Unraveling Eosinophilic Granulomatosis With Polyangiitis
Sharing Patients’ Perspectives to Improve Clinician Awareness, Diagnosis, and Management

A CME/CE-certified supplement to CHEST Physician™
In Summary

After completing this activity, the participant should be better able to

- Identify signs and symptoms that may be indicative of EGPA and evidence-based approaches to evaluating and diagnosing EGPA in patients who present with those signs and symptoms.
- Summarize the latest data on the efficacy, safety, tolerability, and indications for approved and late-stage investigational agents for EGPA. This comprehensive program provides up-to-date information regarding EGPA—and its recognition, diagnosis, and treatment—and incorporates the patient perspective to raise awareness of patients' needs, heighten urgency, and, ultimately, educate on the disease.
- In addition, given the nature of EGPA, a multidisciplinary approach to care is necessary to achieve optimal outcomes; however, clinicians may not be familiar with effective strategies for multidisciplinary care of patients with EGPA and, similarly, may lack the skills to engage patients with EGPA in shared decision making. This activity will include a discussion of not only the roles of members of the multidisciplinary team, but also the need for and strategies to facilitate shared decision making in the treatment of EGPA.

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Letter From the Editors

The past decade has seen more advances in our understanding of eosinophilic granulomatosis with polyangiitis (EGPA) than all the preceding years since 1951, when Churg and Strauss first identified the condition that long carried their names. Although EGPA remains a difficult disease to diagnose and manage, the condition slowly is yielding its secrets through genomic, histologic, and epidemiologic analysis, as bench scientists and clinical researchers delve into its pathogenesis, presentation, and prognosis.

This enhanced understanding of EGPA is shaping approaches for optimal use of existing treatments and strategies for developing new agents. A new therapeutic class has joined the armamentarium in recent years, with the US Food and Drug Administration’s 2017 approval of the anti-interleukin (IL)-5 monoclonal antibody mepolizumab for use in EGPA, making that biologic agent the first therapy specifically approved to treat the condition.

The years just ahead are likely to see even more advances. Other biologics are being evaluated, with a phase 3 trial now assessing the efficacy and safety of another anti–IL-5 monoclonal antibody, benralizumab. Meanwhile, genome-wide association studies and population analyses are identifying phenotypes and patient subgroups that will enable clinicians to further individualize care. These findings are being translated into evidence-based recommendations from groups such as the EGPA Consensus Task Force and the American College of Rheumatology, which is scheduled to release its first-ever vasculitis guidelines in 2020.

The focus of all these efforts is, of course, the patient. If ever a disease depended on an effective patient-physician alliance for its successful management, it’s EGPA. The chronic course, changing nature, serious consequences, and evolving treatment strategies that characterize EGPA necessitate frank and frequent communication between patient and physician. In recognition of that fact, we are proud to have collaborated with the American Partnership for Eosinophilic Disorders to share the insights and experience of 3 people with EGPA. Their observations provide valuable perspectives on our efforts to diagnose, treat, and effectively manage EGPA, and we are pleased to provide their commentary alongside the latest scientific evidence and guideline recommendations.

To close a discussion of a complicated subject on a simple—but simply vital—note: if you don’t look for EGPA, you won’t find EGPA.

Sincerely,

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The Epidemiology of EGPA

Almost 25 million people in the United States have asthma. Over 5000 people in the United States have a rare autoimmune disease known as eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as the Churg-Strauss syndrome), many of whom initially presented with asthma. An analysis of 2000 patients with asthma identified 21 incident cases of EGPA, or roughly 1 case of EGPA for every 100 people with asthma.10

On average, these patients will have symptoms for 50 months before they are diagnosed with EGPA.11 Those “lost” 4 years can be critical in determining outcomes for a disease that can lead to multi-organ dysfunction and even death when untreated.4,12,13 Because asthma is a prominent presenting symptom of EGPA, it is imperative that primary care providers (PCPs), allergists, and pulmonologists consider the possibility of EGPA when evaluating patients with asthma—particularly those with late-onset asthma. The multifaceted nature of EGPA often poses diagnostic challenges for rheumatologists, cardiologists, nephrologists, dermatologists, and other physicians.

Even before grappling with diagnostic criteria and treatment strategies, however, the challenge of EGPA starts with defining what it is. In characterizing the condition that previously bore their names, pathologists Jacob Churg and Lotte Strauss in 1951 described EGPA as “a clinical syndrome of severe asthma, fever, and hypereosinophilia, together with symptoms of vascular embarrassment in various organ systems.”11 In the last decade, the medical community has replaced the eponym “Churg-Strauss syndrome” with the descriptive name “eosinophilic granulomatosis with polyangiitis.”14 The Chapel Hill Consensus Conference, an international panel of experts, described EGPA as an “eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. [Antineutrophil cytoplasmic antibody] ANCA is more frequent when glomerulonephritis is present.”14 That description speaks to the wide-ranging manifestations of EGPA. Indeed, the broad array of presenting constitutional and organ-specific symptoms can contribute to diagnostic delay and complicate treatment decisions.

EGPA appears to affect men and women in roughly equal measure.13,15 While pediatric cases have been reported, EGPA overwhelmingly is a disease of adults, usually arising in middle age.13 In 3 recent studies, the mean age at diagnosis ranged from 45.7 years to 54.2 years.8,9,11

