# Exploring Best Practices for Diagnosis and Management of Hypereosinophilic Syndrome

## OVERVIEW

Hypereosinophilic syndromes (HESs) are a broad group of disorders that can lead to serious complications, including cardiovascular disease, cerebrovascular disease, and death. Due to their rarity, however, HESs are challenging to diagnose and treat. In this in-depth review, presented by Princess Ogbogu, MD, and developed in collaboration with Michael Wechsler, MD, MMSc, the wide-ranging presentations of HES will be reviewed, along with pathophysiology, classification, and acute and chronic management. Learnings from the presentation will be tied together with a case-based presentation of idiopathic HES, allowing learners to see how guideline recommendations and novel clinical trials can be applied in a real clinical setting.

## TARGET AUDIENCE

This activity is intended for allergists, immunologists, pulmonologists, along with other specialists and clinicians involved in the diagnosis and management of patients with hypereosinophilic syndrome.

## LEARNING OBJECTIVES

- Describe the mechanism of eosinophilia in HES and how this can be targeted using biologic agents
- Perform differential diagnosis of eosinophilic disorders to identify patients with hypereosinophilic syndrome (HES)
- Develop patient-specific treatment plans based on HES subtype
- Discuss the safety and efficacy of new and emerging biologic treatments for HES

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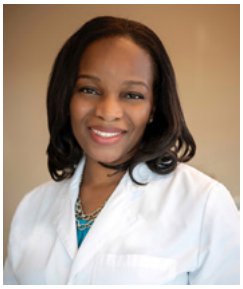

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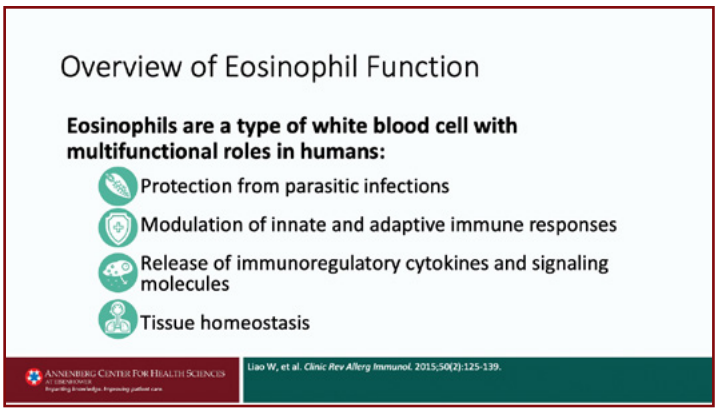
Princess Ogbogu, MD

# Mechanism and Pathophysiology of Hypereosinophilia

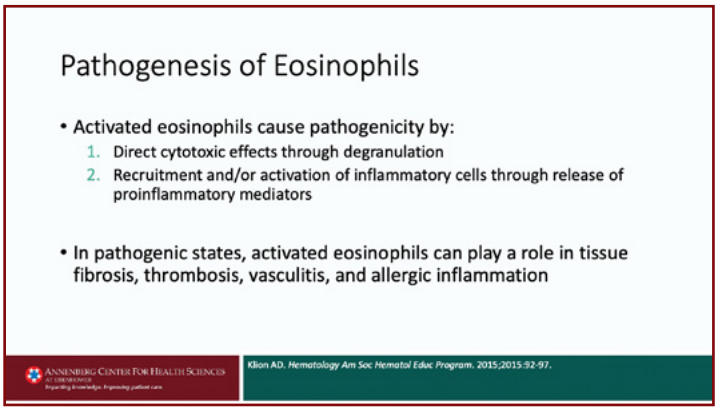
We're going to start with mechanism and pathophysiology of hypereosinophilia. Going back to the basic immunology, we're going to start with reviewing the overall eosinophil function. As you know, eosinophils are a type of white blood cell, and they really have multifunctional roles in humans. One of the best-known roles of eosinophils is that they can protect us from parasitic infections. They also help to modulate both innate and adaptive immune responses and they release a plethora of immunoregulatory cytokines and signaling molecules, and they help us to maintain tissue homeostasis.



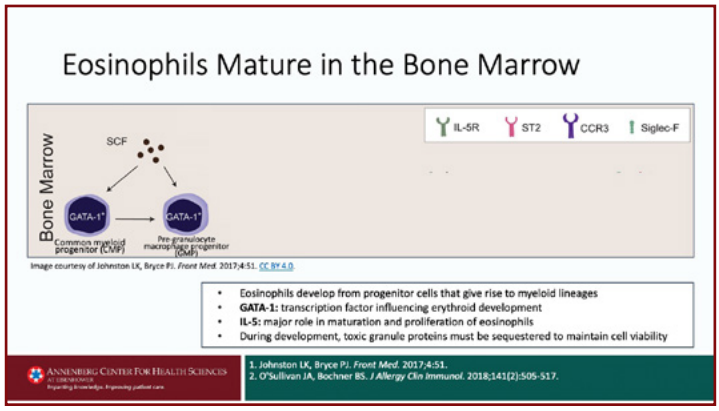

Looking at a cross-section of an electron micrograph for an eosinophil. Eosinophils contain bilobed or multilobed nuclei and they have large red-stained cytoplasmic secretory granules, so they give it that bright pink look that we are all familiar with. Eosinophils contain granules that have cytotoxic proteins.

Intact granules have cores and matrices, and this is an eosinophil that hasn't degranulated. The cytotoxic proteins often contain major basic protein, eosinophil cationic protein, eosinophil peroxidase, eosinophil-derived neurotoxin, and other cation proteins, chemokines, cytokines, growth factors, and enzymes. So, eosinophils are really dynamic cells, and a lot is contained in these core secretory granules.

