

Monitoring patients with vasculitis

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ABSTRACT

Granulomatosis with polyangiitis is a common form of small-vessel vasculitis, remarkable for its tendency toward multisystem manifestations. Standard induction treatment calls for the use of low-dose daily cyclophosphamide (CYC) and glucocorticoids. Treatment goals for newly diagnosed patients include increased survival, induction of remission, reduction of relapse frequency, and minimization of treatment toxicity. Induction and maintenance treatments with CYC, glucocorticoids, and other immunosuppressive therapies improve the disease course, but relapse- and treatment-related toxicity and infections demand consistent, patient-specific monitoring.

Granulomatosis with polyangiitis (GPA), is one of the most common types of small-vessel vasculitis, with an estimated prevalence in the United States of 3 per 100,000 people. It is distinguished from other necrotizing vasculitides by its tendency to affect the upper and lower respiratory system and the kidneys. Despite the success of induction and maintenance treatments with cyclophosphamide (CYC), glucocorticoids, and less toxic immunosuppressive alternative therapies in improving the disease course, significant treatment-related toxicities and frequent disease relapses demand stringent patient-specific monitoring in order to provide early treatment of relapses and prevent or decrease morbidity.

SMALL-VESSEL VASCULITIS MANAGEMENT OVERVIEW

Granulomatosis with polyangiitis (formerly Wegener's granulomatosis, or WG) is an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis that often affects the respiratory system and kidneys across a broad spectrum of clinical presentations, from mild through life-threatening disease. Patients with severe disease present with significant multisystem manifestations, which, in addition to the respiratory system and kidneys, may involve the joints, eyes, and other organs.

Managing patients diagnosed with systemic small-vessel vasculitides such as GPA and microscopic polyangiitis (MPA) is an inexact science. The goals of treatment

are to increase survival, induce and maintain remission, reduce relapses, and minimize treatment-related toxicity. Inducing and maintaining remission have become realistic goals because of the availability of medications that prolong life. On the other hand, extended periods of treatment associated with prolonged life increase the risk of treatment-related toxicity in patients who are inadequately monitored.

The initial CYC protocol published in 1992¹ called for use of CYC for 1 year after remission. The observed permanent morbidity for patients on this treatment course was 100%, whether from the disease or from the medication, with 86% of patients suffering a disease-related morbidity and 42% having a treatment-related toxicity. Complete remission was achieved in 75% of patients, but 50% suffered a relapse (Table 1).¹ Careful, continuous monitoring can help reduce morbidity and relapse.

MONITORING CONSIDERATIONS

Achieving treatment goals requires long-term monitoring of both disease activity and treatment-related toxicities, with constant adjustments to meet the needs of the individual patient and address the often rapidly changing disease and treatment course. The monitoring protocol consists of regularly scheduled follow-up office visits, urine sediment analyses at every office visit whether or not the patient has relapse symptoms, laboratory tests at regular intervals as indicated by the patient's medication plan and disease presentation, additional tests such as lung computed tomography (CT), and patient education regarding new symptoms and the frequency of office visits. A consistent monitoring strategy will help detect a relapse before it can produce more severe morbidity, identify treatment-related complications, and—equally important—identify the achievement of remission. An example of the consequences of inconsistent monitoring is presented in “Relapse in a nonadherent patient,” page S35.

Because there is no definitive cure for small-vessel vasculitis, relapse is always a possibility. The early diagnosis and treatment of relapse may prevent or decrease morbidity from disease, but strict monitoring is needed to identify relapse and initiate treatment before morbid-

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TABLE 1
Cyclophosphamide-related treatment outcomes¹

| Morbidity | Effect |
|--|------------------|
| Permanent morbidity | 100% |
| Disease-related morbidity | 86% |
| Chronic renal insufficiency | 42% |
| Hearing loss | 35% |
| Nasal deformities | 28% |
| Tracheal stenosis | 13% |
| Visual loss | 8% |
| Disease and/or treatment-related morbidity | |
| Chronic sinus dysfunction | 47% |
| Pulmonary insufficiency | 17% |
| Treatment-related morbidity | 42% |
| Infertility | 57% |
| Cystitis | 43% |
| Hair loss | 17% |
| Bladder cancer | 3% |
| Myelodysplasia | 2% |
| Risk of bladder cancer | 33-fold increase |
| Risk of lymphoma | 11-fold increase |
| Relapse | 50% |

ity occurs (see “Relapse in a patient with new symptoms,” page S36). Repeat induction therapy following a relapse introduces risk of drug toxicity and requires careful monitoring, as does long-term maintenance therapy.

In addition to induction and maintenance therapy, several other situations, including prior therapeutic complications, serum creatinine levels, and risk of cardiovascular disease, require special monitoring attention.

Induction therapy: monitor response

Response to treatment during induction must be monitored to identify whether remission is achieved. Induction monitoring requires complete assessment of organ-system involvement at every visit with tools such as the Birmingham Vasculitis Activity Score (BVAS) and, when appropriate, the BVAS/WG. If new or worsening symptoms develop during induction therapy, then the patient needs assessment for continued disease activity as well as treatment complications such as infections related to immunosuppressive therapy.

During induction therapy with daily oral CYC, monitoring should include weekly complete blood cell counts to ensure early identification of leukopenia and other cytopenias. The risk of morbidities increases with the cumulative dose, so a stable blood count for 2 months does not obviate the risk of leukopenia. If persistent hematuria

Relapse in a nonadherent patient

A 58-year-old woman with granulomatosis with polyangiitis (GPA) presents for a routine follow-up visit. Her GPA was diagnosed 2 years earlier with lung nodules, glomerulonephritis, myalgias, fever, sinusitis, and positive proteinase-3–antineutrophil cytoplasmic antibodies. Her serum creatinine level was not increased at the time of diagnosis, and it remained stable (0.9 mg/dL) following treatment. She has been receiving maintenance therapy with methotrexate.

