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive arthritis involving two or more joints, characterized by tenderness, swelling, or effusion</td>
</tr>
<tr>
<td>Serositis</td>
<td>a) Pleuritis with history of pain, rub heard by physician, or effusion or b) Pericarditis as evident on electrocardiogram, or the presence of a rub or pericardial effusion</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>a) Persistent proteinuria &gt;0.5 g/d or &gt;3+ qualitatively or b) Cellular casts (red cell, hemoglobin, granular, tubular, or mixed)</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures or psychosis in the absence of offending drugs or metabolic derangements</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>a) Hemolytic anemia with reticulocytosis or b) Leukopenia: &lt;4,000 cells/μl on two or more occasions or c) Lymphopenia: &lt;1,500 cells/μl on two or more occasions or d) Thrombocytopenia: &lt;150,000 cells/μl in the absence of offending drugs</td>
</tr>
<tr>
<td>Immunologic disorders</td>
<td>a) Positive antiphospholipid antibody or b) Anti-DNA antibody in abnormal titer or c) Anti-Sm antibody or d) False-positive serologic test for syphilis known to be positive for ≥6 mo and confirmed by a negative Treponema pallidum immobilization or fluorescent treponemal antibody absorption test</td>
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<tr>
<td>Antinuclear antibody (ANA)</td>
<td>An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome</td>
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</table>

The classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person is said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.


However, more recent publications have reported a relatively lower mortality rate in the SLE cohort than those published 10 years ago. Thus, one recent work demonstrated that the ICU mortality rate in the SLE cohort was 20% and the survivability of this cohort was similar to the survivability of other systemic rheumatic diseases (91). According to another study, evaluation of the outcome of SLE patients in one ICU revealed that the mortality rate decreased from 42.6% in 1999 to 2000 to 31.2% in 2007 to 2008 (92). These trends may be a result of recent advances in diagnostic and therapeutic strategies in critically ill patients, which have led to a better management of SLE patients in ICUs.

Although the disease affects virtually all organ systems with different degrees of severity, this section focuses on the literature regarding the most common causes for ICU admission. In addition, this section reviews the changes in patients’ characteristics during the recent decade.
### TABLE 141.3 Slicc Criteria for the Classification of Systemic Lupus Erythematosus

Four of 17 criteria, including at least one clinical criterion and one immunologic criterion
OR
Biopsy-proven lupus nephritis needed for diagnosis

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tr>
<td><strong>Clinical Criteria</strong></td>
<td></td>
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<tr>
<td>Acute cutaneous lupus</td>
<td>Lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash (in the absence of dermato-myositis) OR Subacute cutaneous lupus (noninflamed dermato-myositis and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)</td>
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<tr>
<td>Chronic cutaneous lupus</td>
<td>Classic discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematosus tumidus; chilblains lupus OR discoid lupus/lichen planus overlap</td>
</tr>
<tr>
<td>Nonscarring alopecia</td>
<td>Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes, such as alopecia areata; drugs, iron deficiency, and androgenic alopecia)</td>
</tr>
<tr>
<td>Oral or nasal ulcers</td>
<td>a) Palate, buccal, tongue, OR b) Nasal ulcers (in the absence of other causes, such as vasculitis, Behçet disease, infection (herpes virus), inflammatory bowel disease, reactive arthritis, and acidic foods)</td>
</tr>
<tr>
<td>Joint disease</td>
<td>a) Synovitis involving two or more joints, characterized by swelling or effusion OR b) Tenderness in two or more joints and at least 30 min of morning stiffness</td>
</tr>
<tr>
<td>Serositis</td>
<td>a) Typical pleurisy for more than 1 d, pleural effusions, or pleural rub OR b) Typical pericardial pain (pain with recumbency improved by sitting forward) for more than one day, pericardial effusion, pericardial rub, or pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, and Dressler’s syndrome</td>
</tr>
<tr>
<td>Renal</td>
<td>a) Urine protein-to-creatinine ratio (or 24-hr urine protein) representing 500 mg protein/24 hr OR b) Red blood cell casts</td>
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<tr>
<td><strong>Neurologic</strong></td>
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<td>a) Seizures; psychosis; mononeuritis multiplex (in the absence of other known causes, such as primary vasculitis); myelitis; peripheral or cranial neuropathy (in the absence of other known causes, such as primary vasculitis, infection, and diabetes mellitus) OR b) Acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)</td>
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<tr>
<td><strong>Hemolytic anemia</strong></td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Leukopenia or lymphopenia</td>
<td>a) Leukopenia (&lt;4,000 cells/mm³ at least once) (in the absence of other known causes, such as Felty syndrome; drugs, and portal hypertension) OR b) Lymphopenia (&lt;1,000 cells/mm³ at least once) (in the absence of other known causes, such as glucocorticoids; drugs, and infection)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Thrombocytopenia (&lt;100,000 cells/mm³) at least once in the absence of other known causes, such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td><strong>Immunologic criteria</strong></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>ANA level above laboratory reference range</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>Anti-dsDNA antibody level above laboratory reference range (or more than twofold the reference range if tested by ELISA)</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>Presence of antibody to Sm nuclear antigen</td>
</tr>
<tr>
<td>Antiphospholipid</td>
<td>Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticogulant; false-positive test result for rapid plasma reagin; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); or positive test result for anti-beta 2-glycoprotein I (IgA, IgG, or IgM)</td>
</tr>
<tr>
<td>Low complement</td>
<td>Low C3; low C4; OR low CH50</td>
</tr>
<tr>
<td>Direct Coombs’ test</td>
<td>Direct Coombs’ test in the absence of hemolytic anemia</td>
</tr>
</tbody>
</table>

