Wegener’s Granulomatosis: Evolving Concepts in Treatment

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ABSTRACT

Wegener’s granulomatosis (WG), the most common of the pulmonary granulomatous vasculitides, typically involves the upper respiratory tract, lower respiratory tract (bronchi and lung), and kidney, with varying degrees of disseminated vasculitis. Major histological features include a necrotizing vasculitis involving small vessels, extensive “geographic” necrosis, and granulomatous inflammation. Clinical manifestations of WG are protean; virtually any organ can be involved. Further, the spectrum and severity of the disease is heterogeneous, ranging from indolent disease involving only one site to fulminant, multiorgan vasculitis leading to death. The pathogenesis of WG has not been elucidated, but both cellular and humoral components are involved. Circulating antineutrophil cytoplasmic antibodies (cANCA) likely play a role in the pathogenesis and often correlate with activity of the disease. Treatment strategies are evolving. Cyclophosphamide (CYC) plus corticosteroids (CS) is the mainstay of therapy for generalized, multisystemic WG. Historically, the combination of CYC plus CS was used for a minimum of 12 months, but concern about late toxicities associated with CYC has led to novel treatment approaches. Currently, short-course (3–6 months) induction treatment with CYC plus CS, followed by maintenance therapy with less toxic agents (e.g., methotrexate, azathioprine) is recommended. Further, recent studies suggest that methotrexate combined with CS may be adequate for limited, non–life-threatening WG. The role of other immunomodulatory agents (including trimethoprim-sulfamethoxazole) is also explored.

KEYWORDS: Wegener’s granulomatosis, granulomatous vasculitis, pulmonary vasculitis, capillaritis, antineutrophil cytoplasmic antibodies, geographic necrosis

Objectives: The reader will understand: (1) the spectrum of clinical manifestations in patients with Wegener’s granulomatosis; (2) the most recent interpretation of the pathophysiology of Wegener’s granulomatosis; and (3) the concept of the ‘‘induction-maintenance’’ approach to therapy.

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WEGENER’S GRANULOMATOSIS

Wegener’s granulomatosis (WG), the most common of the pulmonary granulomatous vasculitides, typically involves the upper respiratory tract (e.g., sinuses, ears, nasopharynx, oropharynx, trachea), lower respiratory tract (bronchi and lung), and kidney, with varying degrees of disseminated vasculitis. Major histological features include a necrotizing vasculitis involving small vessels (i.e., arterioles, venules, and capillaries), extensive “geographic” necrosis, and granulomatous inflammation. Clinical manifestations of WG are protean; virtually any organ can be involved. Further, the spectrum and severity of the disease are heterogeneous, ranging from indolent disease involving only one site to fulminant, multiorgan vasculitis leading to death. Many of the “classical” features of the disease may be lacking early in the course, but may evolve months or even years after initial presentation. Given the rarity of WG, and nonspecificity of symptoms, the diagnosis is often missed for several months after the initial symptom(s).

Epidemiology

The estimated prevalence of WG in the United States is between 13 and 30 cases per million persons per 5-year period. In a national survey in the United States from 1979 through 1988, WG was listed as the cause of death in 1784 death certificates. WG may be more common in northern Europe. Annual incidence rates of WG (per million) were 10.3 in England and 4.1 in Spain. A study from Norway cited annual incidence rates as high as 12 per million (prevalence ~95 per million). The peak incidence is in the fourth through sixth decades of life; children or adolescents are rarely affected. There is no gender predominance.

Pediatric Age Group

Few publications have focused on WG in children. Two series comprising 23 and 17 children with WG cited subglottic stenosis in 48% and 41% of cases, respectively, which is higher than the incidence in adults. In contrast, kidney involvement was observed less frequently in childhood cases (53–79%) compared with adults (>80%).

Historical Aspects

WG was first described in 1931 by Klinger, who reported a patient with severe destructive sinusitis and uremia who had glomerulonephritis and disseminated vasculitis at necropsy. In 1936, Wegener incorporated both clinical and histological criteria to describe what he believed represented a unique and distinctive syndrome. In 1954, Goldman and Churg described seven new cases, reviewed 22 previously reported cases, and established pathological and clinical criteria for the diagnosis. The classic histopathologic criteria included three major features: necrotizing granulomatous lesions in the upper or lower respiratory tract, generalized necrotizing vasculitis involving both arteries and veins, and glomerulitis. In 1966, Carrington and Liebow described 16 patients with classic histological features of WG but sparing the kidneys (i.e., “limited WG”). Subsequent studies affirmed that this subset of patients had a more favorable prognosis compared with those with generalized WG. Recognizing the differing prognoses among subsets of patients with WG, DeRemee and colleagues proposed a staging classification based on the presence or absence of three specific anatomic sites [i.e., ears, nose, throat (E); lung (L), and/or kidney (K)] to stratify patients with single- or multiorgan involvement. Treatment strategies discussed in detail later developed in the 1970s and 1980s dramatically improved the prognosis of what previously had been a fatal disease.

Clinical Features

UPPER AIRWAY INVOLVEMENT

Upper respiratory tract (e.g., sinuses, ears, nasopharynx, oropharynx, trachea) symptoms occur in more than 90%
of patients with WG and are often the presenting features.\textsuperscript{1–4,40–42} The upper respiratory tract is the predominant or only site of involvement in some patients.\textsuperscript{29,43} Chronic persistent sinusitis, epistaxis, or otitis media are often the presenting and dominant clinical features of WG but are often mistaken for allergic or infectious etiologies.\textsuperscript{2,6} Sinus x-rays or thin section computed tomographic (CT) scans are abnormal in over 85% of patients with WG.\textsuperscript{1,2,41} Characteristic features include thickening or clouding of the sinuses (75%) and erosion or destruction of sinus bones (25–50%).\textsuperscript{2,41,44} Magnetic resonance imaging (MRI) scans of the sinuses and orbits most often reveal high-intensity lesions on T2-weighted images, consistent with mucosal thickening.\textsuperscript{45} Granulomas are depicted as low-signal-intensity lesions on T1- and T2-weighted images. Lesions typically enhance following gadolinium.\textsuperscript{45} MRI scans are less sensitive than CT in detecting bony destruction.\textsuperscript{45} The combination of sinus bone destruction with new bone formation on CT is nearly diagnostic of WG, especially when accompanied by an MRI scan showing a fat signal from the sclerotic sinus wall.\textsuperscript{46} Air–fluid levels suggest secondary pyogenic infections, which are difficult to distinguish from exacerbations of WG.\textsuperscript{2,6,42} Orbital involvement (often with proptosis) occurs in up to one third of patients with severe sinus WG.\textsuperscript{18,45–49} Clinical features of orbital involvement are discussed later in the ocular section.

Otolgic involvement occurs in 30 to 50% of patients with WG.\textsuperscript{2,6,41,50,51} Otalgia and refractory otitis media are common early symptoms of WG.\textsuperscript{2} Chronic otitis media, chronic mastoiditis, or hearing loss occurs in 15 to 25% of patients.\textsuperscript{2,4,50} Hearing loss may reflect vasculitis of the cochlear artery, chronic otitis media, perforation of the tympanic membrane, or chronic mastoiditis with granulation tissue or destruction of the middle ear.\textsuperscript{2,50,51} Consultation with an otolaryngologist is critical because adjunctive surgical procedures (e.g., myringotomy tubes) may be helpful in patients with chronic mastoiditis and otitis media.\textsuperscript{42} Facial nerve paralysis may reflect either or both granulomatous involvement of the middle ear and involvement of the seventh cranial nerve at the preauricular site.\textsuperscript{52–56} Involvement of salivary\textsuperscript{57–59} and parotid\textsuperscript{54,60,61} glands, associated with otological or nasopharyngeal involvement, is rare. One recent review cited only 18 published cases of major salivary gland involvement in WG.\textsuperscript{61}

The nasopharynx is involved in 60 to 80% of patients with WG.\textsuperscript{2,4,41,46,50,62} Clinical manifestations include epistaxis, nasal septal perforation, persistent nasal congestion or pain, nasal crusting, and mucosal ulcers.\textsuperscript{2,4,42} Saddle nose deformity, due to destruction of the nasal cartilage, occurs in 10 to 25% of patients with WG.\textsuperscript{2,4,41,50} Reconstruction of external nasal deformities (e.g., saddle nose) can be successfully accomplished, for either cosmetic reasons or to improve airway patency.\textsuperscript{62} In one study, favorable outcomes were achieved with surgical reconstruction in 12 of 13 (92%) patients.\textsuperscript{62} Surgery was performed when WG was quiescent; no flare or acceleration of the course was noted.\textsuperscript{62}

Sore throat or hoarseness may reflect ulcerations or granulomatous involvement of the pharynx or vocal cords.\textsuperscript{2,41,50} Oropharyngeal ulcers involving the throat or larynx may give rise to pain, crusting, bleeding, or hoarseness.\textsuperscript{42} “Strawberry gingival hyperplasia” is a rare, but nearly pathognomonic, oral lesion of WG.\textsuperscript{42,63}