Because of the patient’s nonadherence with her monitoring protocol, laboratory tests that would ordinarily be performed monthly are instead performed every 3 months; however, the patient missed her appointment 3 months earlier.

She presents for her follow-up visit with fatigue but is otherwise asymptomatic. Urine sediment analysis shows hematuria (2+ blood) and several red blood cell casts, serum creatinine is 5.2 mg/dL, and computed tomography of her chest shows new lung nodules.

Relapse is diagnosed and treatment is started. A few days later, the patient loses kidney function and dialysis, once initiated, becomes permanent.

Comment. This patient was being monitored less frequently than recommended and presented for her follow-up examination with no new symptoms. Had she adhered to the monitoring protocol, which included monthly checks of kidney function, the abnormality could have been detected in time to prevent the need for permanent dialysis.

is present without cellular casts, cystoscopy is indicated to look for signs of hemorrhagic cystitis. Prophylaxis against *Pneumocystis jirovecii* is recommended in all patients who receive immunosuppressive therapy. Finally, bone density measurements should be done at baseline.

Maintenance therapy: frequency can be extended

Monitoring during maintenance therapy is similar to induction monitoring; however, when the dosage of methotrexate or azathioprine is stabilized, the frequency of some tests can be extended to monthly rather than weekly. For example, a complete blood cell count, comprehensive metabolic panel, sedimentation rate, C-reactive protein measurement, and urinalysis should be performed monthly. Follow-up visits should include urine sediment analyses and monitoring for cardiovascular disease risk factors. Medication monitoring should include cystoscopy for persistent hematuria without cellular casts, bone density measurements, and ophthalmologic examinations as frequently as indicated for each individual’s

TABLE 2
Recommendations for prevention and treatment of glucocorticoid-induced osteoporosis: Postmenopausal women and men aged 50 years and older⁵

| Low risk | Medium risk | High risk |
|--|--|---|
| GC < 7.5 mg/d for ≥ 3 mo: no pharmacologic treatment | GC < 7.5 mg/d for ≥ 3 mo: alendronate or risedronate | GC < 5 mg/d for ≥ 1 mo: alendronate, risedronate, or zoledronic acid |
| GC ≥ 7.5 mg/d for ≥ 3 mo: alendronate, risedronate, or zoledronic acid | GC ≥ 7.5 mg/d for ≥ 3 mo: alendronate, risedronate, or zoledronic acid | GC ≥ 5 mg/d for ≤ 1 mo or any dose for > 1 mo: alendronate or risedronate |

GC = glucocorticoid

Relapse in a patient with new symptoms

A 72-year-old woman previously treated for granulomatosis with polyangiitis (GPA) presents for an urgent evaluation of new symptoms. She was diagnosed with GPA 3 years previously after presenting with nasal ulcer, sinusitis, polyarthralgias, lung infiltrates, and glomerulonephritis. She had positive proteinase-3–antineutrophil cytoplasmic antibodies and her initial serum creatinine was 3.2 mg/dL. After treatment, her serum creatinine remained between 1.8 and 2.0 mg/dL; she has not taken any medication in the past year.

The patient's new symptoms include a 1-week history of ear pain and daily sinus drainage. Although her urine has been normal for 1 year, an in-office urine sediment analysis reveals 2+ blood, microscopic hematuria, and several red blood cell casts. Chest computed tomography is normal, erythrocyte sedimentation rate is 78 mm/hr, and serum creatinine is 2.0 mg/dL.

The patient's serum creatinine level is stable, but her urine is abnormal for the first time since treatment. A diagnosis of GPA relapse is made and the patient is started on treatment.

Comment. Continuous frequent monitoring of urine sediment in this patient resulted in a diagnosis of relapse involving the kidneys before loss of renal function occurred.

needs. *P jirovecii* prophylaxis should continue as long as the patient receives immunosuppressive medication.

Therapy-related complications

Bladder complications. In a retrospective analysis of 145 patients with GPA treated with CYC and followed for 0.5 to 27 years (median 8.5 years), nonglomerular hematuria developed in 50% of the patients and bladder

carcinoma in 5%.² The cumulative CYC dose (19 to 251 g) in this group was much higher than what is currently used. Cytologic examination of the urine showed 43% sensitivity for dysplasia (specificity 100%) and 29% sensitivity for atypia (specificity 89%). In contrast, in a retrospective outcomes analysis involving newly diagnosed patients with GPA treated with CYC or methotrexate, 82 patients followed for up to 12 years had no incidents of cystitis or bladder cancer.³ Patients in this study were treated with CYC for only 3 to 6 months and there-

fore received a lower cumulative dose.

To prevent cystitis during treatment with CYC, the patient should be well hydrated, especially in the morning when CYC should be taken. The bladder should be emptied frequently. The addition of mesna when administering intravenous CYC decreases the risk of cystitis. Serial cystoscopy and urine cytology should be used only in patients with nonglomerular hematuria.

Infertility. Preservation of ovarian function is a concern with CYC therapy in women of childbearing age. The cumulative dose threshold for gonadal failure is unknown, because data from cancer studies⁴ demonstrating gonadal failure involve higher cumulative CYC doses than are typical for vasculitis treatment. It is also unknown whether duration of amenorrhea predicts the recovery of menses or fertility. The primary option for preservation of ovarian function is the use of gonadotropin-releasing hormone agonists. Oral contraceptives also may be used, but the best prevention is to avoid CYC in these patients if possible.

Osteoporosis. At glucocorticoid dosages of 5 mg/day or greater, bone mineral density begins a rapid decline within the first 3 months and peaks at 6 months.⁵ The American College of Rheumatology has provided recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis.⁵ **Table 2** presents recommendations for postmenopausal women and men aged 50 years and older who will use glucocorticoids for 3 months or more.⁵ Recommendations are also available for premenopausal women and men younger than 50 years of age who have a history of fragility fracture.

Leukopenia. Leukopenia should be avoided during CYC treatment. The target white blood cell count should be within the normal range. During treatment with daily oral CYC, the patient should be monitored with a weekly complete blood cell count and medication should be adjusted to maintain the target white blood cell count.

