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ICON-Eosinophilic Disorders-An Update on HES and CSS

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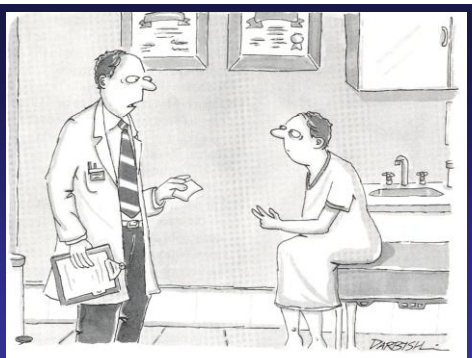


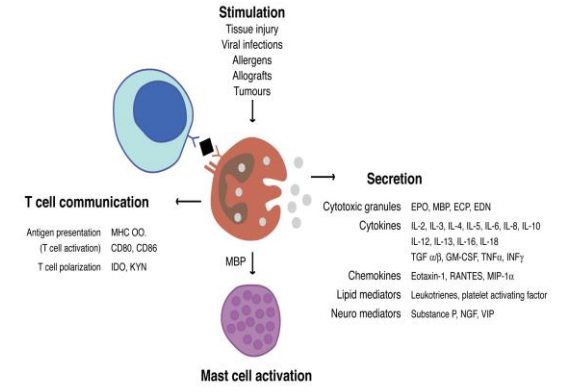
"Try this—I just bought a hundred shares."

Disclosure Statement
Lanny J. Rosenwasser, MD

- RESEARCH STUDIES
  Alcon, A-Z, GlaxoSmithKline, Genentech, Novartis MBBH/MacArthur Foundation, National Institutes of Health
- CONSULTANT
  Alcon, , A-Z, Genentech, GlaxoSmithKline, Novartis, Regeneron, Sanofi-Aventis
- SPEAKERS' BUREAU
  Alcon, A-Z, Genentech, Novartis

Learning Objectives

- Understand the biology of eosinophils
- Understand the role of eosinophils in allergic disease,asthma, and eosinophilic disorders
- Understand treatment of eosinophilic disorders and allergy/asthma including the use of biotherapeutics



Biology of Eosinophils

Origin	Bone Marrow derived myeloid cell development driven by cytokines IL-3, IL-5, and GMCSF
Tissue Distribution	Widespread, primarily epithelial and subepithelial tissues, responsive to chemokines for movement and adhesion
Functions	Host Defense and Tissue Remodeling
Factors/Product	Cationic Proteins – (MBP, ECP, EDN, EPO) Cytokines, Chemokines, PAF, Prostaglandins Leukotrienes

Degrees of Eosinophilia

Severity	Level (Eos/ul)	Differential Diagnosis
Mild	500-1000	allergic diseases, atopy, asthma, drug, allergy, bacterial and viral infections
Moderate	1500-5000	Parasitic Infection, HES Churg-Strauss Syndrome, cancers, Sezary's Sydrome
Severe	>5000	HES, eosinophilic leukemia, myeloproliferative disorders, and cancer

Treatment of Eosinophilia

- Treat Underlying disorders as primary treatment
- For HES:
  - Steroids
  - Interferon alpha
  - Hydroxyurea
  - Imatinib
  - Anti IL-5 (Mepolizumab, Reslizumab)
  - Anti IL-5 receptor (MEDI-563)

ICON Documents

- iCAALL - WAO,AAAAI,ACAAI,EAACI
- Consensus Documents on Critical Topics in Allergy/Immunology
- Advocacy

Causes of Reactive Eosinophilia/HE

Common Causes:
Helminth Infections
Allergic Reactions
Atopic Diseases
Drug-Reactions (Allergic or Toxic)

Rare Causes:
Chronic Graft-versus-Host Disease
Hodgkin's Disease
B or T Cell Lymphoma/Leukemia
Langerhans Cell Histiocytosis
Solid Tumors/Malignancy
Scabies, other infestations
Allergic Bronchopulmonary Aspergillosis
Chronic Inflammatory Disorders (e.g. IBD)
Autoimmune Diseases