In any patient with suspected WG, a careful ear-nose-throat (ENT) exam by an experienced otolaryngologist is warranted to look for mucosal ulcerations or evidence for granulomatous inflammation; any suspicious lesions should be biopsied.\textsuperscript{42,64} Despite the propensity for WG to affect the upper respiratory tract, histological confirmation may be difficult. Biopsies of upper airway lesions often demonstrate non-specific findings of necrosis and chronic inflammation.\textsuperscript{11,65–69} The cardinal histological features of vasculitis or granulomatous inflammation may be lacking. A review of 126 biopsies from upper airway or nasopharyngeal lesions in patients with WG seen at the National Institutes of Health (NIH) revealed the triad of granulomas, vasculitis, and necrosis in only 16% of specimens.\textsuperscript{11} Dual features of vasculitis plus granulomas were noted in 21% of biopsy specimens; vasculitis plus necrosis in 23%.\textsuperscript{11} Biopsies of nasal septal perforations are rarely diagnostic.\textsuperscript{55} In one study, 43 biopsies from clinically appearing benign nasal septal perforations demonstrated only non-specific inflammatory changes; vasculitis was never documented, even among 12 patients with suspected WG.\textsuperscript{67} Generous biopsies of involved sites are critical to substantiate the diagnosis. In one study of 11 WG patients with nasal involvement, the most common histological features included palisading granulomas, microabscesses, granulomatous inflammation, leukocytoclastic vasculitis (LCV) or capillaritis, and fibrinoid necrosis.\textsuperscript{69} Histological features may have prognostic value.\textsuperscript{69} The presence of LCV on nasal biopsy heralds disseminated disease and a poor prognosis.\textsuperscript{69} If upper respiratory tract biopsies are nondiagnostic, biopsies of other sites may be required.

Treatment of WG involving the upper respiratory tract warrants the use of CS and cytotoxic agents (discussed in detail later). However, adjunctive therapy may be necessary. Recurrent sinus infections may require repeated courses of antibiotics for control. Patients with persistent sinus disease refractory to medical therapy may require percutaneous drainage or more definitive surgical drainage procedures.\textsuperscript{2,41,50}

**OCULAR INVOLVEMENT**

Ocular involvement occurs in 20 to 50% of patients with WG.\textsuperscript{1–4,47,48,70–72} Up to 30% of patients with ocular WG have no evidence for systemic involvement.\textsuperscript{48,70,72}
Clinical symptoms may result from primary vasculitis of the retinal vessels or from extension of the granulomatous process from the soft tissues or sinuses into the orbit. 49,73,74 Conjunctivitis, episcleritis, and scleritis occur in 15 to 20% of patients with WG. 1,3,47,71 Recurrent flares of conjunctivitis and episcleritis may parallel flares of systemic disease. 1,47 More serious complications, although rare, include necrotizing keratitis, corneoscleral perforation, posterior uveitis, or optic neuritis. 37,75,76 Retinal hemorrhages and exudates or papilledema on ophthalmological examination suggest retinal vasculitis. 47 The superficial ocular complications (e.g., conjunctivitis, episcleritis) often respond to topical corticosteroids; involvement of the deeper ocular structures warrants both systemic CS and cytotoxic therapy. 1,47,77 Proptosis from a retroorbital granulomatous inflammatory process develops in 10 to 22% of patients during the course of the disease and may result in permanent sequelae. 1,2,18,47,48 Compression or primary involvement of the optic nerve may lead to blindness in 2 to 9% of patients. 1,3,47,48,70,71 Granulomatous involvement of the orbit may cause anterior displacement of the eye, pain, swelling, proptosis, oculomotor palsies, blurred vision, diplopia, and reduction of eye motility. 1,18,47,70,71 In some cases, impingement on the blood supply to the optic nerve by large mass lesions warrants surgical decompression. 47 Primary vasculitis of the posterior ciliary arteries supplying the optic nerves may also lead to visual loss. 1,2,47 CT or MRI scans are important to distinguish these entities. 45,48 Nasolacrimal duct obstruction occurs in 25 to 52% of patients with orbital WG. 48,71,78 Disease localized to the orbit may be difficult to diagnose because serum cANCA are often negative. 70 In a series of 29 patients with orbital WG, circulating cANCA were detected in nine of 10 with generalized disease but in only six of 19 (32%) with limited WG. 48 Orbital biopsies in WG demonstrate the cardinal features of necrosis, granulomatous inflammation, and vasculitis in fewer than 50% of patients. 48,79,80 Frequently, orbital biopsies demonstrate nonspecific findings of mixed inflammatory cells, areas of necrosis, and microabscesses. 48,79 However, sinusitis is present in >85% of patients with proptosis due to WG. 48 In such cases, biopsies of sinuses may substantiate the diagnosis. 48 Early consultation with an ophthalmologist is essential in any patient with suspected WG to assure prompt diagnosis of any ocular abnormalities and provide long-term follow-up.

INVOLVEMENT OF TRACHEA AND BRONCHI

Granulomatous involvement of the trachea or major bronchi leads to stenosis in 10 to 30% of patients with WG. 2,6,41,81–84 Symptoms are nonspecific and include dyspnea, wheezing, stridor, and change in voice. 82,83,85 Stenosis of large airways may develop years after the initial diagnosis of WG and may develop in the absence of manifestations of WG at other sites. 83,85 However, concomitant involvement of the nasopharynx or sinuses is nearly invariably present. 31,82 Among 43 patients with subglottic stenosis (SGS) seen at the NIH, 42 (98%) had sinus involvement; saddle nose deformity was present in 47%. 82 The site of tracheal stenosis is usually circumferential and localized, extending 3 to 5 cm below the glottis. 41,82,83,86 However, more extensive involvement of the distal trachea or mainstem bronchi may occur. 83,84 A study from the Mayo Clinic cited endobronchial abnormalities in 30 of 51 patients (59%) with WG undergoing bronchoscopy. 83 Four (13%) had tracheal or bronchostenosis. Importantly, extensive endobronchial abnormalities were noted in 11 patients with normal chest radiographs. Ulcerating tracheobronchitis was the most common lesion and eventuated in progressive stenosis in seven patients. Persistent dyspnea or wheezing may reflect cicatricial scarring at the site of previous endobronchial inflammation. Stridor or wheezing suggests stenosis of large airways (trachea or mainstem bronchi). 85 Flow-volume loops may detect physiologically significant upper airway obstruction, but are insensitive. With tracheal (subglottic) stenosis, both inspiratory and expiratory limbs of the flow-volume loop are truncated (flow rate limitation) 82 (Fig. 1 86a). When stenosis is suspected, flexible fiberoptic bronchoscopy (FFB) should be performed. Among 27 WG patients with SGS who had FFB, circumferential narrowing of the trachea due to a mature scar was observed in 20 (74%) cases; friability or acute inflammation was noted in only seven patients (26%). 85 Histological confirmation of tracheal or endobronchial WG is difficult; biopsies usually demonstrate nonspecific changes (e.g., necrosis or inflammation). In one study of 26 WG patients with SGS, dual features of vasculitis and granulomatous inflammation were present in only seven of 140 (5%) subglottic biopsies. 82 In a series from the Mayo Clinic, 26 subglottic biopsies were performed in 16 patients with WG and SGS; granulomatous inflammatory changes were observed in only four biopsies (15%). 85 In another study from the Mayo Clinic, endobronchial biopsies fulfilled specific histological criteria for WG in only three of 17 patients (18%). 83 Serum titers of cANCA did not correlate with endobronchial inflammation. 83 Thus the diagnosis of tracheal or endobronchial involvement in patients with known WG in some cases must be presumed in the appropriate clinical context, even when histology is less than definitive. Importantly, progressive subglottic or bronchial stenosis can develop even when the disease is quiescent at other sites. 82,83,85 The severity and extent of airway narrowing are best evaluated using multiplanar and three-dimensional reconstructions of spiral CT scans using thin sections 86–90 (Figs. 2A,B). Serial CT scans may be useful to follow patients longitudinally. 88 A new three-dimensional image reconstruction and display technique...
called virtual bronchoscopy produced from high-resolution CT is a noninvasive means to assess presence and extent of airway stenoses with sensitivity at least to segmental bronchi.89

Severe stenosis of large airways requires urgent and aggressive intervention.85 Life-threatening upper airway obstruction can develop, not only from the subglottic lesion but also from crusted, thickened secretions from mucosal inflammation in the upper or lower respiratory tract.82,83 The impact of medical therapy in altering the course of endobronchial or endotracheal WG is not clear. Aggressive immunosuppressive therapy is warranted when an active inflammatory component is demonstrable or when disease is present at other sites. However, disease localized to the airways may not respond to medical treatment. In this circumstance, alternative treatment modalities include carbon dioxide (CO₂) or neodymium-yttrium-aluminum-garnet (Nd:YAG) laser, dilatation, intratracheal CS injections, placement of Silastic airway stents, tracheostomy, laryngeal–tracheal reconstruction, and partial tracheal resection.2,41,81–83,85,91,92 When possible, surgical intervention or manipulation of the airways should be minimized during flares of systemic disease activity.85 Silastic stents may provide sustained relief of symptoms in some patients but are associated with numerous complications (e.g., migration of the stent, granuloma formation, mucus hypersecretion, fungal colonization, bronchomalacia in the area of the stent).83 Tracheal reconstruction has been successfully performed in patients with severe tracheal stenosis refractory to medical therapy but is a formidable undertaking.82,85 Intralesional injection with long-acting CS and intratracheal dilatation is efficacious in treating SGS. Utilizing this approach, two series comprising 2185 and 2193 patients, respectively, noted that luminal patency was maintained and no patient required tracheostomy. Long-term follow-up by an otolaryngologist is essential to monitor response to medical therapy.

