EOSINOPHILIA

Normal mean eosinophil count in the circulating blood is 400/mm3. Normally, most of the eosinophils reside in the connective tissue located in the immediate proximity of the epithelial lining of the gut, respiratory tract and urogenital tract. Their number and activation increase as a response to antigens, especially when these antigens are deposited in the above tissues. A response is characterized by immediate hypersensitivity reaction, mediated by IgE or delayed hypersensitivity reaction, mediated by T-lymphocytes. Severity of eosinophilia is graded according to the presence of their absolute number in the circulating blood as follows:

- **Mild eosinophilia: 400–1,500/mm3**
- **Moderate eosinophilia: 1,500–5,000/mm3**
- **Severe eosinophilia: greater than 5,000/mm3.**

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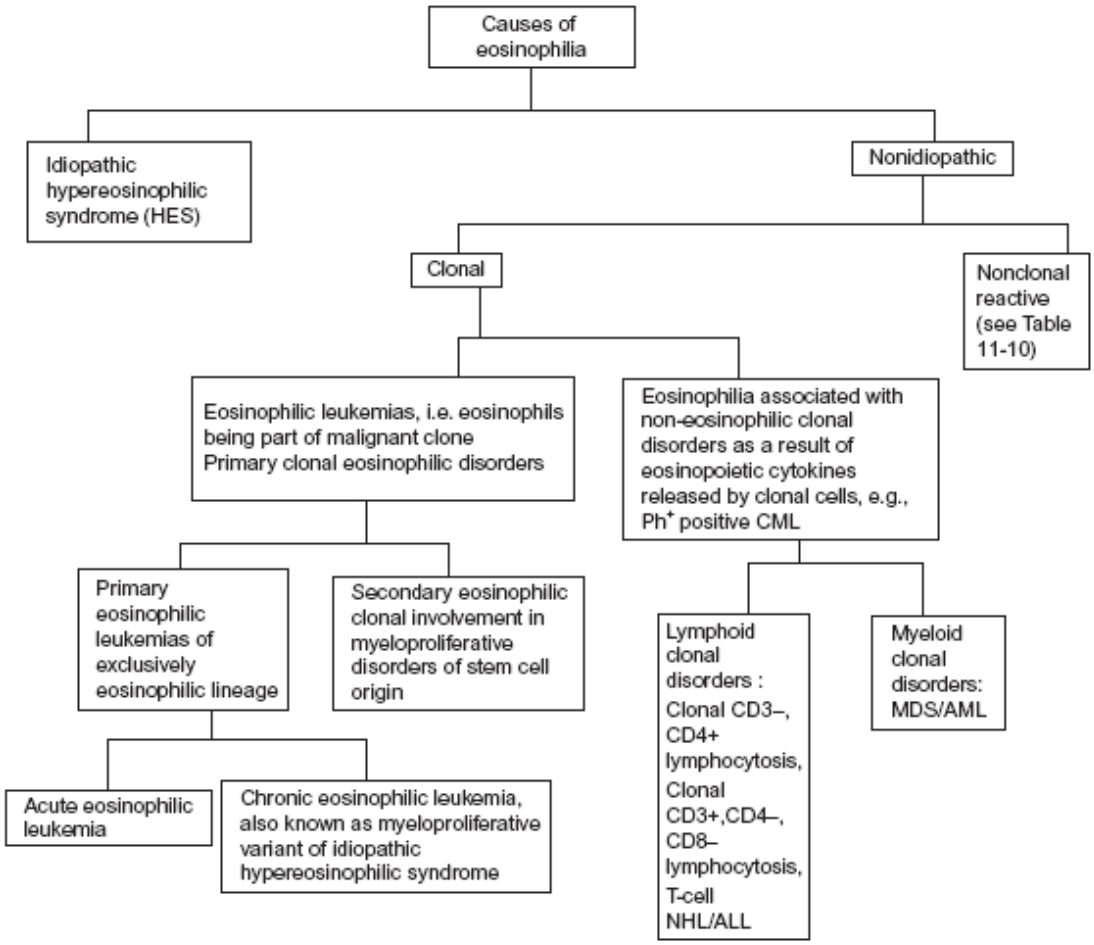

Etiologic Classification of Eosinophilia.