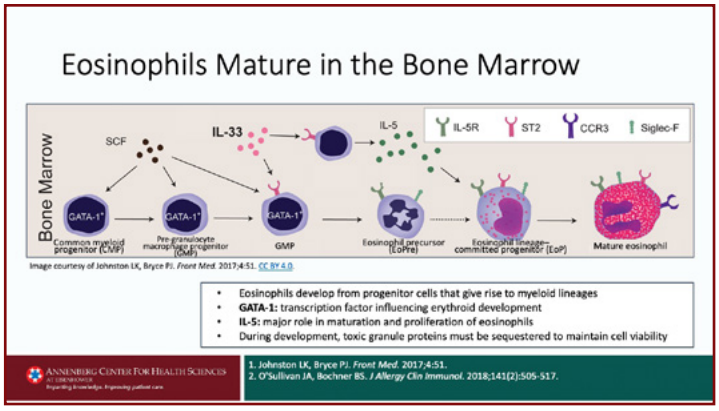
In terms of pathogenesis, activated eosinophils can cause pathogenicity by a few different mechanisms. Because eosinophils contain all of these cytotoxic granules—chemokines, cytokines—they can affect direct cytotoxic effects through the degranulation, but they can also recruit and activate other inflammatory cells through the release of proinflammatory mediators. And in pathogenic states, eosinophils really can play a role in tissue damage through fibrosis, thrombosis, vasculitis, and through allergic inflammation.




We are going to look at how eosinophils mature in the bone marrow, so eosinophils derived from pluripotent hematopoietic stem cells that differentiate into common progenitors. And here, you can see a common myeloid progenitor. Eosinophils and basophils have the same common progenitor, which is influenced by transcription factors such as GATA-1.




It's also important to note that eosinophil and basophil activation can be influenced by various cytokines as well. GM-CSF, IL-3, and IL-5 are all involved in the maturation of eosinophils and basophils, but it's really important to know that IL-5 is very specific for eosinophils, and IL-33 aids in this function as well. IL-5 essentially forces the eosinophil precursors to become mature eosinophils.




When we talk about regulation of eosinophils in terms of production, trafficking, and apoptosis, again, it's dependent on interaction between transcription factors like GATA-1. Cytokines and IL-5 are really paramount for eosinophils and other immune-signaling proteins. Eosinophil differentiation and migration is mediated by IL-5, eotaxin, which is a chemokine that directs eosinophils where to go, non-chemokine factors such as complement, and then other immune cells that are in the milieu, including lymphocytes, mast cells, and other eosinophils.

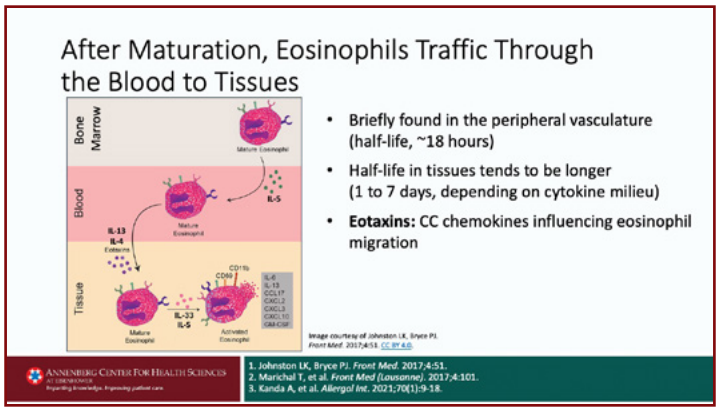
Esinophils are important to know that they're tissue-dwelling cells. The tissue-to-blood ratio of eosinophils is about 100:1. And

eosinophils tend to go to tissues that are connected to the outside environment such as the gut and the lungs. Eosinophils essentially pass through the circulation on their way to the tissues. And they're formed in about 3 to 4 days in the bone marrow, but then they live in the blood for only about 8 to 18 hours before they get to the tissues.

Once they get to the tissues, the half-life tends to be a lot longer, so between 1 and 7 days, depending on whether or not they have other supporting cytokines in the milieu. And, of course, certain chemokines, especially eotaxin, influence this migration.

## Summary

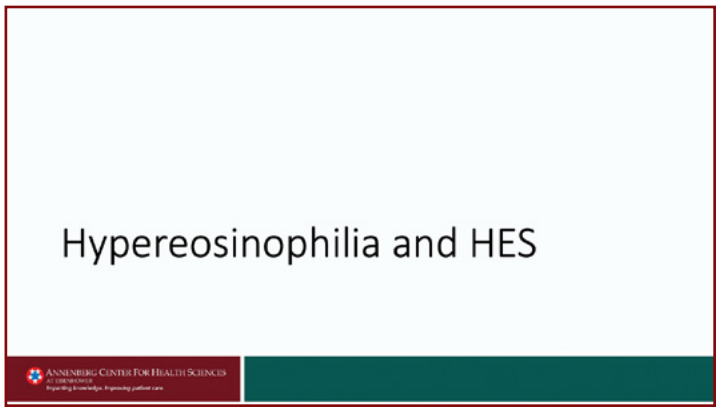
Eosinophils are white blood cells that have multifunctional roles. They differentiate and mature through cytokines, such as IL-5 and IL-33, through nonchemokine factors such as complement, and through other immune cells such as lymphocytes, mast cells, and eosinophils themselves.

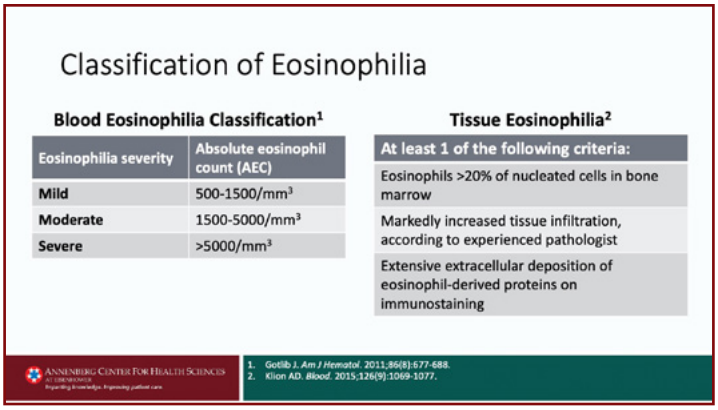



After maturation, eosinophils migrate through the blood to the tissues, which is a fairly short process of about 8 to 18 hours, and then they can live in the tissues for about 1 to 7 days with the appropriate cytokines in the milieu. And this process is mediated by eotaxin, which helps guide the eosinophils to the correct location.