While an in-depth discussion of the pathogenesis of EGPA is beyond the scope of this publication, various environmental and genetic factors may contribute to disease pathogenesis, and defects in adaptive immunity, as noted below, has been implicated in its onset (Figure 1).16 Allergens, infections, medications, and vaccinations all have been proposed as exogenous contributors to development of EGPA, but the strength of evidence supporting a causative role for each varies considerably.13,16 The high prevalence of asthma and allergies among patients with EGPA provides support for the pathogenic role of allergens, while evidence also indicates a causative role for silica exposure in EGPA.17 Several studies have established a link between EGPA and specific human leukocyte antigen (HLA) polymorphisms, with the HLA-DRB*04 and *07 alleles, as well as HLA-DRB4, associated with an increased risk of developing the disease.18,19 A recent genome-wide association study involving 676 people with EGPA and 6809 controls identified 8 EGPA-associated genomic loci.20 The findings prompted researchers to conclude that EGPA consists of 2 distinct syndromes differentiated by ANCA status.20 Although eosinophilia is a hallmark of EGPA, investigators continue to explore how eosinophils contribute to the disease process. One avenue may be through cross-talk with T cells, as T lymphocytes and the Th-2 pathway long have been seen as central to the pathogenesis of EGPA.16 The role of B lymphocytes is not as well understood, but the humoral response also has been implicated in disease development. Significantly elevated immunoglobulin (Ig) E levels are often seen in EGPA, as are sharp increases in IgG4 in active EGPA. Cytokines, including interleukin (IL)-4 and IL-13, have been shown to boost IgG4 production and the humoral immune response overall.13 Research is exploring the role of chemokines and cytokines. Eotaxin-3, also known as CCL26, is one focus of research because it appears to attract eosinophils to sites of inflammation.16 Recent epidemiologic studies have clarified which clinical characteristics are present at the time of EGPA diagnosis. (Table 1 on page 6) One of the largest such studies was conducted by the French Vasculitis Study Group (FVSG).8 The researchers analyzed data on 383 patients who had been diagnosed with EGPA over a 52-year period ending in 2009; 91% of patients had asthma. The mean age at EGPA diagnosis for the full cohort was 50.3 years, and the mean duration of asthma among those affected by the condition was 9.3 years, indicating that the mean age of asthma on set was 40 to 41 years.8 Another study found that, at the time they were diagnosed with vasculitis, 92% of patients with EGPA had dyspnea on exertion, 65% reported a cough, and 25% had sputum production.21
Although EGPA is classified as one of the ANCA-associated vasculitides (AAVs),\(^{14}\) only about 40% of patients with EGPA are ANCA-positive, generally caused by antibodies against myeloperoxidase (MPO-ANCA).\(^{13}\) The FVSG investigators found that ANCA-positive patients were more likely to have ear, nose, and throat (ENT) signs and symptoms, peripheral neuropathy, and kidney involvement, whereas ANCA-negative patients were more likely to have the cardiac manifestations of EGPA. A higher proportion of ANCA-positive patients had relapses during the study’s 5.5-year mean follow-up period (35.2% vs 22.5% of ANCA-negative patients, \(P<.001\)), but univariable analysis found that a lower proportion of ANCA-positive patients died during follow-up (5.6% vs 12.5% for ANCA-negative patients, \(P<.05\)).\(^8\) The study’s authors added, however, that multivariable analysis showed cardiomyopathy—rather than ANCA status or other factors—to be the main poor-prognosis factor across the patient populations studied.\(^8\)

Just over half of patients (51.4%) had peripheral neuroopathy at diagnosis, whereas just under half (48.0%) had ENT symptoms. Skin lesions (39.7%) and lung infiltrates (38.6%) also were common. Allergies were reported by more than one-quarter of the study population, and cardiomyopathy was identified in 16.4% of patients. Fever and weight loss were also common hallmarks of EGPA.\(^8\)

The prognosis for patients with EGPA depends in large measure on organ involvement and age. Those characteristics have been incorporated into the Five Factor Score (FFS), a prognostic tool developed for ANCA-associated vasculitis and polyarteritis nodosa. The latest version of

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Figure 1. Overview of the interacting factors that purportedly lead to the development of eosinophilic granulomatosis with polyangiitis. Both exposure to factors in the environment and an underlying predisposition (genetics) incite eosinophilic inflammation and inflammation that is mediated by ANCA.\(^8\)

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ANCA, antineutrophil cytoplasmic antibody; APC, antigen-presenting cell; BAFF, B-cell activating factor belonging to the TNF (tumor necrosis factor) family; FcR, FC receptor; GM, granulocyte-macrophage; ILC2, group 2 innate lymphoid cell; MPO, myeloperoxidase; NETs, neutrophil extracellular traps formation; ROS, reactive oxygen species.
the FFS was developed in 2009. The factors considered are listed below.\textsuperscript{22}

- Renal insufficiency, as defined by serum creatinine >1.7 mg/dL
- Myocardial involvement
- Severe gastrointestinal involvement
- Age >65 years
- Absence of ENT manifestations

A study of 72 patients with EGPA who did not have poor prognostic factors identified a 100% survival rate at 1 year and 97% overall survival at 5 years.\textsuperscript{23} Even in patients with poor prognostic factors, 8-year overall survival was 92% in a recent 48-patient, prospective, multicenter trial.\textsuperscript{24} A key point to bear in mind: cardiac involvement is the main cause of death for people with EGPA.\textsuperscript{4}

Although recent years have seen considerable progress in diagnosing and treating EGPA, much remains to be determined—and done. The EGPA Consensus Task Force’s 2015 recommendations identified several areas requiring further research, including those listed.\textsuperscript{4}

1. Enhancing early identification of those patients with late-onset asthma who will develop EGPA
2. Identifying reliable biomarkers to distinguish eosinophilic asthma from hypereosinophilia syndrome (HES) and from vasculitis, and asthma flares from vasculitis flares
3. Enhancing maintenance-treatment regimens to prevent relapses while reducing glucocorticoids use/adverse effects
4. Developing alternatives to the use of cyclophosphamide for patients with EGPA who have an FFS $\geq 1$
5. Optimizing treatment regimens for patients with persistent asthma, particularly in terms of the use of various biologic agents
6. Investigating a potential role in EGPA therapy for drugs currently used to treat some forms of HES
7. Determining the appropriate role of ANCA monitoring in EGPA management
8. Formulating optimal strategies for diagnosing and treating EGPA-related cardiac issues

Beyond those “big picture” issues, clinicians must contend with the following challenges.