**Figure 1** Flow-volume loop demonstrating truncation of both inspiratory and expiratory limbs due to a fixed, anatomic narrowing of the proximal trachea (subglottic stenosis) in a 28-year-old male with Wegener’s granulomatosis (WG). Cyclophosphamide had been discontinued 4 months earlier after he had been in continuous remission for nearly 18 months. Dyspnea, due to subglottic stenosis, was the initial manifestation of recrudescent WG. (Reproduced with permission from Lynch and Quint.86a)

**Figure 2** (A) Coronal helical computed tomographic (CT) reconstruction shows severe stenosis of the left mainstem bronchus in a patient with Wegener’s granulomatosis (WG). (B) Three-dimensional shaded surface display created from helical CT data shows severe stenosis of the left mainstem bronchus in a patient with WG. (Reproduced with permission from Lynch and Quint.86a)
to therapy and assess the need for future therapeutic interventions.

**LUNG INVOLVEMENT**

Pulmonary involvement is noted in 55 to 90% of patients with WG. The spectrum of pulmonary manifestations is broad and includes asymptomatic nodules or infiltrates on chest radiographs or CT scans, cough, hemoptysis, dyspnea, impaired pulmonary function, endobronchial inflammation and bronchostenosis, parenchymal necrosis, and diffuse alveolar hemorrhage. Pulmonary function tests may demonstrate airflow obstruction (particularly when endobronchial involvement is prominent), restriction, or mixed patterns. Abnormalities on chest radiographs are noted in more than 70% of patients at some point during the course of the disease. Single or multiple nodules or nodular infiltrates are characteristic; cavitation is noted in 20 to 50% (usually in lesions > 2 cm in diameter) (Figs. 3–6). Fluffy alveolar or mixed alveolar–interstitial infiltrates or consolidation may reflect alveolar hemorrhage or granulomatous inflammation (Figs. 7, 8) or enlarged intrathoracic lymph nodes are rarely observed (< 2%) on conventional chest radiographs but are detected on chest CT in 20% of patients with WG. Chest CT scans are far more sensitive than chest x-rays in depicting the nature and extent of the pulmonary process. Multiple pulmonary nodules (with or without cavitation) are the most characteristic findings on CT; other features of active WG include focal infiltrates, consolidation, or ground-glass opacities (GGOs).

In one study of pulmonary WG, nodules or masses were detected on chest CT scan in 27 of 30 patients (90%); cavitation was present in one or more nodules in 13 of 27 (58%) patients. The nodules ranged from one to 32 in number (mean 8) and had a predominantly subpleural or peribronchial distribution. Thickening of bronchial walls in the segmental or subsegmental bronchi was noted in 22 patients (73%); large airways were involved in nine patients (30%). Other features included consolidation in seven (22%) and GGOs in seven (22%). With treatment, 16 of 20 (85%) of pulmonary parenchymal lesions regressed. In another series of 28 patients with pulmonary WG, the most common aberrations included nodules (70%), infiltrates (25%), pleural disease (25%), and interstitial pattern (18%). Additional manifestations of WG include focal or diffuse neumonic infiltrates, large mass lesions (Figs. 10A–C), pleural effusions, stenosis of the trachea or bronchi, atelectasis, septal bands,
parenchymal scarring, and irregular pleural thickening.87,90,98,102–104 With treatment, GGOs, cavitating nodules, nodules > 3 cm in diameter, or consolidation typically resolve or regress whereas linear lines or smaller nodules persist, suggesting residual fibrosis.98,103,105 Positive uptake on F-18 positron emission tomography (PET) scans, mimicking malignancy, was noted in one patient with WG.106

Surgical lung biopsy (SLB) is optimal to establish a firm diagnosis of pulmonary WG. When focal pulmonary infiltrates or nodules are present, vasculitis and necrotizing granulomas are found on SLB in more than 90% of patients.10 Micronecrosis or microabscesses containing neutrophils and mononuclear cells appear to be early lesions, followed by accumulation of histiocytes forming so-called palisading granulomas.9 Later findings include geographic necrosis, granulomatous inflammation, vasculitis, and varying degrees of fibrosis.10 A review of 87 SLBs in pulmonary WG cited the following features: vascular inflammation (acute or chronic) in 94%, parenchymal necrosis (84%), scattered giant cells (79%), areas of geographic necrosis (69%), granulomatous microabscesses with giant cells (69%), neutrophilic microabscesses (65%), poorly formed granulomata (59%), capillaritis (31%), and fibrinoid necrosis (11%).10 Bronchiolar abnormalities were more common than previously appreciated. In that study, bronchial or bronchiolar abnormalities included nonspecific chronic inflammation (64%), acute inflammation (51%), bronchiolitis obliterans (31%), and follicular bronchiolitis (28%). Confluent, sarcoid-like granulomas were rarely observed (<5%). Additional nonspecific features that may be found in WG include cryptogenic organizing pneumonia (COP),107,108 eosinophilic infiltration,108 chondritis involving bronchial cartilage,109 and interstitial fibrosis.10,110 Treatment with CS or cytotoxic agents influences the histopathological response.110 In a study of 20 SLBs from patients with WG following treatment with CS or cyclophosphamide (CYC), inflammation or fibrosis was present in all cases, but only four (20%) had macronodular necrosis (a hallmark of WG).110 Histological features may be muted with therapy. Palisading granulomas may convert to giant

Figure 7  Alveolar hemorrhage due to Wegener’s granulomatosis. Posteroanterior chest radiograph from a 50-year-old male demonstrates extensive, confluent, bilateral alveolar infiltrates. He presented with severe dyspnea, microscopic hematuria, a serum creatinine of 4.2 mg%, and serum cANCA > 1:640. Percutaneous renal biopsy demonstrated rapidly progressive glomerulonephritis. His pulmonary disease remitted promptly with cyclophosphamide and corticosteroids, but his renal failure deteriorated, requiring dialysis. Nine months later, his renal function improved (serum creatinine 1.2 mg%), and he was asymptomatic.

Figure 8  Alveolar hemorrhage due to Wegener’s granulomatosis. Posteroanterior chest radiograph from a 67-year-old man demonstrates extensive, bilateral alveolar infiltrates. Complete recovery was achieved with cyclophosphamide and corticosteroid therapy.
cell nodules or micronodular scars. Bronchiolar or pulmonary parenchymal fibrosis may reflect old, but irreversible, disease.110

Because of small sample size, the yield of endobronchial or transbronchial lung biopsies to diagnose WG is low (3–18%).10,83,84,110,111 Cytologies of bronchoalveolar lavage (BAL) fluid in patients with WG may demonstrate nonspecific findings of necrotic debris, acute inflammation, multinucleated giant cells, epithelioid cells, and hemosiderin-laden macrophages.112 BAL

Figure 9  (A) Posteroanterior chest radiograph from a 17-year-old boy with fever, sinusitis, and cough demonstrating bilateral lobulated pneumatic infiltrates. Open-lung biopsy demonstrated necrotizing granulomatous vasculitis consistent with Wegener’s granulomatosis (WG). (Reproduced with permission from Lynch.100a) (B) Photomicrograph: open lung biopsy demonstrates nearly complete obliteration of a blood vessel with granulomatosis vasculitis consistent with WG. Note the multinucleated giant cell within the vascular lumen.

Figure 10  (A) Posteroanterior chest radiograph demonstrating right upper lobe mass in a 36-year-old woman with leukocytoclastic vasculitis, fever, sinusitis, and cough. (B) Computed tomographic scan from the same patient reveals a mass lesion in the anterior segment of the right upper lobe with areas of focal necrosis (see arrows). Transbronchial lung biopsies demonstrated granulomatosis vasculitis with extensive necrosis and a polymorphous inflammatory cell infiltrate consistent with Wegener’s granulomatosis. (C) Posteroanterior chest radiograph from same patient 5 weeks after initiation of therapy with cyclophosphamide and prednisone showing near complete resolution of right upper lobe mass. (Reproduced with permission from Lynch and Raghu.102a)
typically reveals increases in neutrophils (22–42%) and eosinophils (3–4%). BAL lymphocytosis may also occur. BAL fluid from patients with active pulmonary WG reveals high concentrations of cANCA, immunoglobulin G (IgG), IgA, and albumin; elevated myeloperoxidase (MPO), peroxidase activity, eosinophil cationic protein (ECP), and soluble interleukin-2 receptor (sIL-2R). These findings shed light on the pathogenesis of WG but are not specific.

Transthoracic core needle biopsy (guided by CT or fluoroscopy) has demonstrated inflammation or vasculitis in a few cases but specificity is suboptimal. With few exceptions, bronchoscopic or percutaneous needle aspiration biopsies are inadequate to substantiate the diagnosis.