# Hypereosinophila and HES

Now, we're going talk about hypereosinophilia and hypereosinophilic syndrome. As an overview, we'll talk about the classification of hypereosinophilic syndrome, how you diagnose

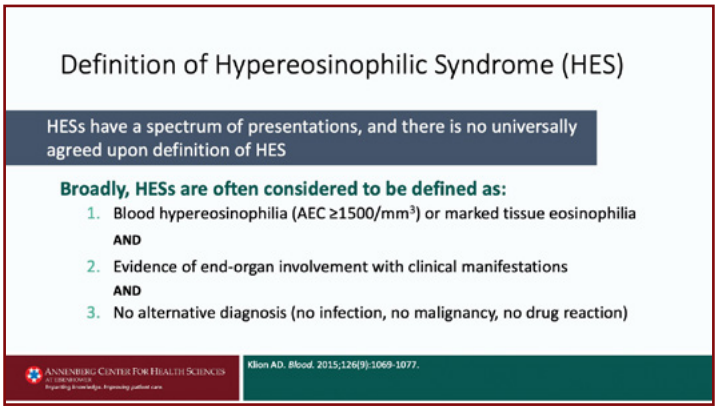



it, what the common presenting symptoms are, and what the secondary causes are. We will start with eosinophilia. And I think this is a really important take-home point for you. When we're looking at eosinophilia severity we're looking at the absolute eosinophil count.

Oftentimes, we are trained to look at the eosinophil percentage, but I want to make the point that you really should look at the absolute eosinophil count, which can help risk-stratify how severe eosinophilia is. The percentage can vary depending on what the white blood cell count is, but the absolute eosinophil count can really let you know if it's mild, moderate, or severe. A normal eosinophil count is anywhere between zero and 500, and then mildly elevated is between 500 and 1,500, moderately elevated is between 1,500 and 5,000, and then severely elevated is greater than 5,000.

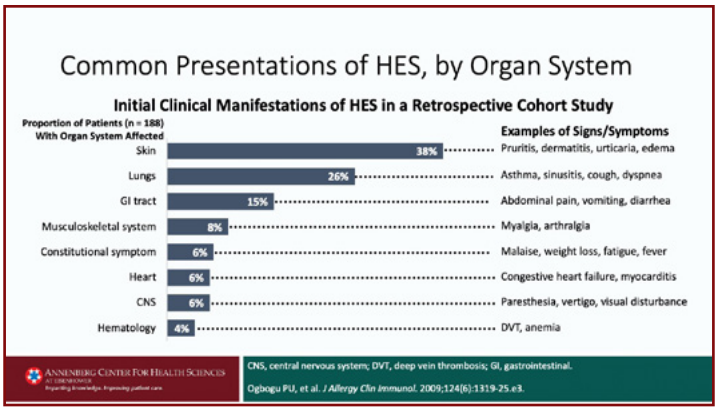
We also look for tissue eosinophilia, and this can be a little bit more tricky. So, you need to meet at least one of the following criteria. Eosinophils greater than 20% of the nucleated cells in the marrow or markedly increased tissue infiltration according to a pathologist that's experienced in looking for eosinophilia, and then really importantly, looking for extensive extracellular deposition of eosinophil-derived proteins on immunostaining—and this is because eosinophils may not be found in the biopsy, but you may find evidence that eosinophils were there and part of the pathogenesis if you can find degranulated proteins. So, staining for the granule proteins is very important for this reason.




Now when we talk about hypereosinophilic syndrome, it's really important to know that this is a diagnosis of exclusion and there are a few criteria that need to be met to call something hypereosinophilic syndrome. One is having blood eosinophilia greater than 1,500 or marked tissue eosinophilia on more than one occasion. The second is ruling out any alternative diagnoses. So,

there shouldn't be another explainable cause, such as infection, malignancy, drug reaction, and so on and so forth, and then seeing that there's evidence of end-organ involvement with clinical manifestations.

I also want to make the point that in older literature for hypereosinophilic syndrome, it was always noted that the eosinophilia should be there for 6 months or longer. We now know that if you wait 6 months to make the diagnosis, this can lead to extreme morbidity and mortality. The blood eosinophilia needs to be documented on more than one occasion with no other discernible cause.

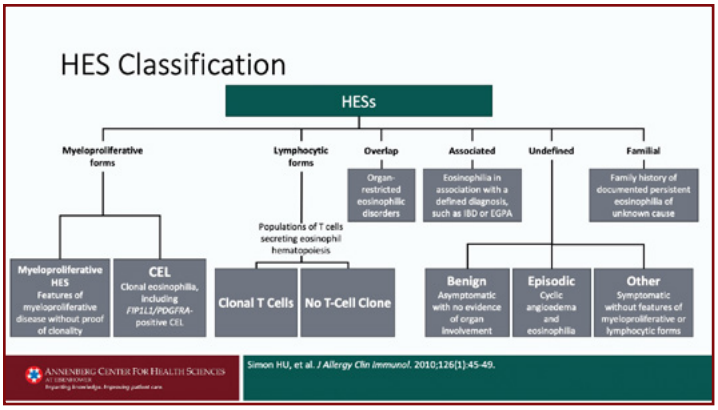



In terms of how patients manifest with hypereosinophilic syndrome, in 2009, we did a retrospective study looking at 188 patients with hypereosinophilic syndromes from 11 sites worldwide, including from the United States and Europe, and found that the majority of the patients presented with skin symptoms—which were varied, anything from pruritus to angioedema,—lung symptoms, GI tract symptoms, followed by musculoskeletal, just general constitutional symptoms, and then heart, lung, and hematologic symptoms.

I also want to bring up the point that 7% of the patients in the study were found to have eosinophilia by routine lab evaluation only. And this is another reason why it's very important to carefully look at the differential on the CBC to look for eosinophilia. What's even more important is the study showed that although most patients frequently present with skin symptoms, lung symptoms, and GI tract involvement, the subsequent manifestations can be quite devastating. So more than 20% of patients can experience cardiovascular and neurologic complications, which can be a major cause of morbidity and mortality.