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*In most cases, eosinophilia is attributable to eosinophilopoietic cytokines
IBD, inflammatory bowel disease

Organ-restricted (inflammatory) conditions accompanied by HE

Eosinophilic Gastrointestinal Disorders (EGID)
- Eosinophilic Esophagitis
- Eosinophiic Gastro-enteritis
- Eosinophilic Colitis

Eosinophilic Pancreatitis
Eosinophilic Hepatitis
Eosinophilic Ascites
Pulmonary Eosinophilic Syndromes
- Eosinophilic Asthma
- Eosinophiic Bronichitis
- Eosinophilic Pneumonia
- Eosinophil Pleuritis

Eosinophilic Nephritis
Eosinophilic Cystitis
Eosinophilic Endometritis and Myometritis
Eosinophilic Mastitis
Eosinophilic Ocular Disorders
Eosinophilic Myocarditis
Eosinophilic Panniculitis
Eosinophilic Synovitis
Eosinophilic Fasciitis (Shulman's Syndrome)
Dermatological Conditions/Diseases*

In addition to the disorders listed in this table, there are many other chronic conditions where blood or/and tissue HE is detectable, such as tissue fibrosis, ocular disorders, atopic dermatitis, nasal polyposis, interstitial nephritis, and acute necrotizing myocarditis, IgE, immunoglobulin E.
*Dermatologic conditions including inflammatory reactions are listed in Table 1.

Dermatological Diseases Accompanied by Eosinophilia

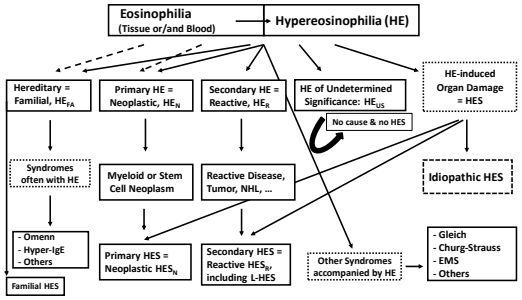
Allergic contact dermatitis
Angiolymphoid hyperplasia with eosinophilia
Annular erythema of infancy
Atopic dermatitis
Bullous pemphigoid
Coccidiomycosis
Drug eruptions
Eosinophilic fasciitis
Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy
Eosiniphilic pustular folliculitis-all variants
Erythema toxicum neonatorum
Eosinophilic ulcer of the oral mucosa
Eosinophilic vasculitis
Granuloma faciale
Infestations (parasites/ectoparasites including scabies, bed bugs and cutaneous larva migrans)
Incontinentia pigmenti
Kimura disease
Langerhans cell histiocytosis
Mycosis fungoides and Sezary syndrome
Pachydermatous eosinophil dermatitis
Pemphigus variants
Pregnancy-related dermatoses
Pseudolymphoma
Urticaria/angioedema
Vasculitis Wells Syndrome (eosinophilic cellulitis)

***Dermatological disorders in which eosinophils are a component of the characteristic histological pattern and often associated with peripheral blood eosinophilia. Evidence for relevant involvement of eosinophils in these cutaneous diseases is provided by observation of intact eosinophils in lesional tissue sections and/or by immunostains for their toxic granule proteins, which are deposited in tissues in the presence of absence of identifiable eosinophils. Note that eosinophils are a predominant inflammatory cell in a brad rang of other cutaneous diseases.**

Selected Defined Syndromes Associated with Eosinophilia or HE

Gleich Syndrome	Cyclic recurrent angioedema, HE, and elevated IgM, often with clonal T cells regarded as one of several possible clinical presentation of lymphoid HES by some of the faculty members)
Churg-Strauss Syndrome	Necrotizing vasculitis with HE (ANCA+ and ANCA-Subvariants)
Eosinopilia Myalgia Syndrome	Severe myalgia plus HE, often accompanied by neurologic symptoms and skin changes; epidemic cases have been attributed to L-tryptophan exposure (Subvariant: Toxic oil syndrome)
Hyper IgE Syndrome	Hereditary immunodeficiency syndrome with HE and elevated levels of IgE, often with eczema and facial anomalies. Known gene mutations: Autosomal dominant, AD-HIES: *STAT3* mutations Autosomal recessive, AR-HIES: *DOCK8* mutations

