Overview
Welcome to this overview of eosinophilic granulomatosis with polyangiitis with Michael Wechsler, MD. In this activity, Dr. Wechsler reviews the pathogenesis, diagnosis, prognosis, and treatment of EGPA. This presentation will help you recognize EGPA and differentiate it from other diagnoses and other small-vessel vasculitides, and develop treatment plans based on the patient's prognosis and response to first-line treatments.

Target Audience
This activity was developed for allergist/immunologists, rheumatologists, pulmonologists, hematologists, dermatologists, cardiologists, EENT specialists and other clinicians involved in the care of patients with EGPA.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Discuss the clinical signs and symptoms that support a diagnosis of EGPA
- Describe the clinical progression of EGPA
- Classify patients' risk based on disease activity and the presence of ANCA
- Select an appropriate therapy for EGPA based on patient's disease activity and characteristics

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GlaxoSmithKline – clinical area: Asthma/EGPA
Regeneron – clinical area: Asthma
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The estimated time to complete the activity is 1.0 hour.

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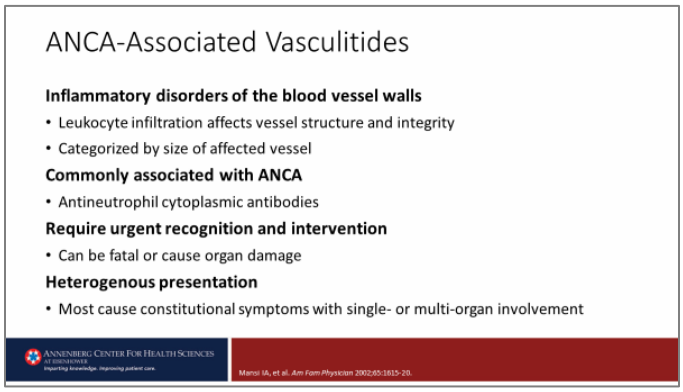
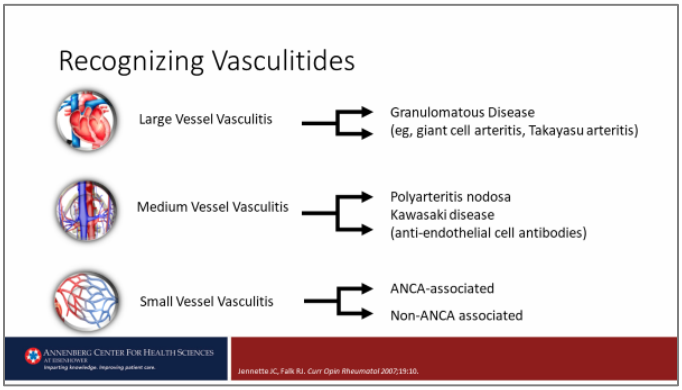
Michael Wechsler, MD: Welcome to this CME program entitled, Eosinophilic in Patients with Asthma: A Sign of Eosinophilic Granulomatosis with Polyangiitis. This program was produced by the Annenberg Center for Health Sciences and this activity is supported by an educational grant from GlaxoSmithKline.

Our goals are to discuss the clinical signs and symptoms that support a diagnosis of EGPA, to describe the clinical progression of EGPA, to classify patients' risk based on disease activity and the presence of antineutrophil cytoplasmic antibodies or ANCA, and to show how to select an appropriate therapy for EGPA based on the patient's disease activity and characteristics.

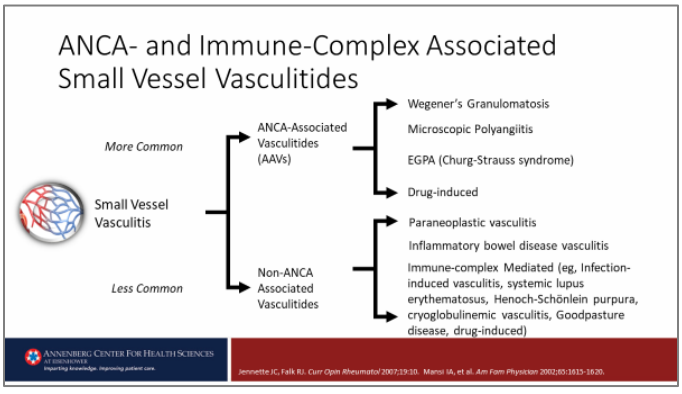


EGPA or Eosinophilic Granulomatosis with Polyangiitis, is an ANCA associated vasculitis. ANCA associated vasculitides are inflammatory disorders of the blood vessel walls and they result from leukocyte or white blood cell infiltration that affects blood vessels' structure and integrity. They're often categorized by the size of the effected blood vessel. Small vessel vasculitides, medium vessel vasculitides, or large vessel vasculitides. There's several entities that are commonly associated with these antineutrophil cytoplasmic antibodies and it's important to recognize, so that one could urgently intervene if needed. Because oftentimes, these vasculitides can be fatal or cause significant organ damage.

One of the challenges with making a diagnosis of ANCA associated vasculitides is that they often have a heterogeneous presentation. They can cause constitutional symptoms and they can have either single or multiorgan involvement. And that's part of the challenge is identifying patients who present with this variegated heterogeneous presentation of a systemic disease with potentially localized manifestations.

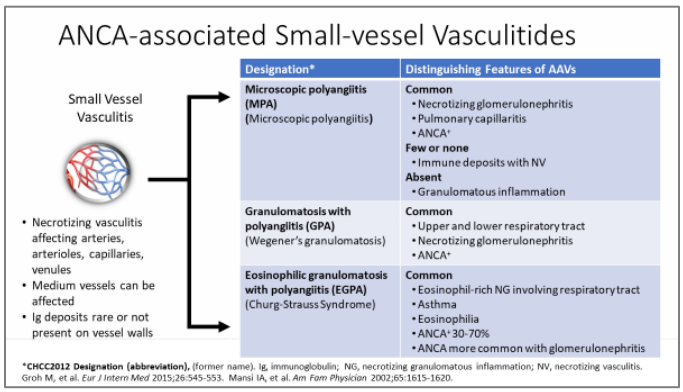


In terms of recognizing vasculitides, we already mentioned that vasculitides can be broken down based on the size of the blood vessels. In terms of large vessel vasculitides, they can often present as granulomatosis disease, such as may occur in giant cell arteritis or Takayasu's arteritis. Medium vessel vasculitides include polyarteritis nodosa, Kawasaki disease, and can have presentation with anti-endothelial cell antibodies. In terms of small vessel vasculitides, one can think of ANCA associated and non-ANCA associated vasculitides.



In terms of the ANCA associate vasculitides, which are more common, one might see Wegener's granulomatosis, which is also known as granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. It used to be called Churg-Strauss syndrome. There are also drug induced vasculitides that are associated with ANCA.

In terms of the small vessel non-ANCA associated vasculitides, which are generally less common, these may occur in association with paraneoplastic syndromes and results in paraneoplastic vasculitis. There can be inflammatory bowel disease associated vasculitis, immune complex mediated vasculitis that may include infection-induced vasculitis, systemic lupus erythematosus, Henoch-Schoenlein purpura, cryoglobulinemia vasculitis, Goodpasture disease, and drug induced vasculitis.