Through advances in molecular diagnostics, we now have identified certain subtypes of hypereosinophilic syndrome. And we'll talk about some of these subtypes in greater detail, but I want to give you an overview of them. M subtype means that the patient presents with myeloproliferative symptoms without proof of clonality or they may present with clonal eosinophilia, including the FIP1L1/platelet-derived growth factor receptor alpha mutation, which leads to chronic eosinophilic leukemia.

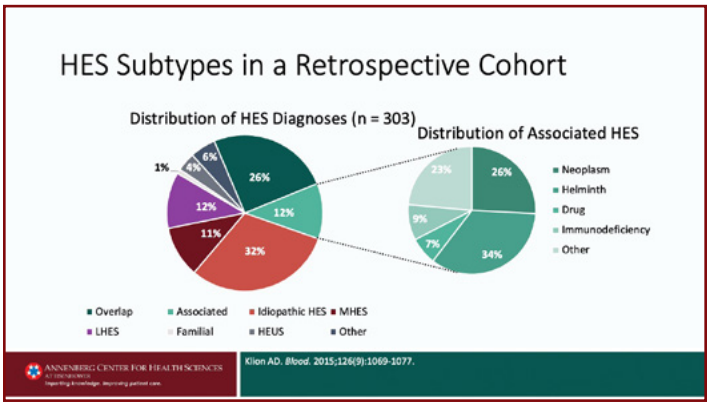
In the lymphocytic variant we see that there are populations of T-cells that secrete eosinophilopoietic cytokines, such as IL-5, which drive eosinophilia. And they may be clonal, or you may not find a discernible T-cell clone. Overlap syndrome is where we see organ-restricted eosinophilic disorders such as a patient




with eosinophilic gastrointestinal disorder that has peripheral eosinophilia or a patient with chronic eosinophilic pneumonia with peripheral eosinophilia.

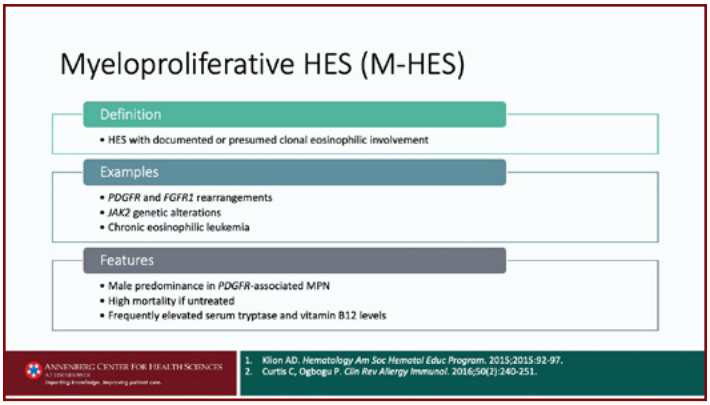
The associated category means that eosinophilia was found in association with a defined disorder such as inflammatory bowel disease or eosinophilic granulomatosis with polyangiitis or sarcoidosis, for example. The undefined category really is the largest category of patients with hypereosinophilic syndrome, and this can be divided into patients with benign eosinophilia, so those that present asymptomatically without evidence of organ involvement, those with episodic eosinophilia with cyclic angioedema, and so this is also known as Gleich's syndrome. And then patients, and this is the most broad category, with symptomatic eosinophilia but they don't have features of myeloproliferative or lymphocytic forms.

And lastly, familial hypereosinophilic syndrome, which is extremely rare. It's been mapped to chromosome 5q31 to 33. And there is a family that is known to have eosinophilia in it, multi-generationally, with varied outcomes.



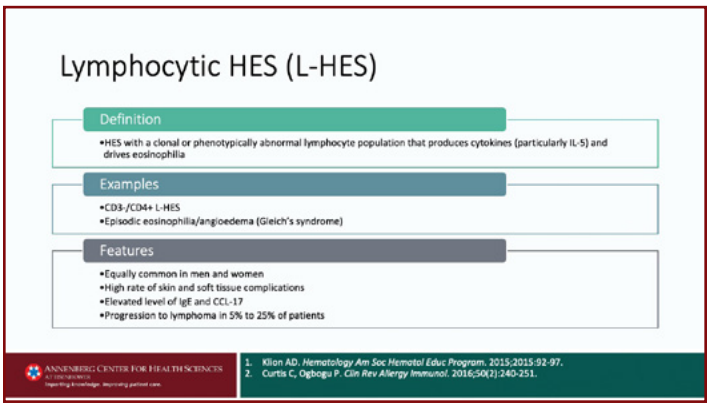

When we look at HES subtypes in a retrospective cohort, we see that 11% to 12% of patients have both lymphoid or myeloid, have either lymphoid or myeloid variants. About 32% of patients have idiopathic HES, which is the largest group in terms of subtypes. About 26% of patients have overlap subtype. And about 12% of patients have associated HES. And when we look at associated HES, this can include neoplasms, helminthic disorders, drug allergy, immunodeficiency, and other causes.

We are going to focus on a few of the subtypes that I mentioned. The first is a myeloproliferative or myeloid subtype, and these patients may have documented or presumed clonal eosinophilic



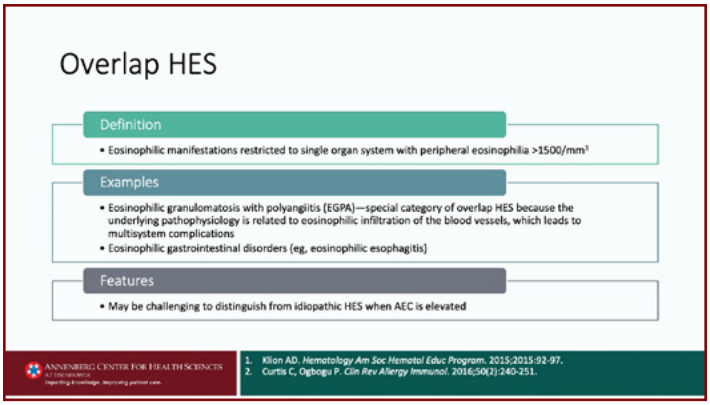

involvement. Some examples include platelet-derived growth factor receptor rearrangements, FGFR1 rearrangements, JAK2 genetic alterations, and chronic eosinophilic leukemia. Just a story … these patients were initially identified in the 1970s and they consisted of young males who presented with cardiovascular and neurologic complications, were extremely sick and, on average, lived only about 6 months.

