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# Evaluation and Management of Infections in Patients with Collagen Vascular Disease

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## 1. Introduction

The clinical outcome of patients with the various manifestations of collagen vascular disease (CVD) has significantly improved over the past two decades with the increased use of diuretics, cytotoxic agents, dialysis, transplantation, and the judicious use of corticosteroids and other antiinflammatory agents directed at altering or delaying end-organ damage by the underlying immunopathologic process.[1–4] A more rigorous definition of the various CVD clinical syndromes and a greater sophistication in the serologic, radiologic, and pathologic diagnostic methods have meant that patients with these diseases are now coming to clinical attention earlier in the course of their illness. Consequently, the physician is now encountering a greater number of clinical problems over a longer time span for each individual patient, rather than just the well-known complications of their end-stage disease. Despite the beneficial aspects of the newer therapeutic interventions to improve the clinical outcome of patients with CVD, the incidence of infection as a cause of both morbidity and mortality in these patients has not changed significantly over the past 30 years.[1–19] A number of factors discussed in this chapter most likely contribute to the persistence of infectious complications in these patients. These include underlying host-defense abnormalities not significantly altered by therapeutic interventions, prolonged therapy with corticosteroids, and alkylating agents that further suppress an already abnormal immune response, and an increased frequency of hospitalizations with more aggressive medical and surgical interventions, thereby increasing the risk of nosocomial infectious complications.

The management of infections in the two most prevalent collagen vascular diseases—systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)—are the principal focus of this chapter. Both SLE and RA are characterized by the fact that they are chronic inflammatory multisystem diseases of unknown etiology, with clinical features common to all the collagen vascular disorders.[4,20,21] SLE and RA, which may begin as early as the second decade of life, exhibit diverse clinical and laboratory manifestations and courses characterized by their unpredictability and by periods of remission and relapse.[20,21] The similarity between the symptoms of infection in a patient with either SLE or RA and those due to a flare of the underlying disease pose a significant challenge to the physician.

## 2. Novel Features of Host–Microorganism Interactions in CVD

The importance of infections in the management of the patient with CVD is underscored by the fact

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**TABLE 1. Interactions between Infections and Collagen Vascular Activity[a]**

1. Clinical symptoms of infection may be indistinguishable from those of CVD (see Table 2).
2. Infection may increase or precipitate CVD activity.
3. Antibiotic therapy for infection may exacerbate CVD activity (penicillins, sulfonamides).
4. Side effects of therapy for infection and CVD may be similar (i.e., diarrhea secondary to gold therapy or antibiotics).
5. Immunosuppressive therapy for CVD may lead to increased susceptibility to infection (see Table 7).
6. Infection increases morbidity and mortality in patients with CVD (see Tables 3 and 4).

[a]CVD, collagen vascular disease.

that the symptoms of the host's response to the microorganisms and the therapy of a particular infection may mimic, alter, or exacerbate the underlying immunologic disease (Table 1). The principal clinical manifestations of both SLE and RA are listed in Table 2 along with examples of those infectious disease categories that commonly cause similar symptoms. The musculoskeletal manifestations of SLE present at some time during the clinical course in as many as 90% of patients[20] may be similar to the arthralgias that are common in patients with infectious endocarditis, disseminated gonoccocemia, rubella, and the prodrome of viral hepatitis.[22–25] As in SLE, major joint swelling, bone destruction, and flexion deformities are uncommon with these infections, and the arthralgias and arthritis are usually transient clinical manifestations of the infectious process. Similarly, the one or two tender, swollen, and

**TABLE 2. Examples of Clinical Symptoms of Systemic Lupus Erythematosus and Rheumatoid Arthritis Compared with Infectious Diseases[a]**

| | SLE | RA | Infectious disease[b] |
|---|---|---|---|
| Weight loss | + | + | Chronic infection (e.g., SBE, TB) |
| Fever | + | + | Most infections |
| Arthralgia, arthritis | + | + | Septic joint (e.g., bacterial, fungal), disseminated gonococcemia, viral infection |
| Skin rash | + | + | Bacterial (e.g., erysipelas, rose spots), fungal, treponemal (secondary syphilis), viral |
| Renal involvement (nephritis) | + | − | Emboli in infectious endocarditis, glomerulonephritis (post-streptococcal, *S. epidermidis*) |
| Gastrointestinal (anorexia, nausea, and vomiting) | + | − | Viral hepatitis, bacterial toxins (*Staph.* sp.), bacterial diarrhea (*Shigella* sp.), antibiotic therapy, pseudomembranous colitis (*C. difficile*), parasites (*Giardia, Amoeba*) |
| Pulmonary (pleurisy, effusions, pneumonia) | + | + | Bacterial, fungal, tuberculous, viral, and parasitic infections |
| Cardiac (murmurs, pericarditis) | + | + | Bacterial, fungal, tuberculous, viral, and parasitic infections |
| Lymphadenopathy | + | + | Bacterial, fungal, tuberculous, viral, and parasitic infections |
| Hepatosplenomegaly | + | + | Bacterial, fungal, tuberculous, viral, and parasitic infections |
| Central nervous system abnormalities | + | + | Bacterial, fungal, tuberculous, viral, and parasitic infections |

[a]Adapted from Schur.[28]
[b]SBE, subacute bacterial endocarditis; TB, tuberculosis.

warm joints characteristic of an acute flare of RA may be indistinguishable from the septic joint, and only analysis and culture of the joint fluid permit distinction between the two processes.[21] Nowhere are the differences between the manifestations of an acute flare of a CVD and those of an infectious process more difficult to resolve than when they involve the pulmonary, cardiac, and central nervous system (CNS). As discussed in the clinical cases, pulmonary symptoms of SLE such as pleurisy, pneumonia, and effusions present in as many as 50% of patients,[20] may mimic most infectious processes involving the lungs. When, on occasion, pneumonias caused by organisms such as *Streptococcus pneumoniae,* the group A streptococcus, *Mycoplasma pneumoniae,* and *Mycobacteria* sp., are associated with scant sputum production, they may exhibit clinical characteristics similar to those of an SLE flare involving the lung. Moreover, in the setting of immunosuppressive therapy with corticosteroids or cyclophosphamide, when infections with *Aspergillus* sp. and *Nocardia* sp. are more prevalent,[3] the hemoptysis and pleuritic chest pain caused by these infections may be identical with the symptoms of SLE–pneumonitis. Cardiac manifestations present in 46% of patients with SLE[20] and in 1–2% of patients with RA[21] and that may be heralded by the onset of a new murmur, pericardial friction rub, or conduction abnormality are findings common to all forms of infectious endocarditis (IE). Consequently, only careful serial bedside examinations for the stigmata of IE in addition to blood cultures will help distinguish between Libman-Sacks endocarditis and IE. A third of patients with SLE and a rare patient with RA, will demonstrate neurologic manifestations such as seizures, behavioral disturbances, cranial nerve abnormalities, and a number of other clinical changes consistent with meningeal and cerebral inflammation.[20,21,26,27] A detailed analysis of the cerebrospinal fluid (CSF) will most often permit exclusion of an infectious etiology as the cause of the observed clinical findings. However, infections such as meningeal tuberculosis and viral encephalitis, for example, which can be characterized by an abnormal mental status, focal neurologic findings, computed tomographic (CT) changes consistent with cerebral infarcts due to vasculitis, and negative routine CSF cultures, may be indistinguishable from a patient with a flare of SLE complicated by neurologic manifestations in addition to steroid-induced psychosis. This not infrequent clinical dilemma can occasionally be resolved by pathologic examination of an appropriate biopsy specimen for infectious organisms and a therapeutic trial with antituberculous or antiviral chemotherapy.

Issues involving the relationship between infections that cause increases in CVD activity, the role of antibiotic therapy in precipitating exacerbations of SLE, and whether immunosuppressive therapy predisposes patients with CVD to specific infections are presented as part of the case discussions.

## 3. Morbidity and Mortality Caused by Infection in Patients with CVD

Infection is a major cause of morbidity among patients with SLE and RA (Table 3). In the series of 70 patients with SLE presenting in the first two decades of life reported by Platt et al.,[7] 55 episodes of infection were documented, with the skin being the principal site of infection. Urowitz et al.[14] described 81 patients with SLE in whom there were 28 instances of proven infection. Eighteen of these were minor, such as cutaneous or urinary tract infections (UTI) requiring only outpatient orally administered antibiotic therapy.[14] In the study by Carpenter et al.,[1] infections complicated the course in 21 patients with SLE, with UTIs affecting 67% of patients, including multiple UTIs in one-half of these. In the 110 patients with SLE reported by Lee et al.,[19] 45 infections were documented in 29 patients. Nine of these patients had multiple infections during the 5-year period of the study. Ten percent had major infections requiring parenteral antibiotics, with pneumonia being the most frequent, and 20% had minor infections, with the most common being UTI and skin infections. In the prospective study of 223 patients with SLE by Ginzler et al.,[12] infection was the major problem leading to hospital admission 100 times, or 29% of all but obstetric hospitalizations among patients in their series. As shown in Table 3, the incidence of infection may vary widely from study to study (26–78%) with the most frequent minor infections involving the skin and urinary tract and major infections most commonly causing pneumonia.