For the Slicc criteria, criteria are cumulative and need not be presently concurrently. A patient is classified as having SLE if he or she satisfies four of the clinical and immunologic criteria used in the SLCc classification criteria, including at least one clinical criterion and one immunologic criterion.

Alternatively, according to the SLCc criteria, a patient is classified as having SLE if he or she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.

involvement in SLE patients appears to be pleural effusion, organizing pneumonia, and acute reversible hypoxemia. Similarly hypertension, DAH, shrinking lung syndrome, cryptogenic ILD, and rare conditions such as lupus pneumonitis, pulmonary manifestations include respiratory tract infection, pleuritis, ARDS, hypoxemia, or suspected DAH, treatment should include intravenous pulse glucocorticoids (i.e., 1 g methylprednisolone per day for 3 days). In addition, immunosuppressants such as CYC should be considered.

**Disease Flares**

Disease flare is a frequent occurrence in SLE patients in addition to systemic manifestations of the disease, and may be life-threatening. The most common reasons for ICU admission following disease flare include pulmonary/airway complications or lupus pneumonitis, diffuse alveolar hemorrhage (DAH), cardiovascular complications such as coronary artery disease (CAD) and vasculitis, and renal complications such as LN (1,77).

**Pulmonary Manifestations of SLE.** Pulmonary complications in SLE may occur in 50% to 70% of patients. According to the last update on ADs, which included seven case series of SLE patients, respiratory compromise was a leading cause of ICU admission for SLE patients (26% of a total 383 patients) (1). Moreover, one of the studies mentioned above reported that the incidence of pulmonary involvement increased from 40.6% to 55.0% between the years 1999–2000 and 2007–2008 (92).

Differential diagnosis of SLE patients with pulmonary manifestations include respiratory tract infection, pleuritis, ARDS, ILD, and rare conditions such as lupus pneumonitis, pulmonary hypertension, DAH, shrinking lung syndrome, cryopyogenic organizing pneumonia, and acute reversible hypoxemia.

**Pleural Involvement.** The most common pulmonary involvement in SLE patients appears to be pleural effusion, which affects about 50% of the patients during their lifetime (107); remarkably, the occurrence of pleuritis and pleural effusion often reflects disease activity (107). Pleural effusions in SLE patients are generally small to moderate, recurrent, often bilateral, and characterized by an elevated level of pleural fluid LDH, a slightly low level of pleural fluid glucose, and low protein levels. The pleural effusion ANA at a titer of ≥1:160 is a sensitive and specific diagnostic biomarker for lupus pleuritis in patients with SLE (108). However, pleural effusion ANA can occasionally be found in other conditions.