We now know that those patients likely had myeloid or myeloproliferative hypereosinophilic syndrome due to the platelet-derived growth factor receptor alpha mutation, where we see a male predominance and a very high mortality if untreated. And there are a few key biomarkers that we may see to clue us in to the fact that someone might have myeloid HES. And this includes an elevated serum tryptase and elevated serum vitamin B12 levels.



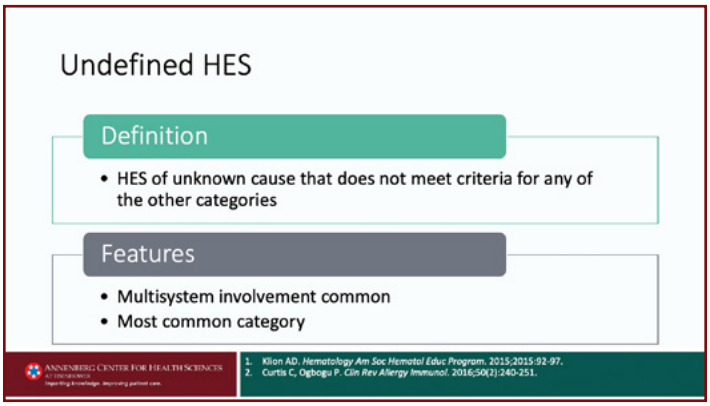

The lymphocytic or lymphoid variant of HES means that you have HES with clonal or phenotypically abnormal lymphocyte populations that produce cytokines, such as IL-5, and this drives the eosinophilia. We know that you can have CD3-negative, CD4-positive lymphocytic HES, and patients with episodic angioedema and eosinophilia, known as Gleich's syndrome, also fall into this category. Unlike the myeloid variant, this is equally common in men and women, and we see high rates of skin and soft tissue involvement. In terms of biomarkers, we see elevated total IgE levels and elevated chemokine levels of CCL17, which is also known as TARC. And it's important to know that these patients can progress to lymphoma in about 5% to 25% of cases.

Overlap HES and these, again, are patients that have peripheral eosinophilia greater than 1,500, but the manifestations are restricted to a single organ. We usually see this with eosinophilic granulomatosis with polyangiitis, which is EGPA. We also see this often with eosinophilic gastrointestinal disorders, specifically



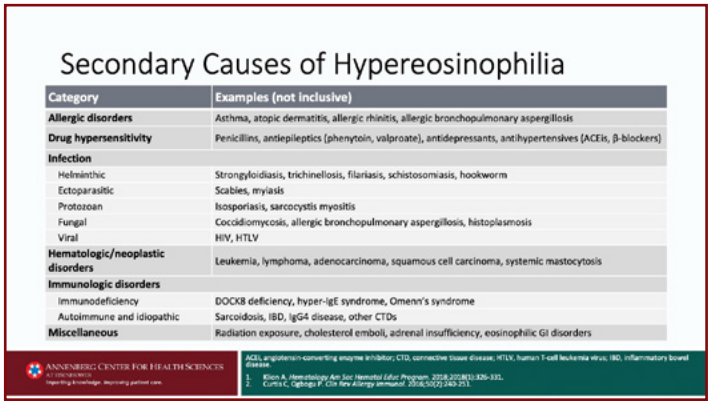

eosinophilic esophagitis and eosinophilic gastritis. This may be challenging to distinguish from idiopathic HES, but generally these patients have single organ-restricted disease, unlike idiopathic HES, where they often have multiorgan disease.

And then undefined HES, this is the largest category. This means HES of unknown cause, and it really doesn't meet criteria for any of the other categories. Again, we often see multisystem involvement, and this is the most frequently diagnosed form of HES.




In terms of secondary causes of hypereosinophilia, and again, this is secondary causes of hypereosinophilia, not HES, they include allergic disorders such as asthma, atopic dermatitis, allergic rhinitis. And I wanted to point out here, though, that allergic disorders rarely cause persistent eosinophilia greater than 1,500, with a few exceptions.

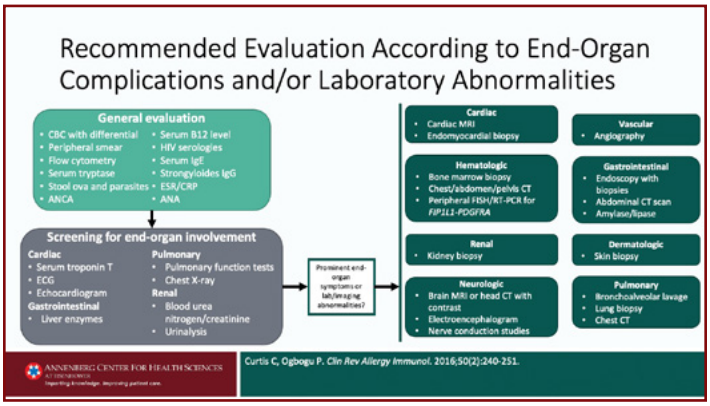
Drug hypersensitivity is the number one cause of hypereosinophilia in the United States. Infection, especially helminthic infection, is the number one cause of hypereosinophilia worldwide. Hematologic and neoplastic disorders can certainly cause hypereosinophilia, and these can include hematologic



malignancies as well as solid tissue malignancies, immunologic disorders such as immune deficiency. For example, DOCK8 deficiency, hyper IgE, and Omenn syndrome are all associated with hypereosinophilia, and then there are other autoimmune disorders that are associated with hypereosinophilia as well. And then there are some miscellaneous causes of hypereosinophilia, and these can include adrenal insufficiency, cholesterol emboli, radiation exposure, to name a few.

When we think about the differential diagnosis, and excluding secondary causes, when we want to make a diagnosis of hypereosinophilic syndrome, the number one thing is to evaluate for drug hypersensitivity reactions. As I mentioned, drug hypersensitivity is the most common cause of hypereosinophilia in the United States and it can be caused by almost any agent. The really important take home point here is to really discontinue any nonessential pharmacotherapies before diagnosis.

