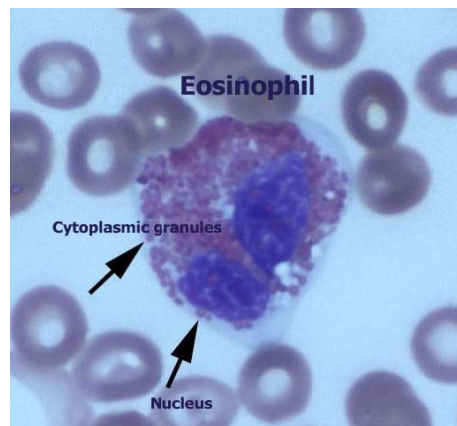


Hypereosinophilic Syndrome

What is an Eosinophil?

An eosinophil is a type of white blood cell that plays an important role in the human immune system. For example, it helps us fight off certain types of infections like parasites. Many different problems can cause high numbers of eosinophils in the blood, including allergies, asthma, some gastrointestinal disorders, parasitic infection, some blood/bone marrow diseases, certain cancers, and other problems. When eosinophils occur in higher than normal numbers in the blood, without a known cause and for a sustained period of time (more than 6 months), an innate disorder of eosinophils may be present.



Eosinophil, Courtesy of Dr. Margaret Collins

Normally, there are less than 4% eosinophils circulating in the blood vessels because they migrate quickly into the tissues and organs of the body. The highest concentration of eosinophils is usually found in the gastrointestinal tract. There is a complex series of chemical events that determine the levels of eosinophils in the blood and tissues. The proper balance and function of these events determines eosinophil production, their activity, and their time to die.

Eosinophil production is governed by several chemicals in blood called cytokines, including interleukin 3 (IL-3), interleukin 5 (IL-5), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Cytokines have many functions. They mediate and regulate immunity, inflammation, and hematopoiesis (production of blood cells) and different cytokines are produced in high amounts in different diseases. IL-5 appears to be the most important and specific cytokine that is responsible for the production and activity of eosinophils. Cytokines bind to specific chemicals on the surface of cells, called membrane receptors. This binding initiates the cascade of changes in other chemicals inside the cell leading toward the change in cell's behavior, including higher activity and multiplication. Many of the membrane receptors and intracellular chemicals belong to a class of chemicals called tyrosine kinases.

Hypereosinophilic Syndrome (HES)

HES is a group of disorders in which there are very high numbers of eosinophils found in the blood, for prolonged period of time for which a cause cannot be found. Continuous presence of high number of eosinophils in blood can eventually cause multiple organ tissue damage as these eosinophils infiltrate different tissues and cause inflammation. Unlike eosinophilic gastrointestinal disorders (EGID), which only affect the digestive tract, HES can affect any organ in the body, including the stomach and intestines, the heart, lungs, skin and other organs. The prognosis in HES depends on the organ systems involved, disease severity and response to therapy. Outcomes can vary greatly from one person to the next. Your doctor can best answers questions about prognosis in HES on an individual basis.

Since many different problems can cause high numbers of eosinophils in the blood, higher than normal blood eosinophil number alone does not mean an individual has, or will develop, HES. Criteria has been developed that must be fulfilled for an individual to be diagnosed with HES.

Criteria for diagnosis of HES

1. Peripheral blood eosinophilia (high numbers of eosinophils in the blood) more than 1500 eosinophils/ μl , for at least six months' duration.
2. End-organ (heart, lungs, GI tract, brain, skin, etc) involvement with eosinophil tissue infiltration (invasion) and injury.

3. Exclusion of known other causes for the eosinophilia such as parasitic infections and certain bone marrow/blood diseases.

Tests are needed to diagnose HES and include a complete blood cell count, including eosinophil count, blood samples for liver and kidney function, and blood tests for Vitamin B12 and tryptase. Depending on symptoms and test results, other studies may be performed. For instance, ultrasound (echocardiography) is used to look at the function of the heart. A chest x-ray may be done to examine the lungs. A bone marrow biopsy is recommended in patients suspected of having HES. It commonly reveals high number of eosinophils and some other abnormalities, suggestive of an innate bone marrow/blood disease of eosinophils. Therefore, HES is classified as hematologic neoplasm (disease of the blood and bone marrow) and is part of the larger group of Myeloproliferative Neoplasms. Closely related disease to HES is chronic eosinophilic leukemia (CEL). Major difference, in simple terms, is that in CEL all eosinophils found in the bone marrow and blood are proven to be identical (also called “clonal”, meaning that all originate from the same, one, abnormal eosinophil).

Standard Treatments for HES

Treatment goals include decreasing blood eosinophil numbers, preventing organ damage, and slowing disease progression. Treatments vary based on organs involved and disease severity, as well as on the presence of other medical problems a patient may have. Therapy for hypereosinophilic syndrome requires careful discussion with your health care providers regarding the risks and benefits of the treatment for your specific HES- related organ involvement.