- Setting an appropriate index of suspicion for EGPA and pursuing a diagnosis in an efficient manner
- Individualizing treatment plans based on ANCA status, organ involvement, and other factors
- Formulating treatment strategies that control the disease and its consequences while limiting the adverse effects of drug therapy
- Monitoring disease progression and treatment response while collaborating effectively with other specialists
- Involving patients in decision making and long-term management to help optimize outcomes.

The pages that follow will examine those topics in detail.

| Table 1. Clinical Characteristics at Time of EGPA Diagnosis From 2 Studies\textsuperscript{8,9} |
|---------------------------------------------------|--------|--------|--------|--------|
| Characteristic                                    | Comarmond Study\textsuperscript{8} | Durel Study\textsuperscript{9} |
|                                                  | ANCA Negative (n=240) | ANCA Positive (n=108) | ANCA Negative (n=57) | ANCA Positive (n=43) |
| Sex                                               |        |        |        |        |
| Male, %                                           | 52     | 56     | 26     | 65     |
| Female, %                                         | 48     | 44     | 74     | 35     |
| Mean age, y                                       | 49.6   | 52.5   | 45.7   | 54.2   |
| History of allergy, %                             | 26.7   | 28.7   | 43.4   | 37.2   |
| History of asthma, %                              | 90.8   | 92.6   | 50.9   | 55.8   |
| Symptoms and manifestations, %                    |        |        |        |        |
| Arthralgias                                       | 26.7   | 34.3   | 61.4   | 76.7   |
| Cardiovascular                                    | 30.4   | 18.5   | 24.6   | 16.3   |
| Cutaneous                                         | 36.3   | 45.4   | 42.1   | 53.5   |
| ENT                                               | 44.2   | 59.3   | 96.5   | 95.4   |
| Fever                                             | 34.6   | 40.7   | 47.4   | 53.4   |
| Gastrointestinal                                  | 23.3   | 22.2   | 25.0   | 25.6   |
| Lung                                              | 91.3   | 92.6   | 61.4   | 44.2   |
| Myalgias                                          | 37.9   | 40.7   | 77.2   | 88.4   |
| Neurologic                                        | 47.5   | 66.7   | 54.4   | 81.4   |
| Ophthalmologic                                    | 5.8    | 8.3    | 19.3   | 23.3   |
| Renal                                             | 16.3   | 26.9   | 16.1   | 37.2   |
| Weight loss                                       | 42.5   | 57.4   | 66.7   | 76.7   |
The classic description of the 3 phases of EGPA can provide the clinician with a useful way to remember the key characteristics of this diagnosis. (Figure 2) Although these phases provide a convenient framework for conceptualizing EGPA, the features associated with each phase often overlap, and a specific patient’s course may not unfold in strict accord with this generalized schema. With that caveat in mind, researchers have found that EGPA tends to arise with a prodromal or allergic phase marked by respiratory issues, including asthma and rhinosinusitis. This phase may last for several years before onset of the eosinophilic phase, which is characterized by blood eosinophilia, eosinophil infiltration of tissues, and organ damage attributable to eosinophils. Finally, the vasculitic phase is characterized by the presence of a systemic necrotizing vasculitis and its consequences in terms of organ dysfunction, morbidity, and mortality.25,26

**Differential Diagnosis and Initial Workup**

The differential diagnosis of EGPA is broad. (Table 2) It can be narrowed considerably, however, through a core set of evaluations, selecting additional assessments based on the patient’s history and clinical findings, and applying the evidence on the natural history of EGPA to diagnose or exclude the condition. A general approach starts with obtaining tests, including a complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, serum Ig level (including IgE and IgG and subclasses), ANCA status, serum B12 level, rheumatoid factor levels, urinalysis, and renal-function screening. Other assessments include *Aspergillus* precipitin test, tryptase levels, stool cultures for parasites, and genetic testing for the *FIP1L1/PDGFRA* fusion genes. Imaging studies, including computed tomography (CT) of the lungs and sinuses (Figure 3 on page 8), with electromyography and other functional studies should also be considered. In patients with severe or fulminant presentations, bronchoscopy with bronchoalveolar lavage and kidney biopsy may be helpful to risk-stratify the patient.16 Troponin levels should be measured, and a screening electrocardiogram should generally be performed, with echocardiogram or cardiac magnetic resonance imaging (MRI) being done when the index of suspicion for cardiac manifestations is high.

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**Table 2. The Differential Diagnosis of EGPA**

The differential diagnosis of EGPA includes other vasculitic and eosinophilic disorders,13 as well as other conditions affecting the organ systems, manifested in the patient’s presenting signs and symptoms.4,13

**Vasculitic Conditions**
- Granulomatosis with polyangiitis
- Microscopic polyangiitis
- Polyarteritis nodosa

**Hypereosinophilic Syndromes**
- Idiopathic hypereosinophilic syndrome
- Myeloid and lymphoid neoplasms with eosinophilia and associated genetic abnormalities
- Chronic eosinophilic leukemia or other myeloid neoplasms with eosinophilia but without clear genetic abnormalities
- Lymphocytic variants of HES
- Familial HES

**Reactive Forms of Eosinophilia**
- Eosinophilic asthma
- Chronic eosinophilic pneumonia
- Eosinophilia associated with
  - HIV, HTLV-1, and other viral infections
  - Toxocariasis and other helminthic infections
  - Medications (eg, antimalarial agents, penicillin)

**Other**
- Allergic bronchopulmonary aspergillosis and other fungal conditions
- Segmental glomerulonephritis
- Acute nephritis
- IgG4-related disease

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**Figure 2. Phases of EGPA Development**

12,16

**Allergic or Prodromal**
- Asthma
- Allergic rhinitis
- Rhinosinusitis

**Eosinophilic**
- Elevated peripheral eosinophil count
- Eosinophilic organ infiltration

**Vasculitis**
- Constitutional symptoms
- Sequelae of necrotizing vasculitis
The EGPA Consensus Task Force recommendations stress the importance of exploring the cause of hypereosinophilia in a patient suspected of having EGPA. This includes consideration of familial hypereosinophilia and consulting databases such as www.pneumotox.com to rule out potential causes of drug-induced eosinophilia.4