Nonclonal (Reactive) Causes of Eosinophilia

Allergic disorders
Asthma, hay fever, urticaria, drug hypersensitivity
Immunologic disorders
Omenn syndrome (severe combined immunodeficiency and eosinophilia)
Skin disorders
Eczema, scabies, erythema toxicum, dermatitis herpetiformis, angioneurotic edema, pemphigus
Parasitic infestations
Helminthic: *Ascaris lumbricoides*,[a] trichinosis, echinococcosis, visceral larva migrans,[a,b] hookworm,[a] strongyloidiasis,[a] filariasis[a]
Protozoal: malaria, pneumocystis, toxoplasmosis
Hematologic disorders
Hodgkin disease, postsplenectomy state, eosinophilic leukemoid reaction, congenital immune deficiency syndromes, Fanconi anemia, thrombocytopenia with absent radii, Kostmann disease, infectious mononucleosis, familial reticuloendotheliosis
Familial eosinophilia
Irradiation
Pulmonary eosinophilia
Eosinophilic pneumonitis (Loeffler syndrome), pulmonary eosinophilia with asthma, tropical eosinophilia
Miscellaneous
Idiopathic hypereosinophilic syndrome,[b] periarteritis nodosa, metastatic neoplasm, cirrhosis, peritoneal dialysis, chronic renal disease, Goodpasture syndrome, sarcoidosis, thymic disorders, hypoxia
Gastrointestinal disorders
Eosinophilic gastroenteritis, milk precipitin disease, ulcerative colitis, protein-losing enteropathy, regional enteritis, allergic granulomatosis
Idiopathic

Non-Idiopathic Eosinophilia
Eosinophilia, for which a cause is ascertained, can be clonal or reactive.

Primary Clonal Eosinophilic Disorders

These include eosinophilic leukemias of exclusively eosinophilic lineage, e.g. acute eosinophilic leukemia and chronic eosinophilic leukemia (also known as myeloproliferative variant of idiopathic hypereosinophilic syndrome). The following karyotypic abnormalities associated with chronic eosinophilic leukemia have been reported: Majority of patientshave t(5;12) (q33:p13).

Secondary clonal involvement of eosinophil lineage can occur in myeloproliferative disorders of stem cell origin, e.g. Ph1-positive chronic myeloid leukemia. Eosinophilia is observed less commonly in polycythemia vera, myelofibrosis and essential thrombocythemia.

Non-Clonal Eosinophilic Disorders

In non-clonal eosinophilic disorders, clonal cells release eosinopoietic cytokines and thus, are associated with eosinophilia. These noneosinophilic clonal disorders may be lymphoid or myeloid in their clonality. Lymphoid clonal disorders associated with eosinophilia include dermatologic patients with abnormal clones of T-cells producing interleukin-5, patients with acute lymphoblastic leukemia and T lymphoblastic lymphoma. Patients who present with T-cell lymphoblastic lymphoma and eosinophilia may be predisposed to developing secondary AML. Myeloid clonal disorders associated with eosinophilia include myelodysplastic syndromes, acute myeloid leukemia with chromosome 16 abnormality, the 8p myeloproliferative syndrome, myelodysplastic syndromes and systemic mastocytosis. The following cytogenetic abnormalities associated with acute myeloid leukemia with eosinophilia have been reported: inv (16) (p13:q22), t(16:16) (p13:q22), t(5;16) (q33:q22) and monosomy 7.

Eosinophilia in Newborn Period

A mild eosinophilia with eosinophil count greater than 700/mm3 is observed in 75% of growing preterm infants. It is present in the second or third week of life and persists for several days or sometimes for weeks. Eosinophilia of prematurity is considered to be benign, although it could be associated with a higher incidence of sepsis, especially, with Gram-negative bacteria.
A complete absence of eosinophils is observed in neonates who fare poorly and subsequently die.

Familial Eosinophilia

Familial eosinophilia is an autosomal dominant disorder. A genome wide search showed evidence of linkage on chromosome 5q31-33 between markers D55642 and D55816. Some of the affected members are found to have high white blood cell counts, lower red cell counts, intermittent thrombocytopenia, cellular infiltration with mast cells in the liver and bone marrow,or involvement of the heart and nervous system. The levels of IL-3, IL-5 and GM-CSF are normal

Idiopathic Hypereosinophilic Syndrome (HES)

Definition
HES includes a heterogeneous group of disorders defined by:
• A persistent eosinophilia of .1,500/mm3 for longer than 6 months
• Absence of evidence of known causes of eosinophilia despite a comprehensive work-up for such causes
• Signs and symptoms of organ involvement, directly attributable to eosinophilia, including hepatomegaly, splenomegaly, heart disease, diffuse or focal central nervoussystem (CNS) abnormalities, pulmonary fibrosis, fever, weight loss, or anemia (i.e.
evidence of end organ damage with histologic demonstration of tissue infiltration by eosinophils or objective evidence of clinical pathology in any organ system associated

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with eosinophilia and not clearly attributable to another cause).

Epidemiology

HES most commonly occurs between the ages of 20 and 40 years with a male to female ratio of 4:1. Clinical manifestations of HES in pediatric age group are similar to HES in adult patients. In children, HES may be associated with trisomy 8 or trisomy 21.