Upon completion of induction therapy, after 3 to 6 months, the patient is switched to maintenance therapy

Relapse presenting as thrombosis

A 45-year-old man presents with bilateral thigh swelling and pain but no other symptoms. He is diagnosed with bilateral deep vein thrombosis and hospitalized for anticoagulation.

The patient was diagnosed with granulomatosis with polyangiitis (GPA) 10 years previously with alveolar hemorrhage, glomerulonephritis, and sinusitis. He has been receiving treatment with azathioprine and has no history of relapse. His urine sediment and serum creatinine levels have been normal over the years.

During this hospitalization, the urine sediment shows blood and red blood cell casts, and chest computed tomography shows bilateral nodular infiltrates.

The patient is diagnosed with asymptomatic GPA relapse whose only clinical presentation was deep vein thrombosis.

Comment. Given the increased risk of thrombosis in patients with active GPA, any patient diagnosed with thrombosis should be fully evaluated for possible concurrent GPA relapse.

with an alternative immunosuppressive agent such as azathioprine or methotrexate, depending on the serum creatinine concentration and other factors. This transition, characterized by full-dose immunosuppressive therapy when the bone marrow has been previously suppressed by CYC treatment, may induce pancytopenia. Monitoring with weekly complete blood counts for at least 4 weeks after initiating maintenance therapy can help ensure stability during the transition period.

Monitor serum creatinine and adjust dosages

The serum creatinine concentration may increase as CYC treatment progresses; in some cases, the serum creatinine concentration increases before a response to treatment is seen. The CYC dosages should be adjusted as necessary in response to serum creatinine changes. Careful monitoring of serum creatinine is necessary during methotrexate therapy, as methotrexate treatment in the setting of renal insufficiency increases the risk of bone marrow suppression.

Cardiovascular disease in GPA and MPA

Premature atherosclerosis has been well described in patients with GPA.⁶ Within 5 years of diagnosis of GPA

or MPA, a cardiovascular event will occur in 14% of patients.⁷ In the absence of specific guidelines for prevention of cardiovascular disease in patients with vasculitis, it is essential to monitor patients and treat modifiable traditional risk factors aggressively, especially in younger patients. Suppiah et al found that independent determinants of cardiovascular outcome included older age, diastolic hypertension, and positive proteinase-3-ANCA status in patients without prior cardiovascular disease.⁷

In the Wegener's Clinical Occurrence of Thrombosis (WeCLOT) study, Merkel et al showed an increased incidence of thrombosis in patients with active GPA⁸ (see "Relapse presenting as thrombosis," left). As with cardiovascular disease, there are no specific guidelines for monitoring asymptomatic patients for thrombosis or for duration of anticoagulation in patients with GPA. It is recommended that patients be evaluated for active GPA or relapse in the setting of acute thrombosis whether or not symptoms of active GPA are present.

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Safety issues in vasculitis: Infections and immunizations in the immunosuppressed host

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■ ABSTRACT

Infectious diseases are a significant cause of morbidity and mortality in immunosuppressed patients, including those with connective tissue diseases. Both disease and treatment contribute to a predisposition to infection in immunocompromised patients. Significant infection and morbidity occur in 25% to 50% of these patients with a median mortality of 5.2% due to common bacterial infections, such as pneumonia or bacteremia, and opportunistic fungal infections such as *Pneumocystis*. The lungs, skin, urinary tract, blood, and central nervous system are commonly affected. Pathogens such as *Pneumocystis jirovecii*, *Histoplasma capsulatum*, *Aspergillus* species, herpes zoster, JC virus, *Nocardia asteroides*, and *Nocardia* species are increasingly prevalent in immunocompromised patients. Improved recognition, diagnosis, and prevention of these infections are needed to enhance outcomes in these patients.

In 2007, Falagas et al¹ provided a systematic review of studies focusing on infection-related morbidity and mortality in patients with connective tissue diseases. Many of the studies reviewed were published prior to the introduction of biologic agents for the treatment of rheumatologic disorders. In 39 studies focusing on infection incidence, patient outcomes, or both in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polymyositis/dermatomyositis, granulomatosis with polyangiitis (GPA, [Wegener's granulomatosis]), and systemic sclerosis, serious infection developed in 29% of patients and 24% of these died due to the infection with a median attributable mortality of 5.2%. Most of the reported infections were common bacterial syndromes such as pneumonia or bacteremia, and opportunistic fungal (*Pneumocystis*) infections.

Similarly, in 2006 Alarcón² reported that 25% to 50% of patients with SLE had significant morbidity primarily from common bacterial infections, with viral, fungal, and parasitic infection less common. *Staphylococcus aureus* was a common cause of soft tissue infection, septic arthritis, and bacteremia. *Streptococcus pneumoniae*

typically caused respiratory infections, although meningitis and sepsis were reported with SLE. Gram-negative bacteria such as *Escherichia coli*, *Klebsiella* species, and *Pseudomonas* species usually caused urinary tract infections and nosocomial pneumonia. Other bacterial infections included *Nocardia* species, *Mycobacterium tuberculosis*, and, rarely, *Listeria monocytogenes*. The most common viral infection was herpes zoster. Fungal infections included *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) and *Candida* species.

In scleroderma, another connective tissue disease evaluated in the literature by Alarcón,² reports of bacterial, viral, and fungal infections are limited to case reports. In scleroderma patients, viral infections with cytomegalovirus (CMV), parvovirus B19, and *P jirovecii* were similar to pathogens observed with SLE.