**Pulmonary Imaging Findings Indicative of EGPA**

- Transient opacities with bilateral and nonsegmental distribution, mostly in peripheral areas
- Areas of ground-glass opacity, with a bilateral symmetrical distribution, again mainly peripherally
- Bronchial wall thickening
- Small centrilobular and peribronchial nodules
- Bronchial dilatation
- Interlobular septal thickening

![Image](image-reprint.png)

**Figure 3.**
A 50-year-old female with EGPA and allergic asthma, rhinitis, and peripheral neuropathy. Chest radiograph results show hazy areas of increased opacity in the middle and right lower lobes (a, b). Computed tomography images, obtained 10 days after the chest radiographs, show diffuse and irregular bronchial wall thickening (arrows in c) associated with the presence of nodules with endobronchial (arrows in d, arrow in e) and peribronchial (f) distribution. Results from CT imaging of the facial bones (g) show bilateral meatal antrostomy of maxillary sinuses with signs of chronic sinusopathy.

Other steps to consider based on a patient’s history and clinical findings include4:
- Testing for human T-lymphocyte virus-1 (HTLV-1) in patients who have traveled or lived in areas where the retrovirus is endemic.
- Beyond Toxocara serology, determining the need for other serologic testing for parasitic infections based on the patient’s travel history, country of origin, and dietary habits.
- In patients with rash, hives, or other cutaneous manifestations, hypergammaglobulinemia, or recurrent angioedema that follows a cyclic pattern, conducting lymphocyte immunophenotyping and analysis of T-cell rearrangement at a specialized laboratory to look for lymphocytic variant reactive hypereosinophilia, previously called L-HES.

Other recommendations and observations include4:
- When a patient’s presentation is marked by eosinophilia, sinus disease, asthma, pulmonary infiltrates, extra pulmonary evidence of vasculitis, and histologic findings of eosinophilic infiltration, granulomatous inflammation, or vasculitis, the diagnosis of EGPA is secure.
- Normal serum levels of IgE in untreated patients rule out allergic bronchopulmonary aspergillosis.
- Splenomegaly, hepatomegaly, thrombocytopenia, and anemia may be indicative of neoplastic hypereosinophilia, whereas lack of response to glucocorticoids may also suggest neoplastic (or clonal) hypereosinophilia.
- Paraneoplastic eosinophilia is a consideration in patients with lung cancer, cervical cancer, and lymphoma, among other patients.
- Chronic eosinophilic pneumonia can be confused with EGPA because both conditions are marked by chronic sinusitis, peripheral blood hypereosinophilia, and pulmonary infiltrates in their early stages; however, people with this form of pneumonia usually do not experience systemic manifestations of hypereosinophilia.

When EGPA is suspected, performing both biopsy and ANCA testing are encouraged. In patients with asthma and eosinophilia with systemic manifestations, and those with eosinophilia and extrapulmonary disease, biopsies showing vasculitis of the small-sized or medium-sized vessels strongly support a diagnosis of EGPA.4

Antineutrophil cytoplasmic antibody testing may be performed with indirect immunofluorescence or enzyme-linked immunosorbent assay (ELISA). The most common finding in ANCA-positive patients is a perinuclear immunofluorescent pattern (P-ANCA) along with detection of antibodies to myeloperoxidase by ELISA (MPO-ANCA). In the presence of asthma and eosinophilia, these antibodies point toward a diagnosis of EGPA, but it is important to remember that the absence of ANCA does not exclude the diagnosis of EGPA.4
Making the Diagnosis

Although several approaches for identifying EGPA have been put forward, there are no universally accepted diagnostic criteria for this condition.13 Many clinicians look to the American College of Rheumatology’s (ACR) 1990 classification criteria when trying to identify EGPA. The ACR created these criteria for purposes of classification rather than for diagnosis, per se, and emphasize that they should be applied only to patients with histologic evidence of vasculitis.28 When applied to a population known to have systemic vasculitis, the presence of ≥4 of the following 6 criteria has an 85% sensitivity and 99.7% specificity for identifying EGPA.28

- Asthma
- Eosinophilia >10% on differential white blood cell count
- Mononeuropathy or polyneuropathy
- Lung infiltrates
- Paranasal sinus abnormalities
- Extravascular eosinophils on biopsy

More recently, the Groupe d’Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and a task force of the European Respiratory Society have proposed a nomenclature for EGPA that focuses on ANCA-positivity and features of polyangiitis.29 Following diagnosis, guidelines recommend that clinicians look beyond the presenting features of the disease to evaluate the patient for pulmonary, renal, cardiac, gastrointestinal, and peripheral nerve involvement.4

Evaluation and Diagnosis

The Patient Perspective

“...I was ANCA-negative, and because of that, they did not think of Churg-Strauss initially,” IM says of the physicians investigating why, at age 38 years, she was experiencing decompensated heart failure and mononeuritis, among other problems. Eventually, she adds, the various specialists caring for her “came together, and they really worked hard to figure out what was going on” to arrive at a diagnosis of EGPA.

Meet the Patient Providing Perspective on EGPA: CC

CC noticed some hearing loss just days after retiring from an administrative position with an integrated healthcare system, where she had worked for 25 years. She sought care for the issue in June 2016, but the cause of the problem wasn’t clear. In September of that year, she experienced aches and other constitutional symptoms that she thought were influenza, followed by what appeared to be a sinus infection, her first in 55 years of life. Several months of chronic sinusitis, with persistent cough and intermittent flu-like symptoms, followed. The cough was attributed to postnasal drip from the sinusitis, and she attributed her general malaise and weight loss to the persistent infection.