Secondly, is evaluation for parasitic infections, and this can be dictated by exposure, clinical signs and symptoms, travel history. And strongyloides, I want to raise the point, is an important one to rule out, especially in that it's endemic in the southeastern United States. It is not something that you have to travel to get strongyloides, and it can be asymptomatic. And then certainly evaluating for neoplasms, because eosinophilia can precede both blood and solid organ neoplasms.




This is a helpful slide because this can give you a guide in terms of recommended evaluation for hypereosinophilia and end-organ complications. We start off with the general evaluation, and the general labs that you want to get are CBC with differential, again, looking at the absolute eosinophil count, a peripheral smear, flow cytometry on the peripheral blood, and this is really looking for clonal populations of T-cells. A baseline serum tryptase and serum vitamin B12 because we want to screen for myeloid HES, serum stool ova and parasites and strongyloides antibody because we want to screen for for parasitic disease, HIV, screening for infection serum IgE, which, if it's elevated, can help point us towards a lymphoid variant of HES, and then a sedimentation rate, CRP, ANA, and ANCA because we are looking for autoimmune connective tissue disorders which could contribute to eosinophilia.

In terms of screening for end-organ involvement, cardiac screening generally includes checking of serum troponin, ECG, and echocardiogram, GI screening includes checking liver enzymes, pulmonary screening, checking PFTs, chest X-ray, or other chest imaging as indicated, renal screening, looking at BUN and creatinine and a urinalysis.

And then if there is something that raises concern on the initial screening for end-organ manifestations, then you can look further into screening with cardiac MRIs, bone marrow biopsies, kidney biopsies, further neurologic imaging, endoscopy and biopsies, skin biopsies, bronchoalveolar lavage, lung biopsy, and chest CT, to name a few. This gives you a really good framework of how to start the evaluation, how to do basic screening, and then how to follow up on any screening abnormalities.

### Summary

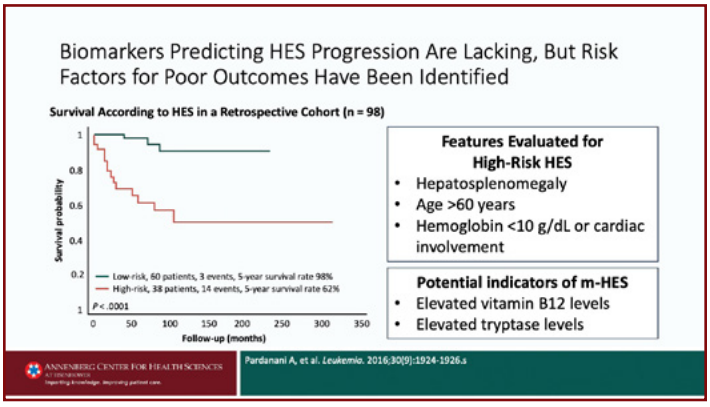
HES is characterized by hypereosinophilia either in the tissue or blood, clinical symptoms, and end-organ involvement with the absence of other diagnoses that could be causing it. Dermatologic and pulmonary and GI manifestations are really common initial presentations of HES. But if HES is not diagnosed promptly and treated promptly, it can cause irreversible cardiovascular and neurologic complications, and so this is why it's important to make the diagnosis.

## Treating Hypereosinophilic Syndromes

Moving on to treating hypereosinophilic syndromes. We'll talk about acute treatment. We will talk about HES treatment regimens, including conventional treatments and novel and emerging treatments, specifically focusing on anti-IL-5 biologic therapy.

In terms of the initial approach to HES treatment, the severity and type of presentation really guides treatment decisions. When someone presents with life-threatening HES, it's really important to promptly initiate high-dose glucocorticoids to prevent the risk of end-organ damage. If someone presents with life-threatening HES, it's very difficult to take the time to get a full diagnostic evaluation, but a limited diagnostic evaluation is appropriate, and then steroids really shouldn't be withheld while waiting for the evaluation if symptoms are rapidly progressing.

In terms of high-dose glucocorticoid dose, we generally say prednisone 1 mg/kg/day as the initial treatment of choice. Consider giving empiric ivermectin for any patient who might



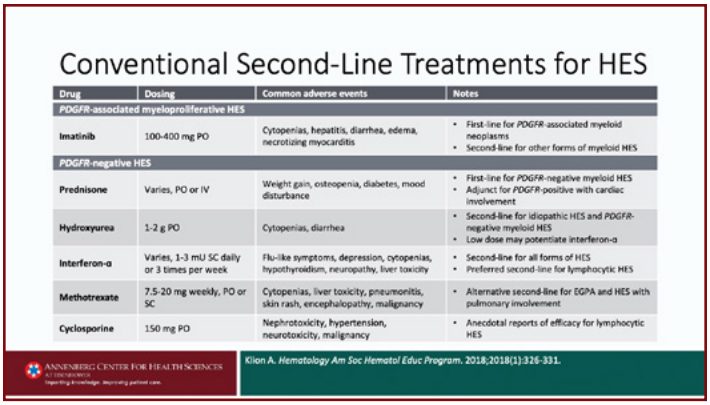
have potential exposure to strongyloides, especially because it takes a few days for strongyloides antibody results to return. And then IV glucocorticoids are appropriate for those who are acutely ill or that may have other issues, such as GI involvement that could impair absorption.

As I mentioned before, we don't have a lot of biomarkers for HES, but we do know that there are some risk factors that have been identified that can give a clue to whether a poor outcome may occur.

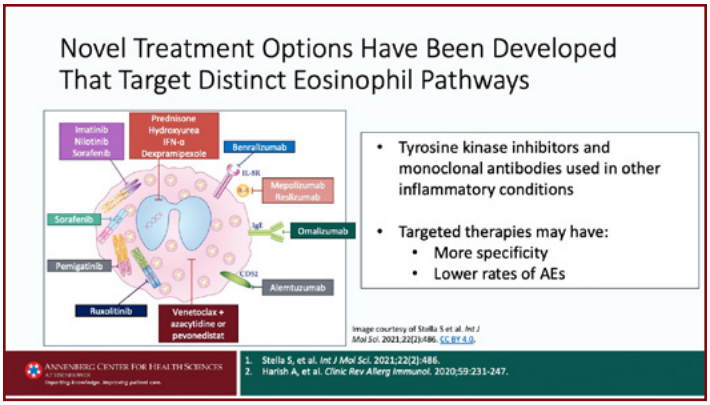
High-risk HES patients often have hepatosplenomegaly. They may be older, so age greater than 60 years, and then may have hematologic involvement such as anemia or cardiac involvement. And these 3 things, hepatosplenomegaly, anemia, and cardiac involvement, all make you think of myeloid HES, but in general these patients tend to be more high risk. And then potential indicators of myeloid HES, again, include elevated serum vitamin B12 levels and elevated tryptase levels.