The principal infectious complication causing significant morbidity in patients with RA has been their propensity to develop septic arthritis. The eight

**TABLE 3. Infection as a Cause of Morbidity in Systemic Lupus Erythematosus and Rheumatoid Arthritis[a]**

| Series | Period | Number of patients | Number with infection | | Number of infections | Principal site of infection |
|---|---|---|---|---|---|---|
| | | | *N* | Percent | | |
| | | Systemic lupus erythematosus | | | | |
| Platt et al.[7] | 1958–1981 | 70 | 55 | 78 | | Skin (45%) |
| Carpenter and Sturgill[1] | 1958–1965 | 40 | 21 | 53 | | Urinary tract (67%) |
| Urowitz et al.[14] | 1970–1975 | 81 | 21 | 26 | 28 | Pneumonia/sepsis |
| Lee et al.[19] | 1970–1975 | 110 | 29 | 26 | 45 | Pneumonia (18%); skin (30%) |
| Ginzler et al.[12] | 1966–1976 | 223 | 150 | 67 | 384 | Urinary tract (20%)<br>Pneumonia (11%) |
| Staples et al.[15] | 1960–1969 | 23 | 13 | 57 | 25 | Urinary tract (28%) |
| | | Rheumatoid arthritis | | | | |
| Huskisson and Hart[30] | | 12 | | | 24 | Tissue abscesses (58%) |
| Mitchell et al.[29] | 1964–1974 | 2500 | 8 | 1 | | Septic arthritis (100%) |

[a]Adapted from Perez and Goldstein.[3]

patients with RA in the study by Mitchell et al.[29] all developed indolent septic arthritis frequently after concurrent skin infections. Other studies in patients with RA have documented increased morbidity from recurrent soft tissue abscesses[30] and respiratory infections.[31]

In patients with SLE, infectious complications have been major contributors to the increased mortality of that disease (Table 4). Clinical studies conducted during the preantibiotic era[32,33] found that 30–40% of deaths were caused by infections, with a significant number due to *S. pneumoniae* bronchopneumonia. As described by Dubois[34] and others,[35] bronchopneumonia and pneumonitis continued to be the principal infectious disease complication leading to death in patients with SLE during 1950–1973, despite the introduction of antimicrobial chemotherapy and the improved survival due to advances in the management of CNS damage and uremia. During that period, infections as the cause of death remained unchanged at 5–14% of patients with SLE, whereas uremia declined from 26% to 14%, and death due to CNS damage declined from 26% to 8%. The recent studies of Urowitz et al.[14] and Ginzler et al.[12] underscore the fact that infection contributes to mortality principally during the early phases of SLE. Of the six patients who died in Urowitz's study within the first year after diagnosis, five died from sepsis, whereas in all five of the late deaths, none was attributable to infection, but rather to myocardial infarction. Factors associated with early death from infection were active lupus nephritis and large doses of corticosteroids. A similar pattern was observed by Ginzler et al.[12] in the 30 patients in their study who died from infection. A majority had their fatal infection early in their clinical course, frequently associated with active lupus nephritis, especially when manifested by red blood cells (RBCs) or cellular casts in the urine sediment.[12] The most recently reported data by Platt et al.[7] and Rosner et al.[8] confirm these earlier observations. Of the 11 deaths in Platt's report caused by infection, five died within one year of diagnosis and two of these patients had diffuse proliferative lupus nephritis. The early deaths from infection were also seen by Rosner and co-workers, however, nearly half of their patients who died primarily of infection did not have active SLE at the time of death, a finding opposite those in earlier series. Nevertheless, in SLE the number of deaths overall due to infection range widely between 3% and 80% and are caused principally by pneumonia (Table 4). The contributions of underlying host-defense abnormalities and immunosuppressive therapy to the increased morbidity and mortality due to infections in SLE are discussed in Section 4.

Infection has also played a major role in the mortality of patients with RA (Table 4). The recent studies by Vanderbroucke et al.[16] and Prior et al.[18] demonstrate that infections were a significant cause of death in RA patients who were hospitalized more

**TABLE 4. Infection as a Cause of Death in Systemic Lupus Erythematosus and Rheumatoid Arthritis[a]**

| Series | Period | Number of deaths | Deaths due to infection | | Principal site or type of infection | Time of fatal[b] infection relative to duration of CVD | |
|---|---|---|---|---|---|---|---|
| | | | *N* | Percent | | Early in disease (%) | Late in disease (%) |
| | | | Systemic lupus erythematosus | | | | |
| Klemperer et al.[32] | 1930–1941 | 20 | 8 | 40 | Pneumonia | — | — |
| Ropes[33] | 1932–1944 | — | — | 27 | — | [c] | — |
| | 1945–1963 | 5 | 3 | 60 | — | [c] | — |
| Harvey et al.[35] | 1940–1954 | 38 | 1 | 3 | Pneumonia | — | — |
| Dubois and Tuffanelli[2]; Dubois et al.[34] | 1950–1955 | 57 | 9 | 16 | Pneumonia | — | — |
| | 1956–1962 | 100 | 12 | 12 | Pneumonia | — | — |
| | 1963–1973 | 92 | 17 | 18 | Pneumonia | — | — |
| Carpenter and Sturgill[1] | 1958–1965 | 8 | 4 | 50 | Pneumonia | 60 | 40 |
| Platt et al.[7] | 1958–1981 | 11 | 9 | 81 | Pneumonia/sepsis | 55 | 45 |
| Hashimoto and Shiokawa[37] | 1955–1968 | 17 | 6 | 36 | — | — | — |
| | 1969–1971 | 16 | 4 | 20 | — | — | — |
| | 1971–1976 | 7 | 1 | 14 | — | — | — |
| Estes and Christian[36] | 1963–1971 | 53 | 10 | 18 | Pneumonia | — | — |
| Rosner et al.[8] | 1965–1978 | 222 | 74 | 30 | Sepsis/pneumoia | 78 | 22 |
| Ginzler et al.[12] | 1966–1976 | 55 | 30 | 60 | Pneumonia | [c] | — |
| Lee et al.[19] | 1970–1975 | 13 | 4 | 30 | Pneumonia/sepsis | 100 | — |
| Urowitz et al.[14] | 1970–1975 | 11 | 5 | 45 | Sepsis | 100 | — |
| | | | Rheumatoid arthritis | | | | |
| Vandenbroucke et al.[16] | 1954–1981 | 165 | 4 | 2 | Sepsis | — | [c] |
| Allebeck[38] | 1971–1978 | 473 | 5 | 1 | — | — | [c] |
| Prior et al.[18] | 1964–1978 | 199 | 4 | 2 | — | 25 | 75 |
| Koota et al.[39] | 1959–1976 | 176 | 23 | 13 | Pneumonia | — | — |

[a]Adapted from Perez and Goldstein.[3]
[b]CVD, collagen vascular disease. Early in disease: within first 2 years of coming to clinical attention. Late in disease: more than 2 years of clinical follow-up.
[c]Present.

than 5 years after the onset of their disease. In contrast to SLE, infections in patients with RA occur late in the course of the disease. Furthermore, as in patients with SLE, pneumonia and urogenital sepsis were the principal infectious complications leading to death, findings which are even more striking when autopsy series are examined.[38–41]

## 4. Host Abnormalities as Potential Contributing Factors to Infections in Patients with CVD

A detailed discussion of abnormal host defenses in CVD is beyond the scope of this chapter, and can be found in several recent scholarly references.[3,42–44] However, a number of both humoral and cellular immune abnormalities have been described in patients with SLE and RA that may predispose them to infectious complications and these will be described within the context of this chapter (Table 5).

The biologic activities of the various components of complement that contribute to the maintenance of normal host defenses include lysis of bacteria (C5, C6, C7, C8, C9), stimulating chemotaxis of phagocytic leukocytes (C5a, C567), opsonization of bacteria (C3b), oxidative metabolism (C3b, C5a), and degranulation of leukocytes (C3b, C5a).[3,45,46] In both SLE[47] and RA,[48] reduction of serum C4 due to increased consumption has been observed con-

**TABLE 5. Immunologic Abnormalities in Systemic Lupus Erythematosus and Rheumatoid Arthritis**

| | SLE | RA |
|---|---|---|
| Complement | Decreased levels of C4, C1q, C3, C9, and factor B due to increased consumption and turnover<br>Inherited abnormalities of factors (C1, C4, C2)<br>Decreased heat-labile opsonic capacity for *E. coli* and *S. aureus* | Increased catabolism of C4 |
| Antibodies | ± altered antibody response to bacterial antigens<br>Hypergammaglobulinemia | Increased antibody production to native type II collagen |
| PMN leukocytes | Decreased complement-derived chemotactic activity in endotoxin-activated serum<br>Decreased chemotactic response to ascorbic acid<br>Presence of inhibitor of C5-derived chemotactic activity<br>Decreased phagocytic activity<br>Decreased oxidative metabolism | Altered chemotaxis and phagocytosis |
| Lymphocytes | Deficient autologous MLR (active SLE)<br>Lymphopenia (decreased number and function of suppressor/cytotoxic T lymphocytes)<br>B-lymphocyte hyperreactivity (polyclonal)<br>Increased T lymphocytes with Ia antigen<br>Decreased NK cell activity (hyporesponsive to interferon)<br>Increased number of antilymphocyte antibodies | Decreased T-lymphocyte production of γ-interferon<br>Increased mononuclear leukocyte activation in synovial tissue<br>Increased T-lymphocyte sensitivity to type II and III collagen<br>Decreased NK cell activity |

sistently, in addition to occasionally depressed serum levels of Clq,[49] C3,[49] C9,[59] and factor B,[48,51] all of which lead to decreased serum levels of total hemolytic complement.[52,53] These deficiencies of C3, and other early components of the classic pathway have been associated with an increased incidence of infections with encapsulated bacteria such as *N. meningitidis, S. pneumoniae,* or *H. influenzae.*[54] Systemic infections caused by either *N. meningitidis* or *N. gonorrhea,* however, are more typical of late complement component deficiencies.[54] Other complement abnormalities observed in SLE that may predispose to infection include inherited isolated deficiencies of selected complement components[54] and, in certain patients, decreased heat-labile opsonic capacity for *Escherichia coli* and *Staphylococcus aureus.*[55]