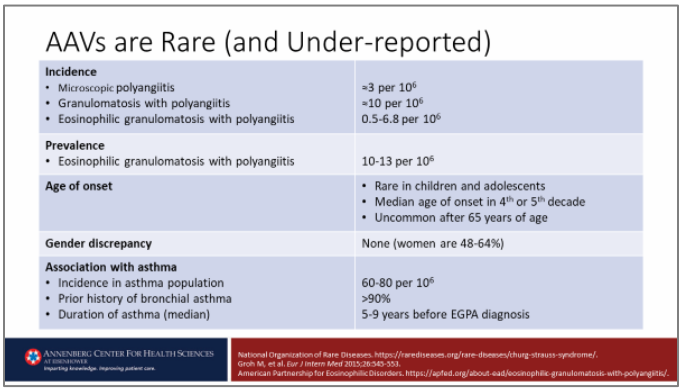


In terms of ANCA-associated small-vessel vasculitides, there are 3 key entities that need to be recognized. These include microscopic polyangiitis, granulomatosis with polyangiitis, that used to be known as Wegener's granulomatosis, and eosinophilic granulomatosis with polyangiitis, that used to be known as Churg-Strauss syndrome. All 3 of these entities affect small vessels, and they're associated with necrotizing vasculitis that affects the arteries, the arterials, the capillaries, and the venules. However, these entities can also affect medium sized blood vessels as well.

Immunoglobulin deposits are rare, or they're not present on blood vessel walls, and so they can be distinguished from other entities. So how do we distinguish these 3 entities? Well, microscopic polyangiitis is generally associated with necrotizing glomerulonephritis, and can be associated with pulmonary capillaritis. It has antineutrophil cytoplasmic antibodies in almost all cases, and most of the time it's p-ANCA or myeloperoxidase antibody positive. Few patients may have immune deposits with necrotizing vasculitis, but granulomatosis inflammation is essentially absent from all of these kinds of patients.

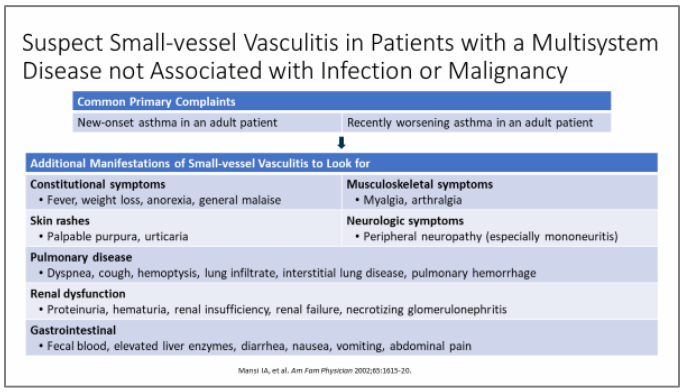
In contrast to MPA, granulomatosis with polyangiitis, it's a bit more common in terms of its presentation with both upper and lower respiratory tract symptoms, as well as necrotizing glomerulonephritis. In contrast to microscopic polyangiitis, the antineutrophil cytoplasmic antibody profile in GPA is generally associated c-ANCA or PR3 antibodies.

Eosinophilic granulomatosis with polyangiitis is a completely distinct entity from the other 2. It's associated with eosinophilia, and almost all patients have asthma. Fewer patients are ANCA-positive. Only somewhere between 30% to 70% of patients are ANCA-positive, and they generally have a p-ANCA or myeloperoxidase profile. ANCA is more common in these patients who have glomerulonephritis. So this are helpful ways to distinguish between these 3 entities in the context of vasculitis.



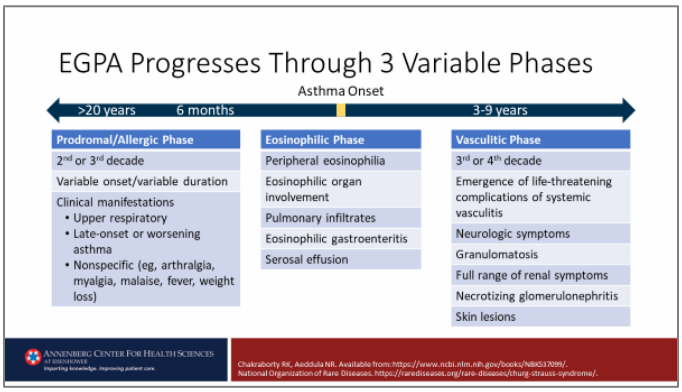
Now, ANCA-associated vasculitides are somewhat rare. Microscopic polyangiitis has a incidence of 3 per million, granulomatosis with polyangiitis has an incidence of 10 per million, and eosinophilic granulomatosis with polyangiitis has an incidence somewhere in between, generally around 5 to 6 cases per million. The prevalence of eosinophilic granulomatosis with polyangiitis is a little bit higher, and that includes all the people who come into this entity with new disease. And it generally reflects around 10 to 13 cases per million population.

In general, this is a disease of adulthood. The median age of onset is in the fourth or fifth decade. It's relatively rare in children and adolescents, but it can occur. And it's also uncommon after age of 65, but it can occur in that age group as well. There's really no gender discrepancy in these patients. It will affect males almost as frequently as females, with a general range in female prevalence of 48% to 64%. In terms of the association with asthma, the incidence in the asthma population of EGPA is 60 to 80 cases per million. And over 90% of patients with EGPA have a prior history of bronchial asthma. And the duration of asthma is generally 5 to 9 years before an EGPA diagnosis.



One should consider a diagnosis of small-vessel vasculitis in patients who present with multisystem disease that's not associated with infection or malignancy. So, when a patient presents with new-onset asthma in an adult patient, or if there's recently worsening asthma in an adult patient, one should start asking and do a detailed history to identify whether or not there are other signs and symptoms of vasculitis. These may include asking about constitutional symptoms. Does the patient have fever, weight loss, anorexia, or malaise? Does the patient have musculoskeletal symptoms, including myalgias and arthralgias? Has the patient had a skin rash with palpable purpura or urticaria? Has the patient presented with neurologic symptoms, such as peripheral neuropathy, or especially mononeuritis multiplex.

It's also important to ask about pulmonary disease manifestations. Does the patient have shortness of breath, cough, hemoptysis, pulmonary infiltrates? Is there evidence of interstitial lung disease or pulmonary hemorrhage? Or does the patient have renal dysfunction? Do they have proteinuria, hematuria, renal insufficiency, or renal failure, or necrotizing glomerulonephritis? Lastly, does the patient have gastrointestinal manifestations? Do they have blood in their stool, elevated liver enzymes, nausea, vomiting, diarrhea, or abdominal pain? These are all important symptoms and signs to ask patients about. In the context of evaluating patients' new asthma, adult-onset asthma, or any of these symptoms, you want to ask a broad range of questions to try and identify whether or not a patient has small-vessel vasculitis.

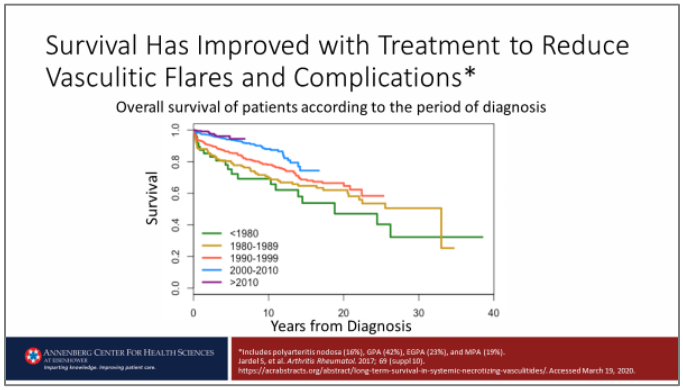


Now, in terms of EGPA, eosinophilic granulomatosis with polyangiitis, there are generally 3 phases that may occur variably in all patients. There's a prodromal or allergic phase that generally starts off in the second or third decade of life, and has variable onset with variable duration, with clinical manifestations including upper respiratory symptoms, late onset or worsening asthma, and then some nonspecific symptoms of arthralgias, myalgias, malaise, fever, and weight loss.