The diagnosis of lupus pleuritis is a clinical one, made by excluding other causes on the basis of pleural fluid analysis or pleural biopsy. Effusions often respond to therapy with NSAIDs. In nonresponders, moderate- to high-dose glucocorticoids are usually effective (107). However, immunosuppressive therapy with high-dose steroids and CYC may be required in rare cases of refractory massive pleural effusion due to SLE exacerbation (109). Local measures such as talc pleurodesis should be employed if systemic measures fail, or when pleural effusion is the only manifestation of SLE. In addition, fibrothorax, or trapped lung, is a rare complication that may require decortication (110).

**Acute Pneumonitis.** Acute lupus pneumonitis (ALP) is an uncommon manifestation of SLE, occurring in about 1% to 4% of patients. It is one of the most life-threatening manifestations of SLE, with a short-term mortality rate of 50% to 90% (111). Acute injury to the alveolar capillary unit may be the central pathology in ALP. It is characterized by nonspecific manifestations including cough with or without expectoration, hemoptysis, pleuritic pain, dyspnea, hypoxemia, fever, fatigue, anorexia, chills, and constitutional symptoms of malaise; lung involvement may be unilateral or bilateral. Physical examination may reveal crepitations, bronchial breath sounds, or decreased breath sounds in the basal regions owing to effusion. Chest radiographs may show diffuse acinar infiltrates, especially in the lower lung zones. The HRCT scan usually shows a ground-glass opacification and/or fibrosis (112). BAL may show either a lymphocytosis or granulocytosis. An open or VATS lung biopsy may be necessary to establish the diagnosis. Distinguishing between lupus pneumonitis and alveolar hemorrhage may be difficult, and lung biopsy is helpful in differentiating between ALP and DAH, but this procedure is usually not recommended. Additionally, it is critically important to differentiate ALP from infectious pneumonitis. Both ANA and anti-dsDNA tests are commonly positive in ALP. The ESR and C-reactive protein (CRP) level may also be useful in differentiating diagnosis. Unlike ESR, a high CRP level (>5 to 6 mg/dL) is a strong predictor of infection while modest rise of CRP is more associated with active SLE without infection (111).

Empiric antibiotics are often started early and then discontinued as cultures return negative for infections. The mainstay of ALP treatment is systemic glucocorticoids (prednisone 1 to 1.5 mg/kg/d in divided doses), although the mortality of ALP remains high. If the response to oral glucocorticoids is not adequate within 72 hours or the patient has marked tachypnea, hypoxemia, or suspected DAH, treatment should include intravenous pulse glucocorticoids (i.e., 1 g methylprednisolone per day for 3 days). In addition, immunosuppressants such as CYC should be considered.

**Interstitial Lung Disease.** ILD is seen in 3% to 13% of patients with SLE, primarily in patients with long-standing
Treatment of PAH in patients with SLE is similar to that of pulmonary arteries, and immunoglobulin and complement angiomatous lesions, thickening of the media layer of the pathic PAH (128). Histopathology usually shows plexiform was 16.8% in comparison to 68.2% in patients with idiopathic PAH (128). Diabetic nephropathy, hypertension, and smoking are recognized risk factors for PAH (129, 130). Histopathology of pulmonary arteries in patients with PAH may show a proliferative pattern with perivascular fibrosis, intimal thickening, and medial hypertrophy (131). In some cases, patients with PAH may have evidence of pulmonary hypertension associated with congenital heart disease (132). However, the management of PAH in SLE patients is complex, and further studies are needed to better understand the pathophysiology of PAH in these patients.