ALVEOLAR HEMORRHAGE

Diffuse alveolar hemorrhage (DAH) is a rare but potentially fatal complication of WG, reflecting diffuse injury to the pulmonary microvasculature. In this setting, rapidly progressive glomerulonephritis is present in more than 90% of patients. By contrast, fewer than 40% manifest upper airway symptoms. Chest radiographs in DAH demonstrate bilateral alveolar infiltrates; the classic nodular or cavitary lesions of WG are lacking. The role of SLB in the setting of DAH is controversial. Histopathological features of alveolar hemorrhage and inflammation and necrosis of the alveolar capillaries and walls (termed capillaritis) predominate, but these are nonspecific (Fig. 13). Interestingly, in most cases of WG that manifest as DAH, granulomatous vasculitis or extensive parenchymal necrosis are absent. For severe DAH, we believe the risk of SLB outweighs the benefit. A presumptive diagnosis of DAH can often be made on the basis of clinical and radiographic features, circulating cANCA, and bronchoscopy with BAL. Large numbers of hemosiderin-laden macrophages, bloody or serosanguinous BAL fluid, and absence of infectious etiologies support the diagnosis of DAH (Figs. 14A,B). Biopsy of extrapulmonary sites of involvement may also help substantiate the diagnosis. Percutaneous renal biopsy is warranted if the urinary sediment demonstrates microscopic hematuria, or renal insufficiency is present. Rapidly progressive glomerulonephritis (GN), with negative immunofluorescent stains (i.e., pauci-immune) is characteristic of WG in the context of DAH. DAH is a medical emergency requiring aggressive therapy with intravenous “pulse” methylprednisolone (1 g daily for 3 days), while pursuing a diagnostic workup and awaiting the results of biopsies and ancillary laboratory results. Conventional therapy with oral CYC and a tapering regimen of CS is appropriate once the diagnosis of WG has been confirmed.

RENAL INVOLVEMENT

Glomerulonephritis (pauci-immune) occurs in 70 to 85% of patients at some point in the course of the disease, but only 11 to 17% of patients exhibit severe
Figure 13  Capillaritis and pulmonary hemorrhage in Wegener’s granulomatosis. (Upper left) Numerous neutrophils hug alveolar capillaries associated with recent alveolar hemorrhage. (Upper right) Early fibrinoid necrosis of alveolar wall associated with capillaritis. (Lower left) Pulmonary hemorrhage with capillaritis. (Lower right) Linear band of degenerating neutrophils from zone of necrotizing capillaritis.
renal insufficiency at presentation.\textsuperscript{1–4,6,118,119,121} Extra-
renal manifestations usually precede the renal mani-
festations, often by several months. In contrast to
Churg-Strauss syndrome (CSS) or PAN, hypertension
is uncommon in WG, cited in fewer than 10\% of
patients at presentation.\textsuperscript{1,2} The characteristic renal
lesion of WG is a segmental focal GN.\textsuperscript{2,122} Microscopic
hematuria, proteinuria, or red cell casts precede detect-
able elevations in serum creatinine.\textsuperscript{1,2,118,119} Althought
abnormalities in renal function often parallel the severity
of lesions on renal biopsy, abnormalities on renal biops-
ies may be observed even in patients with normal
urinary sediment and renal function.\textsuperscript{1,123} With more
fulminant forms, a necrotizing, crescentic GN is ob-
served\textsuperscript{118,119,122} (Fig. 15). Immune complexes are absent
or infrequent, consistent with "pauci-immune GN."\textsuperscript{124}
These histological findings are nonspecific and can be
found in diverse immune-mediated or infectious disor-
ders. Granulomatous vasculitis is observed in only 6 to
15\% of renal biopsies from patients with WG.\textsuperscript{1,2,121,122}
In a retrospective review of 94 renal biopsies from
patients with WG and renal involvement, most common
features included segmental necrotizing GN and extra-
capillary proliferation, present in 85\% and 92\% of
biopsies, respectively.\textsuperscript{122} Serum creatinine at biopsy
correlated with the percent of glomeruli with crescents
or with necrosis.\textsuperscript{123} The onset and course of renal
involvement are variable. In some patients, the course
is indolent (progressing over months to years)\textsuperscript{2,122,125}
whereas others manifest rapidly progressive GN, pro-
gressing to end-stage renal failure (ESRF) within days to
weeks.\textsuperscript{118,119} Aggressive and prompt institution of ther-
apy with CS and cytotoxic agents is mandatory to avert
irreversible renal damage. Even in oliguric renal failure,
substantial recovery of renal function can be achieved in
many patients.\textsuperscript{122} The initial serum creatinine does not
predict long-term outcome (i.e., loss or restoration of
renal function).\textsuperscript{126} Unfortunately, 11 to 32\% of patients
with WG develop ESRF requiring chronic dialy-
sis.\textsuperscript{2,119,122,125,127,128} Chronic dialysis-dependent renal
failure is more common in patients with severe loss of
glomeruli on initial renal biopsy.\textsuperscript{122,129} Prognosis with
dialysis-dependent renal failure is poor.\textsuperscript{126} One retro-
spective study followed 23 patients with WG requiring
dialysis.\textsuperscript{126} At long-term follow-up, 11 (48\%) had died;
seven (30\%) remained dialysis-dependent; only five
(22\%) had substantially improved renal function.\textsuperscript{126}
Chronic renal failure months or years after the initial
injury may reflect nephrosclerosis from the original renal
injury rather than recurrent WG.\textsuperscript{1,125} Renal transplanta-
tion may be considered for patients with ESRF and no
evidence for active WG.\textsuperscript{125,128} Recurrence of WG has
been rare following transplantation.

Figure 14  (A) Photomicrograph. Hemosiderin-laden macrophages. Bronchoalveolar lavage fluid demonstrating numerous hemosi-
derin-laden macrophages with adjacent red blood cells indicating alveolar hemorrhage (Wright stain, low power). (Reprinted with
permission from Lynch and Raghu.\textsuperscript{102a}) (B) Photomicrograph. Hemosiderin-laden macrophages (siderophages) are prominent in the
alveolar interstitial in a patient with recurrent alveolar hemorrhage (hematoxylin-eosin). (Courtesy of Joseph Fantone, M. D., Department
of Pathology, University of Michigan Medical Center). (Reprinted with permission from Lynch and Leatherman.\textsuperscript{99})

Figure 15  Photomicrograph. Percutaneous renal biopsy in a 65-
year-old man with Wegener’s granulomatosis presenting with
alveolar hemorrhage, rapidly progressive glomerulonephritis
(RPGN), and serous otitis media. Note the typical crescent
formation indicative of RPGN. (Reprinted with permission from
Lynch et al.\textsuperscript{100a})
Other rare urological complications of WG include anecdotal reports of necrotizing vasculitis involving the ureters, ureteral stenosis, renal artery aneurysms with rupture, penile necrosis or ulcers, acute urinary retention, bladder pseudotumor, and renal masses. Involvement of the prostate is rare. One recent review identified 18 cases in the literature with histological evidence of WG in the prostate gland: 13 patients (72%) had symptomatic urinary tract obstruction, three (17%) had microscopic hematuria, and two (11%) had no urinary tract symptoms. Medical therapy for WG involving the urinary tract is usually efficacious. Surgical intervention (e.g., suprapubic cystotomy; ureteral stents, transurethral prostatic resection, etc.) may be required in selected cases.

CENTRAL OR PERIPHERAL NERVOUS SYSTEM INVOLVEMENT

Central or peripheral nervous system involvement occurs in fewer than 4% of patients at initial presentation, but eventually develops in 10 to 54% In a classical review of 104 patients with WG, Drachman identified three patterns of central nervous system (CNS) involvement: (1) vasculitis (28%); (2) granulomatous lesions from contiguous invasion from nasal, paranasal, or orbital disease (26%); and (3) granulomatous lesions remote from nasal granulomas (involving paranasal, or orbital disease (26%); and (3) granulomatous lesions from contiguous invasion from nasal, paranasal, or orbital disease. Involvement of the CNS is rarely confirmed histologically because of inaccessibility or risks associated with biopsies. The diagnosis is usually supported by histological confirmation at extraneural sites or by noninvasive studies (e.g., electromyogram (EMG), MRI, or CT scans of the brain or spinal cord) in patients with neurological symptoms and previous documentation of WG. MRI scans reveal a wide spectrum of findings including diffuse or focal dural thickening and enhancement, discrete lesions, infarcts, nonspecific white matter areas of high signal intensity, enlarged pituitary gland with infundibular thickening, and cerebral atrophy. Cerebral angiography is ill advised because the small vessels affected in WG are below the sensitivity of angiography.

SKIN INVOLVEMENT

Cutaneous lesions are present in 14 to 50% of patients during the course of the disease. Manifestations are protein and include palpable purpura, subcutaneous nodules, papules, petechiae, ulcers, and nonspecific erythematous or maculopapular rashes. Severe ulcerating lesions resembling pyoderma gangrenosum have been described. Skin biopsies may demonstrate granulomatous vasculitis with necrosis; however, leukocytoclastic vasculitis (LCV) (a nonspecific lesion) is more common. In a series of 46 patients with WG and dermatological manifestations, the most common features on skin biopsies were LCV (31%), chronic inflammation (31%), granulomatous inflammation (19%), acute inflammation without vasculitis (9%), and miscellaneous (11%). Importantly, granulomatous vasculitis was never observed. Another series of 35 patients with WG involving skin or mucous membranes cited the following aberrations: palpable purpura (n = 26), oral ulcers (n = 15), skin nodules (n = 6), skin ulcers (n = 5), gingival hyperplasia (n = 3), and miscellaneous (n = 5). Subcutaneous nodules and popular lesions reflect granulomatous inflammation of the dermis. Petechiae and purpuric or hemorrhagic lesions indicate vasculitis with necrosis and fibrinoid change. Skin changes may parallel the course of the systemic disease and have prognostic significance. In a cohort of 46 patients with WG and dermatological involvement, LCV correlated with a younger age at the onset of disease, active disease, more rapid progression of disease, higher frequency of articular and musculoskeletal symptoms compared with patients with no skin involvement.
In contrast, only 64% of patients with granulomatous inflammation on skin biopsies had evidence for active systemic disease. Cutaneous lesions in WG are associated with a higher incidence of articular and renal involvement compared with WG patients without cutaneous involvement.