Systemic steroids are often needed to treat HES with organ involvement or with systemic symptoms, like severe rash, fluid retention, and similar. Steroids are medications that fight (suppress) many types of inflammation. They are not specific for suppressing eosinophils, although eosinophils are particularly sensitive to them. Systemic steroids, those that are absorbed into the bloodstream (oral or IV), are very effective for treating a number of eosinophilic disorders. Steroids are very effective for controlling eosinophil numbers in blood and most HES patients can be maintained on oral steroid medication (called prednisone) for long period of time with good control of the disease. However, the blood eosinophils and disease symptoms generally return once steroids have been stopped. Long-term steroid use (especially when used in high doses) has, unfortunately, been associated with certain side

effects. Serious side effects can include osteoporosis (brittle bones from bone loss), infections, adrenal insufficiency (body becomes unable to properly respond to illness or stress), avascular necrosis (collapse of the bones in a joint, usually the hip), and stunted growth. Common side effects may include fluid retention (swelling), increased appetite, “moon-face”, and irritability.

Interferon alpha (IFNa) is used for a variety of diseases including infections (like hepatitis) and malignancies (like certain types of leukemia). IFNa has been shown to be effective in HES by suppressing the symptoms related to the disease. Toxicity, however, is a major obstacle to the use of this therapy. IFNa is commonly injected into the fatty tissue under the skin 3-5 times a week. Upon the initiation of therapy most patients experience influenza-like symptoms such as fever, chills, muscle aches, headaches, and joint pain. Other side effects of IFNa are low blood counts and elevated liver enzymes that require careful monitoring. These side effects usually lessen over time, but other toxicities can manifest themselves in various forms after long-term therapy. Overall experience with IFNa in myeloproliferative neoplasms is that about 25-30% of patients require discontinuation of therapy due to side effects. New long-acting forms of IFNa (pegylated interferons) have been developed over last few years and are now approved as therapy for hepatitis. These medications are administered only once a week and may, therefore, be better tolerated.

Cyclosporine is a potent medication that suppresses the immune system and it is used primarily to prevent organ rejection in people who have had organ transplants. In some patients with HES there might be evidence that the immune cells have a role in supporting the diseases existence (so called T cells) and cyclosporine may have a role as therapy in such cases.

Anti-neoplastic agents (chemotherapy) provide an alternative approach to therapy of advanced cases of HES. These are chemotherapeutic agents that may control the disease. They are used to treat many malignancies and are not specific for eosinophilic disorders. They are potent medications that kill cells that grow the fastest (eosinophils in HES) but may potentially have harmful side effects and are reserved only for more severe cases. Careful monitoring while taking these medications is essential. Chemotherapeutic agents that have

been used in HES include: Hydroxyurea, Methotrexate, Etoposide, Cyclophosphamide, Vincristine, and Cladribine.

Gleevec (Imatinib Mesylate) is a tyrosine kinase inhibitor. As a result of cell growth research, scientists have been able to develop a group of therapeutic agents known as tyrosine kinase inhibitors (TKI). Tyrosine kinases are enzymes in the cells with a variety of functions. By blocking the ability of tyrosine kinases to function, TKI provide a valuable tool for controlling malignant cell growth. Several years ago a discovery was made in some patients with HES of a genetic abnormality involving tyrosine kinase called PDGFR α . In these cases it seems that PDGFR α abnormality is responsible for disease existence. Gleevec is TKI that inhibits PDGFR α and may eliminate the disease in HES patients with PDGFR α abnormality. Genetic testing for PDGFR α abnormality is usually part of the bone marrow evaluation and can help determine if Gleevec is best first therapy. Not all patients with HES will respond to Gleevec as about 10-20% of patients may have PDGFR α . In HES patients without PDGFR α abnormality Gleevec can be tried as therapy but it is unlikely to eliminate the disease; it may help control the disease signs and symptoms for a period of time.

New therapies for HES

For patients who are refractory to conventional therapies, use of monoclonal antibody therapy (medications that selectively bind to specific proteins) should be considered. Two drugs are currently available: mepolizumab that targets interleukin-5, a cytokine in blood that is recognized as very important protein that governs eosinophil growth, and alemtuzumab that targets the CD52 protein expressed on the surface of eosinophils (its function not yet known). Mepolizumab, therefore, by blocking interleukin-5 eliminates a cytokine from blood that provides signal for eosinophil growth. Alemtuzumab, on the other hand, by binding to CD52 kills the eosinophil. Mepolizumab is not approved therapy yet and is currently available in a compassionate-use program (<http://clinicaltrials.gov>) sponsored by GlaxoSmithKline, for patients with life-threatening HES that is not responding to usual therapy. Alemtuzumab is currently approved by the Food and Drug Administration for use in B-cell chronic lymphocytic leukemia.

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