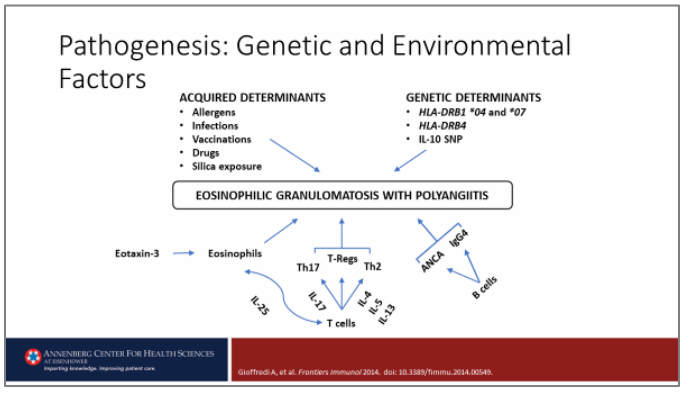
Later on, usually months later, a patient will enter the eosinophilic phase. They may have evidence of peripheral blood eosinophilia, eosinophilic organ involvement. And that may manifest in terms of pulmonary infiltrates, eosinophilic gastroenteritis, and serosal effusions.

In the vasculitic phase, which can often occur years later, and generally in the third or fourth decade of life, there can be emergence of potentially life-threatening complications of systemic vasculitis. And these may

include neurologic symptoms, if the vasculitis affects the nerves, granulomatosis, a full range of renal symptoms, including necrotizing glomerulonephritis, skin lesions, and involvement of other organ systems in the GI tract, in the heart, or in the central nervous system.



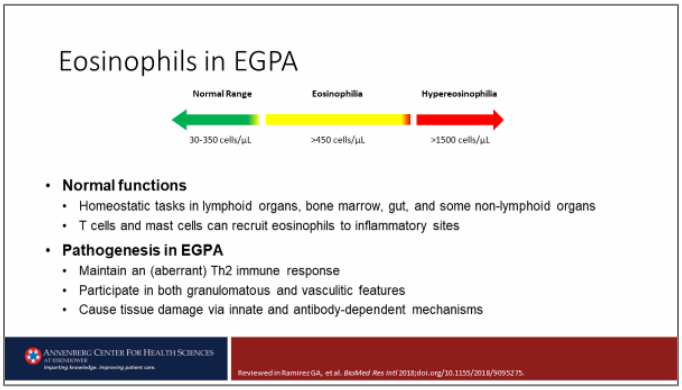
Now, survival of EGPA has improved with treatment as we've been able to demonstrate that we can reduce vasculitic flares and complications. Overall survival of patients has changed over time, and what we've seen is that over the last couple of decades we've significantly improved outcomes in these patients. From before the 1980s to the last decade, 2010 to 2020, survival has improved dramatically, and we've been able to significantly reduce vasculitic flares and complications.



The pathophysiology of vasculitides and of EGPA in specific is generally very complex, and there are environmental as well as genetic determinants that can help identify what is going on and what are the processes involved in the pathophysiology of this complex syndrome. In terms of environmental factors, allergens, infections, vaccines, drugs, and silica exposure have all been implicated, on top of an underlying genetic profile that often includes mutations in the HLA-DRB1 gene HLA-DRB4 gene, and in the IL10 gene. In general, these result in the manifestations of eosinophilic granulomatosis with polyangiitis and associated with that are the underlying pathophysiological findings that may include eosinophilia in a variety of different organs.

How does eosinophilia emerge? Well, eosinophils are produced from the bone marrow and stimulated to release into circulation through eotaxin-3. This is generally stimulated from different cytokines, including TSLP, IL4, IL5, IL13, IL25, amongst others. And there is a complex interaction between T regulatory cells in type 2 as well as non-type 2 pathways.

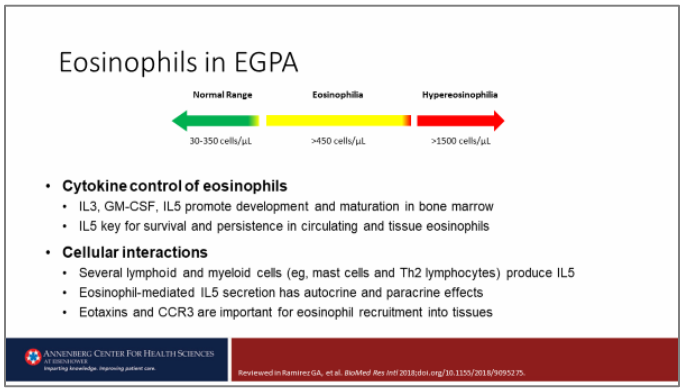
In addition, EGPA is unique in that it's characterized by not only the eosinophilic component of the pathophysiology, but also in terms of the ANCA association and the presence of blood vessels. B cells that are stimulated by interleukin 4, interleukin 13, and Th2 cells will produce antibodies, including antineutrophil cytoplasmic antibodies, and IgG4, all of which can cause some of the complicated pathophysiology that is occurring in these patients.



In terms of understanding eosinophilia and EGPA, it's important to recognize when is it considered to be normal? In general, we think that eosinophils that are less than 300 to 400 are in the normal range. Eosinophils that are about 400 to 500 are considered to be moderate eosinophilia. And then eosinophils that are greater than 1,500 are considered to be associated with high levels of hypereosinophilia.

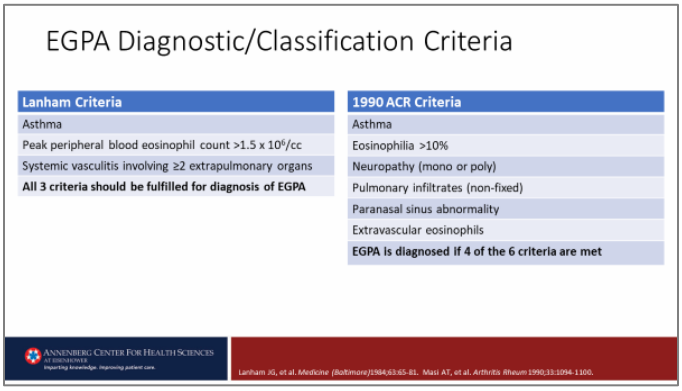
Now, eosinophils play a role in terms of homeostasis. They're involved in homeostatic tasks in lymphoid organs, the bone marrow, the gut, as well as some lymphoid organs, and T cells and mast cells can recruit eosinophils to inflammatory sites.

In terms of the pathogenesis in EGPA, it's important to recognize that eosinophils may result from an aberrant Th2 immune response, and that eosinophils can participate in both granulomatosis, as well as vasculitic features of the disease, and they cause damage by innate and antibody- dependent mechanisms. Eosinophils can release different mediators, including eosinophilic cationic protein, eosinophil-derived neurotoxin, and major basic protein that can all cause tissue damage.