**CARDIAC INVOLVEMENT**

Cardiac involvement is rarely documented antemortem, but prevalence rates of 8 to 15% have been estimated. Any portion of the heart may be involved, but coronary arteritis and pericarditis are the most common clinical features. Classic ST and T wave changes may reflect pericarditis. Necrotizing vasculitis or granulomatous inflammation involving the myocardium or coronary arteries may give rise to conduction defects, fatal arrhythmias, or cardiomyopathies. Necrotizing vasculitis affecting cardiac valves has been described. In one study, echocardiography detected valvular abnormalities in eight of nine patients with WG; severe aortic insufficiency requiring surgical valve replacement was documented in three patients. An inflammatory mass involving aortic valve and myocardium mimicking atrial myxoma has been described.

**INVOLVEMENT OF LARGE VESSELS**

Involvement of the aorta or large arteries is common in Kawasaki’s syndrome, Behçet’s syndrome, giant-cell (temporal) arteritis, and Takayasu’s arteritis, but is rare in WG. However, case reports of WG involving the internal carotid artery leading to stenosis, abdominal aorta (with dissection), or mesenteric arteries have been published.

**GASTROINTESTINAL INVOLVEMENT**

Gastrointestinal (GI) manifestations (e.g., abdominal pain, diarrhea, hemorrhage, and perforation) were cited in 4 to 10% of patients with WG. Two series cited GI involvement in four of 45 and four of 36 patients with WG. Histological confirmation of WG involving the GI tract is rarely documented antemortem. However, in a review of 59 necropsies in patients with WG, granulomatous or vascular lesions within the GI tract were detected in 23 (39%). Rarely, GI involvement (e.g., colitis, bleeding) may be the presenting feature of WG. Hepatic involvement is not a feature of WG. However, isolated case reports of patients with WG and incomplete septal cirrhosis, primary biliary cirrhosis, and portal inflammatory granuloma, vasculitis, and fibrosis have been published. Splenic involvement is rarely diagnosed antemortem, but splenic infarcts have been documented at necropsies or on abdominal CT (low attenuation lesions with peripheral enhancement).

**OTHER ORGAN INVOLVEMENT**

Constitutional symptoms (e.g., malaise, fatigue, fever, weight loss) occur in 30 to 80% of patients with WG and may be the presenting features. Nondeforming polyarthritis involving medium- and large-size joints occurs in two thirds of patients and parallels activity of the systemic disease. Articular symptoms usually remit with cytotoxic or CS therapy.

**HISTOPATHOLOGY**

The cardinal histopathologic features of WG include a necrotizing vasculitis affecting arterioles, venules, and capillaries; granulomatous inflammation; foci of parenchymal necrosis; microabscesses; and areas of fibrosis with acute and chronic inflammation. Irregularly shaped (geographic) necrosis surrounded by granulomatous inflammation is characteristic (Fig. 16). Well-formed sarcoidlike granulomas are rare, but multinucleated giant cells, epithelioid cells, and collections of histiocytes impart a granulomatous character to the inflammatory process (Fig. 9B). Vascular walls are infiltrated (and may be destroyed) by mononuclear cells and neutrophils, with occasional multinucleated giant cells and eosinophils (Fig. 17). Both acute and healing phases of the vasculitic lesions may be observed.

Figure 16 Photomicrograph. (Top) Early Wegener lesion with features of a microabscess (arrow) comprised by a collection of neutrophils in a fibrotic background with giant cells. (Bottom) Fully developed necrotizing granuloma with irregular (“geographic”) borders surrounded by a background of fibrosis and chronic inflammation with giant cells.
in individual patients. Fibrinoid necrosis and thrombosis within vascular lumens are early findings (Fig. 18). Later, fibrosis of vascular walls may result in stenosis or obliteration of the lumens (Fig. 19). Elastic stains may be required to identify remnants of destroyed vascular walls. A pronounced fibroblastic component, with concentric rings of collagen and connective tissue matrix, may be present. These histological features may not be found if small or nonrepresentative biopsies are obtained. Granulomas and vasculitis of small vessels may be observed with infections (particularly due to mycobacterial and fungal etiologies). Thus special stains should be performed in any granulomatous or necrotic lesion to exclude infectious causes. With infectious granulomas, vasculitis is a secondary phenomenon contiguous with foci of necrosis; sarcoidlike granulomas are frequently observed.

Laboratory Features

Anemia, thrombocytosis, or leukocytosis can be identified in 30 to 40% of patients with WG. Leukopenia or thrombocytopenia is rare in untreated patients, but may develop as a consequence of cytotoxic therapy. Peripheral blood eosinophilia is not a feature of WG. Polyclonal hypergammaglobulinemia occurs in up to 50% of patients. Serum complement levels are normal or elevated. Renal function tests (serum creatinine, blood urea nitrogen) and urinalysis should be obtained in all patients initially. Striking increases in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are characteristic of active, generalized disease and usually correlate with disease activity. CRP concentrations change more rapidly than ESR in response to changes in disease activity. However, ESR or CRP can be normal with active disease, particularly when only a single site is involved. Serial determinations of the ESR or CRP are useful in monitoring the disease but are nonspecific because elevations may occur in the presence of coexisting infections. Autoantibodies directed against cytoplasmic components of neutrophils (cANCA) are helpful in the initial diagnosis of WG and in monitoring response to therapy. Increases in cANCA were noted in more than 90% of
patients with active generalized WG, and in 40 to 70% of patients with active regional disease. Among WG patients with circulating ANCA, >90% are directed against proteinase 3 (PR3); <10% are directed against MPO or other antigenic epitopes. Changes in ANCA usually correlate with disease activity and are unaffected by intercurrent infections. However, cANCA titers may persist in 30 to 40% of patients even after complete clinical remissions have been achieved. Further, increases in cANCA titers do not necessarily presage relapse. Serial determinations of cANCA provide useful adjunctive information to the clinical data, but treatment decisions should not rely exclusively on cANCA titers.

RADIONUCLIDE SCANS
Gallium citrate scintigraphy may show uptake in lung or sinuses in patients with active WG, but clinical value is unproven. In one retrospective study, Ga scans were examined from 40 episodes of presumed active WG in 28 patients. Positive (increased uptake) Ga scans were noted in eight episodes (20%). Negative predictive value was 100%, but positive predictive values for lungs or paranasal sinus involvement were 24% and 63%, respectively. False-positive findings were related to bacterial or viral infections. A strongly negative scan strongly supports inactive disease, Ga scans are expensive, nonspecific, and logistically difficult (scanning is done 72 hours after injection). We see no role for radionuclide testing in the diagnosis or follow-up of WG.

STAGING OF ACTIVITY
The Birmingham Vasculitis Activity Score (BVAS) has been used as a disease-specific activity index for WG. Parameters are weighted according to minor or major components. A modified BVAS was shown to be a valid, disease-specific activity index for WG, with good inter- and intraobserver variability. The use of objective scoring systems may be invaluable in longitudinal follow-up.

PATHOGENESIS OF WG
The cause of WG is unknown. Two key histopathologic features of granulomas and vasculitis suggest an exaggerated cellular immune or hypersensitivity response, but no identifiable antigen or pathogen has been identified. The preponderance of disease in the upper and lower respiratory tracts suggests that inhaled antigen(s) may initiate the cellular immune response. T cells, monocytes, and neutrophils constitute key cellular elements in the infiltrate in WG, suggesting that both cell-mediated and neutrophil-mediated immune mechanisms are operative. Early injury is likely mediated primarily by polymorphonuclear leukocytes (PMNs) but late phases of the vasculitic process involve principally mononuclear cells (both mononuclear phagocytes and lymphocytes). The granulomatous component in WG is mediated by CD4+ T cells that produce Th1 cytokines [e.g., interleukin-2 (IL-2), γ-interferon (IFNγ)], but not IL-4, IL-5, or IL-10. Circulating cANCA suggests a role for PMNs and these autoantibodies in the pathogenesis and evolution of WG. The binding of PR-3 ANCA activates PMNs and endothelial cells, eliciting cytokine release and injury. Increases in serum immunoglobulins, B cell activity, and cANCA suggest that humoral mechanisms are also operative. Immune complexes (ICs) have been identified in serum and skin in some patients with WG but are generally absent in involved lung or renal tissue. Activation of the coagulation cascade may play a role. Deposition of fibrin, platelets, and activated coagulation products may modulate glomerular injury. Chronic suppurative disease in the upper or lower respiratory tracts may provide an antigenic source, leading to an exaggerated immune response mediated by cANCA. Exacerbations of WG during intercurrent infections and the frequent relapses observed in WG patients who are chronic nasal carriers of Staphylococcus aureus suggest that infections may amplify the inflammatory process, possibly by eliciting an antibody and acute phase response.