Vanishing Lung Syndrome. This peculiar syndrome is seen in some patients with SLE; it is characterized by a progressive decrease in lung volume without evidence of interstitial fibrosis or significant pleural disease. Symptoms include progressive dyspnea and episodes of pleuritic chest pain (117). It should be suspected in patients with dyspnea, a clear chest radiograph, and elevated diaphragms. The pathogenesis of this disorder is unclear; one possible mechanism is poor function and elevation of the diaphragm secondary to myositis or myopathy (118). However, other reports have documented restrictive lung volumes with normal diaphragmatic strength (119). Theophylline, glucocorticoids, and/or immunosuppressive therapy including AZA, MTX, CYC, and RTX may improve the symptoms and overall lung functions (117, 119–122).

Diffuse Alveolar Hemorrhage. DAH is a rare manifestation that occurs in about 2% to 5.4% of SLE patients, and is associated with a mortality rate of 50% to 80% (123); the etiology remains unknown. Patients typically present acutely with dyspnea, cough, and sometimes hemoptysis; bleeding may be severe enough to produce anemia. Chest radiograph and CT frequently show bilateral alveolar infiltrates that may mimic pulmonary edema or infection. BAL fluid may be increasingly bloody on consecutive BAL specimens; hemosiderin-laden macrophages may also be present. An elevated DLCO is strongly suggestive of pulmonary hemorrhage but is nonspecific, and definitive diagnosis may only be established by open-lung biopsy. Concomitant CYC given with high-dose glucocorticoids improves the prognosis significantly (124). In cases of DAH in SLE patients, plasmapheresis has been shown to improve survival rate (125). In addition, RTX has been used successfully in a small number of patients in combination with CYC (as part of initial therapy), or alone. RTX may also be used following failure or intolerance to CYC in patients with recurrent DAH (126). Furthermore, a successful use of activated recombinant factor VIIa by inhalation with a jet nebulizer has been described in a case report of an SLE patient with pulmonary hemorrhage refractory to standard therapy (127).

Pulmonary Arterial Hypertension (PAH). Mild-to-moderate PAH is frequently seen in SLE patients and tends to have a worse prognosis than idiopathic PAH. It has been demonstrated that the 5-year survival in SLE–PAH patients was 16.8% in comparison to 68.2% in patients with idiopathic PAH (128). Histopathology usually shows plexiform angiomatous lesions, thickening of the media layer of the pulmonary arteries, and immunoglobulin and complement deposition in the walls, along with vasculitis (rarely) (129). Treatment of PAH in patients with SLE is similar to that of patients with idiopathic PAH. SLE patients may benefit from the use of oxygen, anticoagulants, vasodilators (prostacyclin, calcium channel blockers), Bosentan, Sildenafil, and intermittent IV CYC (130–132). In general, PAH associated with SLE is resistant to treatment and this fact may explain the poor prognosis (128).

Acute Reversible Hypoxemia. Acute unexplained hypoxemia is a recognized phenomenon in SLE patients (133). Chest radiographs are negative, and pulmonary emboli are not identified. Plasma C3a levels have been noted to be markedly elevated, suggesting the involvement of pulmonary leukoaggregation and complement activation in this disorder. Further supporting this theory of leuko-occlusive vasculopathy is the noted upregulation of adhesion molecules, E-selectin, VCAM-1, and ICAM-1. Treatment includes glucocorticoids alone or in combination with aspirin; gas exchange has been shown to improve within 3 days (133–134).

Pulmonary Embolism in Systemic Lupus Erythematosus. Patients with SLE and antiphospholipid (aPL) antibodies can suffer from a variety of thromboembolic events, including deep venous thrombosis, chronic thromboemboli causing PAH, and acute pulmonary embolism with or without infarction. Most patients are treated with anticoagulation; immunosuppressive regimens are generally ineffective.

Bronchiolitis Obliterans with Organizing Pneumonia (BOOP). BOOP is seen in SLE and RA patients, along with other disorders. Therapy with prednisone is usually effective; however, the addition of CYC may be necessary in some cases (135).

Acute Respiratory Distress Syndrome (ARDS). ARDS can occur due to APL, DAH, or pulmonary infection. In a small cohort of 19 patients with SLE and ARDS, recent treatment with glucocorticoids was a risk factor for infectious ARDS and the overall prognosis was poor with a high mortality rate of 68% (136). Patients with ARDS secondary to SLE tend to be younger and have more rapid ARDS progression than non-SLE patients.