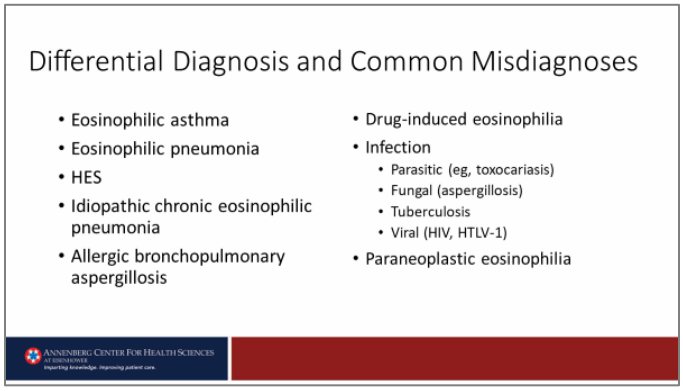
What is controlling the eosinophils are different cytokines. As we mentioned, IL3, GMCSF, and IL5 promote the development and maturation of eosinophils in the bone marrow. Interleukin 5 is key for survival and persistence in circulating and tissue eosinophils. And other cytokines, including interleukin 4 and interleukin 13 play a role along with IL5 in terms of eosinophil trafficking into the tissue.

In addition to the complexities of cytokines that are associated with eosinophilic tissue infiltration, there are a lot of other cellular interactions. Several lymphoid and myeloid cells can produce IL5, eosinophil-mediated IL5 secretion has autocrine and paracrine effects, and eotaxins and chemokines like chemokine CCR3 are important for eosinophil recruitment into tissues.

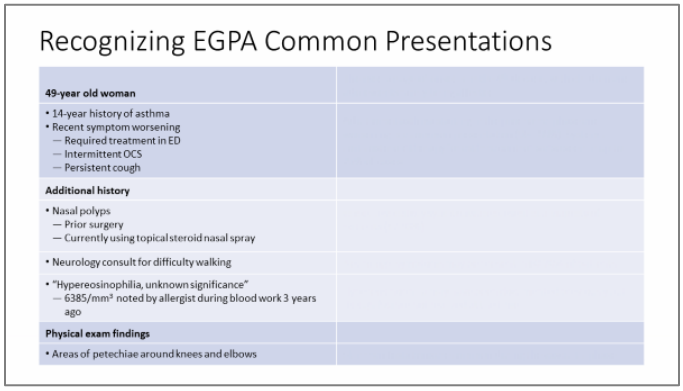


We've talked about eosinophils. We've talked about vasculitides. Now let's talk a little bit about EGPA. What is EGPA, eosinophilic granulomatosis with polyangiitis? Well, when this entity was first described on an autopsy series back in the 1950s by Jacob Churg and Lotte Strauss, it was defined based on pathologic criteria. It was actually described at the time as allergic angiitis with granulomatosis. When Churg and Strauss identified patients on an autopsy series who had features of asthma, eosinophilia, and granuloma, as well as what they called embarrassment of different blood vessels in different organs.

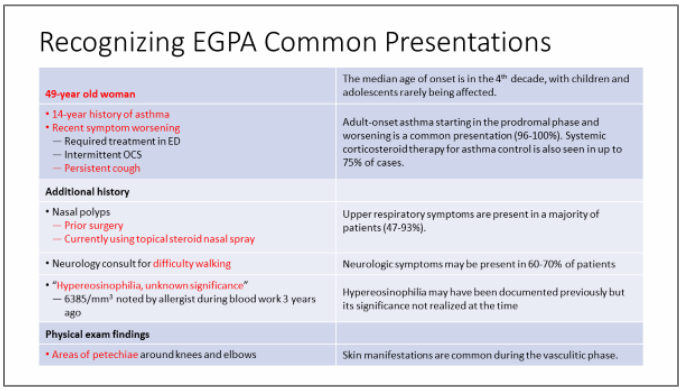
In the 1980s, the Lanham criteria were developed, and this was more of a clinical diagnosis. EGPA was defined as patients who had asthma, eosinophilia, systemic of vasculitis involving 2 or more extra pulmonary organs. And one needed to have all 3 criteria to fulfill a diagnosis of EGPA. In 1990, the American College of Rheumatology said that we need to be able to distinguish EGPA from other entities. And they said, "Well, if you have vasculitis and you meet 4 of the following 6 criteria, then we can confidently say that you have EGPA." Those criteria included asthma, eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extra vascular eosinophils, or eosinophilic vasculitis. And a diagnosis of EGPA was attained if one had 4 of the 6 criteria met. These were meant to be classification criteria in the context of vasculitis. They weren't necessarily meant as diagnostic criteria.



So what else can complicate the diagnosis of patients with EGPA? What's the differential diagnosis and what are some common misdiagnoses? Well, certainly patients with EGPA present with asthma and eosinophilia. So eosinophilic asthma can be a differential. Patients with eosinophilic pneumonia present with asthma, eosinophilia, and pulmonary infiltrates, as well as sometimes sinus disease. And those are all part of the diagnosis of EGPA. Hypereosinophilic syndrome can present with eosinophilic tissue infiltration variety of organs, idiopathic chronic eosinophilic pneumonia presents with pulmonary infiltrates in eosinophilia, allergic bronchopulmonary aspergillosis presents with pulmonary infiltrates, eosinophilia and is often IgE-mediated with antibodies towards aspergillus. That can be drug-induced eosinophilia, infection associated eosinophilia with lung manifestations that include parasitic disease, fungal disease, TB, and viral infections. And then there can be paraneoplastic eosinophilia.



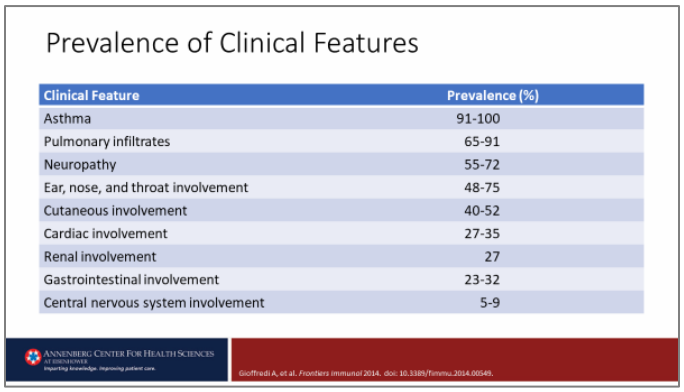
It's important to take a good history and to do a thorough evaluation of our patients to figure out what is going on in them. In order to help us recognize some common presentations, let's review a case of a 49-year-old woman who presented with EGPA. She had a 14-year history of asthma and she had recent symptom worsening requiring treatment in the emergency room, intermittent oral corticosteroids, and she had persistent cough. On top of that, she also had nasal polyps and she had prior surgery for them. She was currently using topical steroid nasal spray. She began to have difficulty walking and she ended up seeing a neurologist for that. And she was found on blood work to have hypereosinophilia. 6,385 was her eosinophil count. If you recall, we mentioned the hypereosinophilia is any eosinophil count above 1500. So she had very high eosinophils and this was noted by her allergist during blood work over the prior 3 years. On physical exam, she had areas of petechiae around her knees and elbows on top of that.