In polymyositis/dermatomyositis, gram-positive pneumonia affected 15% to 20% of patients and *S aureus* occurred frequently in the juvenile form of the disease. Herpes zoster was commonly observed, but CMV was relatively rare. Other viral infections included Coxsackie virus, parvovirus B19, and hepatitis C in polymyositis/dermatomyositis. Infection with *P jirovecii* is frequently fatal in these patients. Other fungal infections seen in polymyositis/dermatomyositis include candidiasis and histoplasmosis.²

Since the approval of antitumor necrosis factor (anti-TNF) agents for RA in the late 1990s, as well as other more recent biologic agents, there has been heightened awareness of infectious complications in rheumatologic patients. A major concern with the anti-TNF agents is the risk of granulomatous infection, particularly mycobacterial disease and dimorphic fungal infections such as histoplasmosis and coccidioidomycosis. Formation of granulomas is the major host defense against mycobacterial infection and is mediated in large part by TNF-alpha. The precise risk of infection associated with each of the various biologic agents is still under study, and rates from randomized trials have differed from postmarketing surveillance studies. Important pathogens associated with biologic agents include *Nocardia*, CMV, *Listeria*, *Aspergillus*,

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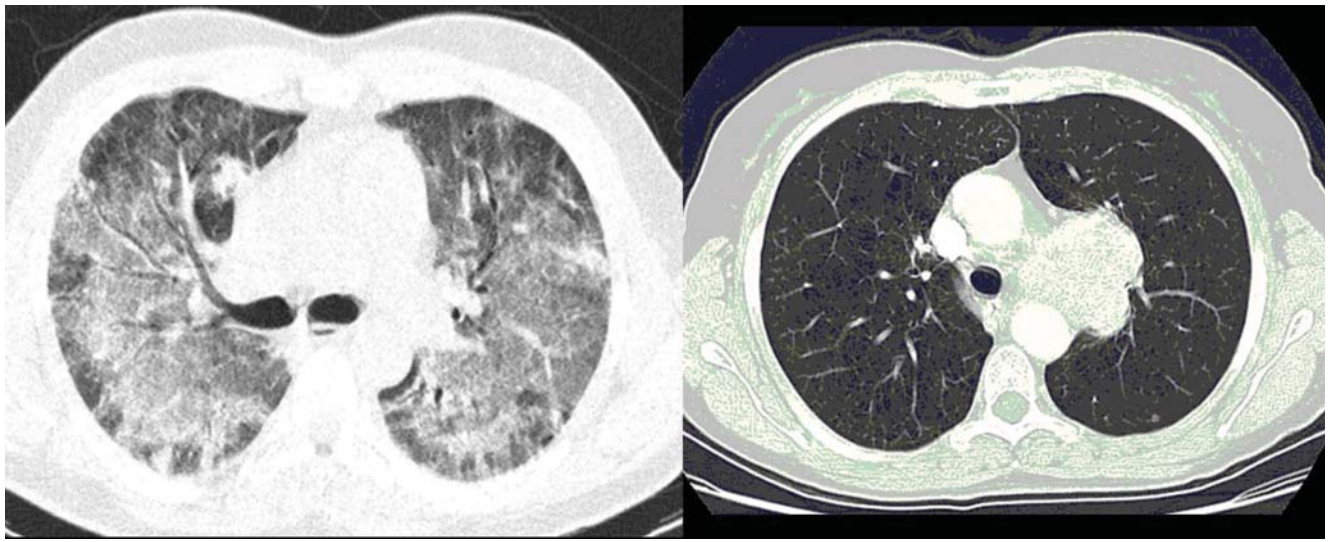


FIGURE 1. Chest computed tomography in non-HIV-infected patients demonstrating ground glass opacities. If ground glass opacities are present (left), sputum or bronchoalveolar lavage fluid should be obtained. If the image is clear (right), *P jirovecii* is unlikely.

and JC virus (JCV).^{3,4} Delays in the diagnosis of these infections in immunocompromised patients have led to poor outcomes.

■ KEY PATHOGENS IN INFECTIONS OF IMMUNOCOMPROMISED HOSTS

Pneumocystis jirovecii

For many decades, *P jirovecii* was classified as a protozoan but, based on gene sequencing, the organism has been reclassified as a fungus. *P jirovecii* is a low-virulence, unicellular organism that is the causative agent of *Pneumocystis pneumonia* (PCP). Epidemiologically, primary infection most likely occurs in infants and children. Colonization may be transient, entering the airways and then resolving over a period of weeks or months. Alternatively, the organism may enter a latent state similar to tuberculosis with reactivation occurring during times of intense immunosuppression. However, molecular epidemiology studies show that new cases of PCP are likely environmentally acquired through multiple exposures rather than reactivation of latent infection.^{5,6} Transmission is thought to be airborne from person to person. Pathogenically, the trophic form of the organism attaches to type 1 alveolar cells and remains in the extracellular compartment of the alveoli. This colonization evokes an influx of inflammatory cells (CD8 cells, neutrophils, and macrophages). However, not all colonizations result in pneumonia—even in advanced human immunodeficiency virus (HIV) infection. While there is an innate immunity through alveolar macrophages and pulmonary surfactant, alveolar macrophage response is impaired in HIV when the CD4 count is low. Cell-mediated immunity is the main defense against progression to pneumonia with assistance from costimulatory

molecules (such as CD28 and CD2) as well as B cells.

Pathogenesis and clinical presentation of PCP. In HIV-infected patients with CD4 counts less than 200 cells/mm³, foamy eosinophilic interstitial debris may develop.⁷ HIV patients often present with subacute PCP after having symptoms for days to weeks. In non-HIV patients, the presentation is often more acute, at times with severe fulminant infection. Infected patients often experience dyspnea as well as nonproductive cough and fever. Examination may reveal crackles. Chest x-ray shows diffuse bilateral interstitial infiltrates and, less commonly, nodules, cavities, unilateral infiltrates, effusions, and spontaneous pneumothoraces. Lung examination can be clear, however, confounding the diagnosis. If chest x-ray shows reticular or interstitial infiltrates, one approach would be to obtain a bronchoalveolar lavage (BAL) or sputum sample. If the chest x-ray is clear but the suspicion of PCP is still high, the next step would be high-resolution computed tomography (CT). The finding of ground glass opacities is highly suggestive of *P jirovecii*, particularly in HIV patients. Sputum or BAL fluid should still be obtained to confirm the diagnosis of *P jirovecii* (Figure 1). If the CT is clear, then *P jirovecii* is unlikely, particularly in HIV-positive patients where, in one study, the sensitivity of the CT approaches 100%.⁸