In January 2017, she experienced 3 days of intense back pain that sent her to the emergency department, where a physician diagnosed her with pancreatitis and asthma, and admitted her. Vague numbness and tingling in her fingers and toes progressed quickly to significant neurologic symptoms; her heart rate accelerated, and she was put on oxygen to ease her labored breathing. Following nerve-conduction studies, results from blood work showing eosinophilia, lung CT images showing granulomas, and other assessments, her physicians recognized that she had vasculitis and soon thereafter diagnosed her with ANCA-negative EGPA. Treatment was initiated with IV methylprednisolone and cyclophosphamide and then transitioned to high-dose prednisone.

After 9 days in the hospital and 12 days in a multidisciplinary rehabilitation center, CC came home with walker and wheelchair. She made a rapid recovery in the months that followed, and after 5 additional cycles of cyclophosphamide, transitioned to mycophenolate mofetil while tapering her prednisone dose. Her respiratory and sinus symptoms resolved completely, and she continued to make progress with mononeuritis multiplex. By June 2018, she tapered off glucocorticoids altogether so that today she is taking only an agent for neuropathy and mycophenolate mofetil, which she and her rheumatologist are working together to taper.

She has had no flares since she was declared in remission in June 2017, 1 year after her initial symptoms. However, her hearing loss, tinnitus, and neuropathy have worsened. She also has been diagnosed with early cataracts and osteopenia; whether her prednisone use caused or contributed to those conditions is unclear.

“I carefully track medical appointments, laboratory results, and medication changes, and keep a log of what I do every day,” CC says of her approach to monitoring her health. “For instance, did I wake up with pain in my legs or numbness in my hands? Was I especially tired today? I assume that I will have a disease flare at some point, and I want to be able to identify any patterns.”
The goals of therapy for EGPA include all of the following listed below.4,12,16

- Inducing remission
- Avoiding or reducing relapses
- Preventing organ damage and dysfunction and related morbidity and mortality
- Avoiding or limiting the toxicities of treatment
- Maintaining or enhancing quality of life

Glucocorticoids are the cornerstone of therapy for EGPA, according to the EGPA Consensus Task Force. When patients are facing organ-threatening or life-threatening symptoms, methylprednisolone pulses of 7.5 mg/kg to 15 mg/kg per day are recommended in combination with another immunosuppressant, such as cyclophosphamide.4

The group also endorses use of adjunctive cytotoxic agents in high-risk EGPA patients with an FFS ≥1. Similarly, use of immunosuppressants such as cyclophosphamide should be considered when patients have conditions such as mononeuritis multiplex that, while not included in the FFS, are associated with a poor prognosis.4 Cyclophosphamide can be administered orally or intravenously. The recommended oral dosage for patients facing organ-threatening or life-threatening disease manifestations is 2 mg/kg per day, whereas intravenous pulses would start with infusions of 15 mg/kg or 0.6 g/m² (to a maximum of 1.2 g per infusion) administered every 2 weeks for 3 cycles, followed by pulses of 15 mg/kg or 0.7 g/m² every 3 weeks through cycle 6. Adjusting the cyclophosphamide dose based on renal function is important. Additionally, screening for drug-induced neutropenia should be conducted every 1 to 2 weeks, and semen cryopreservation for men and gonadotropin releasing hormone (GnRH)-analogue treatment for women is recommended due to the gonadal toxicity associated with the agent. Prophylaxis against Pneumocystis jiroveci pneumonia should also be provided.4

For maintenance therapy, one may consider treatment with methotrexate, azathioprine, mycophenolate, rituximab, or anti–IL-5 therapy. Azathioprine 2 mg/kg per day has been shown to be effective for remission maintenance in ANCA-associated vasculitides.30 However, in patients with mild disease, it has been found to be no better than glucocorticoid monotherapy in terms of reducing relapses and improving lung function or reducing glucocorticoid dosing.31 Methotrexate 10 mg/week to 25 mg/week with folic acid replacement of 1 mg/week to 5 mg/week has also been shown to be effective in some studies. Although the optimal duration of maintenance therapy has not been established, a minimum of 18 months to 24 months of treatment following remission should be considered.4

For remission induction in patients with nonsevere disease, the Task Force suggests initiating prednisone at 1 mg/kg per day for 2 to 3 weeks, followed by tapering to 0.3 mg/kg per day after 3 months and by 0.15 mg/kg per day after 6 months until the minimal effective dose is identified or withdrawal of glucocorticoids is possible.4 Maintenance therapy with glucocorticoids alone may be sufficient for some patients, but selecting the optimal dose for ongoing use involves a balancing act between preventing relapses and controlling asthma on the one hand and minimizing the risk or extent of glucocorticoid-induced side effects on the other. The Task Force identifies a maintenance dose of <7.5 mg/day as optimal but notes that roughly 85% of patients will require a mean dose of 12.9 mg/day of prednisone to control their asthma, arthralgias, or other EGPA disease manifestations, highlighting the need for adjunctive immunosuppressants to maintain disease control while tapering glucocorticoids.4 In particular, the use of additional immunosuppressants may warrant consideration in patients who cannot have their prednisone dose reduced to <7.5 mg/day after 3 or 4 months, those who have recurrent disease, and those with peripheral neuropathy. There currently is uncertainty about whether cytotoxic agents should be used in patients requiring ≥7.5 mg/day of prednisone to control asthma or ENT manifestations of EGPA.4

Other recommendations include the following.4

- Intravenously administered immunoglobulin (IVIG) should be considered as a second-line therapy for patients on glucocorticoids and/or other immunosuppressants who continue to have EGPA flares, who are pregnant, or who have drug-induced hypogammaglobulinemia associated with severe or recurring infections.
- Interferon-α therapy should also be considered as a second-line or third-line therapy for selected patients.
- Leukotriene-receptor antagonists can be prescribed for patients with EGPA, when appropriate.