Abnormal immunoglobulin homeostasis has been reported in patients with both SLE[56–58] and RA.[44] Although some studies have detected an abnormally increased antibody response to bacterial antigens in patients with SLE,[59] others have not, [60] suggesting that whatever regulatory defect is present is probably multifactorial in origin. The hyperreactivity of the immune system observed in many patients with SLE[19,36,42] may be manifested by hyper-

gammaglobulinemia principally of the IgG and IgA isotypes.[50] In addition, numerous antibodies directed against the surface antigens of a number of different leukocytes have also been detected in patients with SLE.[61,62] Although it is difficult to assess the role of the hypergammaglobulinemia of SLE in predisposing these patients to infection, it is possible that the antileukocyte antibodies may significantly alter the host's response during periods of increased disease activity.[63]

Altered chemotaxis of polymorphonuclear (PMN) leukocytes has been observed in patients with CVD. In SLE, a number of abnormalities of PMN leukocyte chemotaxis have been detected, including reduced complement-derived chemotactic activity in endotoxin-activated serum,[64] altered responses to ascorbic acid,[65] and the presence of an inhibitor of the chemotactic peptide C5a.[3,66] Of interest is that patients with the heat-stable inhibitor of C5a had a greater number of infectious episodes than did patients without the inhibitor.[67] Other defects of PMN leukocyte function in SLE include defective opsonization,[68] and impaired oxidative metabolism leading to decreased production of hydrogen peroxide and superoxide anion,[69] factors essential to cellular microbicidal activity.[70]

The role of cellular-mediated immunity directed by activated lymphocytes and macrophages in combating infections caused by intracellular organisms (viruses, *Listeria, Mycobacteria* sp.) and opportunistic bacteria has been extensively documented.[71] In SLE and to a lesser degree in RA, a multiplicity of abnormalities in cellular immunity have been described (Table 5). To what extent these lymphocyte abnormalities directly contribute to infectious complications in patients with SLE and RA is difficult to establish.

In patients with SLE, conflicting results have been reported on the degree to which delayed hypersensitivity responses to *Candida,* PPD, and other antigens are depressed.[72,73] However, what is clear is that when patients are immunized with specific antigens during periods of SLE activity, they fail to become sensitized.[74] In addition, a number of specific lymphocyte abnormalities have been reported in SLE, which include a deficient autologous mixed lymphocyte response (MLR) during periods of disease activity,[75] a decrease in T-suppressor-cytotoxic lymphocytes,[76] altered B-lymphocyte responses to pokeweed mitogen,[77] inability of T lymphocytes to generate suppressive signals that turn off B-lymphocyte function,[78] and deficient natural killer (NK) cell function.[79] Parallel abnormalities in cell-mediated immunity have been described in patients with RA, including decreased T-lymphocyte production of γ-interferon ($IF_\gamma$),[80] increased T-lymphocyte sensitivity to type II and III collagen,[81] and decreased NK cell activity.[82] The exacerbations and remissions of SLE and RA over time that have been shown to alter different aspects of immunologic function, most likely predispose the host to varying types of infections depending on which part of the host's response is most severely affected at any one moment by the underlying disease activity. In addition, many of the drugs used to treat RA and SLE can perturb the immune system, altering the host's response even further.

## 5. Role of Immunosuppressive Therapy in Predisposing Patients with CVD to Infections

The wide use of immunosuppressive therapy in the management of SLE and RA over the past two decades has led to a greater appreciation of the significant interactions between corticosteroids, cytotoxic agents, and gold compounds with various elements of the immune response. Many studies, the results of which are summarized in Table 6, have now established both in vitro and in vivo the extensive degree to which the above classes of drugs inhibit host defenses. In general, glucocorticoids have a greater effect on leukocyte traffic within the circulation and sites of soft tissue inflammation than on their function, and more effect on cellular than humoral processes.[83,84] The ability of glucocorticoids to inhibit recruitment of PMN leukocytes and monocyte–macrophages at sites of inflammation is probably their single most important antiinflammatory effect.[83] Other functions such as lymphokine-mediated recruitment,[85] delayed-type hypersensitivity responses,[86] antigen processing,[88] monocyte bactericidal activity,[89] lymphocyte proliferation,[90] and NK cell activity,[91] are altered by corticosteroid therapy. As will be discussed below, it is not surprising that in addition to the underlying immune alterations that are part of the CVD complex, corticosteroid ther-

**TABLE 6. Effects of Immunosuppressive Therapy on the Immune Response of Patients with Collagen Vascular Disease[a–c]**

| Effect | Corticosteroids | Cyclophosphamide | Azathioprine | Gold |
|---|---|---|---|---|
| Lymphocytes | | | | |
| Lymphocytopenia | +[85] | +[99] | +[102] | |
| Suppression of DTH | +[86] | +[100] | +[103] | |
| Suppression of proliferation | +[90] | +[100] | ±[104] | +[111] |
| Lysis of activated cells | +[85] | | | |
| Decreased cellular recruitment by lymphokines | +[85] | | | |
| Inhibition of suppressor T-cell function | | +[101] | | |
| Monocyte/macrophage | | | | |
| Monocytopenia | +[85] | | | |
| Inhibition of accumulation at inflammatory site (MIF antagonism) | +[87] | | +[105] | +[110] |
| Altered bactericidal activity | +[89] | +[100] | | |
| PMN leukocyte | | | | |
| No significant change in function | ±[83] | | | |
| Accelerated release from bone marrow | +[92] | | | |
| Increase in antibody-dependent cellular cytotoxicity | +[83] | | | |
| Neutropenia | | +[98] | | |
| Altered phagocytic activity | | | | +[110] |
| Immunoglobulins/mediators | | | | |
| Inhibition of antibody production | ±[93] | +[97] | +[106] | |
| Inactivation of complement system | +[94] | | | +[107] |
| Decreased synthesis of PG and LTs | +[95,96] | | | +[109] |
| Potentiation of catecholamine action | +[83] | | | |
| Inhibition of lysozomal enzymes | | | | +[108] |

[a]Adapted from Parillo and Fauci.[83]
[b]Superscript numbers are references.
[c]DTH, delayed-type hypersensitivity; MIF, migration inhibition factor; PG, prostaglandins; LT, leukotrienes.

apy further inhibits responses that enable the host to combat common pathogenic gram-positive cocci, gram-negative enteric bacilli and intracellular organisms.[3]

Cytotoxic agents such as cyclophosphamide and azathioprine exhibit many of the same alterations of leukocyte function as glucocorticoids. However, the major differences include a more profound inhibition of B-lymphocyte function resulting in significant suppression of immunoglobulin levels in patients on chronic therapy,[97] and marrow suppression resulting principally in neutropenia.[98] The mechanisms in which gold compounds alter host defenses are still controversial. Gold compounds have been shown to inactivate complement,[107] and a number of lysosomal enzymes,[108] in addition to other leukocyte functions (Table 6).

The question as to whether immunosuppressive therapy acting by the above described mechanisms increases the incidence of infection in patients with CVD, is an extremely complex one. This complexity is multifactorial and is caused by the poorly understood interrelationships between a number of interacting elements, including level and extent of disease activity, length of time disease has been present, and degree of immunosuppression secondary to therapy in addition to that already caused by the underlying illness. A number of studies have attempted to examine the various factors associated with infectious complications in patients with CVD and whether they contribute to the commonly held clinical impression that these patients do have an increased incidence of infection as compared with a similar cohort of non-CVD patients.[3] The first study to carefully examine which factors were associated with an increased incidence of infection in patients

with CVD was by Staples et al.[15] Their report described 23 patients with SLE, 20 with RA, and 11 with the nephrotic syndrome (NPS), hospitalized at the National Institutes of Health during 1960–1969. The number of infections in each group per 100 days of hospitalization (infection rate, IR) was almost ten times greater in the SLE cohort (1.22) than in the RA (0.0), NPS (0.23), and RA + NPS (0.16) groups, respectively. Of the total of 30 infections that they observed, only 15% occurred during periods of antibiotic therapy or neutropenia. The only other factors associated with disseminated and deep tissue infections was daily prednisone therapy in excess of 20 mg and significant azotemia (BUN >60 mg%). In addition, the IR in SLE was noted to increase with increasing steroid dose from a rate of 0.43 on no steroids to 1.63 on >50 mg prednisone per day. They were able to conclude that patients with SLE on no or low doses of steroids were susceptible to infections as compared with RA and NPS patients and that corticosteroid therapy further increased the risk with increasing dosage. Moreover, azotemia, but not proteinuria or active urine sediment, increased the risk of infection still further. The studies by Urowitz et al.[14] and Lee et al.[19] also noted the association of major infections with corticosteroid therapy and active renal disease. In particular, the former study also showed that the greatest number of fatal infections occurred within one year after diagnosis of CVD had been made, and that these patients had active SLE involving three or more organ systems, including positive renal biopsies for SLE nephritis. These results further underscore the association of increased rate of infection during periods of CVD disease activity, when in vitro studies have demonstrated the greatest degree of functional PMN leukocyte and lymphocyte abnormalities. The association of azathioprine with an increased incidence of infections was noted by Lee et al.[19]; however, in a subsequent study by Ginzler et al.,[12] azathioprine was only associated with an increased incidence of herpes zoster in patients with SLE. Ginzler et al.[12] further noted that with increasing prednisone doses, the rate of bacterial infections and opportunistic infections increased from 10.3/100 patient years of follow-up to 87/100 patient years, and from 0.8/100 patient years to 42/100 patient years, respectively.