Laboratory diagnosis. *P jirovecii* cannot be grown in culture for clinical purposes, and it is extremely difficult to culture even in the research setting. Cytologic stains such as the Wright-Giemsa and methamine silver stains are the mainstay of laboratory diagnosis. The yield for *P jirovecii* from routine expectorated sputum is very low and some laboratories discourage this approach. The sensitivity of nebulized sputum using hypertonic saline ranges from 50% to 90%.⁹

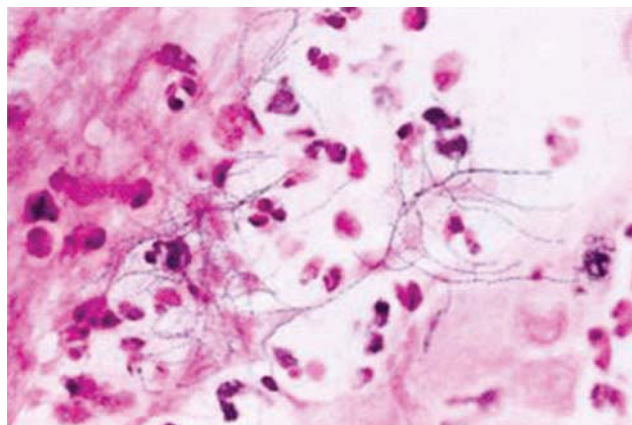


FIGURE 2. *Nocardia asteroides* acid-fast stain showing filamentous branching rods.

In patients with acquired immune deficiency syndrome (AIDS), bronchoscopy provides 90% to 98% sensitivity by BAL. Transbronchial biopsy may provide some additional yield over BAL in a few situations, such as patients who have been receiving partial *P jirovecii* prophylaxis. Immunofluorescence techniques using monoclonal antibodies to *P jirovecii* are commercially available and are first-line diagnostic tools in some laboratories. Recently, polymerase chain reaction (PCR) assay has been introduced into clinical practice as a reproducible test with high sensitivity.

Primary therapy. Primary therapy for PCP consists of trimethoprim-sulfamethoxazole (TMP-SMX) or pentamidine. TMP-SMX is considered the drug of choice and is usually administered intravenously for 21 days in HIV patients and 14 days for non-HIV patients. The oral form may be used in patients with less severe PCP with a functioning gastrointestinal tract. Common adverse reactions to TMP-SMX include rash, Stevens-Johnson syndrome, neutropenia, changes in pulmonary function, and nausea/vomiting/diarrhea.¹⁰ Pentamidine is as effective as TMP-SMX, but is associated with renal toxicity, hypotension, severe hypoglycemia, cardiac arrhythmias, and diabetes.¹¹ It is generally reserved for severe cases of PCP in patients who are allergic to or otherwise intolerant of sulfa. Other treatments include atovaquone and trimethoprim-dapsone. Adjunctive corticosteroids have been shown to be beneficial in moderate to severe PCP in HIV patients to reduce the local host inflammatory response to dead or dying organisms. Recent guidelines have recommended corticosteroids for HIV patients with PCP who have an arterial oxygen pressure of 70 mm Hg or less on room air, or an alveolar-arterial (A-a) gradient of oxygen 35 mm Hg or greater.¹² Little is known about the role of adjunctive corticosteroids in non-HIV patients, given a lack of clinical studies.

Prevention. Recent estimates of disease burden from a meta-analysis of 11,900 patients with connective tissue diseases found PCP in 12% of patients with GPA, in

6% of those with polydermatomyositis, in 5% of those with SLE, and in 1% of those with RA.¹ Mortality due to PCP is higher in patients with rheumatic diseases, ranging from 30% in RA to 63% in GPA, than in those with HIV (10% to 20%).¹³ One key risk factor predisposing patients with connective tissue diseases to infection with *P jirovecii* is recent corticosteroid use. Among patients with connective tissue disease, more than 90% of those infected with *P jirovecii* have recently received steroid therapy.¹⁴ Additionally, in almost all patients with *P jirovecii*, lymphopenia with absolute lymphocyte counts less than 1,000/mm³ is present.¹⁵

In patients with HIV, prophylaxis is initiated at a CD4 level of 200/mm³.¹³ However, the cutoff is less clear for non-HIV rheumatic patients. A cutoff of less than 300 cells/mm³ has been proposed for prophylaxis of PCP. However, at that range, approximately 50% of patients with connective tissue disease would remain above the threshold.¹³ One possible solution is to screen by PCR and treat colonization. Other algorithms have been proposed, but there is no general consensus on treatment of non-HIV rheumatic patients.^{13,16} Generally, prophylaxis should be considered in patients at the highest risk for PCP. These include patients taking prednisone at doses greater than 20 mg/day for 1 month plus a cytotoxic agent, a TNF inhibitor plus glucocorticoids, and methotrexate plus glucocorticoids in GPA.¹³

***Nocardia asteroides* and *Nocardia* species**

Nocardia species are ubiquitous bacteria found worldwide in soil, dust, and decaying material. On Gram stain the organism is weakly gram-positive with a filamentous “beaded” and branching appearance (Figure 2). Disease results from inhalation of contaminated material in the environment with subsequent lung colonization. Nocardiosis is an opportunistic infection generally seen in persons with defective T-cell (cell-mediated) immunity. Cases have been reported in patients with connective tissue diseases, including SLE, and RA treated with corticosteroids alone and corticosteroids plus methotrexate.^{17–19} Nocardiosis has been increasingly recognized with anti-TNF therapy. Animal models have demonstrated that TNF plays an important role in clearance of *Nocardia* infections.²⁰ In one review, eight cases of nocardiosis were identified from some 300,000 patients receiving an anti-TNF agent.²¹