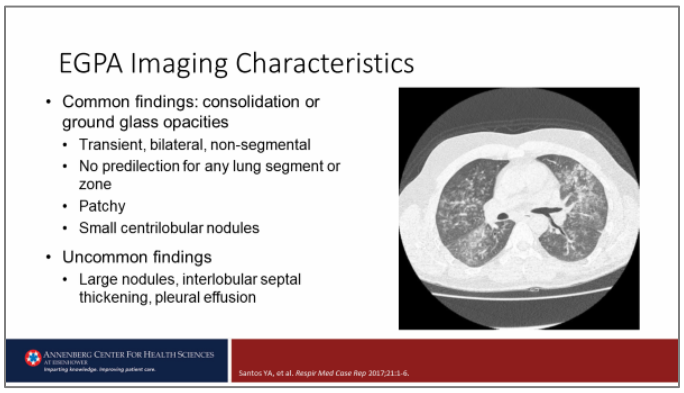
Well, let's review how this patient fits into the overall spectrum of EGPA. Well, first of all, she's 49 and she fits into the category of the median age of onset of EGPA being in the fourth decade, with children and adolescents rarely being affected. On top of that, as we discussed, she's got a 14-year history of asthma with increased symptom worsening. This fits into the paradigm of adult onset asthma starting in the prodromal phase and worsening as a common presentation in many, many patients. And systemic steroids therapy for asthma control is seen in up to 75% of patients as well.

In terms of our nasal polyp surgery, upper respiratory tract symptoms are present in the majority patients ranging from 47% to 93% of patients. As for her difficulty

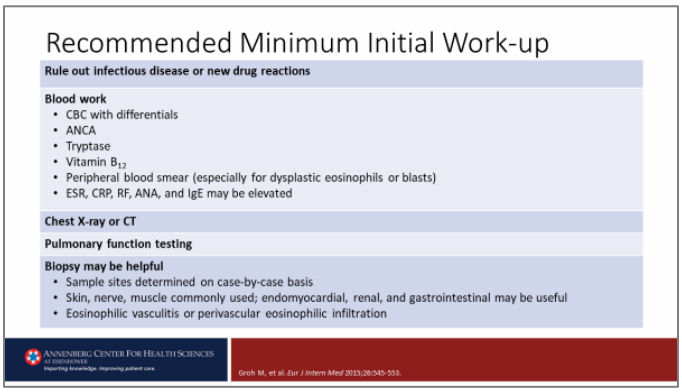
walking and neurologic symptoms, these can be present in 60% to 70% of patients. And the hypereosinophilia that she's seeing may have been documented previously, but significance wasn't realized at the time, and that can really play a role in terms of delaying a diagnosis of EGPA. The skin manifestations that we report here of petechiae are common during the vasculitic phase and need to be recognized by all clinicians.



In terms of the prevalence of different clinical features that we've talked about, asthma occurs in over 90% of patients. Pulmonary infiltrates occurs in over two thirds of patients. Neuropathy occurs in over half of patients. ENT involvement occurs in up to three quarters of patients. Skin involvement occurs in about half of patients. Cardiac involvement occurs in about a third of patients. Kidney involvement occurs in about a quarter of patients. GI involvement occurs as well, around 30% of patients, and central nervous system involvement occurs in 5% to 9% of patients.

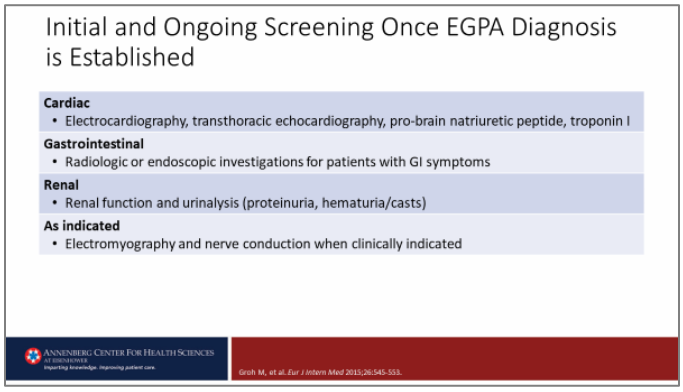


In terms of imaging, it's really important to do a good workup radiologically when you identify patients who could have EGPA. Common findings on chest CT can include consolidation or ground glass opacities. And oftentimes these manifestations will be transient, bilateral, and nonsegmental, and there's no predilection for any lung segment or zone. They're patchy and associated with small central lobular nodules. Uncommonly, there can be large nodules or interlobular septal thickening, as well as pleural effusions. That isn't what is observed here on this CT image, where you can see ground glass opacities bilaterally, as well as some small central lobular nodules that are generally patchy in nature.

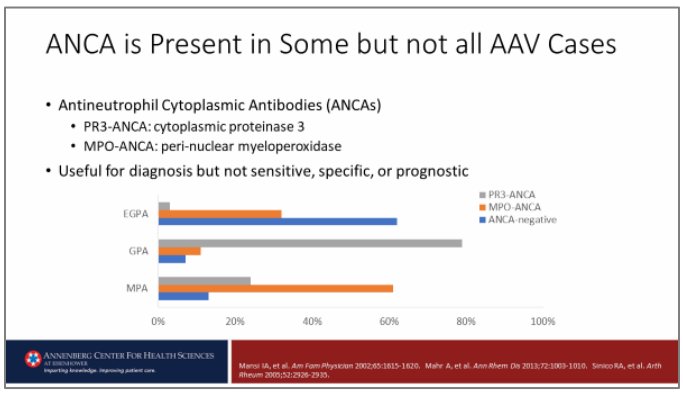


So how should we work up a patient for whom we suspect EGPA or in any patient with eosinophilia? Well, it's important to rule out infectious disease or any new drug reaction. You can do that based on history or checking stool for ova and parasites as needed. And then the basic workup includes a CBC with differential, antineutrophil cytoplasmic antibody, tryptase, vitamin B12, peripheral blood smear. And then I usually check for nonspecific inflammatory markers, including erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, A&A, and an IgE. All of which may be elevated. A chest x-ray or chest CT can be very helpful in terms of identifying pulmonary infiltrates. And then I generally do pulmonary function testing to evaluate the degree of airflow obstruction that's occurring. If there is something to be biopsied, I generally will biopsy it. And the sample sites can be determined on a case-by-case basis. Skin, the nerve and the muscle are most commonly used. Endomyocardial, renal and GI biopsies can be useful in specific symptoms and with specific patients. In general,

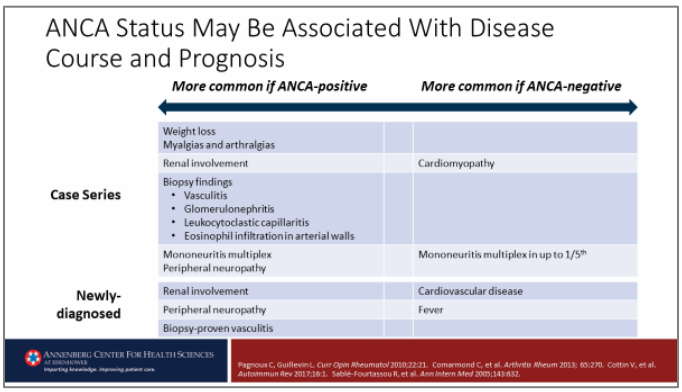
eosinophilic vasculitis presents on biopsy with peri vascular eosinophilic tissue infiltration.



Other workup that can be done initially or an ongoing basis include a cardiac workup. You can do EKGs, echocardiogram, check a BNP and troponin levels to evaluate for myocardial ischemia and myocardial involvement. GI manifestations can be worked up by doing radiologic imaging or doing endoscopic evaluations for patients who have GI symptoms. Renal workup includes measurement of renal function, such as the creatinine, and evaluation of your analysis. Lastly, when patients have neuropathy or myopathy, one can do electromyography and nerve conduction size when they're clinically indicated.