Cardiac Manifestations in SLE. Cardiac disease is common in patients with SLE and may involve the pericardium, myocardium, valves, conduction system, and coronary arteries (137). According to the last update on ADs in ICUs, cardiovascular or hemodynamic involvement was the third most frequent reason for ICU admission in SLE patients, following infection and pulmonary compromise (19.8%, 76 of 383 patients from 7 SLE series) (1). Moreover, according to one recent study, the incidence of cardiovascular dysfunction in SLE patients admitted to an ICU increased from 9.6% to 14.5% between the years 1999–2000 and 2007–2008 (92). This trend may be associated with a higher incidence of CAD in SLE patients that has become a recognized cause of mortality (138).

Pericardial Disease. Pericardial involvement, the most common cardiac manifestation, is seen in approximately 25% of all SLE patients, and is often associated with pleuritis (137). It may be asymptomatic or present with positional substernal chest pain and an audible rub on auscultation. On histopathologic specimens, the pericardium may reveal foci of inflammatory lesions with immune complexes. Large effusions, tamponade, and constrictive pericarditis are rare. Pericardiocentesis is recommended in patients with suspicion of infection. This is especially true for patients that are febrile, immunocompromised, or have persistent symptoms or effusion despite treatment. Pericardiocentesis is also needed when
Several changes in the morbidity and mortality patterns of SLE patients with LN have been reported in the past several years. According to the last update on ADs in ICUs, renal involvement was the reason for the admission of 19% of the SLE patients (74 of 383 patients from 7 SLE series) (1). One of the studies included in the update demonstrated a high prevalence of acute renal dysfunction (46.2%) and necessity for hemodialysis (54.2%) in SLE patients (88). Conversely, a later report that evaluated the changes in the characteristics and outcome of SLE patients in an ICU, found that the incidence of renal dysfunction decreased from 36.2% to 28.8%, and the necessity for hemodialysis decreased from 37.3% to 28.7% between the years 1999–2000 and 2007–2008 (92). While early studies stated that renal involvement is a major cause of mortality in SLE patients hospitalized in ICUs (82–83), later studies disclosed that mortality rate due LN has decreased (146).

The optimal treatment of LN varies with the type of renal histology that is present in renal biopsy specimens (147). Immunosuppressive therapy is usually not required for minimal mesangial and mesangial proliferative LN, but should be in patients with diffuse or focal proliferative LN (class III or IV LN) (147). Induction regimen usually includes MMF (2 to 3 g/d orally) or CYC along with glucocorticoids. MMF and CYC are considered equivalent based on recent high-quality studies, a meta-analysis, and expert opinions (148–149). MMF is preferable to CYC for patients who express a major concern with fertility preservation, since high-dose CYC can cause permanent infertility in both women and men. There are two regimens of intravenous (IV) CYC:

1. Low dose “Euro lupus” CYC (500 mg IV once every 2 weeks for a total of 6 doses)
2. High-dose CYC (500 to 1000 mg/M² IV once a month for a total of 6 doses) (150).

AZA or MMF may be used for maintenance therapy in patients who improved after 6 months of either high-dose CYC or MMF (151). The recommendation of initiating induction therapy with pulse glucocorticoids (500 to 1000 mg methylprednisolone daily for a total of three doses) is based primarily on expert opinion; some recent prospective trials have employed pulse steroids at treatment initiation (750 mg methylprednisolone daily for 3 days) (150) whereas others have not done so (148).

**Catastrophic Antiphospholipid Syndrome.** Antiphospholipid syndrome (APS) is characterized by recurrent arterial and/or venous thrombosis or pregnancy loss, in association with antibodies directed against plasma proteins that are bound to anionic phospholipids. Antibodies that may be detected include anticardiolipin antibodies, lupus anticoagulants, and anti-B₃ glycoprotein-I antibodies. APS is often associated with SLE or other AD, but may also occur alone. A patient with APS may present with a widespread thrombotic disease and end-organ damage, referred to as “catastrophic” APS. Diagnostic criteria include involvement of three or more organ systems, abrupt onset, confirmation by histopathology of small-vessel occlusion in at least one organ or tissue, and the presence of antiphospholipid (aPL) antibodies (152).