Classically, *Nocardia* infection results in abscess formation with infiltrates of polymorphonuclear cells, debris, and thin-walled abscesses. The most frequent site of primary infection is pulmonary. Characteristically, multiple pulmonary nodules or cavities are seen, and *Nocardia* should be considered in the differential diagnosis of an immunocompromised patient with nodular pneumonia. The nodules can also be masslike in appearance (greater than 2 cm). The presentation of new cavitory lung opacities with systemic symptoms

may be mistaken for GPA.²² *Nocardia* may disseminate to the central nervous system (CNS), skin, joints, and spine, usually causing suppurative infection at these sites. *Nocardia* has a very strong tropism for neural tissue. In the CNS, *Nocardia* can cause single or multiple brain abscesses that may be asymptomatic; patients with pulmonary nocardiosis require imaging to rule out occult CNS involvement.

Nocardia species are resistant to several antibiotics. The treatment of choice for *Nocardia* species is TMP-SMX, but imipenem, amikacin, third-generation cephalosporins, and other options such as minocycline and linezolid may be considered depending on the species and the antimicrobial susceptibility pattern.

Histoplasma capsulatum

Histoplasma capsulatum is a dimorphic fungus that causes disease in both healthy and immunocompromised hosts. The organism differs from other pathogenic fungi in that it is an intracellular organism, mainly involving the reticuloendothelial system, and is rarely in the extracellular space. In the United States, infections are clustered endemically in areas such as the Mississippi and Ohio River Valleys, but infections are common worldwide. The fungus is found in soil, mulch, bird excrement, and bat guano. Asymptomatic or mild infections are common in healthy persons residing in endemic areas and occur on a sporadic basis. Epidemics can occur when contaminated material is aerosolized. Histoplasmosis is also an opportunistic infection in patients with impaired T-cell immunity such as persons with AIDS, organ transplant recipients, hematologic malignancies, and corticosteroid use. Clinically significant cases of histoplasmosis have been described in patients with RA while receiving methotrexate alone, corticosteroids alone, and combinations of disease-modifying agents.²³ Histoplasmosis was recently identified in 240 patients in association with TNF inhibitors, translating to 17 per 100,000 patients treated with infliximab.^{21,24}

Pathogenesis. Infection initially occurs through inhalation of contaminated material from the environment, primarily causing pulmonary infection. The organism converts from a mold form in the environment to a pathogenic yeast form in the host. Once inhaled, the mediastinal lymph nodes provide the first line of defense. Following draining of the lymph nodes, the organism enters the bloodstream in both immunocompetent and immunosuppressed patients. It is spread hematogenously into the spleen, liver, and reticuloendothelial system, where it is eventually cleared. In immunocompetent patients, cellular immunity limits infection within 7 to 14 days and humoral immunity is not protective.²⁵ Granuloma formation is the hallmark of host defense.

Spectrum of illness. Histoplasmosis is associated with a wide spectrum of illness, with presentation rang-

ing from asymptomatic to mild pulmonary illness to overwhelming pneumonia. Symptomatic pulmonary histoplasmosis typically presents with fever, flulike symptoms, and cough, often with retrosternal chest pain. X-rays show patchy or nodular infiltrates, with hilar or mediastinal lymphadenopathy. In some cases the lung parenchyma is clear and the main feature is fever and bilateral hilar adenopathy. Pulmonary histoplasmosis may be difficult to distinguish from sarcoidosis and tuberculosis. Extrapulmonary disease can present as hepatitis, infective endocarditis, and chronic meningitis. In immunocompromised patients, histoplasmosis can present as a progressive disseminated disease which can be acute, subacute, or chronic. Chronic disseminated histoplasmosis is characterized by cough, persistent fever, wasting, hepatosplenomegaly, oral ulcerations, and progressive cytopenias. Acute disseminated histoplasmosis has a much more fulminant course characterized by respiratory insufficiency, hypotension, multisystem organ failure, coagulopathies, and encephalopathy. Histoplasmosis is primarily a pulmonary disease, but in disseminated disease more than 50% of patients have no pulmonary symptoms and 30% may have normal chest x-rays.²⁶ In one series of infliximab-related cases (n = 10), all came from an endemic area 1 week to 6 months after the first dose of infliximab. Patients presented with cough, fever, and shortness of breath.²⁷ The pathogenesis of histoplasmosis in patients receiving TNF inhibitors is not entirely clear; such patients may be suffering a new primary infection, a reinfection, or, least likely, reactivation of latent infection.

Definitive diagnosis requires culture confirmation from appropriate body fluids or identification of characteristic yeast forms from histopathologic sections of tissue biopsies. Serologic tests may also be used to confirm the diagnosis. Detection of H and M precipitins or bands by immunodiffusion is a routine test in many laboratories. M bands are present in 50% of acute cases but their presence does not distinguish acute from remote infection. H bands are present in only 10% of all acute cases, but their presence is very specific for acute histoplasmosis.²⁸

When looking at complement fixation antibodies to yeast (HY) and mycelial (HMy) forms in pulmonary histoplasmosis, a fourfold rise in titer establishes the diagnosis retrospectively, and a single titer greater than 1:32 is strongly suggestive of active infection. However, in progressive disseminated histoplasmosis, the complement fixation antibodies are frequently negative.²⁹ Detection of antigen in urine and serum by enzyme immunoassay has become a mainstay of diagnosis, with a sensitivity of approximately 90% in progressive disseminated disease.³⁰ Of note, most cases of histoplasmosis associated with biologic agents have detectable urinary antigen tests.