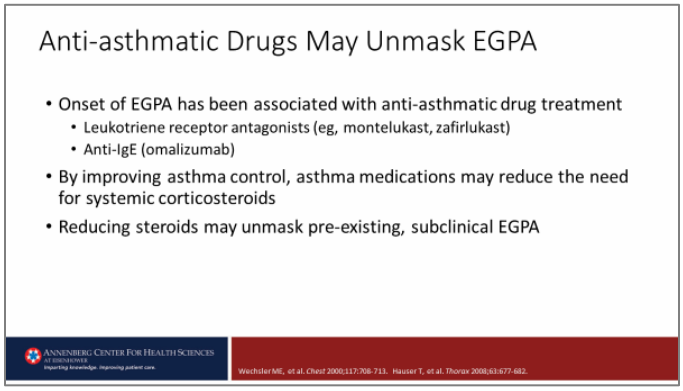


Now, antineutrophil cytoplasmic antibodies occur in some, but not in all ANCA associated vasculitides. The 2 types of ANCA that we've talked about include PR3 antibody or cANCA, and then myeloperoxidase antibody, or pANCA. Now these are useful for diagnosis, but they're not sensitive, they're not specific, and they're not prognostic. As you can see here that the vast majority of patients with EGPA are ANCA negative. Whereas those who are ANCA positive, the vast majority are NPO, myeloperoxidase, pANCA positive. In GPA, it's the exact opposite. Very few patients are ANCA negative. And the vast majority of these patients are PR3 ANCA positive or showing cANCA positivity. Lastly, in terms of microscopic polyangiitis, this study demonstrated that very few patients who are ANCA negative, only about 15% or so. And the vast majority of patients who are ANCA positive, who've got MPA, are MPO ANCA, or pANCA positive.

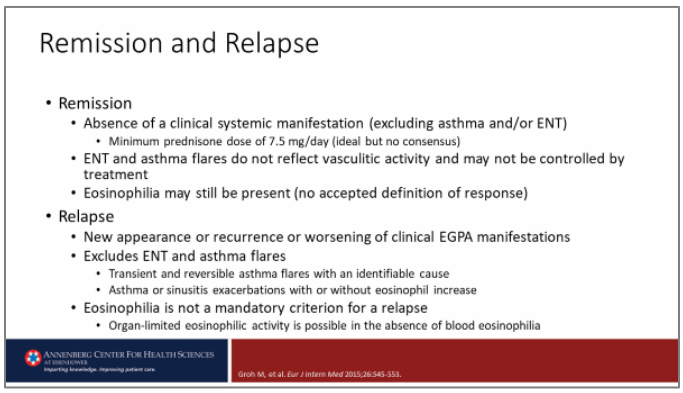


Now ANCA status can be associated with disease course and progression as well. And it's important to recognize that because one can follow ANCA status and treat accordingly. Patients can also be predicted in terms of what manifestations may be occurring based on their ANCA positivity. So ANCA positive patients tend to have more weight loss, myalgias, arthralgias, renal involvement, and you'll often see biopsy findings include vasculitis, glomerulonephritis, leukocytoclastic capillaritis, and eosinophilic infiltration in the arterial walls with mononeuritis multiplex and peripheral neuropathy, renal involvement, as well as biopsy proven vasculitis.

In ANCA negative patients, it's actually more common to see cardiomyopathy. Mononeuritis multiplex occurs in only about 20% of patients. Cardiovascular disease and fevers can often be present. And many of these patients will also have a predilection for asthma and upper airway disease.

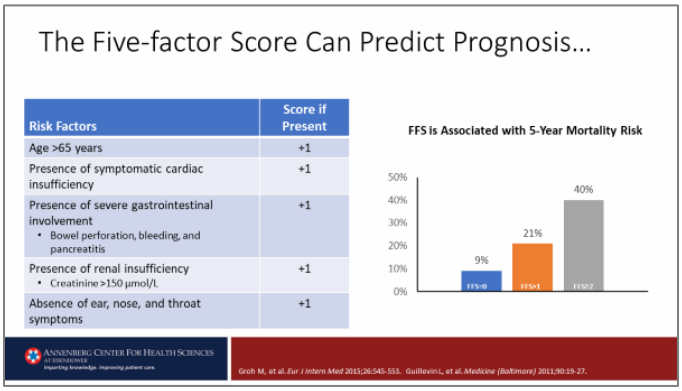


It's important to recognize that there can be unmasking of EGPA. This is when onset of asthma is associated with anti-asthma drug treatments. So just look to try a receptor antagonist or anti IgE. This has been demonstrated to occur in many patients who get improved asthma control, is novel therapies, and then they may reduce their systemic corticosteroids. And by that they may get an unmasking. It hasn't been shown that any of these asthma therapies are directly related, but it's more of an indirect association where patients were having worsening disease. And instead of either getting put on corticosteroids, they got put on one of these therapies or when they got put on one of those therapies and happened to have been on corticosteroids as they tapered down the corticosteroids, it results in decreased suppression of the inflammation that's going on and resulting in an unmasking of the preexisting subclinical EGPA that's occurring.



The 2 key outcomes that we follow in patients with EGPA are remission and relapse. Remission is defined as the absence of a clinical systemic manifestation, excluding asthma or ENT manifestations, and in general is treated and identified when patients are on 7 mg a day of prednisone or less. The European League Against Rheumatism uses the 7.5 mg threshold. However, other entities have defined remission as when one can get down to 4 mg or less of prednisone and have no significant symptoms. Rheumatologists generally consider that ENT and asthma flares or exacerbations don't reflect vasculitis activity and may not be controlled by specific treatment for the vasculitis. And eosinophilia may still be present, but there's no accepted definition of response at this point.

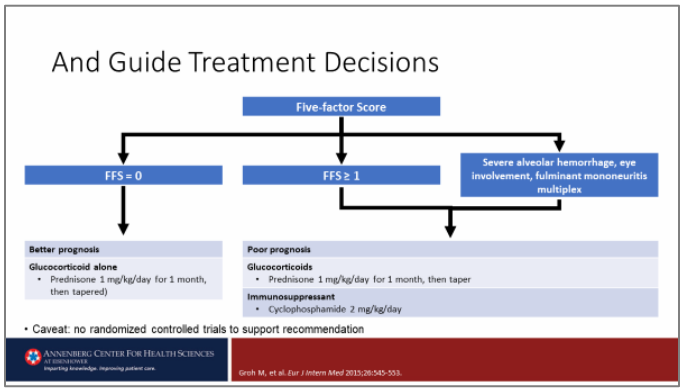
The other major outcome is relapse. And one of the goals of therapy is to achieve remission of disease, getting down to no symptoms and less than four to 7.5 mg of prednisone, but also to prevent the relapses. Relapses include new appearance or recurrence of worsening of clinical EGPA manifestations. They generally exclude ENT and asthma flares, but some people consider asthma and sinus flares as a significant manifestation of these types of patients. In general, the transient reverse for asthma flares are associated with an identifiable cause and they may or may not be associated with an eosinophil increase. It's also important to recognize that eosinophils in the blood are not a mandatory criteria for relapse. One can have organ limited eosinophilic activity, that's possible even in the absence of blood eosinophilia.