The etiology of CAPS is uncertain; however, several triggering factors have been recognized. The hypothesis of “molecular mimicry” tried to explain the role of infectious diseases in the development of CAPS. According to this hypothesis, aPL

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**Table 141.4** Classification of Glomerulonephritis in SLE

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Minimal mesangial lupus nephritis: Normal on light microscopy; mesangial immune deposits on immunofluorescence</td>
</tr>
<tr>
<td>II</td>
<td>Mesangial proliferative lupus nephritis: Mesangial hypercellularity or matrix expansion, with mesangial immune deposits on immunofluorescence</td>
</tr>
<tr>
<td>III</td>
<td>Focal lupus nephritis: Glomerulonephritis involving less than 50% of glomeruli, typically with subendothelial immune deposits</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse lupus nephritis: Glomerulonephritis involving greater than 50% of glomeruli, typically with subendothelial immune deposits; can be segmental or global</td>
</tr>
<tr>
<td>V</td>
<td>Membranous lupus nephritis: Global or segmental subendothelial immune deposits</td>
</tr>
<tr>
<td>VI</td>
<td>Advanced sclerotic lupus nephritis: Greater than 90% of glomeruli globally sclerosed without residual activity</td>
</tr>
</tbody>
</table>

antibodies may be produced after the exposure to peptides from bacteria and viruses that resemble β2-GPI (153–154).

Without treatment, the prognosis is poor. The recommended management includes the treatment of any precipitating factor (i.e., infection), anticoagulation with heparin followed by long-term warfarin, and high-dose glucocorticoids (methylprednisolone 1 g daily for 3 days) followed by prednisone (1 to 2 mg/kg/d) (155). Plasma exchange and/or IV immunoglobulin (IVIG) (400 mg/kg/d for 5 days) should be used if there are features of microangiopathy. Other treatments in the follow-up period may include CYC (155), RTX (156), and Eculizumab (anti-C5a) (157).

**Neurologic Manifestations of SLE.** The prevalence of distinct neurologic and/or psychiatric symptoms in SLE patients varies from 10% to 80%. Neuropsychiatric manifestations seen in SLE include cognitive dysfunction, headaches, mood disorders, cerebrovascular diseases, seizures, polyneuropathy, anxiety, and psychosis. The last update on ADs showed that of 383 SLE patients admitted to an ICU, 54 (14%) were admitted due to neurologic involvement (1). Additionally, the incidence of neurologic dysfunction in SLE patients admitted to an ICU increased from 2.5% in 1999 to 2000 to 5.1% in 2007 to 2008 (92).

### THE VASCULITIDES

Vasculitis is defined by the presence of leukocytes in the vessel wall with reactive damage to mural structures. The various vasculitides, in general, vary by the size and location of affected vessels (Table 141.5). The recent update on ADs in the ICU demonstrated that in last 10 years systemic vasculitis was the most frequent AD after SLE and RA (1). Thus, 31 of 203 (15%) patients in case-series reports of ADs had diagnosis of systemic vasculitis. Mortality rates in patients with systemic vasculitis range from 10.5% to 33.0%, according to four studies included in the update (158–161). A higher mortality rate of 52% was found in one recent study that included 31 adult patients with systemic vasculitis admitted to ICUs (162).

This illness may be severe and life-threatening, warranting the need for prompt recognition and treatment. Clinical manifestations of systemic vasculitis are usually variable and depend on the involved site. Unfortunately, the diagnosis of vasculitis is often delayed because the clinical manifestations can be mimicked by a number of other disorders.