Treatment. Acute pulmonary histoplasmosis is usu-

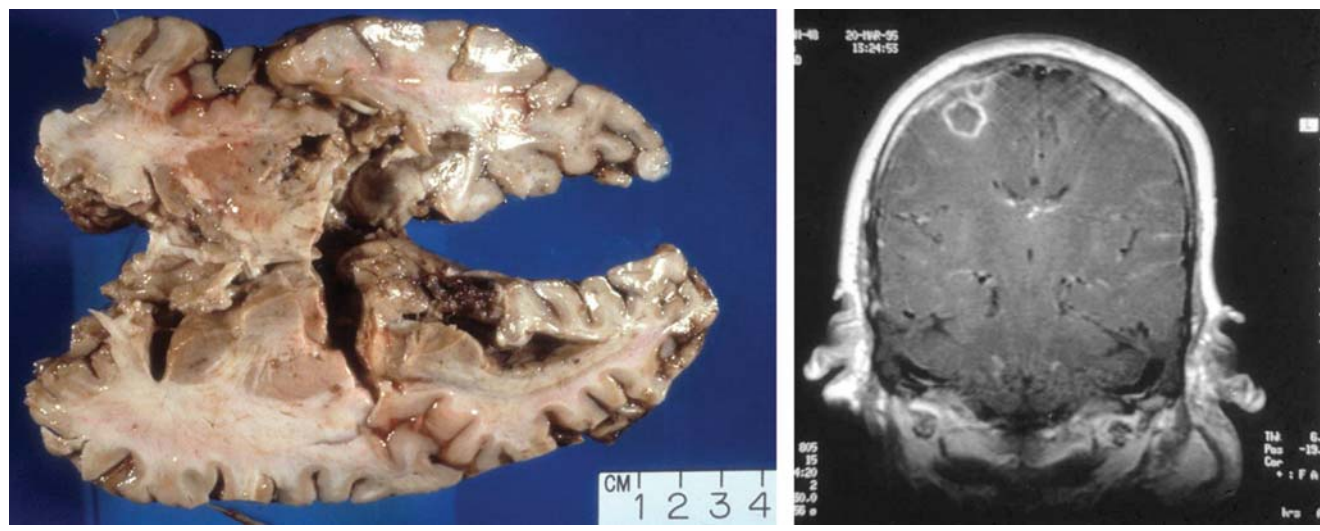


FIGURE 3. Disseminated central nervous system aspergillosis in immunosuppressed patients showing brain abscesses.



FIGURE 4. Manifestations of herpes zoster include localized disease, disseminated cutaneous zoster, and disseminated visceral zoster.

ally self-limited, requiring no treatment. The 2007 Infective Diseases Society of America (IDSA) guidelines recommend observation alone in most cases of mild to moderate pulmonary histoplasmosis unless symptoms persist longer than 1 month. For moderately severe or severe acute pulmonary histoplasmosis, the IDSA recommends lipid formulations of amphotericin B (3.0 to 5.0 mg/kg/day) or deosycholate amphotericin B (0.7 to 1.0 mg/kg/day) for 1 to 2 weeks followed by itraconazole 200 mg twice daily for a total of 12 weeks. Methylprednisolone at a dose of 0.5 to 1.0 mg/kg/day intravenously for 1 to 2 weeks is also recommended. For moderately severe to severe disseminated histoplasmosis, the IDSA

recommends lipid formulations of amphotericin B (3.0 mg/kg/day) for 1 to 2 weeks followed by oral itraconazole 200 mg three times daily for 3 days and then 200 mg twice daily for a total of at least 12 months.³¹ Commonly, the immunosuppressive agent is held during treatment.

***Aspergillus* species**

Another emerging pathogen is *Aspergillus* species—a ubiquitous mold spread by aerosols of spores. There are many different species of *Aspergillus*, but the most common human pathogens include *A fumigates*, *A niger*, and *A flavus*. To date, 39 cases of *Aspergillus* infection associated with infliximab and etanercept have been reported

in the Adverse Event Reporting System, translating to 9 to 12 cases per 100,000 patients.²¹

Manifestations of the various types of *Aspergillus* infection include invasive pulmonary aspergillosis, which is classically a cavitary disease with a halo effect; chronic necrotizing pneumonia, which has no specific identifying characteristics; and disseminated CNS aspergillosis, causing abscesses in immunosuppressed patients (Figure 3).

Varicella zoster

Herpes zoster infection is caused by reactivation of latent infection. In the United States, 95% of adults are seropositive for herpes zoster with a 10% to 30% lifetime risk of zoster reactivation.³² It is the most common viral infection in multiple series of patients with connective tissue diseases. In a multivariate analysis by Wolfe et al³³ of patients with RA, cyclophosphamide (hazard ratio [HR] 4.2), azathioprine (HR 2.0), and prednisone (HR 1.5) were significant predictors of herpes zoster. TNF inhibitor risk (HR 1.82) is less clear, with studies demonstrating no definitively increased risk. Manifestations of herpes zoster include localized disease (thoracic zoster as the most common presentation), disseminated cutaneous zoster, and disseminated visceral zoster (with encephalitis, myelitis, and angiitis) (Figure 4).

JC virus

More than 80% of adults are seropositive for JCV, a DNA virus of the genus *Polyomavirus* that causes lytic infection of oligodendrocytes.³⁴ In immunocompromised hosts, JCV causes progressive multifocal leukoencephalopathy (PML), a rare but devastating demyelinating disease. PML was first described in malignancy, leukemia, and various other immunocompromised states, prior to its strong association with AIDS in the 1980s. More recently, JCV has been associated with natalizumab for multiple sclerosis and Crohn disease, rituximab for oncology patients, efalizumab for psoriasis,³⁵ and mycophenolate mofetil for transplant recipients.³⁶

In 2006 the US Food and Drug Administration issued a safety alert regarding PML in two patients with SLE treated with rituximab and other immunosuppressives.³⁷ In a review of PML in rheumatic disease, 36 cases were identified in patients who had not previously received a biologic agent. Most of these patients (60%) had SLE.³⁸ Of these, many had little or no immunosuppression over the 6 months prior to the diagnosis of PML, suggesting that SLE itself may predispose to PML. Interestingly, PML is rarely associated with TNF inhibitors.