Abbreviations: HE, hypereosinophilia; HES, hypereosinophilia syndrome; ANCA, anti-neutrophil cytoplasmic antibodies



Valent et al. Figure 1

Hypereosinophilic syndromes: diagnostic criteria

- Eosinophil counts > 1500/mm^3 for at least 6 months, or less than 6 months with evidence of organ damage
- Lack of evidence for parasitic, allergic, or other recognized causes of eosinophilia
- Symptoms and signs of organ system involvement

Hypereosinophilic syndromes: clinical features

Myeloproliferative	Lymphoproliferative
FIP1L1-PDGFRA gene; other as yet unidentified mutations possible	T-cell clone producing Th2 cytokines
"Classical HES" – males with endomyocardial disease; increased number of atypical mast cells or systemic mast cell disease variant (with peripheral blood eosinophilia) or overlap	
High serum tryptase level, tissue fibrosis, elevated vitamin B12 levels, splenomegaly and bone marrow biopsies with increased numbers of CD25+ atypical spindle-shaped mast cells	

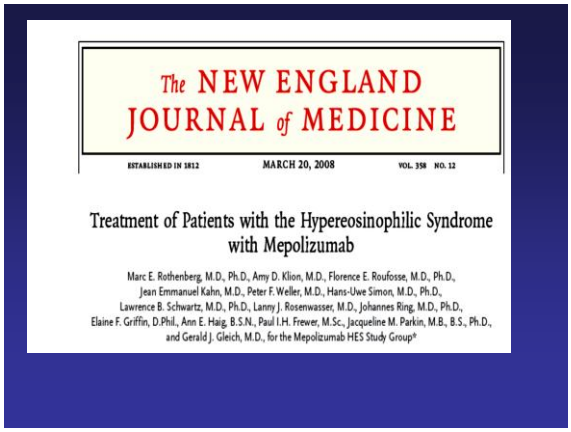
Clinically Distinguishing Characteristics of the Sub-types of Hypereosinophilic Syndrome (HES)

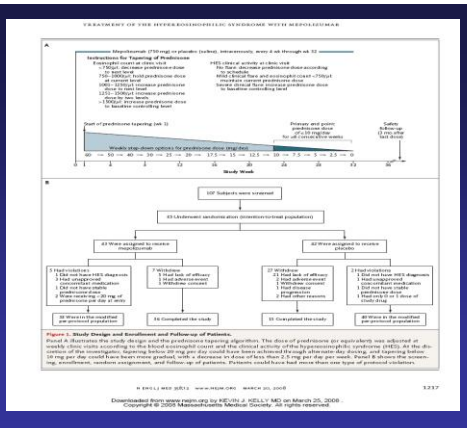
Myeloproliferative HES	Lymphocytic HES
Cardiac complications	Cutaneous manifestations (pruritus, eczema, erythroderma, urticaria, angioedema)
Anemia and/or thrombocytopenia	Increased serum immunoglobulin E levels
Abnormal leukocyte alkaline phosphatase score	Increased interleukin-5-producing T-cell population with cytogenetic changes
Increased serum vitamin B_{12}	Polyclonal hypergamma-globulinemia
Chromosomal abnormalities Hepatomegaly, splenomegaly Splenomegaly	

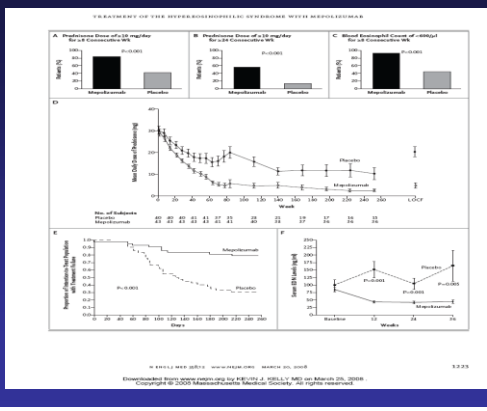
Treatment Options for Hypereosinophilic Syndrome