Role of Biologic Therapies

Several ILs have been implicated in the pathogenesis of EGPA.16 These include IL-5, which plays a role in the production and development of eosinophils. Patients with EGPA generally have elevated levels of IL-5.32 The efficacy of biologics directed against IL-5 for the treatment of severe eosinophilic asthma prompted investigators to question whether this therapeutic class could also be efficacious in EGPA.
The phase 3 MIRRA trial compared mepolizumab with placebo in 136 adult patients with relapsing or refractory EGPA. Study subjects had been on a regimen of prednisone or prednisolone (≥7.5 to ≤50.0 mg/day, with or without adjunctive immunosuppressants) for ≥4 weeks. They were randomized 1:1 to 300 mg of mepolizumab every 4 weeks or matching placebo while they continued to receive their standard care of glucocorticoids with or without other immunosuppressive therapy. Patients’ glucocorticoid dose had to remain stable from randomization to study week 4, but investigators then were allowed to reduce the dose. The study had 2 primary endpoints: accrued weeks of remission over 52 weeks and proportion of patients in remission at both week 36 and week 48. Secondary endpoints included average daily glucocorticoid use and time to first relapse. Safety and annualized relapse rate also were evaluated.

At the end of the study period, 28% of patients receiving mepolizumab had ≥24 weeks of accrued remission vs 3% of those receiving placebo (odds ratio [OR] 5.91; 95% confidence interval [CI] 2.68 to 13.03; P<.001). (Figure 4) Further, 32% of mepolizumab-treated patients were in remission at week 36 and week 48, vs 3% of patients receiving placebo (OR, 16.74; 95% CI, 3.61 to 77.56; P<.001). Just under half of patients in the mepolizumab group (47%) did not achieve remission, compared with 81% of patients receiving placebo.

Forty-four percent of patients in the mepolizumab group and 7% in the placebo group were able to taper to an average daily prednisone or prednisolone dose of ≤4.0 mg during the last 4 weeks of the study (OR, 0.20; 95% CI, 0.09 to 0.41; P<.001) Eighteen percent of patients in the mepolizumab group were able to stop their prednisone or prednisolone altogether, whereas 3% of placebo group were able to discontinue their glucocorticoid.

The annualized relapse rate was 1.14 for patients receiving mepolizumab vs 2.27 among patient receiving placebo. The incidence and nature of adverse events in patients receiving mepolizumab were similar to those seen with the use of the monoclonal antibody for severe eosinophilic asthma (Table 3 on page 12).

In another trial, in terms of response, as many as 87% of subjects benefited from mepolizumab therapy with regard to achieving remission or 50% glucocorticoid reduction or being relapse free over the course of a year. The US Food and Drug Administration (FDA) cited the MIRRA trial’s findings in its December 2017 decision to expand the approved uses of mepolizumab to include treatment of adults with EGPA. That indication made mepolizumab the first agent approved specifically for treatment of EGPA. Now, however, a second anti–IL-5 monoclonal antibody approved for use in severe eosinophilic asthma is in late stages of investigation for use in EGPA.

The phase 3 MANDARA trial is assessing the efficacy and safety of benralizumab relative to mepolizumab in 140 patients with relapsing or refractory EGPA who are on glucocorticoids with or without stable immunosuppressive therapy. The primary endpoint of the 52-week trial is the proportion of patients in remission at both week 36 and week 48. Secondary outcome measures include patients in remission; average daily prednisone/prednisolone use during weeks 48 to 52; annualized relapse rate; and change from baseline in Birmingham Vasculitis Activity Score (BVAS), Vasculitis Damage Index (VDI), and pulmonary function, as well as safety measures. The study began in October 2019 and has an estimated completion date of August 2023.

Researchers also are examining whether rituximab, an anti-CD20 agent that causes significant B-cell depletion, may also have a role to play in EGPA. Rituximab has been approved by the FDA for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis.
but, at the time of this publication, is not FDA-approved for EGPA.\textsuperscript{37} The EGPA Consensus Task Force notes that "rituximab can be considered for selected ANCA-positive patients with renal involvement or refractory disease."\textsuperscript{34} Other investigators are exploring whether the anti-IL-5 agent reslizumab, a monoclonal antibody approved for the treatment of severe eosinophilic asthma, is efficacious against EGPA.\textsuperscript{38}

### Ongoing Management

The EGPA Consensus Task Force offered several recommendations and observations on the long-term management of patients with EGPA.\textsuperscript{4}

- There currently is no reliable biomarker for measuring EGPA activity, although total eosinophil count, ESR, and CRP may be informative.
- Remission can be defined as "the absence of a clinical systemic manifestation" of EGPA, excluding asthma and/or ENT symptoms. Asthma flares and nonspecific ENT manifestations of disease should be excluded from consideration when assessing whether a patient has achieved remission, most panel members held.
- Relapse can be defined as "the new appearance or recurrence or worsening of clinical EGPA manifestations requiring the addition, change, or dose increase of glucocorticoids and/or other immunosuppressants," with asthma and ENT symptoms again excluded.
- There is not consensus on a total eosinophil count that can serve as a threshold for defining remission.
- An increased eosinophil count does not necessarily represent a flare but does warrant intervention and close monitoring.
- Live-attenuated vaccines should not be employed in patients on immunosuppressant therapies or those taking ≥20 mg/d of prednisone.
- People with EGPA should receive inactivated vaccines against influenza and pneumococcal pneumonia.

### Treatment and Ongoing Management

**The Patient Perspective**

- “One thing that can be really helpful” throughout the course of managing EGPA, says IM, “is for the provider to make an effort to explain what each lab test is and what it means. The patient typically doesn’t know what it is, and a brief written explanation of what each lab is, perhaps on a patient portal, would be good.”
- Although she declined to take 2 medications that her physicians had recommended due to a desire to employ holistic nonpharmacologic approaches to the greatest extent possible, JS says, “I’m still open to the drugs, if needed. I told my doctors that if I get sick again, I will consider them. Prednisone saved my life.”
- “I actually got all the way off prednisone. I’m in that minority of patients able to do that, and all my respiratory issues went away, which is really unusual,” says CC.