Abundant experimental, in vitro, and clinical data suggest that CANCA play critical roles in the development of WG and other ANCA-associated vasculitides (e.g., MPA and CSS) (discussed in depth by Dr. Jeannette in this issue). PR3, one of the neutral serine proteinases in azurophilic granules of human PMNs and monocytes, is the target antigen for ANCA in WG. Parameters directed against MPO (MPO-ANCA) are rare in WG but are detected in >50% of patients with MPA, CSS, or pauci-immune GN. PR3-ANCA is infrequent (10–20%) in these disorders. Experimental in vitro data suggest that PR3-ANCA induces a sequence of events including recruitment and activation of PMNs and monocytes, release of oxygen (O2) radicals and lysosomal enzymes, and endothelial cell (EC) injury. BAL demonstrates marked increases in PMNs in patients with active WG and circulating cANCA. Further, plasma tumor necrosis factor-α (TNFα) is elevated in patients with active WG. “Priming” of PMNs by cytokines such as TNFα or IL-1 is necessary for expression of PR3 or MPO on cell membranes. PR3-ANCA stimulates production of the chemokines monocyte chemotactic peptide-1 (MCP-1) and IL-8 by monocytes. ECs, mesangial cells, epithelial cells, and PMNs are capable of producing IL-8, particularly
following cytokine stimulation.\textsuperscript{211} IL-8 plays a key role in neutrophil sequestration in the microvasculature. TNF\textsubscript{\alpha}-primed PMNs downregulate expression of the IL-8 receptor CXCR2, reducing their ability to respond to a chemotactic gradient,\textsuperscript{229} favoring retention of PMNs with the microvasculature. In vivo, these processes may trap PMNs within glomerular capillaries or other sites of disease.\textsuperscript{211} Exposure of cytokine-primed PMNs and mononuclear phagocytes to ANCA IgG induces full activation with a respiratory burst, release of O\textsubscript{2} radicals, degranulation, and release of proinflammatory cytokines.\textsuperscript{229,230} After degranulation of PMNs, release of PR3 causes EC injury and tissue damage.\textsuperscript{209,222,231,232} The cytotoxic effects of PR3 on ECs are mediated by both lytic necrosis\textsuperscript{209} and apoptosis.\textsuperscript{233} Scavenging macrophages engulf apoptotic PMNs that express ANCA on the cell surface.\textsuperscript{234} Phagocytosis of PR3-ANCA-opsonized PMNs by macrophages (MOs) elicits the release of TNF\textsubscript{\alpha} and other pro-inflammatory mediators, and may prime and recruit additional PMNs\textsuperscript{235} and augment tissue damage.\textsuperscript{211} In addition, diverse nonimmune cells express PR3 and may contribute to the inflammatory process.

The endothelium is not an innocent bystander in the vasculitis process but plays an active role in augmenting tissue injury.\textsuperscript{211,236} Upregulation of adhesion molecules [e.g., intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1)] contributes to the PMN-mediated cytotoxic process.\textsuperscript{237} Endothelial cells produce platelet activating factor (PAF) and IL-8 following stimulation by proinflammatory cytokines\textsuperscript{238} or reactive O\textsubscript{2} intermediates.\textsuperscript{211} Both PAF and IL-8 mediate increased EC/PMN adhesion by triggering increasing affinity for CD11b/CD18.\textsuperscript{211,237} These molecules are chemotactic for PMNs, prime PMNs, and trigger PMN adhesion. In addition, cANCA-induced stimulation of IL-1\beta, TNF\textsubscript{\alpha}, IFN\textgamma, and chemokines augments EC expression of the leukocyte adhesion molecules ICAM-1, VCAM-1, and E-selectin.\textsuperscript{239,240} Serum concentrations of ICAM-1, VCAM-1, and E-selectin are elevated in WG and correlate with disease activity.\textsuperscript{241} Elevation levels of soluble (s) E-selectin, sICAM-1, and sVCAM-1 were demonstrated in active WG and MPA compared with healthy controls.\textsuperscript{242} Further, the levels of sE-selectin, sICAM-1, and sVCMA-1 correlated with disease activity and normalized as the disease remitted. Human ECs express PR3, and anti-PR3 antibodies activate ECs in vitro.\textsuperscript{243,244} Upregulation of PR3 by proinflammatory cytokines (e.g., TNF\textsubscript{\alpha} and IL-1) induces PR3,\textsuperscript{224} leading to tissue damage.\textsuperscript{245} Both PR3 and elastase were detected extracellularly in renal tissue in patients with WG and crescentic GN\textsuperscript{246} suggesting that non–immune cells expressing PR3 are important in the development of ANCA-associated pauci-immune GN.\textsuperscript{247} PR3 and elastase also induce EC apoptosis.\textsuperscript{233,248} Activated ECs also contribute to a procoagulant environment.\textsuperscript{211} Intraglomerular fibrin deposition and enhanced tissue factor (TF) expression are prominent in ANCA-associated GN.\textsuperscript{211,249} Thrombosis and platelets play key roles in the pathogenesis of early lesions in ANCA-associated vasculitis.\textsuperscript{230}

The later phases of the vasculitic process in WG are mediated primarily by mononuclear cells. T-lymphocytes (primarily CD4\textsuperscript{+} cells) in WG are activated and produce diverse cytokines/chemokines that favor a proinflammatory milieu.\textsuperscript{208,251,252} Biopsies from lung, kidney, or upper respiratory tract in WG patients contain CD3\textsuperscript{+} cells (predominantly CD4\textsuperscript{+}), many of which express human leukocyte antigen (HLA-DR) (indicating activation).\textsuperscript{253} CD8\textsuperscript{+} cells likely play contributory roles.\textsuperscript{254} Circulating PR3 and MPO antigen-specific T cells are present in peripheral blood (PB) in patients with ANCA-associated vasculitis.\textsuperscript{255,256} Antigen-specific T cells persist in the PB in patients in remission,\textsuperscript{255} suggesting that T cells contribute to late relapses.

Th1-like cytokines appear to be pivotal to the pathogenesis of WG. Peripheral blood mononuclear cells (PBMCs)\textsuperscript{208} or T cells (CD4\textsuperscript{+} cells) isolated from blood, BAL, or granulomatous lesions from patients with WG display increased secretion of IFN\textgamma but not IL-4, IL-5, or IL-10, consistent with a Th1 response.\textsuperscript{257} Furthermore, TNF\textsubscript{\alpha} production from PBMCs and CD4\textsuperscript{+} T cells isolated from patients with WG is elevated when compared with healthy donors.\textsuperscript{208} In vitro production of IFN\textgamma by WG PBMC is inhibited in a dose-dependent manner by exogenous IL-10.\textsuperscript{208} Large numbers of CD3\textsuperscript{+} T cells, IFN\textgamma-staining cells, and CD4\textsuperscript{+}/CD26\textsuperscript{+} cells (CD26 is a Th1 marker) were identified in granulomatous lesions of nasal biopsies from patients with WG.\textsuperscript{258} In contrast, CD30\textsuperscript{+} cells (a Th2 marker) were uncommon.\textsuperscript{258} The immune response may be compartmentalized and may differ in localized versus disseminated disease. For example, Th1 cells predominated in nasal biopsies from patients with localized WG compared with generalized WG.\textsuperscript{258} By contrast, PB mononuclear cells from localized WG displayed a Th2 phenotype when compared with generalized disease.\textsuperscript{258} These data suggest a polarized Th1-like response in localized disease. The Th1 cytokine profile observed in WG is consistent with an immune response to antigens. T cells reacting to bacterial antigens produce a Th1 cytokine profile.\textsuperscript{259} A shift in the bias from Th1 to Th2 profiles may occur at different phases of the disease.\textsuperscript{258} Such a shift in T cell phenotype has been described in systemic vasculitis\textsuperscript{260} and lepromatous leprosy.\textsuperscript{261} The T cell bias in WG is neither straightforward nor static. In one study, Th2 bias
(increased IL-4), decreased IFNγ, increased expression of CCR3) predominated in nasal mucosal biopsies from patients with WG.262 Interestingly, renal biopsies demonstrated both Th1 and Th2 responses (increased IL-2 and IL-10).262

Expression of the chemokines monocyte chemoattractant peptide-1 (MCP-1), macrophage inflammatory protein (MIP-1x), MIP-1β, and RANTES (regulated upon activation in normal T cells) is enhanced in ANCA-associated vasculitis.263 These chemokines favor T cell recruitment.264 Monocytes from patients with active WG secrete greater amounts of IL-12,208 which favors the Th1 phenotype. Upregulation of B7–1 and B7–2 on activated T cells, with a lower expression which favors the Th1 phenotype. Upregulation of B7–1 and B7–2 on activated T cells, with a lower expression that stimulates RANTES production by MOs; few B lymphocytes (either CD19 or CD20) were present.263 Further, the chemokine RANTES (produced mainly by MOs) and the gene encoding for IFNγ were expressed at a higher level in lung tissue from WG patients than in controls.263 One can theorize that cANCA triggers an initial pathological event, which induces production of inflammatory cytokines, chemokines, and adhesion molecules. Later, T cells produce IFNγ that stimulates RANTES production by MOs, which then recruits additional memory T cells and MOs.263 Interestingly, corticosteroids inhibit T cell production of IFNγ and RANTES production by MOs.263