Clinical Presentation
The disease generally has a gradual onset. The chief complaints include anorexia, fatigue, weight loss, recurrent abdominal pain, fever, night sweats, persistent non-productive cough, chest pain, pruritus, skin rash and congestive heart failureOrgan Involvement
Cardiovascular Disease

HES-associated heart disease evolves through three stages:
• Early acute phase, associated with degranulating eosinophils in the heart muscle (5–6 weeks into eosinophilia)
• Subacute thrombotic stage (10 months into eosinophilia)
• Chronic stage of fibrosis (24 months into eosinophilia). Cardiac disease involves both ventricles and can cause incompetence of mitral and tricuspid valves.

Coagulation System
Eosinophilia can cause a hypercoagulable state, the etiology of which is unclear. Eosinophil major basic proteins inactivate thrombomodulin, thus, resulting in unavailability of activated protein C. Intracardiac thrombus, deep venous thrombosis, dural sinovenous thrombosis and/or arterial thrombosis can occur.
Nervous System Complications

1. Encephalopathy (altered behavior and cognitive function).
2. Thrombotic strokes.
3. Peripheral neuropathies including mononeuritis multiplex, symmetrical sensory-motor neuropathy and radiculopathy.
4. Retinal hemorrhages.
Gastrointestinal Complications

1. Hepatomegaly due to eosinophilic infiltration of the liver results in liver function abnormalities.
2. Enteropathy due to blunting of the villi and cellular infiltration in the lamina propria results in diarrhea and fat malabsorption.
3. Eosinophilic infiltration of colon results in colitis.
Spleen

Splenomegaly with disruption of its architecture can occur.

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Dermatologic Manifestations
The most common lesions include pruritic papules and nodules, urticarial plaques and angioedema. Vesiculobullous lesions, generalized erythroderma and aquagenic pruritus occur in some patients. Digital necrosis may result from vasculitis and microthrombiPulmonary Complications

Nocturnal cough, fever, diaphoresis can occur due to accumulation of eosinophils in the lungs. Pulmonary fibrosis can also occur.
Treatment

Treatment

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Treatment of reactive or non-clonal eosinophilia: Treat the underlying cause e.g. treatment of parasitic infections with appropriate anti-parasitic drugs

Treatment of clonal disease: Myeloid clonal disease: Treat with appropriate chemotherapy±hematopoietic stem cell transplantation. Lymphoid malignancies: Treat with appropriate chemotherapy CD3−, CD4+ Lymphoid clonal disease with high levels of IL-5, usually associated with dermatologic manifestations: Treat with cyclosporine A, glucocorticoids or 2CDA CD3+, CD3−, CD8− Lymphoid clonal induced eosinophilia with high levels of IL-5 and usually associated with dermatologic manifestations: Treat with glucocorticoids, cyclosporine A

Treatment of HES caused by interstitial deletion of 4q12 resulting in a fusion gene FIP1L1-PDGFRA: Imatinib mesylate, adult dose: 400 mg/day. Pediatric dose: not established

Treatment of idiopathic HES: Glucocorticoids, Hydroxyurea, α-interferon, vincristine, thioguanine, or etoposide.[a] Use these agents sequentially. If the response is unsatisfactory, then treat with imatinib mesylate at doses of 100–200 mg/day (of interest is that patients with normal serum Interleukin-5 values respond to imatinib, but not the ones with high values). During acute life threatening presentation of HES, high dose 10–20 mg/kg of solumedrol (methylprednisolone) may be required, but usually 1–2 mg/kg of prednisone may be sufficient. Treatment with allogeneic hematopoietic stem cell transplantation is reserved for patients with HES refractory to above mentioned therapies. Treatment of patients with idiopathic HES but without organ involvement: None. Treatment is not necessary, but continuous periodic monitoring for organ involvement and emergence of clonality is warranted. Also, continue search for rare reactive causes of eosinophilia.

The following eosinophilic disorders with single organ involvement may progress into HES:

- Eosinophilic gastroenteritis
- Gleich syndrome (episodic eosinophilia with angioedema)
- Loeffler syndrome
- Schulman syndrome (eosinophilic fascitis)
- Well syndrome (eosinophilic cellulitis)
- Parasitic infections with eosinophilia

[a]Doses of some of the drugs: Thioguanine, 40–60 mg/m^2/day orally, Vincristine, 1.5 mg/m^2/week IV, Etoposide, 60–100 mg/m^2/day for 3–5 days IV every 3–6 weeks, Hydroxyurea, 10–20 mg/kg/day orally, Cyclosporine 6 mg/kg/day orally (trough level 100–200 μg/L), α-Interferon 5×10^6 units/m^2/day subcutaneously or IM.