Classic presentation of PML includes motor weakness, aphasia, dysarthria, vision loss, and cognitive loss. Atypical presentation includes seizures, headaches, and brainstem involvement. PML usually spares the optic nerves, spinal cord, peripheral nerves, and muscles. In persons with underlying rheumatic diseases, PML can be difficult to distinguish from neuropsychiatric SLE or

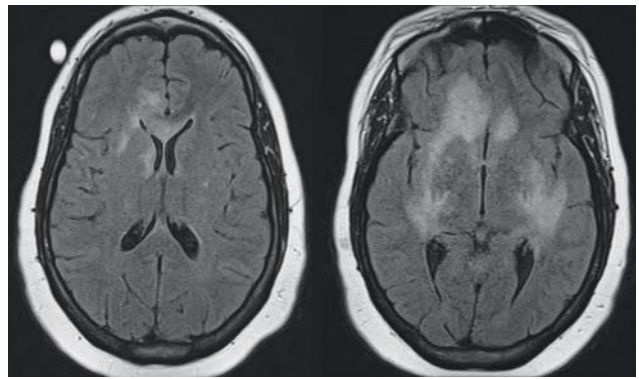


FIGURE 5. Brain magnetic resonance image of a patient with progressive multifocal leukoencephalopathy.

CNS vasculitis.

Diagnosis. On magnetic resonance imaging, typical presentation of PML shows T2 and fluid attenuated inversion recovery hyperintense regions in the white matter, asymmetric parietal and occipital radiations, and occasional cerebellum and basal ganglia involvement (Figure 5). If magnetic resonance imaging is normal, PML usually can be excluded. Cerebrospinal fluid examination shows a mean of 7 white blood cells/ μ L. PCR for JCV in cerebrospinal fluid has a specificity of close to 100% in persons with advanced HIV based on data prior to the use of highly active antiretroviral therapy.³⁹ Sensitivity using older assays is approximately 70% to 90% while the sensitivity of newer quantitative “ultrasensitive” PCR assays is greater than 90%.^{40,41}

Treatment. In clinical trials no antiviral agent has been effective in the treatment of PML. In HIV patients who develop PML, highly active antiretroviral therapy should be initiated (if antiretroviral-naïve) or existing antiviral regimens optimized. Antiretroviral therapy in this situation may stabilize disease and possibly increase survival.⁴² For HIV-negative patients who develop PML, the cornerstone of management is immediate decrease or discontinuation of immunosuppression.⁴³ Several adjunctive measures have been reported mainly in natalizumab-associated PML, including corticosteroids, mirtazapine, plasma exchange, and others.

VACCINES

Vaccination is important in the prevention of infectious disease in immunocompromised patients with connective tissue diseases. Because live vaccines are contraindicated in immunocompromised patients, inactivated or component vaccines should be used. It is recommended that patients who will start immunosuppressive therapy be vaccinated 2 to 4 weeks before beginning therapy. If this is not possible, vaccination should be administered during disease remission, 3 months after immunosuppression and 1 to 3 months after administration of high-dose corticosteroids.

TABLE 1
Live versus inactivated vaccines

| Live vaccines (attenuated) ^a | Inactivated vaccines |
|--|---|
| Live-attenuated influenza—nasal spray | Influenza (trivalent inactivated vaccine) |
| Measles-mumps-rubella | Pneumococcal |
| Varicella | Meningococcal |
| Herpes zoster vaccine | Haemophilus influenza B |
| Rotavirus | Hepatitis A and B |
| Yellow fever | Tetanus-diphtheria-pertussis |
| Others: oral polio vaccine (not available), BCG, typhoid fever, yellow fever | Human papilloma virus |

BCG = Bacillus Calmette–Guérin

^aLive vaccine contraindicated in immunocompromised patients with connective tissue disease.

Table 1 lists common live (attenuated) vaccines and inactivated vaccines. Live influenza vaccine is available as a nasal spray, but that route of administration is contraindicated in immunocompromised patients and those aged over 50 years. To further define the contraindications in immunocompromised patients, corticosteroids are not a contraindication to live-virus vaccines when corticosteroid administration is:

- Short-term (less than 14 days)
- At a dose of less than 20 mg/day of prednisone or equivalent
- Long-term on alternate days with short-acting preparations
- At a physiologic dose of prednisone
- Topical, inhaled, intra-articular, bursal, or via tendon.⁴⁴

No data are available to guide immunization while a patient is taking anti-TNF agents, but the Centers for Disease Control and Prevention (CDC) recommend “caution in the use of live vaccines” with these drugs with “avoidance” unless the benefit, by case, greatly outweighs the risk.⁴⁴ Similarly, there are no data on vaccine safety or specific recommendations with rituximab treatment. However, following the recommendations for “functional asplenia” in the CDC guidelines, pneumococcal, meningococcal, and *Haemophilus influenzae* type b (Hib) vaccine (if not given in infancy) would be indicated. Table 2 summarizes the CDC recommendations for vaccinating immunocompromised adults (excluding those with HIV).

Until definitive guidelines are developed, practitioners must evaluate and treat each patient individually to maximize the efficacy of disease treatments while preventing infection morbidity and mortality in their patients with connective tissue diseases.

TABLE 2
Vaccines indicated for immunocompromised adults (excluding HIV)

| Vaccine | Dose |
|--|--|
| Influenza | 1 dose trivalent inactivated vaccine annually |
| Tetanus, diphtheria, pertussis (Td/Tdap) | Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years |
| Varicella | Contraindicated |
| Human papillomavirus | 3 doses through age 26 years |
| Herpes zoster | Contraindicated |
| Measles, mumps, rubella | Contraindicated |
| Pneumococcal (polysaccharide) | 1 or 2 doses |
| Meningococcal | 1 or more doses ^a |
| Hepatitis A | 2 doses ^a |
| Hepatitis B | 3 doses ^a |

^aRecommended if some other risk factor is present (eg, on the basis of medical, occupational, lifestyle, or other indications).

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