T lymphocytes lacking CD28 expression may play a pathogenic role in some autoimmune disorders including ulcerative colitis,265 rheumatoid arthritis,266,267 and WG.252,254 Expansion of the CD28(-) subset of CD4+ or CD8+ cells in PB has been noted in WG252,254 and corresponds with greater extent of disease.254 In addition, the proportion of CD28 negative T cells (both CD4+ and CD8+) in granulomatous lesions and BAL is increased in WG compared with active sarcoidosis or healthy controls.268

Although T cells play a pivotal role in the inflammatory process in WG, B lymphocytes contribute. CD20+ B lymphocytes and CD38+ plasma cells were present in nasal biopsies from patients with untreated WG.269 Activated CD4+ cells of the Th2 type are present in PB in patients with generalized WG.270 CD4+ Th2 cells show B cell helper activity and stimulate antibody production.271 B-lymphocyte production of cANCA is polyclonal.272,273 During active disease, IgG1 and IgG4 predominate,274 with a slight increase in IgG3 as well.272 The presence of antibodies of the IgG4 subclass suggests that ANCA production is antigen-triggered and T cell dependent.274 One may speculate that B cells promote ANCA production elicited by S. aureus–reactive T cell clones.275

Chronic infection may play a role in orchestrating the inflammatory/immune process in WG. Intercurrent bacterial or viral infections increase the risk for relapses in WG.275 Chronic nasal carriage of S. aureus is a risk factor for disease relapses.213 Mayet et al examined PB lymphocyte responses to PR-3, S. aureus, and other bacterial antigens.275 Reactivity to S. aureus was increased in patients with WG compared with controls. Further, S. aureus–specific T cell clones from patients with WG were of the γδ TCR+CD4+ phenotype and HLA-DR restricted.275 In addition, S. aureus–specific T cell clones recognized the PR3 antigen. The authors speculated that specific HLA-DR restricted CD4+ T cells play a key role in triggering immune responses in WG.

Genetic Factors
The role of genes in influencing susceptibility to WG has not been extensively studied. A Caucasian racial bias has been suggested;2 but this could reflect referral patterns. Studies of the distribution of major histocompatibility complex (MHC) alleles among patients with systemic vasculitis (various forms) have yielded disparate results. Associations with DR2,276,277 DR1-DQw1,277 B8,278 DR9,279 with a weaker association with B55280 have been described in WG. Other studies cite no significant associations between MHC class II and WG.281,282 Genetic polymorphisms may influence susceptibility to autoimmune disorders (including WG). Certain polymorphisms of receptors for the Fc fragment of IgG (FcγR) (i.e., homozygosity for the R131 form of (FcγRIIa) for the R158 form of (FcγRIIa) were associated with a higher propensity to relapse in the first 5 years after diagnosis of WG.283 These polymorphisms are associated with decreased FcR-mediated clearance, which may be relevant to the chronic nasal carriage of S. aureus. A link between α-1-antitrypsin proteinase inhibitor (Pi) Z allele and WG has been cited.285–287 An increased frequency of the α-1-antitrypsin allele PIZ and members of the serpin gene cluster was noted in patients with WG.288 α-antitrypsin (α-AT) is the main inhibitor of PR3 and elastase.211 PR3-ANCA interferes with the binding of PR3 to α-AT, and may inhibit the clearance of PR3.211 In one study, the inhibitory effect of ANCA on PR3/α-AT correlated more closely with disease activity than serum levels of ANCA.286

Treatment
Over the past 30 years, WG has gone from being a fatal disease for which there was no known treatment to one
in which there are therapeutic options capable of bringing about long-term survival. With the expansion of therapeutic alternatives, management decisions in WG are increasingly being guided by disease severity, organ manifestations, and individual patient factors that take into account past treatment history and drug toxicities.

Prior to the introduction of effective therapy, mean survival among patients with untreated active WG was less than 6 months; more than 80% of patients died within 3 years of onset of symptoms, usually of progressive renal failure. Corticosteroids were initially employed and ameliorated many of the inflammatory manifestations of WG. However, gains in survival were modest (mean survival of only 12.5 months).

Early experience at the NIH affirmed that CS alone were not adequate to treat severe WG. In an early cohort of patients at that institution, 57 had initially been treated with CS. Although partial improvement was sometimes cited, none of 45 patients with renal involvement achieved complete remissions with CS alone. Further, excessive cumulative doses of CS may lead to long-term adverse effects (particularly osteoporosis and opportunistic infections).

The seminal studies employing daily CYC combined with CS represented a major advance in the treatment of WG. This regimen dramatically improved survival but underscored the need to broaden the therapeutic goals to include relapse prevention and minimization of treatment-related toxicity. In the original regimen by Fauci and Wolff, patients were treated with oral CYC (1–2 mg/kg/d) combined with prednisone (1 mg/kg/d, with gradual taper). Among responders, prednisone was gradually tapered to an alternate schedule and discontinued by 6 to 9 months. CYC was continued for a minimum of 1 year past remission and was then tapered and discontinued. From the NIH cohort spanning 1229 patient-years, 91% of patients treated with this regimen improved, 75% achieved complete remission (CR), and mortality was only 20%. Unfortunately, relapses occurred in 50% of patients, and 42% experienced serious morbidity from the side effects of treatment. Subsequent studies employing this regimen reported remissions rates of 70 to 90% and early mortality rates less than 15%. Relapses were noted in 30 to 70% of patients following cessation or tapering of therapy, but reinstitution of therapy was usually efficacious. However, late sequelae of vasculitis (e.g., cerebrovascular accidents, myocardial infarction, renal failure, hypertension) or complications of CYC (e.g., opportunistic infections, neoplasms) contributed to long-term mortality and morbidity. The search has remained ongoing for safer and effective therapies associated with acceptable rates of relapse.

### Intermittent “Pulse” CYC

The exploration of intermittent high-dose intravenous (IV) “pulse” CYC in WG was prompted by the potential for reduced toxicity as well as favorable experience with this approach in other autoimmune diseases. Although data are limited, pulse CYC appears to be less effective than daily oral CYC for WG. Several studies showed that remission rates were similar with oral or IV pulse CYC, but relapses were more common with pulse CYC. It is possible that reducing the time between cycles or extending the total length of IV pulse therapy may improve long-term prognosis, but this has not been studied. Currently, we believe daily oral CYC combined with CS is optimal therapy for generalized WG. Recent treatment strategies advocate initial treatment with oral CYC and CS for 3 to 6 months (until CR are achieved), followed by maintenance therapy with less toxic agents (e.g., methotrexate or azathioprine) (discussed later).

### Methotrexate

Oral or IV methotrexate (MTX), administered once weekly, may be used for patients developing serious adverse effects from CYC or for non-life-threatening WG. In an open-label prospective trial, investigators at the NIH treated 42 patients with oral MTX (20–25 mg once weekly) combined with prednisone (initial dose 1 mg/kg/d, with gradual taper). All patients had active disease at entry, including GN in 21 (50%) and lung involvement in 22 (52%). Exclusion criteria included acute renal failure, pulmonary hemorrhage, serum creatinine > 2.5 mg%, and chronic liver disease. With this regimen, remissions were achieved in 30 patients (71%); overall survival was 93%. Late relapses occurred in 11 of 30 (36%), but reintroduction of MTX plus CS led to second remissions in six of eight patients. Toxicity was generally mild, but four patients developed Pneumocystis carinii pneumonia (PCP) (two of whom died). Long-term follow-up (median of 76 months) of 21 patients with active GN in that study cited durable remissions in 20 patients (95%). At late follow-up, the serum creatinine rose > 0.2 mg% from baseline in only two patients. In another open-label trial, these investigators treated 31 patients with WG with CYC plus prednisone. After CRs were achieved (at a median of 3 months), CYC was discontinued and MTX was substituted to maintain remissions. Exclusion criteria for MTX included serum creatinine > 2.5 mg% or chronic liver disease. Late relapses occurred in five of 31 patients (16%); all relapses occurred more than 1 year after initiation of MTX. All five patients were taking only MTX at relapse; all five responded to intensification of therapy. In a similar study, de Groot and colleagues treated patients initially with either oral or IV pulse CYC and switched to weekly IV MTX with or without concomitant CS after remissions had been achieved with
CYC.\textsuperscript{309} Median duration of CYC in that study exceeded 24 months. Partial or complete remissions were maintained in 86% of 22 patients who received MTX alone and in 10 of 11 (91%) of patients receiving MTX plus prednisone. A subsequent report from these investigators documented favorable responses to IV pulse MTX in 10 of 17 patients (59%); in that study, low-dose CS was administered concomitantly (mean prednisone dose < 7 mg/d).\textsuperscript{303} All 17 patients had active disease at entry; 11 had never been treated; six had relapsed after initial remission with CYC and CS. By 2000, these same investigators had treated 45 patients with IV pulse MTX for either initial or maintenance therapy for non-life-threatening WG.\textsuperscript{4} Patients with impaired renal function were excluded. Among the entire cohort of 155 patients (92% received CYC at some point), overall mortality was only 14% after a median of 5.6 years. These various publications\textsuperscript{4,303,304,306,307,309,310} are encouraging and support the use of MTX plus prednisone in patients experiencing adverse effects from CYC or as initial therapy for mild WG. Additional data are required to evaluate the role of MTX as therapy for severe cases of WG. Because the kidneys are the major route of MTX elimination, toxicity is increased in the presence of renal insufficiency.\textsuperscript{311} Additionally, the concomitant use of MTX and therapeutic doses of 160 mg trimethoprim/800 mg sulfamethoxazole (T/S) twice daily may cause severe pancytopenia.\textsuperscript{307,311} Thrice weekly T/S (80/400) plus MTX can be safely administered\textsuperscript{308} and is recommended as prophylaxis against PCP.\textsuperscript{106,307,310,312}