### Table 3. Mepolizumab vs Placebo in Relapsing or Refractory EGPA: Adverse Events\textsuperscript{33}

<table>
<thead>
<tr>
<th>Event</th>
<th>Mepolizumab (n=68)</th>
<th>Placebo (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>66 (97)</td>
<td>64 (94)</td>
</tr>
<tr>
<td>Considered by investigator to be related to trial agent</td>
<td>35 (51)</td>
<td>24 (35)</td>
</tr>
<tr>
<td>Leading to trial-agent discontinuation or trial withdrawal</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1)*</td>
<td>0</td>
</tr>
<tr>
<td><strong>Serious adverse event, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>12 (18)</td>
<td>18 (26)</td>
</tr>
<tr>
<td>Considered by investigator to be related to trial agent</td>
<td>3 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td><strong>Systemic or local-site reaction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic reaction</td>
<td>4 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Local-site reaction</td>
<td>10 (15)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Anaphylaxis considered by investigator to be related to trial agent</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiovascular adverse event, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Myocardial infarction or unstable angina</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

\*The death resulted from cardiac arrest, which the physician did not consider to be related to the trial regimen.

Effective Multidisciplinary Care

The complexity and multiple-organ manifestations of EGPA make collaborative care essential. Five steps can facilitate that process.

1. Draw on vasculitis centers of excellence to the greatest extent possible. Ideally, this would entail having the center’s physicians manage the patient’s EGPA, while keeping the referring physician informed of their assessments and therapeutic approaches. In other instances, it may mean a consultation to confirm the diagnosis or obtain input on changes to a treatment plan. (The Vasculitis Foundation provides a list of centers. See page 14.)

2. When symptoms extend beyond your area of expertise, have other specialists confirm the diagnosis. A pulmonologist may feel comfortable diagnosing EGPA in a patient whose symptoms are predominantly or exclusively respiratory in nature, but consulting a nephrologist when renal values are out of the normal range can be critical in confirming EGPA or identifying other possibilities.

3. Assemble your care team based on your post-diagnosis assessment of organ system involvement. As noted earlier, guidelines recommend that newly diagnosed patients be evaluated for pulmonary, renal, cardiac, gastrointestinal, and peripheral nerve involvement.

4. Establish a reliable platform for communicating, and a few ground rules for collaborating. Understanding whether you and other specialists use the same electronic medical record (EMR) system is an important first step in this regard. Perhaps the most important “rule” for collaboration is considering the potential impact on conditions within another specialist’s area of expertise when contemplating medication changes and consulting that specialist before proceeding.

5. Keep the PCP in the mix. The PCP is likely to have important insights into the patient’s overall condition, as well as valuable perspective on comorbidities and other factors that need to be considered.

Meet the Patient Providing Perspective on EGPA: JS

JS was leading a very active life at age 73 years, taking 4-mile hikes, swimming, practicing yoga, painting, and enjoying the company of family and friends. In late 2017, she began to feel a bit wobbly in some yoga poses. “I actually fell a couple of times, and I just never fall,” she says. She also began noticing pain in the center of her chest and weakness in her legs, as well as frequent belching. Other than well-controlled asthma that had been diagnosed 30 years earlier, JS had always enjoyed good health up to that point.

The chest pain—now accompanied by fatigue—eventually brought her to the hospital. Her blood work results showed elevated troponin levels, but the results of an angiogram were negative. Discharged after an overnight stay, JS continued to experience chest pain and soon began having daily episodes of visual distortions—seeing strange colors and prisms of light—that lasted for 15 or 20 minutes. Her eye doctor attributed the symptoms to stress. They subsequently were recognized as manifestations of ocular migraines.

By January 2018, she was quite ill, and results from a new round of bloodwork revealed an elevated overall white blood cell count and significantly elevated eosinophil count, triggering further assessments. The results of bone marrow biopsies ruled out leukemia, but imaging results revealed eosinophilic infiltration in her heart and lungs.

JS’s health was declining precipitously. “I thought I was dying. I could sense my body shutting down,” she recalls. A course of prednisone helped and was augmented at discharge with a methotrexate regimen that she discontinued a few months ago. She also has had intravenously administered Ig treatments, but has declined some other proposed medications in favor of following a comprehensive holistic approach that encompasses a plant-based diet, avoiding sugar, taking vitamin and nutrient supplements, acupuncture, and exercise. “I’m not where I was, but I’m doing much better,” says JS.
Expert panels issuing recommendations on EGPA management endorse patient education and engaging patients in shared decision making, or SDM, which has been described as “a model of patient-centered care that enables and encourages people to play a role in the medical decisions that affect their health.” The Agency for Healthcare Research and Quality (AHRQ) recommends a 5-step approach for implementing shared decision making.

1. Seek your patient’s participation
2. Help your patient explore and compare treatment options
3. Assess your patient’s values and preferences
4. Reach a decision with your patient
5. Evaluate your patient’s decision

Studies have shown that SDM improves adherence to drug therapy in a number of chronic conditions, including asthma, Crohn disease, rheumatoid arthritis, and psoriatic arthritis.

The management of EGPA presents several opportunities for SDM.

- The pace and extent of glucocorticoid-tapering strategies
- Introduction of adjunctive therapies, including biologic agents
- Management of EGPA among patients trying to conceive, during pregnancy, and while breastfeeding
- The need to involve other specialists in the patient’s care, as well as decisions regarding imaging studies, biopsy, and surveillance regimens
- The quality-of-life considerations most important to patients

Of course, the better informed patients are about their condition, the better equipped they are to participate in SDM. Clinicians can draw upon several resources to help educate patients about EGPA.