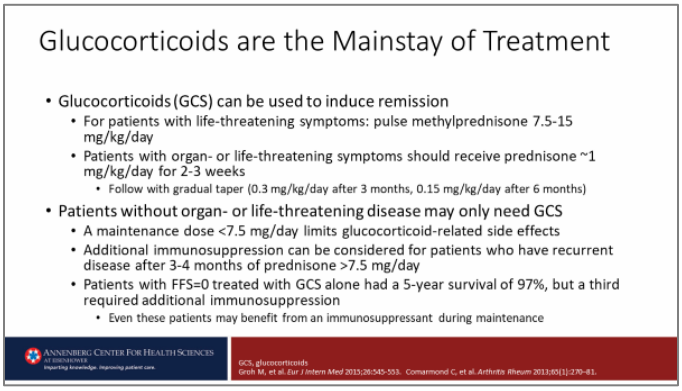
How can we predict which patients will do well with regard to their underlying disease? The five-factors score and patients can be stratified based on these 5 factor: age greater than 65, presence of symptomatic cardiac insufficiency, presence of severe gastrointestinal involvement including bowel preparation, bleeding and

pancreatitis, presence of renal insufficiency with a creatinine greater than 150, and the absence of ear nose and throat manifestations. Patients who have more than one of these manifestations have significantly worse prognosis.

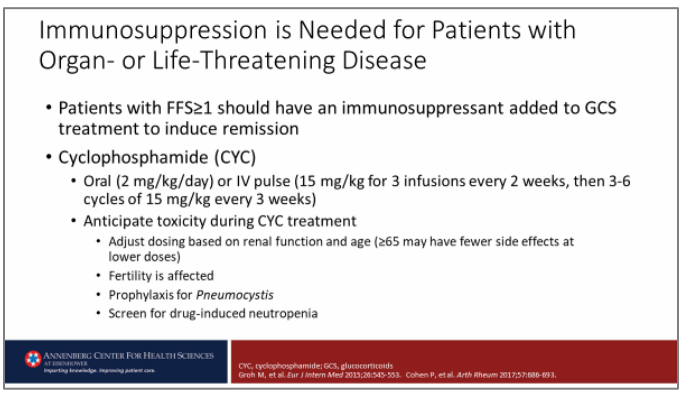
If you have 2 or more of these, your 5-year mortality goes up to 40%. Whereas if you have none of these features, you're less than 65, you don't have GI, cardiac, renal involvement, and you do have ear nose and throat manifestations, the 5-year survival is over 90%. It's important to evaluate what the manifestations are to look for different manifestations in different organ systems, so that one can give a sense to the patient of what his or her prognosis is.



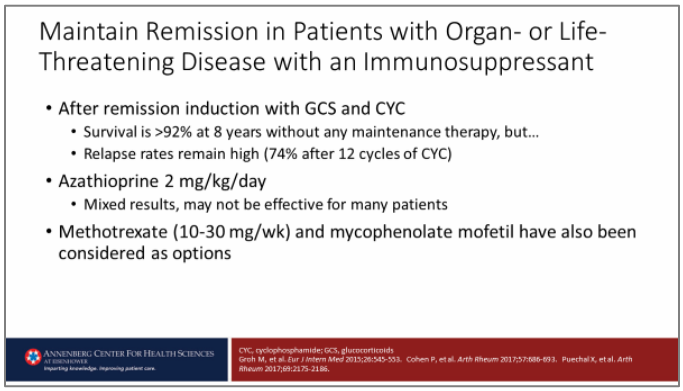
The five-factor score can also be helpful in terms of guiding treatment decisions. Patients who have a five-factor score of zero can often be treated with glucocorticoids alone, generally starting off with one mg per kg per day, treating for a month and then tapering. Patients who have a five-factor score of one or more, or patients who have severe alveolar hemorrhage, eye involvement, or mononeuritis multiplex generally should be treated with induction therapy with glucocorticoids and immunosuppressants, such as cyclophosphamide, given intravenously. One of the issues, however, is that no randomized controlled trials are there to support recommendations, but this was published 5 years ago by consensus group at the European Respiratory Society.



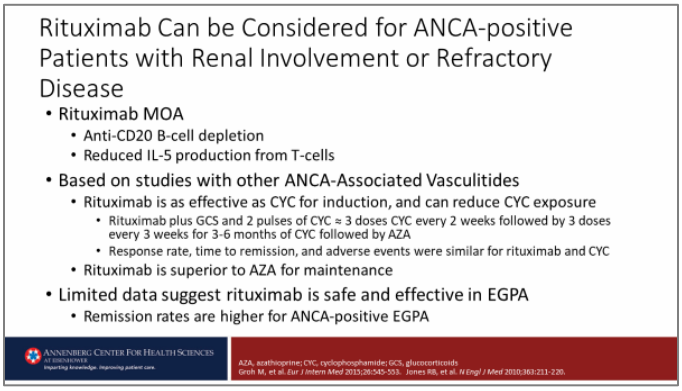
Overall, glucocorticoids are the mainstay of treatment for patients with EGPA. Glucocorticoids can be used to induce remission, and generally one will start off with methylprednisolone, 7.5-15 mg per kg per kilogram per day. And patients with organ or life-threatening symptoms to receive prednisone one mg per kg per day for a few weeks, all with a gradual taper. Patients with organ or life-threatening disease may only need glucocorticoids, and a maintenance dose less than 7.5 mg a day limits glucocorticoid related side effects, things like cataracts, glaucoma, weight gain, osteoporosis, hypertension amongst others. And additional consideration may be given to giving immunosuppressants for patient who have recurrent disease after 3 to 4 months of prednisone, more than 7.5 mg a day. For patients who can't taper below 7.5 mg a day, these therapies should also be considered. And patients with a five-factor score of zero can be treated with glucocorticoids alone, and they tend to have a pretty good survival of up to 97%. However, as many as a third of these patients require additional immunosuppression in order to maintain a healthy life.



What are some of the add-on therapies that one could consider for patients with EGPA? Well, for patients who've got organ or life-threatening disease, immunosuppression is critically needed and any patient with a five-factor score of one or more should have an immunosuppressant as glucocorticoid treatment to induce remission. For induction of remission, cyclophosphamide is generally the therapy that we reach for first, and we could give either oral or IV pulse therapy, and however one should anticipate some toxicity during cyclophosphamide treatment, and therefore adjust dosing based on renal function and age. Fertility can be affected, prophylaxis for pneumocystis can occur, and one should screen for drug induced neutropenia, which can also occur quite commonly.

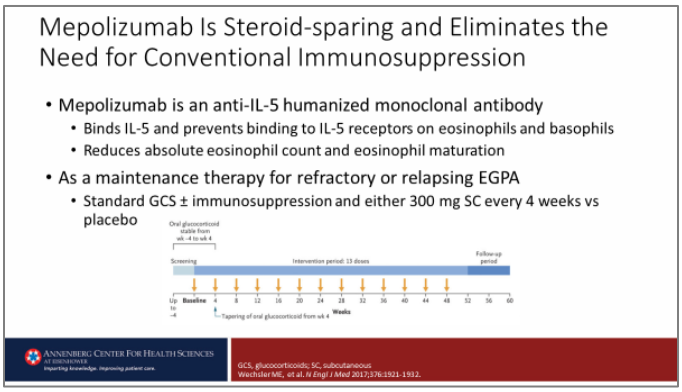


It's important not only to achieve remission by using induction therapies, such as steroids and cyclophosphamide, but also work on maintaining remission in patients with organ or life-threatening disease. And one does that best with immunosuppressant. So what are some of the options? Well, after remission induction with steroids and cyclophosphamide, one could consider azathioprine, methotrexate, mycophenolate, and others.