In terms of conventional second-line treatment for HES, here is where we really need to try to identify what subtype we think they have. Patients who are found to have a myeloid or myeloproliferative subtype are appropriate to try imatinib with, and imatinib is a tyrosine kinase inhibitor. And so, again, these are for patients with platelet-derived growth-factor-receptor-associated myeloproliferative HES or other myeloid features. And common adverse events here could be cytopenias, hepatitis, diarrhea, edema, and necrotizing myocarditis.

For patients that are PDGFR-negative, prednisone is a common therapy, and 2 other common therapies are hydroxyurea and interferon-alpha. Interferon-alpha, in particular, is really preferred as a second-line agent for lymphoid HES, but it is very difficult to tolerate because of flu-like symptoms and depression. And then there are other therapies that can be used and that have been used in a limited format or case-report format, such as methotrexate and cyclosporine. And so, these are more anecdotal in terms of the data we have on efficacy.



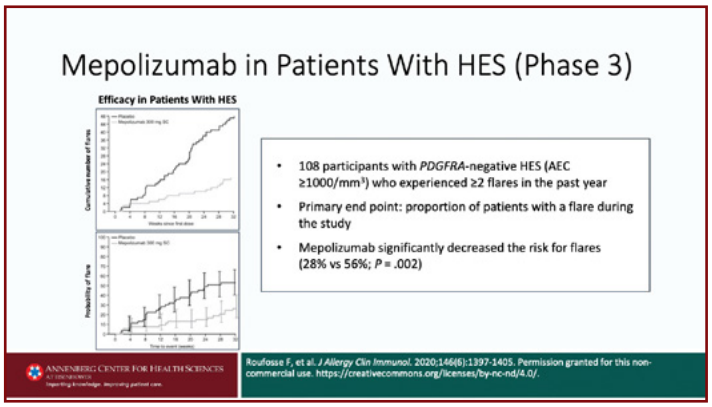

What's really exciting, is that novel treatment options have been developed that target the eosinophil pathways. And so, as I mentioned, tyrosine kinase inhibitors can be used, especially when someone presents with the myeloid-variant HES. Those aren't appropriate, generally, for patients who present with PDGFRA-negative HES. There are many monoclonal antibodies that have been used for HES and these are more targeted therapies that have more specificity and lower rates of adverse events. We will talk about these coming up.




In terms of targeted therapies for HES, as we discussed, IL-5 is the number one cytokine that's involved with eosinophil differentiation, proliferation, and maturation, and so targeting IL-5 makes a lot of sense for HES. The 3 agents that have been used include mepolizumab, which is an anti-IL-5 monoclonal antibody, and benralizumab and reslizumab, which are anti-IL-5 receptor monoclonal antibodies. Mepolizumab has been approved for both eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, and now for HES.

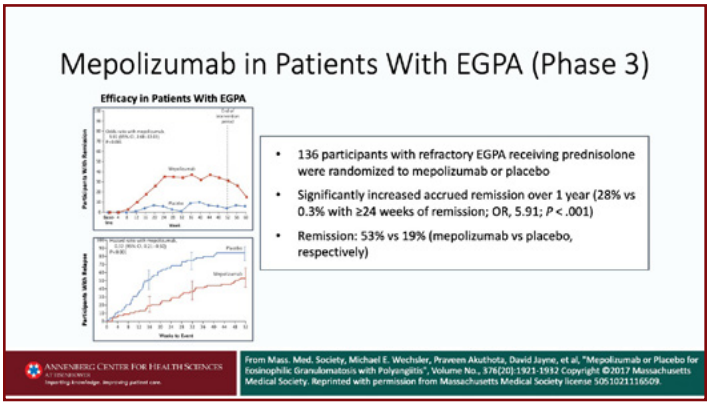
Benralizumab has had positive studies for the phase 2, and phase 3 studies are ongoing, and then reslizumab is approved for eosinophilic asthma and has been studied in hypereosinophilic syndrome as well. Other monoclonal antibodies that have been used in HES are omalizumab, and so this is approved for both allergic asthma and idiopathic urticaria, and alemtuzumab, an anti-cyclic 8 molecules, have also been studied.

In terms of small molecules for HES, JAK-STAT inhibitors are being studied currently, tyrosine kinase inhibitors, again, I mentioned imatinib, but there are other tyrosine kinase inhibitors that are studied for use in myeloid HES, and then other small molecules. And dexpramipexole is interesting because it is a molecule that was originally studied for amyotrophic lateral sclerosis and, in the studies, was found to have a profound effect on eosinophils and so has now been studied in eosinophilic asthma.

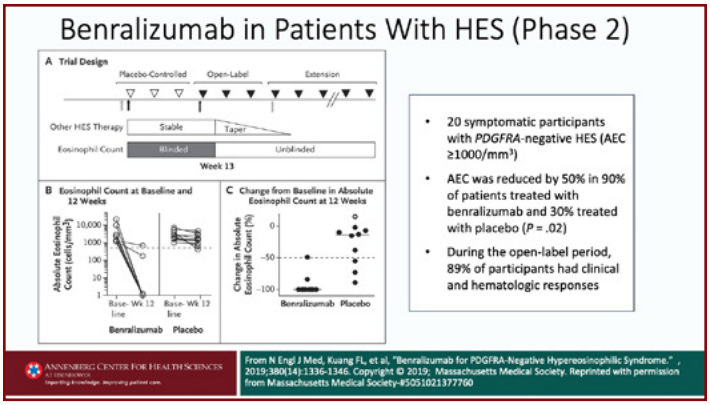



Specifically talking about mepolizumab in patients with HES, so in the phase 3 study, 108 participants with PDGFRA-negative HES who had persistent eosinophilia greater than 1,000 and had greater than 2 flares per year were included, with the primary endpoints of looking at the proportion of patients with a flare during the study. And the study found that there was a much lower probability of both flare and cumulative number of flares, so it decreased the risk of flares in the patients who received mepolizumab vs placebo.