The most recent study to examine the question of infection and immunosuppressive therapy in patients with CVD, described 22 patients with antiglomerular basement membrane antibody disease (GBM), 19 with SLE, 18 with Wegener's granulomatosis (WG), and 16 with other forms of systemic vasculitis (SV).[112] The 75 patients had a total of 277 infections, with the IR being significantly lower in patients with SV and higher in those with SLE, when compared to the group as a whole. Of importance was that the mean time from the onset of immunosuppression to the first infection for the entire group was 12.7 days but in the SLE group was significantly shorter at 7.8 days ($p < 0.05$). Once again, the association of increased risk of infection with worsening renal failure and corticosteroid therapy was noted. The results of all the above studies therefore support the conclusion that immunosuppressive therapy predisposes patients with CVD to infectious complications. However, it is only one of several important interrelated factors, which include level of disease activity, and time of onset of disease manifestation (Table 7).

**TABLE 7. Factors Associated with Increased Susceptibility to Infection in Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis[a]**

| |
|---|
| Late in the course of RA disease activity[114] |
| First 2 years after diagnosis of SLE (early in the course of disease activity)[14] |
| Increase in disease severity (increase in manifestations of disease/patient)[14] |
| Azotemia (BUN >60 mg%)[15] |
| Active SLE nephritis (RBCs, cellular casts in sediment; positive kidney biopsy for SLE nephritis)[14] |
| Vascular lesions consistent with sclerosis[113] |
| Corticosteroid dose >20 mg prednisone/day[15] |
| Azathioprine therapy (herpes zoster infections only)[12] |
| Cyclophosphamide therapy (only in the presence of neutropenia)[112] |

[a]Superscript numbers are references.

## 6. Spectrum of Infection in Patients with CVD

In most clinical studies over the past decade, bacteria have accounted for the majority of infections in patients with CVD (Table 8). In the recent series by Cohen et al.,[112] clinically significant bacterial

**TABLE 8. Types of Infections in Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis[a]**

| Infection | Number of patients | SLE/RA[b] |
|---|---|---|
| Pneumonia | | SLE = RA |
| *S. pneumoniae* | 5 | |
| *S. pyogenes* | 2 | |
| *S. aureus* | 2 | |
| *H. influenzae* | 2 | |
| Gram-negative rods (not specified) | 35 | |
| *Klebsiella* sp. | 4 | |
| *P. mirabilis* | 1 | |
| *Enterobacter cloacae* | 1 | |
| *M. tuberculosis* | 7 | |
| *Aspergillus* sp. | 5 | |
| *C. albicans* | 1 | |
| *Aspergillus* sp., *C. albicans* | 1 | |
| *Cytomegalovirus* | 5 | |
| *P. carinii* | 5 | |
| Total | 76 | |
| Bacteremia | | SLE > RA |
| *S. pneumoniae* | 2 | |
| *S. pyogenes* | 4 | |
| *S. aureus* | 5 | |
| *E. coli* | 3 | |
| *P. mirabilis* | 2 | |
| *S. enteriditis* | 1 | |
| *Acinetobacter* | 1 | |
| *B. fragilis* | 1 | |
| *S. typhimurium* | 1 | |
| *C. albicans* | 1 | |
| *C. neoformans* | 1 | |
| Total | 22 | |
| Meningitis | | SLE > RA |
| *N. meningitidis* | 3 | |
| *E. coli* | 1 | |
| *Klebsiella* sp. | 1 | |
| *Aspergillus* sp. | 1 | |
| *C. neoformans* | 2 | |
| Total | 8 | |
| Skin infections/cellulitis | | SLE = RA |
| Varicella zoster | 21 | |
| *S. aureus* | 15 | |
| *S. pyogenes* | 1 | |
| *E. coli* | 1 | |
| *C. albicans* | 1 | |
| Total | 39 | |
| Urinary tract infections | | SLE = RA |
| *E. coli* | 18 | |
| *Klebsiella* sp. | 1 | |
| *Enterococcus* | 2 | |
| *Proteus* sp. | 2 | |
| Total | 23 | |
| Pyelonephritis/perinephric abscess | | SLE = RA |
| *E. coli* | 2 | |
| *Klebsiella* sp. | 1 | |
| Total | 3 | |
| Pharyngitis/thrush | | SLE > RA |
| *C. albicans* | 24 | |
| Peritonitis/intraabdominal abscess | | SLE > RA |
| *P. aeruginosa* | 1 | |
| *Klebsiella* sp. | 1 | |
| Retroperitoneal tuberculosis | 1 | |
| Total | 3 | |
| Soft tissue abscesses | | RA > SLE |
| *S. aureus* | 2 | |
| *S. pneumoniae* | 2 | |
| *C. albicans* | 1 | |
| Total | 5 | |
| Prosthetic joint infection | | RA > SLE |
| *Staphylococcus* sp. | 22 | |
| *S. pyogenes* | 5 | |
| Diphtheroids | 2 | |
| *S. pneumoniae* | 1 | |
| Gram-negative bacilli | 6 | |
| Anaerobes | 3 | |
| Mixed infections | 14 | |
| Total | 53 | |

[a]Summarized from Refs. 3, 7–9, 12, 14–17, and 19.
[b]Comparative frequencies.

infections were responsible for 73% of the 277 infections observed in their 75 patients with immunologically mediated disease. Gram-negative enteric bacilli comprised 68% of the bacterial infections in their patients with SLE, whereas in that same group viral, fungal, and *M. tuberculosis* and *P. carinii* accounted for 7%, 15%, and 4% of infections, respectively. In this study, the 15% incidence of fungal infections in patients with SLE was significantly ($p < 0.05$) greater as compared with the other patients

studied which included patients with SV, WG, and GBM disease. The principal sites of infection were the urinary tract, lungs, and blood, with ear, nose, and throat (ENT) infections also being present. UTIs were the most frequent infections in patients with SLE, with *Klebsiella* sp. and *E. coli* the most common isolates. Pneumonias were the second most frequent infection, with gram-negative enteric bacilli again the most common isolates (40%). In addition, pneumonias exhibited the highest mortality, being responsible for 70% of the deaths, with *Aspergillus fumigatus* responsible for 4 of the 5 fatal fungal pneumonias, and cytomegalovirus (CMV) complicating 30% of the fatal pneumonias. Other organisms responsible for fatal pneumonias included *M. tuberculosis, P. carinii,* and *Pseudomonas* sp. Of the SLE patients who developed septicemia (5 of 19), only 1 died of *Cryptococcus neoformans* fungemia, whereas the other four with septicemia caused by *S. aureus* (2), *Acinetobacter* (one), and *Salmonella enteritidis* (one), respectively, survived. Furthermore, this study points out the important fact that half of the patients with serious opportunistic infections also became infected with another serious opportunist pathogen, often simultaneously. For example, one patient had a *C. albicans* fungemia rapidly followed by CMV pneumonia, while in another case both *Aspergillus* sp. and *P. carinii* were found in a bronchial biopsy specimen. This type of complication, not unique to immunosuppressed SLE patients, has been observed in renal transplant patients (see Chapter 21) and more recently in those with the acquired immunodeficiency syndrome (see Chapter 15).

The pattern of infections in patients with SLE in the first two decades of life is slightly different from those described above.[7] Infections of the skin (31% with varicella-zoster virus, 13% with *Staphylococcus* sp.) accounted for 44% of all infections, and septicemia with or without endocarditis caused by *Staph.* sp., *S. pneumoniae,* gram-negative bacilli, and *C. albicans* another 20%. The study by Ginzler et al.[12] made the additional observation that in this population, oral thrush was the leading type of opportunistic infection, with pneumonia due to CMV, *P. carinii,* and *Aspergillus* sp. the second most common opportunistic infection. Furthermore, it was noted that a significant number of patients with deep fungal infections had received prior antibiotic therapy for gram-negative sepsis.[12] This study and those by Lee et al.[19] and by Staples et al.[15] also confirmed that the urinary tract, the lungs, and the skin are the major sites of infection in patients with SLE, with gram-positive cocci and gram-negative enteric bacilli the most frequently isolated organisms. These studies all suggest a progression toward increasing microbial pathogenicity, depending on the level of CVD activity. Patients with inactive SLE have mainly a higher incidence of gram-positive bacterial infections. In the setting of active SLE, however, which involves two or more organ systems, the infections are more aggressive and are caused mainly by gram-negative enteric organisms. In active SLE, when the degree of immunosuppression is furthered by corticosteroid or cyclophosphamide therapy, infections with opportunistic pathogens such as *Aspergillus* sp., *Nocardia* sp., and *Cryptococcus neoformans* become more prevalent.