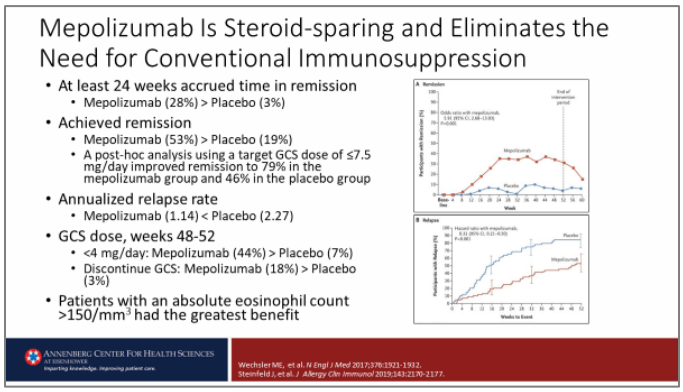


Rituximab is another therapy that could be considered for ANCA positive patients with renal involvement or refractory disease. Rituximab is an anti-CD20 B-cell depleter that reduces IL-5 production from T-cells. And based on studies with other ANCA associated vascular disease, rituximab is an effective therapy and is as effective as cyclophosphamide for induction and can reduce cyclophosphamide exposure, which can be associated with toxicity that we discussed above.

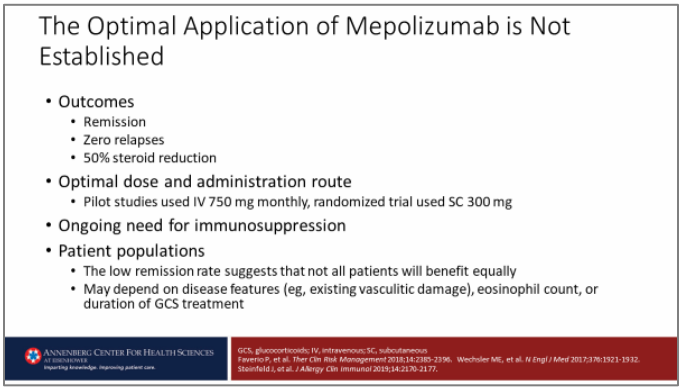
Rituximab plus glucocorticoids, and 2 pluses of cyclophosphamide or three doses every two weeks followed by 3 doses of every 3 to 6 months of cyclophosphamide followed by azathioprine is one strategy that's been employed and response time, response rate, time to remission and adverse events were similar for rituximab and cyclophosphamide. In general, rituximab is considered to be superior to azathioprine for maintenance. And there are limited data suggesting that rituximab is safe and effective in EGPA, but can be associated with worsening asthma, and remission rates are generally higher for ANCA positive EGPA compared to ANCA negative patients.



The newest therapy, and the only one that's actually approved by the FDA for management of EGPA, is mepolizumab. Mepolizumab has been shown to be a steroid-sparing therapy that eliminates the need for conventional immunosuppression. It's an anti-IL-5 humanized monoclonal antibody that binds IL-5 and prevents binding to the IL-5 receptors on eosinophils and basophils. It reduces absolute eosinophil count and eosinophil maturation, and as a maintenance therapy for refractory or relapsing EGPA, it was studied and published in 2017 the *New England Journal of Medicine*, in which 300 mg subcutaneously every 4 weeks was administered vs placebo to patients with EGPA.



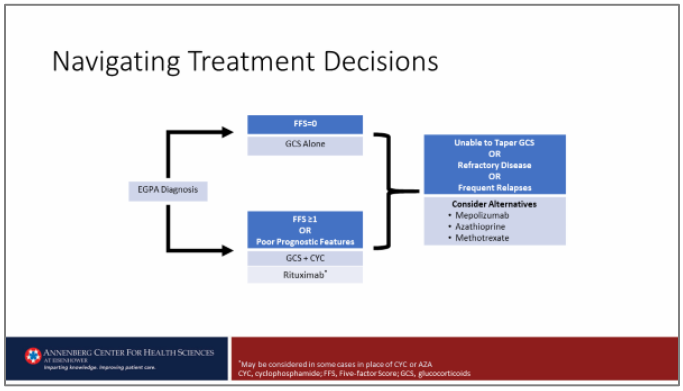
In that study, it was demonstrated that there was a significant benefit in terms of mepolizumab vs placebo and was able to eliminate the need for conventional immunosuppression. Patients were able to achieve remission at a greater rate with mepolizumab compared to placebo, over 50% of patients were able to achieve permission vs less than 20% of patients on placebo. Secondly, the relapse rate was cut in half, 1.1 with mepolizumab vs 2.2 with placebo. Glucocorticoid dosing was reduced significantly to less than 4 mg a day with mepolizumab. And the number of patients who discontinue glucocorticoids was almost 19% with mepolizumab and only 3% with placebo. Lastly, in doing a postdoc analysis, it turns out the patients with an absolute eosinophil count of greater than 150 didn't tend to have the greatest benefit in terms of their efficacy in these patients.



It's important to recognize that the optimal application of mepolizumab has yet to be established. In terms of outcomes, the goals are to achieve remission, to get patients to have zero relapses, and to achieve 50% steroid reduction. In early studies, 750 mg was administered monthly. However, in the randomized studies that have been approved by the FDA, 300 mg subcutaneously is what's administered now.

In some patients, there can be an ongoing need for immunosuppression, and one of the key things that was demonstrated, in a postdoc analysis by Steinfeld and colleagues, is that mepolizumab resulted in not just a 50% reduction in remission, but there was a large proportion of patients who, even if they didn't meet the criteria for remission, either had zero relapses or 50% steroid reduction.

Almost 80% of patients achieved one of these outcomes with mepolizumab, if you use the threshold for remission of getting down to 4 mg or less per day, and almost 90% of patients had achieved at least one of these outcomes and were able to get down to a remission based on getting down to less than 7.5 mg a day of prednisone. Not all patients will benefit equally. It's important to recognize that. And it may depend on disease features, eosinophil count, duration of glucocorticoid treatment, and then other patient-related factors.



So how do we navigate all these complex treatment decisions of EGPA? Well, one of the first things to do is to evaluate whether or not the patient has any of the five-factor score criteria. And if the patient has a five-factor score of zero, then one could consider glucocorticoids alone. And if someone has a five-factor score of one or more, or has poor prognostic factors, one should add on cyclophosphamide on top of the glucocorticoids and consider rituximab in some patients who are ANCA positive. Furthermore, in terms of disease maintenance, for patients who are unable to taper glucocorticoids or who have refractory disease, or who have frequent relapses, one should consider alternatives, including anti-IL-5 therapy with mepolizumab, and in some patients azathioprine or methotrexate.

So what we've talked about today is that EGPA is a complex syndrome. It's a vasculitis that's characterized by asthma, eosinophilia, pulmonary infiltrates, neuropathy, sinus disease, and vasculitis of at least one end organ. The pathophysiology is complex, and one needs to recognize that eosinophils are involved. Antibodies are involved, different cells are involved, including neutrophils and mast cells. And so the pathophysiology is complex. One should do an extensive workup for patients with EGPA. One needs to treat aggressively because this disease can be life-threatening, potentially. And for patients who can't taper steroids or have refractory disease, one should add other immunosuppressants or anti-IL-5 therapy.

Thank you so much for participating today. It's been great to present this important topic to you. EGPA is a complex syndrome characterized by a host of different organ system involvement, and can have long-term damage. So I'll leave you with this. It's important to recognize, it's important to treat EGPA, it's important to recognize and distinguish it from other eosinophilic disorders. It's important to distinguish it from other vascular diseases as well.