Mepolizumab was also studied in patients with EGPA. The study involved 136 participants with refractory EGPA receiving prednisolone, and they were randomized to either getting mepolizumab or placebo, and they were found to have significantly increased remission over 1 year in the mepolizumab group. The remission was 53% vs 19% in the mepolizumab vs placebo group respectively.




Benralizumab, which is an anti-IL-5 receptor monoclonal antibody, has been studied in patients with HES in a phase 2 study, which included 20 symptomatic participants with PDGFRA-negative HES, again, with an absolute eosinophil count greater than 1,000, it was found that the absolute eosinophil count was decreased by 50% in 90% of the participants who received benralizumab and only 30% in those who were treated with placebo. And during the open-label period, 89% of participants had clinical and hematologic responses. Benralizumab is now in phase 3 studies.




In terms of common adverse events with these IL-5 therapies, they're really well tolerated in general. So anti-IL-5 and anti-IL-5 receptor therapies have been relatively well tolerated in all the studies. Common adverse effects include nasopharyngitis, injection site reactions, headache, and upper respiratory tract infections. And serious adverse effects were really rare in the studies, but they did include asthma worsening, anaphylactic reactions, and pneumonia.

## Summary

For HES diagnosis and treatment, at presentation, we want to identify the onset of eosinophilia, identify the magnitude or severity of eosinophilia so that we are able to determine if it's mild, moderate, or severe, understand how it's temporarily associated to medications or exposures.

It's important to get a great clinical history, so identifying if the patient has a travel history, what medications they are on, including over-the-counter medications and supplements, or any other comorbid conditions, performing a complete physical exam looking for signs and symptoms of organ dysfunction, performing an initial diagnostic workup which could include getting a CBC, troponins peripheral smear, serum vitamin B12 and tryptase flow cytometry.

And then if there is anything that flags on the initial diagnostic workup, a subsequent diagnostic workup could include additional imaging such as CAT scans, MRIs, endoscopies, biopsies, etc. Additional, or subsequent diagnostic workup could include additional imaging such as cardiac MRIs, CAT scans, endoscopies, colonoscopies, skin biopsies, lung biopsies, etc. This allows us to understand what organs are involved. We want to make sure that we've ruled out other alternative diagnoses such as autoimmune conditions, drug hypersensitivity, malignancy, and parasitic infections among others.

And then once we've determined that the patient has HES, we want to determine if it needs to be urgently treated or not. If it needs to be urgently treated, then we want to treat with high-dose glucocorticoids including ivermectin if there is concern for strongyloides. Once we have a patient in a stable condition, we want to identify what subtypes they have. This can include lymphoid subtype, myeloid subtype, overlap associated, or idiopathic HES. And then, depending on the subtype, this will help guide therapy. And if a patient is not doing well with initial therapy and/or having adverse side effects and they have PDGFRA-negative HES, considering more targeted therapy such as biologics or considering clinical trials if appropriate.

Prompt treatment with glucocorticoids is recommended for those patients with HES for patients with HES with life-threatening symptoms including use of ivermectin if strongyloides is suspected as well, making sure that treatments are individualized by HES classification, and consideration of using newer targeted agents for HES.

# Case Study

We will talk about HES laboratory workup, differential diagnosis, how we treat, and how we make treatment modifications. Jonathan is a 62-year-old male who presents to a PCP with a rash on his chest and right arm. On questioning, he's also noting that he's had fatigue and shortness of breath. His medical history is significant for hypercholesterolemia which was diagnosed at age 52 and it's controlled with a moderate dose statin. And the CBC results show an absolute eosinophil count of 2,800 with normal hemoglobin and normal platelets and a normal comprehensive metabolic panel.

His rash and hypereosinophilia persist even when his medications are discontinued. The PCP then refers Jonathan to allergy/immunology for further evaluation. As part of his evaluation and based on suspicion for HES, additional testing is requested and this includes laboratory testing. Serum immunoglobulin levels,

troponin, tryptase, serum vitamin B12, HIV, ANCA stool for ova and parasites, and serology for strongyloides, and lymphocyte immunophenotyping. Imaging is obtained including chest, abdomen, and pelvis CT, and echocardiogram. Bone marrow biopsy is obtained including sending for cytogenetics and the biopsy of the skin rash is performed.

Treatment with glucocorticoids is not initiated immediately because his presentation was not life-threatening, and so we waited for results to come back and his bone marrow biopsy shows eosinophil precursors and the rash biopsy shows evidence of eosinophil infiltration and the rest of the test results are negative or within normal limits.

Jonathan is diagnosed with undefined HES. Initial treatment is prednisone 60 mg/day, which is initiated, and he returns 6 weeks later. He wasn't able to taper below 20 mg/day. Every time he tried to taper, his symptoms worsened and hypereosinophilia persisted.

Treatment adjustments were made, and these included continuing prednisone but adding in an anti-IL-5 therapy. Two months later, Jonathan was able to successfully taper off of all steroids, his rash resolved, his eosinophil count normalized to 100, and he no longer had shortness of breath and now had a clear chest X-ray. At a 1-year follow-up, Jonathan reports that he's feeling well, the symptoms have not returned, and he's not had any flares.

## Summary

In summary, HES is characterized by hypereosinophilia in the tissue or blood, clinical symptoms and end-organ involvement, and the absence of any other explanatory diagnosis. Rash, fatigue, and other systemic symptoms often accompany HES. It is important to consider step-up therapy with targeted agents such as biologics for patients who cannot taper their corticosteroids.

# References and Resources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# Resources

**American Partnership for Eosinophilic Disorder (Apfed):** https://apfed.org/about-ead/hypereosinophilic-syndrome/

**NIH's Genetic and Rare Diseases Information Center (GARD):** https://rarediseases.info.nih.gov/diseases/2804/hypereosinophilic-syndrome