The types of infections seen in patients with RA are similar, although less frequent, than in patients with SLE. Nevertheless, a number of important differences emerge from several studies over the past 10 years. Whereas, in SLE the majority of infectious complications occur early in the course of the disease, in patients with RA, the greatest number of infections occur late in their clinical course.[114] Moreover, although infections of the urinary tract, lungs, and skin are still significant in number, septic arthritis,[29] relatively silent and localized tissue abscesses,[30] and infected hip, knee, and elbow arthroplasties are the infectious complications with the greatest clinical impact.[11]

In the eight cases of septic arthritis reported by Mitchell et al.,[29] the principal organism was *S. aureus.* Other reports, however, describe many additional organisms implicated in joint infections in this patient population, including *S. pneumoniae, H. influenzae, Pasteurella multocida, Candida* sp., and *Mycobacteria* sp.[22] An increased incidence of severe soft tissue infections in RA patients has also been noted. One report[30] describes 24 episodes of infection in 12 patients with longstanding RA. Extremity abscesses in association with superficial skin infections (5), Intraabdominal abscess (ovarian, 1; gallbladder, 1; pelvic, 1; perinephric, 4), empyema (5), and pneumonia with abscess formation (3), were caused mainly by *S. aureus,* enteric gram-negative bacilli, and *S. pneumoniae.* The gram-positive organisms principally caused the extremity and pulmo-

nary infections, with the gram-negative ones causing the intraabdominal and pelvic infections.

Patients with RA frequently undergo total joint arthroplasty (TJA) in order to relieve symptoms of pain and improve function of severely damaged joints. Although a detailed discussion of the extensive orthopedic literature surrounding the issue of which factors influence the incidence of infections in this setting is beyond the scope of this chapter, several important points should be made. The overall infection rate for all TJA in most series is approximately 1–2%, with the risk in RA patients two to three times that of the osteoarthritic.[115] The operated joint with the highest incidence of infection is the knee, being ten times more frequently infected than the hip and almost twice more often than the elbow. Of interest is that most infections occur within 2 years of surgery, and furthermore, infections occurring during the first year usually result from perioperative complications, but after 3 years there is an increased likelihood that an infected joint may be seeded hematogenously from a distant site. Early TJA infections are caused principally by *Staph.* sp., with late infections exhibiting an increased percentage of gram-negative enteric bacilli, *Pseudomonas* sp., and mixed infections with gram-positive cocci and gram-negative bacilli.

## 7. Unique Clinical Features of Infection in Patients with CVD

As described in the first part of this chapter, the manifestations of an infectious process in patients with SLE, more often than those with RA, may be identical to a flare of the underlying immunologic illness. Consequently, differentiating between infection and active SLE or RA is a critical aspect of acute medical management in these patients. Relatively few studies, however, have focused exclusively on those clinical features which could be helpful in the early identification of infection in patients with either SLE or RA. The study by Stahl et al.[116] has been particularly useful in helping the physician analyze the etiology of febrile episodes in this population because fever is such a common occurrence in patients with SLE.[4] Their study showed that in 160 patients with SLE who had 63 febrile episodes, the primary cause of febrile episodes was active SLE alone in 60%, infections in 23% and a variety of miscellaneous causes in 17% of their patients. Of the 19 febrile episodes associated with the infections, bacteremia, which had the highest mortality rate (33%), was the most common single cause of fever (48%), with localized bacterial infections (abscesses and pneumonia) causing 31%. The most important point, however, was that the only clinical feature that was helpful in discriminating infectious from noninfectious febrile episodes, were shaking chills (27% in noninfected versus 68% in infected patients, $p < 0.001$) (Table 9). In patients who had active SLE, the laboratory features that were most helpful in identifying an infectious cause of fever were leukocytosis (WBC count greater than 12,000 $mm^3$), neutrophilia, and an active urinary sediment. When the group as a whole was examined (active plus inactive SLE), normal DNA binding was observed more frequently in infectious than in noninfectious febrile episodes.

**TABLE 9. Clinical and Laboratory Features Suggestive of Infection in Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis**

| | SLE | RA |
|---|---|---|
| Atypical flare | + | + |
| Shaking chill | + | + |
| Normalization of previously low WBC count | + | + |
| Leukocytosis (WBC 12,000/$mm^3$) | + | + |
| Neutrophilia | + | + |
| Normal DNA binding (in the absence of SLE flare) | + | – |
| Active urinary sediment (in the presence of SLE flare) | + | – |

Other general clinical features which should alert the physician to an infection in a patient with SLE or RA is a change in the usual pattern associated with a flare of the disease. Manifestations of disease activity in an individual patient will frequently appear as a predictable constellation of signs and symptoms, particularly when the flare occurs in temporal association with efforts to reduce corticosteroid or cytotoxic therapy.[4] Symptoms of pneumonitis and pleurisy, arthritis and skin rashes, or meningitis, will recur repeatedly in patients with SLE on tapering of their prednisone dose. The sudden onset of SLE-like symptoms involving a previously silent organ system should lead to a diligent search for an infectious etiol-

ogy, particularly in the absence of CVD activity in other systems. Thus, the diagnosis of new onset of arthritis, pleurisy, or fever secondary to SLE should be a diagnosis of exclusion reached only after an evaluation for infection is unrevealing.[116]

## 8. Clinical Examples of Infection and Their Management

A number of chapters in this book discuss in depth the management of infections in patients with different degrees of immunosuppression in association with an underlying disease process. The clinical approach to complications such as neutropenia, gram-negative sepsis, and pulmonary infiltrates for example, is very similar in practical terms whether the patient has SLE or has had a kideny transplant. However, the unique features of patients with CVD are that the immunologic diseases may mimic an infectious process, that antibiotic therapy can precipitate a flare of CVD activity, and that therapies to suppress CVD activity may cause symptoms indistinguishable from those of an infection. Consequently, the clinical cases below will focus principally on the possible approaches to these particular clinical dilemmas.

### 8.1. Altered Mental Status in a Patient with SLE

Since the diagnosis of CNS involvement in SLE in any of its forms is largely one of exclusion, it is necessary to rule out other treatable causes of such symptoms or signs.

### Illustrative Case 1

A 24-year-old black woman with a 6-year history of SLE was transferred to our hospital for evaluation of possible viral encephalitis because of progressive impairment of memory and unusual behavior over a 4-day period. Six years prior to this admission, the patient had presented with fever to 100.4°F (38°C), arthralgias, and pleuritic chest pain. Evaluation at that time had revealed a normal physical examination except for a friction rub under the right subscapular area. Her laboratory data had revealed a mild normochromic normocytic anemia, a white blood cell (WBC) count of 4500/mm$^3$, an erythrocyte sedimentation rate (ESR) of 80 mm/hr, a positive antinuclear antibody (ANA) test, and a normal urinalysis. A presumptive diagnosis of SLE had been made and she was begun on 60 mg prednisone/day, with prompt resolution of her symptoms. During the ensuring 6-year period, numerous attempts to decrease her daily dose of prednisone below 20 mg had resulted in flares of her original symptoms. On two of these occasions, when the level of prednisone therapy was increased, she had exhibited a transient period of agitated behavior interpreted as steroid-induced psychosis following unrevealing evaluations for meningitis or SLE as etiologic possibilities. Ten days prior to the present admission, the patient's family stated that she had been suffering from the flu, following a weekend camping trip near a lake, and had complained of a sore throat, a nonproductive cough, fever to 38°C, myalgias, and a mild frontal headache. On advice from her family physician, she took acetominophen and increased her prednisone to 60 mg/day (previous evaluation had revealed her to have no significant adrenal reserves under stress conditions). Forty-eight hr later, her family noticed that she displayed increased irritability and had several verbal altercations with her siblings. The day before transfer to the hospital, she was examined in an outlying emergency room because of altered personality and further emotional outbursts. She had a normal neurologic examination and computed tomographic (CT) examination of the head, the lumbar puncture was normal, except for CSF showing 20 lymphocytes/mm$^3$. An infectious disease consultation raised the possibility of viral encephalitis as a possible etiology, and the patient was transferred for further evaluation and therapy. Examination on admission revealed a cushingoid woman with periods of somnolence alternating with agitation. She was afebrile, and had a normal cardiopulmonary examination. Except for her altered mental status, her neurologic examination was normal. A chest radiograph was normal. A repeat CT examination of the head was normal. Lumbar punction revealed a CSF glucose of 60 mg%, a protein of 100 mg%, and 80 lymphocytes/mm$^3$. India ink, Gram stain, and smears of the CSF for acid-fast organisms were all negative. However, her CSF revealed the presence of cryptococcal polysaccharide capsular antigen, and a diagnosis of cryptococcal meningitis was made. CSF cultures subsequently grew *C. neoformans*. She was treated with the combination of amphotericin B 0.3 mg/kg body weight per day IV and flucytosine 37.5 mg/kg body weight every 6 hr PO for 6 weeks. Her neurologic abnormalities resolved, and a lumbar puncture 2 weeks after discontinuation of therapy was normal and failed to grow *C. neoformans*.