- American Partnership for Eosinophilic Disorders
  https://apfed.org/
- Vasculitis Foundation
  https://www.vasculitisfoundation.org/
- National Organization for Rare Disorders
  https://rarediseases.org/rare-diseases/churg-strauss-syndrome/
- National Institute of Health

Shared Decision Making

The Patient Perspective

- “It’s really important for patients to be active partners in their care,” says CC. “Because of the variable nature of EGPA manifestations, and the fact that laboratory testing is a data point but not typically conclusive, it’s important for patients to communicate symptom changes to their physicians. I used to discount symptoms and not assume they had any relationship to one another. Now if I have a fever, or a rash, or whatever, I monitor it more carefully and usually report it to one of my physicians. Also, because there is so little evidence for treatment decisions in such a rare disease, I really appreciate that my rheumatologist collaborates with me on medication choices and dosage changes.”

- While it’s incumbent on physicians to involve patients in decisions about their care, IM notes that it’s also important for patients to “do your research. You have to put the time in, even though it’s tough and you don’t feel good. Don’t give up.”

- “I talk with my PCP and rheumatologist all the time online,” notes JS, adding that when she expressed a desire to discontinue her prednisone, she and her rheumatologist worked out a strategy for slowly tapering the dose.

A Resource to Facilitate Patient-Clinician Discussions on EGPA Management

Physicians seeking to engage their patients with EGPA in SDM and to enhance communication overall can access the Unraveling EGPA: Clinician-Patient Discussion Reference Guide at https://tinyurl.com/Unraveling-EGPA. Produced in conjunction with this publication, the reference guide will help shape clinician-patient discussions, focusing patients on key considerations in their care and directing them toward reliable sources of information on EGPA.

New Vasculitis Guideline Coming From the American College of Rheumatology

The American College of Rheumatology is scheduled to release its first-ever vasculitis guideline in 2020. Developed in partnership with the Vasculitis Foundation, the guideline will address EGPA and 2 other ANCA-associated vasculitides, granulomatosis with polyangiitis, and microscopic polyangiitis, as well as other forms of vasculitis.
IM was accustomed to running or walking up to 10 miles 3 or 4 times a week. Given that level of activity, she was somewhat surprised in 2013 when she started having a dry cough after her runs and was diagnosed with exercise-induced asthma. The months ahead were quite full, however, as she married and then conceived. Her pregnancy was complicated by her respiratory issues, and at the 37th week of pregnancy, she developed severe preeclampsia accompanied by hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome. Her postpartum recovery following cesarean delivery was protracted and was made more difficult by the demands of caring for and nursing a newborn and by returning to her full-time position as a diettian.

The lack of sleep inherent in tending to a baby was exacerbated by severe back pain of uncertain origin. Then, in August 2014, she awakened with numbness in her left foot and a shooting pain up her left side. A physician in a hospital emergency department prescribed a narcotic and sent her back to the hospital. She was transferred to an academic medical center’s cardiology unit, where she was diagnosed with decompensated heart failure and admitted to the coronary care unit. With high eosinophil and troponin levels, she was transferred to an academic medical center’s cardiology unit, where she spent the next 2 weeks. “They were even talking about a heart transplant,” she recalls.

Results from a cardiac biopsy found eosinophilic infiltrates, whereas the results of a cardiac catheterization—her second—were normal. After being stabilized on intravenous prednisone and cardiac medications, she was discharged home but could not work for another 3 months. In the intervening months, IM saw several specialists at different institutions, but, because she was ANCA-negative, most did not entertain the possibility of EGPA. A bone marrow biopsy results of a cardiac catheterization—her second—were normal. After being stabilized on intravenous prednisone and cardiac medications, she was discharged home but could not work for another 3 months. In the intervening months, IM saw several specialists at different institutions, but, because she was ANCA-negative, most did not entertain the possibility of EGPA. A bone marrow biopsy ruled out other conditions, whereas several assays ordered by her neurologist and rheumatologist yielded inconclusive results. Other imaging studies, biopsies, and lab work followed, as did an August 2015 hospitalization for an asthma exacerbation that led to the diagnosis of EGPA. The period prior to receiving that diagnosis was marked by grave illness and frequent trips to specialists and the hospital, she adds, noting, “My hematologist saved my life three times.”

After having been treated with prednisone, azathioprine, mycophenolate mofetil, and other agents, IM learned about the phase 3 trial of mepolizumab from her participation in a Facebook EGPA support group. After talking with her rheumatologist about the trial, she started mepolizumab in 2016 and has taken the biologic since. Initially, the agent enabled her to discontinue mycophenolate mofetil and greatly reduce her prednisone, but after results from a photon emission tomographic and CT scans showed active disease in her left ventricle, she is now taking all 3 agents again.

“I’m doing really well now,” says IM, noting that she is running again; although her physicians are concerned about the risks, they also know it is important for her quality of life and stress management.

In Summary

EGPA is an uncommon, systemic autoimmune disease characterized by asthma, hypereosinophilia, and the presence of a vasculitis affecting the small-caliber and medium-caliber blood vessels. The condition is associated with considerable morbidity and can be organ-damaging and even life-threatening. The challenges of managing EGPA begin with setting an appropriate index of suspicion for its presence and then pursuing the diagnosis in a comprehensive fashion.

Glucocorticoids long have been the cornerstone of EGPA management and, in some cases, are the only agents needed to induce remission and prevent relapse. However, both the adverse effects of long-term glucocorticoid therapy and the significant proportion of patients who do not attain or maintain adequate disease control with glucocorticoids alone often necessitate the use of other agents. Therapeutic options include cyclophosphamide, azathioprine, methotrexate, and other treatments. More recently, FDA approval of mepolizumab, an anti-IL-5 monoclonal antibody, provides clinicians with another treatment option for patients with refractory or relapsed EGPA. Some clinicians also use rituximab, an anti-CD20 monoclonal antibody approved for use in several cancers and in other vasculitides, but not yet for EGPA. Other biologics that target ILs, including benralizumab and reslizumab, are also being investigated for a potential role in EGPA.

Patients with EGPA require comprehensive, multidisciplinary care, ideally provided at or in collaboration with a vasculitis center of excellence. Involving patients in care decisions to the greatest extent possible is essential not only in respecting patients and their autonomy, but also in promoting adherence to treatment regimens and pursuing the best outcomes possible.