AZATHIOPRINE

Azathioprine (AZA) is less effective than CYC and should not be used as primary therapy for WG. However, AZA (1–3 mg/kg/d orally) has a role as maintenance therapy in patients who remit with CYC and CS. Early studies cited maintenance of remission with AZA in eight of nine\textsuperscript{1} and 10 of 13\textsuperscript{313} patients after initial induction of remission with CYC and CS. Although AZA has myriad potential toxicities, including bone marrow suppression, heightened susceptibility to infections, GI toxicities, stomatitis, and idiosyncratic reactions, serious adverse effects requiring discontinuation of therapy are uncommon (< 10%).\textsuperscript{295} In contrast to CYC, AZA lacks bladder toxicity and has low oncogenic potential.\textsuperscript{295}

STAGED “INDUCTION-MAINTENANCE” THERAPY OF WG

Although CYC remains the cornerstone of therapy for generalized or severe WG, long-term cumulative use or the need for repetitive courses of CYC to treat relapses may be associated with serious potential toxicities (particularly bladder carcinomas and myeloproliferative disorders).\textsuperscript{2,295,296,314–317} Recent strategies advocate treating generalized WG with CYC and CS (to induce remission), followed by less toxic agents (e.g., AZA or MTX) to maintain remissions.\textsuperscript{305,308,309} A recent randomized trial by the European Vasculitis Study Group presented strong evidence in support of this “induction-maintenance” approach in WG.\textsuperscript{305} In that study, 155 patients with ANCA-associated vasculitides were treated with daily oral CYC/CS as induction therapy for a minimum of 3 to 6 months.\textsuperscript{305} Ninety-five patients (61%) had WG; 60 patients (39%) had MPA. Renal involvement was present in 94%. With this induction regimen, CRs were achieved in 119 patients (77%) by 3 months and in 144 patients (93%) within 6 months. After CRs were achieved, patients were randomly assigned to continue oral CYC (1.5 mg/kg/d) (\(n = 73\)) or switch to AZA (2 mg/kg/d) (\(n = 71\)) in addition to low-dose prednisolone (10 mg/d) for maintenance therapy. After 12 months of therapy, both groups received AZA (1.5 mg/kg/d) and prednisolone (7.5 mg/d). Both groups were followed for 18 months from study entry. At 18 months, relapse rates (the primary end point) were similar in the AZA cohort (15.5%) and CYC group (14%) (\(p = 0.65\)). Relapses were more common among patients with WG (18%) compared with MPA (8%), \(p = 0.03\). Other outcome measures (e.g., Vasculitis Damage Index scores, quality of life, CRP, or ESR) were similar between AZA and CYC cohorts. End-stage renal failure developed in two patients in each group. The rate of adverse effects was similar between treatment groups. Only eight patients died (5% mortality). Seven of the eight fatalities occurred within the first 3 months, during the induction phase with CYC/CS. One patient died (from stroke) during the maintenance phase. Although the frequency of toxicity was similar between treatment arms, the short study duration was insufficient to examine the long-term consequences associated with chronic CYC use (particularly malignancies). This experience supports the use of CYC/CS for initial induction therapy, followed by early switch (within 3 to 6 months) to less toxic agents once CRs have been achieved. Although this study did not evaluate MTX, either MTX or AZA are reasonable options for long-term maintenance therapy. The decision about whether to use MTX or AZA for remission maintenance must be made on an individual patient basis because no studies have directly compared these agents. However, MTX is contraindicated in patients with renal insufficiency, hepatic disease, or severe chronic pulmonary functional impairment.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF), an inhibitor of purine synthesis, has been used in small, nonrandomized trials as a remission maintenance agent in WG. In one study, nine patients with WG were treated with MMF (2 g/d) following induction of remission with CYC/CS.\textsuperscript{318} One
patient relapsed during the 15-month study period. In a prospective study, Langford et al treated 14 patients with daily CYC plus CS to induce CR, followed by MMF as maintenance therapy. Relapses occurred in six patients (43%) at a median of 10 months after achieving CR. Experience with MMF is limited; its use should be reserved for patients experiencing or at risk for adverse effects from MTX or AZA.

**CHLORAMBUCIL**

Chlorambucil, an alkylating agent related to CYC, has been used to treat WG, with anecdotal successes, but is oncogenic and has myriad toxicities. We see no role for chlorambucil to treat WG.

**TRIMETHOPRIM/SULFAMETHOXAZOLE**

Trimethoprim/sulfamethoxazole (T/S), one double strength tablet b.i.d., may reduce relapse rates in patients with WG; however, it is of doubtful value as primary therapy. Its mechanism of action is not clear between groups. These data are intriguing, but the impact of T/S on modulating the course of WG remains controversial.

The mechanism of action of T/S is not known but could reflect antimicrobial or immunomodulatory effects. Relapses of WG are more frequent coincident with respiratory infections or in patients with chronic nasal carriage of *S. aureus.* Low-grade bacterial infection may prime neutrophils to express target antigens (e.g., cANCA) on the cell surface and may trigger local immune responses. The antimicrobial effect of T/S may abrogate these effects, thus limiting neutrophil activation and further tissue damage.

In view of its low toxicity, T/S may be considered as adjunctive therapy for persistent, indolent disease despite CYC and CS. Although T/S may be considered as initial therapy for selected patients with isolated upper airways disease, T/S has no primary role for treating WG involving kidneys or other major organs. The most important role of T/S in WG is to prevent pneumonia due to *Pneumocystis jiroveci* (formerly *P. carinii*), a well-known complication of immunosuppressive therapy.

The incidence of PCP in WG ranges from 20% in a French study to 4% in the United States and 1% in Germany; these differences likely reflect more aggressive immunosuppression in the French group. Prophylaxis against PCP with T/S is highly efficacious and should be given to all patients treated with aggressive immunosuppressive therapy. Thrice weekly T/S (160 mg/800 mg) is cost-effective. Other prophylactic regimens employing dapsone, aerosolized pentamadine (one monthly), or atovaquone are far more expensive and have a less favorable adverse effect profile.

**TREATMENT OF FULMINANT DISEASE**

More aggressive therapeutic regimens may be necessary in patients with fulminant disease (e.g., rapidly progressive glomerulonephritis [RPGN], DAH with respiratory failure, or CNS vasculitis). In this context, higher initial doses of CS and CYC can be considered. Pulse methylprednisolone (1000 mg daily IV) combined with IV CYC (3–4 mg/kg/d) for 3 days, followed by CS taper and oral CYC (2 mg/kg/d) has been used, but data are limited to anecdotal cases. This regimen is associated with an increased risk of side effects and should be considered only for life-threatening indications. Plasmapheresis (combined with CYC/CS) has been employed, with anecdotal successes in severe DAH, but its efficacy remains unclear. In the absence of prospective data establishing its efficacy apart from other modalities, plasmapheresis should be reserved for patients with life-threatening disease refractory to conventional therapies.

**Special Considerations**

WG in the elderly (age ≥ 65 years) is associated with an increased mortality rate and incidence of complications of therapy. Because of the heightened...
susceptibility to opportunistic infections in elderly patients, less aggressive immunosuppressive therapy is warranted in this age group. Further, initial induction therapy with agents less toxic than CYC (such as MTX) can be considered in patients with localized or less severe disease and a more favorable prognosis. In one study, elevated serum creatinine ≥ 1.8 mg/dl or age ≥ 57 years were predictors of worse survival. In this context, traditional induction therapy with CYC/CS is appropriate. The dose and duration of immunosuppressive and CS therapy need to be individualized. In one retrospective study from Norway, all 57 patients treated with CS and CYC achieved CRs. However, relapses occurred in 31 patients (60%) after a median of 18 months. Relapses were associated with lower cumulative doses of CYC and prednisolone. Careful longitudinal follow-up incorporating clinical, serological parameters (e.g., CRP, ESR, ANCA), and radiographic parameters are essential to guide efficacy of therapy and appropriate dosing and duration of medical therapy.

Other Therapeutic Options
Anecdotal responses have been cited with cyclosporin A, 15-deoxyspergualin, high-dose intravenous immunoglobulin, monoclonal antibodies targeted against T cells, rituximab (an anti-CD20 chimeric monoclonal antibody directed against B cells), Campath-1H (a monoclonal antibody directed against CD52), humanized anti-CD4 antibodies, anti-thymocyte globulin, and etoposide but data are limited to a few cases in uncontrolled trials.

Biological Response Modifiers
The use of biologic agents in the treatment of WG is currently being investigated. These therapies are intriguing because of the potential to specifically target immunologic components involved in disease pathogenesis while leaving other host defense mechanisms intact. The study of biologic therapies in WG must, however, be approached with caution because of the potential for unexpected effects in a disease that can be life threatening. To date, the efficacy and safety profile associated with biologic agents to treat WG have not been established. A chapter later in this issue by Lanford addresses the rationale and published data for the use of biologic therapies in WG.

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