*Comment.* The dilemma facing the physicians who first saw this patient was to differentiate between infectious meningitis, steroid-induced psychosis, and CNS manifestations of SLE. The fact that the patient's mental status had worsened in association with increasing her prednisone, a pattern that had been previously observed, added to the initial diagnostic difficulties. Nevertheless, several important points can be made to facilitate the management of this case. Although CNS manifestations of SLE can be the sole manifestation of a disease flare,[117] they usually occur when disease activity is manifested in other organs.[117–119] Except for her mild flulike symptoms, this patient did not exhibit any of her usual manifestations of active SLE. Furthermore, her usual symptoms always had responded to increased prednisone therapy and in this situation had in fact been associated with further clinical deterioration. In several series reporting patients with CNS–SLE, none of the neurologic features appears in the absence of other features of SLE.[118,120] Laboratory abnormalities such as hypoglycorrhacia can very rarely be caused by SLE, but usually only when trans-

verse myelitis is present.[121] In addition, CSF pleocytosis may also occur in the setting of CNS–SLE in up to one-third of patients, but usually consists of only a few cells.[118,120] Consequently, in this type of case a search for an infectious etiology is imperative, particularly because the symptoms of cryptococcal meningitis may be similar to those of CNS–SLE.[122] As with this patient, more than one lumbar puncture may have to be performed, since the findings of elevated CSF protein and minimal or no lymphocytosis may be the only findings in both early cryptococcal meningitis and CNS–SLE.[122] In a number of series examining deep fungal infections in SLE, the correct diagnosis of cryptococcal meningitis was made in only 36% of patients antemortum.[123] The combination therapy she received with amphotericin B and flucytosine has been effective in erradicating CNS cryptoccal infections.[124] In patients with SLE, however, azotemia is more likely to develop despite the lowered dose of amphotericin B, causing flucytosine levels to rise. Consequently, renal function and flucytosine levels should be carefully monitored in order to avoid the GI and marrow toxicities of this drug. Despite the success of this therapy, mortality due to CNS cryptococcal infection is still approximately 30%, with nearly one-half the patients cured exhibiting residual neurologic abnormalities, and hydrocephalus an occasional late complication even when the infection has been irradicated.[125]

## 8.2. Pleuritic Chest Pain and Fever in a Patient with SLE

Patients with SLE may develop parenchymal lung disease in addition to pleural and pericardial involvement. In most situations, however, cardiac failure, pulmonary emboli, uremia, and infections play a more important role. A careful and thorough evaluation should provide the basis for a choice between antibiotics and antiinflammatory agents.

## Illustrative Case 2

A 37-year-old white woman with a 2-year history of SLE was admitted to the hospital for evaluation of pleuritic chest pain and fever. The patient had presented to her family physician 2 years earlier with pleuritic chest pain, tachypnea, mild hypoxia, arthralgias, and a malar rash. Her initial laboratory examination revealed a normal WBC count, an ESR of 110 mm/hr, an elevated ANA, and a chest radiograph with bilateral alveolar infiltrates. She was diagnosed as having SLE following extensive evalution, including bronchoscopy with transbronchial biopsy that revealed only acute alveolitis on pathologic examination. Her pulmonary symptoms and chest radiographic abnormalities resolved with the use of oral corticosteroids. Even with the judicious use of corticosteroids and the subsequent addition of cyclophosphamide therapy, she had developed the nephrotic syndrome over the 2-year period, and at the time of this admission her degree of azotemia had progressed to the extent that she was being considered for dialysis. Despite her disease, she had remained physically active and had recently helped her family build an extension to their home. The admission physical examination revealed a visibly tachypneic, cushingoid-appearing white woman, complaining of right-sided pleuritic chest pain. Her temperature was 102.2°F (39°C) and her respiratory rate 24/min. She had dullness to percussion over the right posterior chest with an audible friction rub. Except for mild pitting edema of her lower extremities, the remainder of the physical examination was normal. Her laboratory data revealed a WBC count of 13,000/mm$^3$, an ESR of 60 mm/hr, a urinalysis with 2+ protein, and a chest radiograph with an area of consolidation in the apical segment of the right lower lobe (Fig. 1). Arterial blood gas (ABG) measurements showed her to have a $Pa_{O_2}$ of 74 mm Hg, $Pa_{CO_2}$ of 25 mm Hg, and pH of 7.48 while breathing room air. On further questioning, the patient described several days of a nonproductive cough, intermittent fever to 100.4°F (38°C), and the sudden onset of pleuritic chest pain the day before admission.

Repeated attempts to obtain a sputum sample for examination, including a transtracheal aspirate, were unrewarding. The patient was begun on nafcillin 8 g/day in addition to gentamicin 3 mg/kg per day IV. On her second hospital day, she complained of increasing pleuritic chest pain and had several episodes of a small amount of hemoptysis. Pulmonary arteriography was performed and revealed no changes consistent with pulmonary emboli. Bronchoscopic examination with transbronchial biopsy was performed on the third hospital day because of further clinical deterioration characterized by increasing shortness of breath, and decreasing arterial oxygen content to a $Pa_{O_2}$ of 54 mm Hg on breathing room air. Pathologic examination of the lung biopsy specimen revealed areas of hemorrhagic infarction with abundant hyphal forms growing in blood vessels. The patient's previous antibiotics were discontinued, and she was begun on amphotericin B 0.5 mg/kg per day IV. Aspergillus sp. subsequently were identified in cultures of the biopsy specimen. On the fifth hospital day, the patient suddenly became cyanotic, hypotensive, and unresponsive to stimuli. Resusitation attempts were unsuccessful and she expired. Postmortem examination revealed a saddle embolus obstructing the pulmonary artery, and the right lower lobe of the lung with extensive consolidation and hemorrhagic necrosis, with many hyphal forms seen invading the microvasculature.

*Comment.* Differentiating between SLE pneumonitis, pulmonary emboli, and infectious etiologies to explain this patient's clinical course was the principal difficulty encountered by her physicians. Because the patient had previously demonstrated SLE flares that had exhibited a significant pulmonary component, her present tachypnea, nonproductive cough, fever, and hypoxia were all consistent with acute SLE pneumonitis.[126] When autopsy series have principally examined the lungs in patients with SLE, those pulmonary manifestations attributed to SLE alone were interstitial fibrosis, vasculitis, and hematoxylin bodies in 100% of cases and interstitial pneumonitis and pleuritis in 73% and 61%, respectively.[127] Chest radiographs are usually characterized by unilateral or bilateral alveolar infiltrates with or without effusions.[128,129] It is important to remember however, that pulmonary infections are still the most frequent causes of infiltrates in patients with SLE.[126–131] One feature that may help the physician distinguish between infection and SLE pneumonitis, is that the latter has a predilection for the lung bases.[126] In addition, when pulmonary hemorrhage is present in SLE, there are usually bilateral radiographic abnormalities, again usually more pronounced in the

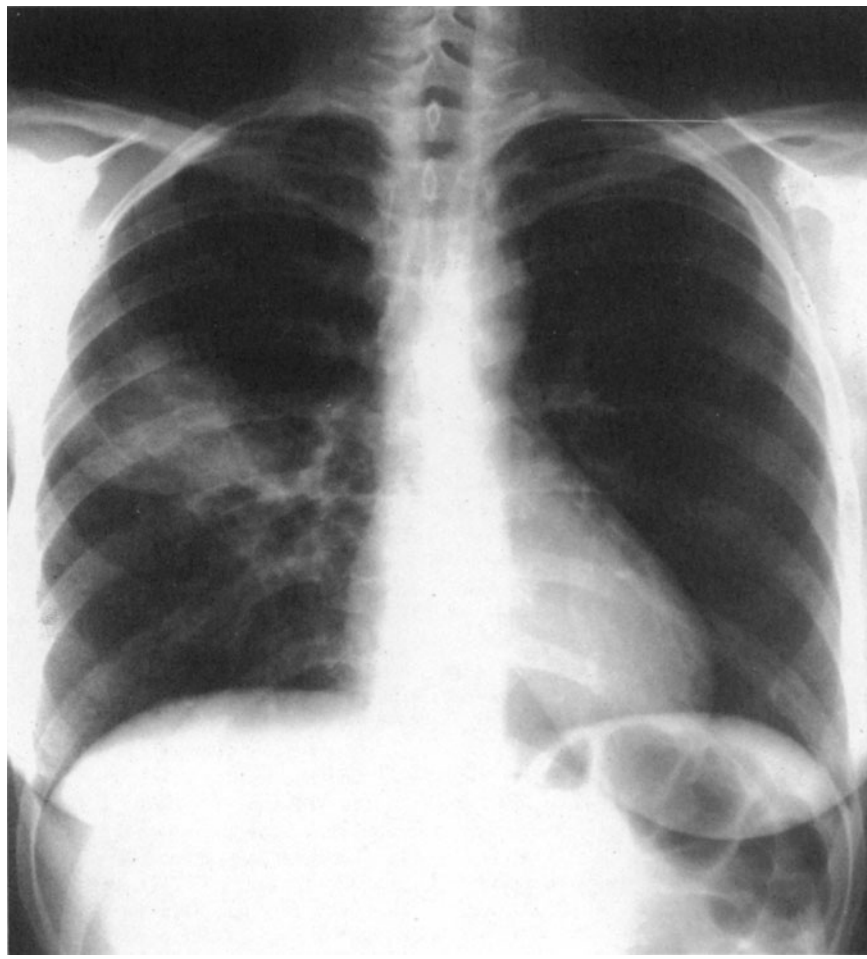

**FIGURE 1.** Admission chest radiograph for Illustrative Case 2. This 37-year-old patient with SLE presented with pleuritic chest pain, a nonproductive cough, and an audible friction rub over the right posterior chest. The posterior apical (PA) chest radiograph demonstrates a right lower lobe (apical segment) pneumonia.