According to an analysis of four case series, the leading causes for ICU admission in vasculitis patients were respiratory compromise, flare of the disease and infection: 36 (32.4%), 33 (29.8%) and 26 (23.4%), respectively, of 111 reported admissions (1). Causes of ICU admission in another study were active manifestation of vasculitis, septic shock, and “miscellaneous” (163). Sometimes, the beginning of systemic vasculitis may be abrupt with life-threatening manifestations requiring ICU admission; in these cases, the diagnosis is usually made in the ICU. For instance, in a series of 26 patients admitted to an ICU with systemic necrotizing vasculitis, 42% were diagnosed as suffering from vasculitis in the ICU (158). Recent work evaluating 90 patients with ANCA-associated vasculitis (AAV) noted that 10 patients (11.1%) were diagnosed in the ICU. The most frequent AAV

<table>
<thead>
<tr>
<th>TABLE 141.5 Classification of Vasculitis</th>
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<tbody>
<tr>
<td><strong>Vasculitis</strong></td>
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<tr>
<td>Large vessel vasculitis</td>
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<tr>
<td>Takayasu arteritis</td>
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<tr>
<td>Giant cell or temporal arteritis</td>
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<tr>
<td>Medium-sized vessel vasculitis</td>
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<tr>
<td>Polyarteritis nodosa</td>
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<tr>
<td>Kawasaki disease</td>
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<tr>
<td>Isolated central nervous system</td>
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<tr>
<td>Small-vessel vasculitis</td>
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<tr>
<td>Churg–Strauss arteritis</td>
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<tr>
<td>Wegener granulomatosis</td>
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<tr>
<td>Microscopic polyarteritis</td>
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<tr>
<td>Henoch–Schönlein purpura</td>
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<tr>
<td>Essential cryoglobulinemic vasculitis</td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
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<tr>
<td>Vasculitis secondary to connective tissue disorder</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Vasculitis secondary to viral infection</td>
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</tbody>
</table>

ANCA, antineutrophil cytoplasmic antibodies; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus.

diagnosed in the ICU was eosinophilic granulomatosis with polyangiitis (EGPA) (60%), followed by granulomatosis with polyangiitis (GPA) (20%) and microscopic polyangiitis (MPA) (20%) (163).

The management scheme for vasculitis generally includes the following components: remission induction, remission maintenance, and monitoring. The goal of the initial treatment is to induce remission of the disease. Initial management usually involves the use of medium to high doses of glucocorticoids, with the use of an additional immunosuppressive agent in some forms of the disease such as AAV, Takayasu’s arteritis, and polyarteritis nodosa. Vasculitis usually progresses rapidly, and early diagnosis and appropriate treatment are crucial and may improve survivability. The initial treatment phase should be more intensive and include glucocorticoids at higher doses and immunosuppressives with higher risk of toxicity. In the remission phase, the dose of glucocorticoids is usually gradually lowered to limit the development of drug-induced toxicity. However, the continuation of glucocorticoids and other immunosuppressives is usually required for a period of time, depending on the clinical condition. The main goals of the remission maintenance phase of the treatment are to prevent disease recurrence and maintain control of disease activity. The secondary goals are the reduction or discontinuation of medications. Patients require monitoring during remission induction, remission maintenance, and also after achieving drug-free remission.

Key Points

- **Careful examination of the patient is essential in the accurate diagnosis of suspected rheumatic disease.** Appropriate serologic testing may be requested and early rheumatologic consultation can be helpful.
- **The morbidity and mortality of a person with a rheumatologic emergency remains high.** Early recognition and appropriate treatment are essential for a better outcome.
- **SLE, RA, and systemic vasculitis are the most frequently seen ADs in patients admitted to the ICU in the last decade.**
- **ADs patients are most commonly admitted to an ICU following an infection.** Several clinical manifestations of SLE or vasculitis may mimic infectious etiologies. Therefore, infection must be excluded before starting immunosuppressive therapy for a presumed disease exacerbation.
- **In patients with ADs, respiratory involvement is another leading cause for admission to an ICU.**
- **Sometimes, the beginning of systemic vasculitis may be abrupt, with life-threatening manifestations requiring ICU admission, and in these cases the diagnosis is usually made in the ICU.**
- **Empiric replacement therapy with glucocorticoids during critical illness or surgical procedures may be required in patients which have been treated with significant doses of glucocorticoids during the previous year.**
- **Placement of an arterial catheter should be avoided in patients with RP.**

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