lower lung fields, with pathologic examination revealing a significant number of patients with immune complex deposition in the alveolar septa and bronchioles.[132] In a number of cases of SLE–pneumonitis, once an infectious etiology has been ruled out, there has been prompt clinical response to corticosteroid and immunosuppressive therapy.[126]

The single most important action that will help the physician manage this type of case in an optimal manner, when no sputum can be obtained initially for microbiologic examination and culture, is a lung biopsy. It should be performed as early in the clinical course as possible to obtain material for culture and pathologic examination. Delays to evaluate the results of empirical therapy frequently lead to further clinical deterioration, and should be avoided. Because in autopsy reports of SLE patients bronchopneumonia is present in one-half of cases and is the most common pulmonary finding,[127] every effort should be made to identify an infectious etiology. Most of these pneumonias are bacterial in origin, but tuberculosis and fungal infections are also common causes. The conspicuous absence of sputum in this case makes a search for tuberculosis and fungal infection particularly urgent.

Tuberculosis (TB) in association with SLE usually presents as fever, cough, hemoptysis, dyspnea, and weight loss, symptoms that frequently initially are attributed to SLE itself.[133] As with most infectious complications of SLE, nearly two-thirds who develop TB will do so within the first 2 years of having had the diagnosis of SLE.[133] Frequently two or more organ systems have manifestations of SLE disease activity at the time TB is detected. Consequently, there usually is an average delay of one to three months in establishing the diagnosis, particularly when extrapulmonary manifestations are present. Therefore, in a patient with SLE, unexplained pulmonary infiltrates, lymphadenopathy, pleural effusion, or ascites should be evaluated aggressively for

active TB and not be attributed to the underlying immunologic disease. Because in most studies severity of SLE and corticosteroid dosage correlate positively with severity of TB and mortality, an individual patient with a course strongly compatible with TB, in whom a tissue diagnosis of TB has been unobtainable, a judicious trial of antimycobacterial drug therapy is probably indicated.[134]

Examination of the lung biopsy specimen and subsequent cultures demonstrated that this patient had developed an invasive fungal infection with *Aspergillus flavus*. In one series that reviewed 33 cases of deep fungal infection in association with SLE, most patients had candidiasis (14 of 33), either disseminated (8 of 14) or localized (pneumonitis, pertinonitis, or esophagitis) (6 of 14).[123] Of the remaining patients, 10 had infection with *Cryptococcus* (disseminated and meningitis), four with *Aspergillus* sp. (disseminated and pneumonitis), and two each with *Coccidiodes immitis* and *Histoplasma capsulatum*. It was not uncommon for fungus infection to supervene in an area previously infected with bacteria. It is clear from published reports and our experience, that despite the high mortality of invasive pulmonary fungal disease, the patients that are the most likely to survive are those in whom the diagnosis is made early in the course of the infection, and who have few if any ongoing manifestations of SLE requiring high doses of corticosteroids. Intravenous amphotericin B is the drug of choice for invasive aspergillosis. The likelihood of a response is increased by its administration early in the course of the disease, with doses being rapidly advanced to therapeutic levels in the range of 0.5–0.6 mg/kg per day.

An additional etiologic possibility considered initially in this case was that of an infection caused by *Nocardia asteroides*, an organism frequently complicating the course of immunosuppressed patients on high doses of corticosteroids.[135] Of interest, however, is that norcardiosis is a distinctly unusual infection in women with SLE, with almost 90% of cases complicating SLE being reported in men.[136] In several studies involving SLE patients, lung involvement by Nocardia presented not infrequently as a pulmonary cavity in women, and pneumonia involving the upper and middle lobes in men.[136] Most of these patients are almost always on high doses of corticosteroids. The striking association of nocardiosis and male patients with SLE seen in the literature suggests that either genetic host factors or hormonal milieu, or both, may contribute significantly to the pathogenesis of this infection.[136]

## 8.3. Abdominal Pain in a Patient with SLE

Thirty-five to 40% of patients with SLE develop signs or symptoms of GI involvement at some point during the course of their illness, and nearly 20% of these patients complain of abdominal pain at some point. Because of the pleomorphic nature of the symptoms and signs of acute abdominal pain in SLE, it may be impossible to distinguish infectious peritonitis from the abdominal syndromes associated with mesenteric vasculitis.

## Illustrative Case 3

The patient was a 31-year-old black woman with a 10-year history of SLE, transferred to our hospital for management of her abdominal pain. The diagonsis of SLE had been made 10 years previously when the patient presented with hematuria, arthralgias, fever, and weight loss. A renal biopsy at that time had been described as being consistent with SLE nephritis. Over the ensuing 10 years, she experienced numerous complications as a result of her SLE, including several episodes of cerebritis, myocarditis, pericarditis, pleuritis, and azotemia. She had received continuous therapy with corticosteroids and intermittent therapy with cyclophosphamide, complicated by insulin-dependent diabetes mellitus and several episodes of hemorrhagic cystitis. She had been hospitalized for 2 months prior to transfer because of abdominal pain, pleuritis, and pericarditis. Radiologic evaluation at the outlying hospital had revealed a normal biliary tree, but a CT examination of the abdomen had raised the possibility of a pancreatic pseudocyst. She had been treated with high doses of corticosteroids with no significant relief and on transfer was taking 160 mg/day prednisone. She denied any alcohol consumption and no use of thiazide diuretics. The admission physical examination revealed a distressed cushingoid black woman, vomiting coffee-ground material. Her temperature was 37°C, her blood pressure was $^{140}/_{100}$ mm Hg and her pulse 126/min. The cardiopulmonary examination was positive for a pleuropericardial friction rub over the upper left sternal border. Her abdomen was diffusely tender with decreased bowel sounds. The rectal examination revealed stool that stained positive for guaiac. The laboratory examination showed a WBC count of 9900/mm$^3$, a Hct of 34.9%, an ESR of 56 mm/hr, normal coagulation parameters, and a fivefold elevation above normal in both serum amylase and alkaline phosphatase. Her urinalysis showed 1+ protein and no cells, and the chest radiograph was normal except for mild cardiac enlargement. A presumptive diagnosis of pancreatitis complicated by upper GI tract bleeding was made and the patient was placed on antacid therapy by mouth and on intravenous fluids.

Initial attempts over the first few days of hospitalization to reduce her dose of prednisone resulted in increased pleuritic chest pain. Further evaluation with a CT examination of the abdomen revealed "fluid collections within the abdomen suggestive of pancreatic pseudocysts," and endoscopy revealed gastritis. Because of persistent abdominal pain, paracentesis was performed that revealed yellowish fluid containing 3400 PMN leukocyte/mm$^3$ and an elevated amylase level. Although the Gram stain was negative for organisms, she was begun on antibiotic therapy intravenously as treatment for possible spontaneous bacterial peritonitis. Eight days after admission, she developed sudden left-sided weakness and blurring of vision. CT examination of the head was normal, as was the laboratory evaluation of her CSF. The following morning, because of severe and sudden dyspnea, she was transferred to intensive care, with chest radiography revealing diffuse bilateral interstitial changes consistent with pulmonary edema. Because of her deteriorating level of oxygenation, she was intubated. All attempts to identify an infectious etiology for the pulmonary infiltrates were negative, and a presumptive diagnosis of adult respiratory distress syndrome (ARDS) was made. Several hours later she complained of severe abdominal pain, became hypotensive and

despite resuscitation attempts, expired. Post mortem examination revealed fulminant pancreatitis with extensive fat necorsis and pseudocyst formation, complicated by ARDS and a large acute myocardial infarct. In addition, there were focal infarcts in her spinal cord with small vessel thrombosis, and ulceration of the large bowel.

*Comment.* The principal problem that significantly complicated this patient's management among the many other complex and interrelated clinical issues involving this case, was the etiology of her abdominal pain. Abdominal pain has long been recognized as a prominent and the most frequent GI manifestation of SLE and other vasculitides such as periarteritis nodosa (PAN)[137] and may have many potential causes such as peritonitis, bowel ulceration and perforation, hemorrhage, and motility disturbances.[138] In a recent series of 140 patients with SLE in whom 11% developed disease-related signs and symptoms of acute surgical abdomen, one-third of this group had nausea, vomiting, diarrhea, and melena, as did our patient.[139] Fever and tachycardia were universally present, and 75% had rebound abdominal tenderness, with hypoactive bowel sounds. In those that underwent laparotomy, more than half had intestinal perforations. Other causes of pain that needed to be considered in this case were peritonitis and pancreatitis.

Acute necrotizing pancreatitis was noted in 4 of 14 SLE patients with severe abdominal pain in Pollack's study.[140] The important points from this and other reviews are that (1) there is little correlation between amylase levels and duration or dosage of corticosteroid therapy in those patients who develop pancreatitis,[141] and (2) diagnosis of an acute surgical abdomen due to SLE could be made with increased confidence only when the patient had concomitant disease activity in other organs. Zizic et al.[139] pointed out that the index of suspicion should be particularly high in those patients who have evidence of peripheral vasculitis, neurologic involvement, thrombocytopenia, or rheumatoid factor positivity, all of which occur significantly more often in those SLE patients with abdominal crises. In the study by Reynolds et al.,[141] which examined 53 SLE patients with abdominal pain, 49% had hyperamylasemia, with only 20% of these caused by extrapancreatic causes. As was described in other studies,[129] 80% of these patients with pancreatitis and hyperamylasemia manifested SLE activity in more than four organ systems. In contrast with our patient, complications such as ARDS, shock, and hemorrhage were not observed in this series. Moreover, recovery usually occurred despite continued steroid therapy. Gram-positive bacterial spontaneous peritonitis in association with SLE has been reported.[142] In SLE patients, this complication has arisen in the setting of marked proteinuria and hypoalbuminemia, although ascites has usually not been demonstrable. The symptoms, as in the case of acute pancreatitis, are not distinctive, with abdominal pain, diffuse tenderness, and guarding present in most cases. In the cases reported by Lipsky et al.,[142] all the patients were bacteremic and had abdominal paracentesis revealing the causative organism.

In managing these patients, it is important not to delay therapy until all the classic signs of an acute abdomen develop, since they may occur late, if not at all, and be masked by the antiinflammatory properties of corticosteroids. Consequently, early analysis of peritoneal fluid for Gram stain and culture to exclude bacterial peritonitis, the judicious use of antibiotics, and prompt laparotomy when clinical symptoms and signs progress despite medical therapy are all indicated.

## 8.4. Painful Knee in a Patient with Rheumatoid Arthritis

The early identification and treatment of an infectious etiology of a painful knee in a patient with RA will lead to a significant improvement in morbidity.

## Illustrative Case 4

A 76-year-old white woman with a long history of seropositive RA was admitted for evaluation of a swollen, painful left knee. Over the previous 35 years, she had developed numerous flares of RA involving both her knees and ankle, and had undergone an uncomplicated left knee synovectomy 10 years earlier. Over the preceding 4 months she had experienced periodic painful swelling of her left knee, and on several occasions small amounts of cloudy fluid had been aspirated with Gram stain and routine bacteriologic cultures being negative. Intraarticular corticosteroids had been administered with temporary relief of her symptoms. She denied any systemic symptoms such as fever or weight loss. The physical examination was characterized by the stigmata of longstanding RA involving both her knees and ankles, with her left knee being warm, mildly erythematous, tender to palpation, and demonstrating decreased arc of flexion. Radiographs of the left knee showed increased bony and joint destruction, which had progressed over the preceding year. Aspiration of the left knee revealed cloudy fluid with 50,000 PMN leukocytes/$mm^3$, a negative Gram stain but positive Ziel–Nielsen stain for acid-fast bacilli. Cultures subsequently yielded *Mycobacterium kansasii*. Surgical exploration of the knee found caseating granulomata with bony and joint destruction and a florid synovitis. On the basis of the diagnosis of tuberculous arthritis, the knee was debrided and an arthrodesis performed. The patient received isoniazid and rifampin therapy for 6 months with resolution of the knee pain and no further radiologic progression.

*Comment.* Patients with chronic RA have a propensity to develop superimposed joint infections. This susceptibility to infection is further increased in the presence of Felty syndrome, severe longstanding disease, and immunosuppressive therapy.[143] Moreover, such patients have been shown to be at risk for opportunistic infections with organisms of low virulence, such as *M. tuberculosis* and *M. kansasii*.[144]

The clinical management of cases such as this is always complicated by the difficulty in diagnosing an infectious process in joints of immunocompromised patients who have an underlying chronic inflammatory process. Frequently, these joints either fail to show a local articular response to infection such as heat and tenderness or have such frequent rheumatoid flares that no distinguishing features of the suppurative process are detectable.

Tuberculous infection of the joints in this population is almost

always a combination of osteomyelitis and arthritis, may be a consequence of remote infection, and is frequently monoarticular, with the weight-bearing joints the most commonly affected. *M. kansasii* has been reported to cause suppurative arthritis in a number of patients with RA.[145] Distinguishing features have included frequent involvement of the tendon sheaths of the hand and wrist, with common involvement of small bones and joints of the hands.[146] Consequently, the granulomatous process often simulates RA. As in our patient, the earliest clinical manifestation may be pain, which can precede other signs or inflammation by weeks or even months. Joint fluid aspirates in this population should always be carefully examined for an infectious etiology. A sample that is cloudy, with variable viscosity, >10,000 PMN leukocytes/mm$^3$ and a low to normal sugar, should not only be Gram stained for bacteria, but a Ziehl–Neelsen stain for acid-fast organisms should be done. Definitive diagnosis almost always requires a biopsy, which should be done as soon as the suspicion of tuberculous joint infection is raised. Early chemotherapeutic intervention frequently is curative, with arthrodesis necessary only for control of pain as well as joint stability.[115]

Although the insidious onset of a suppurative process with an organism of low virulence may present a difficult clinical problem, a far more common complication in RA is septic arthritis caused by organisms such as *Staph. aureus*.[22] Mortality in patients with RA for this complication may be high, occurring in approximately 30% of patients. Moreover, the prognosis is largely determined by the speed of initiating antibiotic therapy, with patients who are untreated for a week or more having a much worse prognosis. Not infrequently, the joint infection will be temporally and anatomically close to an infected skin ulcer.[2,29] Therefore, it is important to vigorously treat skin infections in patients with RA, in the same way that an infected lesion would be treated in a patient with diabetes mellitus.

There are a number of significant clinical differences and similarities between our patient with RA and the septic arthritis in patients with SLE. In patients with SLE, septic arthritis also commonly involves the large weight-bearing joints, with the knee being the most frequent. Characteristically, the septic arthritis is monarticular, accompanied by pain, swelling, and erythema.[147] The onset is usually acute, with systemic symptoms such as fever and chills present in 60% of cases. The most significant difference between SLE and RA, however, is that in SLE a wide variety of bacterial organisms may cause septic arthritis.[147] *Neisseria gonorrheae, Staphylococcus* sp., gram-negative enteric bacilli, *Hemophilus influenzae,* and *Salmonella* sp. are reported far more frequently in SLE than is RA, where 70–80% of the cases of septic arthritis caused by *S. aureus*. The management of these cases should be similar to those already described, with prompt joint fluid analysis and culture, synovial tissue biopsy for definitive diagnosis in the more indolent cases, and early antibiotic treatment to prevent further tissue destruction.

## 9. Conclusions

The management of infections in the immunosuppressed patient with CVD shares many features in common with those in other immunosuppressed groups. Neutropenia and other side effects of cytotoxic therapy, nosocomial infections such as line sepsis, and the complications of corticosteroid therapy are among the many common issues throughout this book. The most distinctive feature, however, that makes infection in the SLE or RA patient difficult to assess is the fact that the manifestation of an infectious process in these patients may be identical to specific aspects of the underlying disease activity. Moreover, infection may not only mimic a flare of SLE or RA but also precipitate one, causing further diagnostic difficulties. In addition, complications of antibiotic and cytotoxic therapy may be indistinguishable from one another, or from the protean manifestations of the immunologic disease.

Patients with SLE are most likely to develop an infection within the first 2 years after diagnosis. These patients have a greater incidence of gram-positive bacterial infections when compared to other patients with immunologically mediated disease. As the level of disease activity increases and immunosuppressive therapy is instituted, infections with enteric gram-negative bacilli and opportunistic pathogens become more frequent. The major causes of morbidity and mortality continue to be pneumonia and sepsis, with minor infections principally involving the skin and urinary tract. By contrast, patients with RA are more likely to develop an infection late in the course of their disease, usually involving the weight-bearing joints. In these patients, joint infections with bacteria commonly causing skin infections, such as *Staph.* sp., are more frequent. In RA patients, when gram-negative organisms are involved, it is principally in the setting of hematogenous spread from the urinary tract.

Atypical flares of disease in the absence of clinical involvement of other organ systems should always raise the possibility that the etiology is an infectious process. Prompt and persistent attempt to obtain a biopsy specimen from the involved area for microbiological analysis is the single most important step in managing infections in these patients. Attempts to evaluate empiric therapy frequently lead to significant delays in the diagnosis, and a far worse prognosis overall. When the appropriate cultures have been obtained, early judicious use of antibiotic therapy most often results in a positive clinical outcome.

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