Treatment:

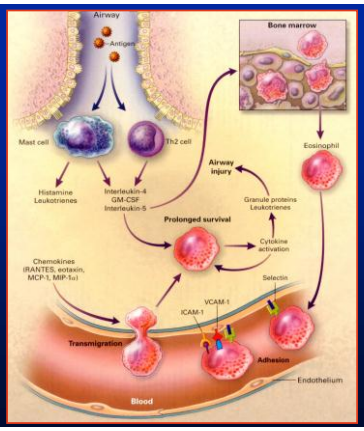
- Corticosteroids
- Cytotoxic agents
  (hydroxyurea, vincristine, cyclophosphamide, busulfan, methotrexate, chlorambucil)
- Biological response modifiers
  Interferon-alpha
- Cyclosporine
- Imatinib mesylate
- Mepolizumab



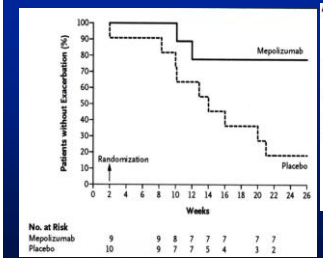


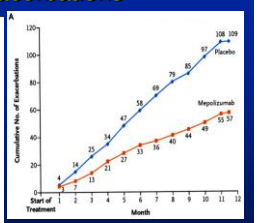


Key Central Role of IL-5 in Asthma



Anti-IL-5 in Human Asthma: Reduction in Exacerbations

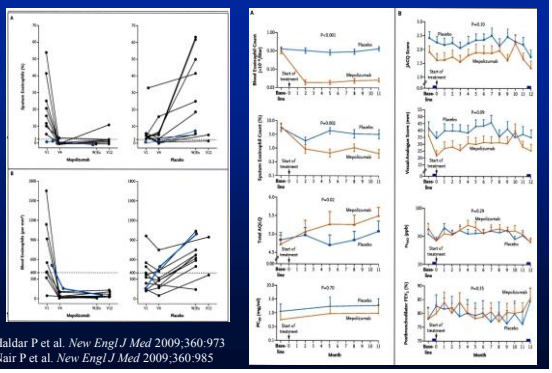




- Severe (CCS-dependent) asthma
- Sputum eosinophilia required for enrollment
- No improvement in FEV1, control, symptoms

Haldar P et al. *New Engl J Med* 2009;360:973
Nair P et al. *New Engl J Med* 2009;360:985

Anti-IL-5 in Human Asthma:



Haldar P et al. *New Engl J Med* 2009;360:973
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Classification of Vasculitis

- Necrotizing Vasculitis
  - Polyarteritis Nodosa
  - Microscopic Polyangiitis
  - Churg Strauss Syndrome
- Granulomatous Vasculitis
  - Wegener's Granulomatosis
  - Lymphomatoid Granulomatosis
  - Temporal Arteritis
  - Takaysau's Arteritis
- Hypersensitivity Vasculitis
  - Drug reaction HSP
  - Infection EMC
  - Auto Immunity Cancer
- Miscellaneous
  - Kawasaki's Disease
  - Bechet's Disease

ANCA - Specificity

cANCA (Proteinase 3)	Wegener's granulomatosis
pANCA	Microscopic polyangiitis
(MPO)	PAN
(Cathepsin)	Churg-Strauss syndrome
(Lactoferrin)	RA
(Elastase)	Hepatitis
	HIV
	Inflammatory bowel disease

Prevalence of ANCA

Disease	cANCA	pANCA
	percent	
WG	80	14
MPA	45	45
CSS	10	60
PAN	5	15

Adapted from R.W. Simms, NEJM 339:775-763:1998

Organ systems involved by Churg-Strauss syndrome

Respiratory tract - Asthma- pulmonary infiltrates, alveolar hemorrhage, sinusitis

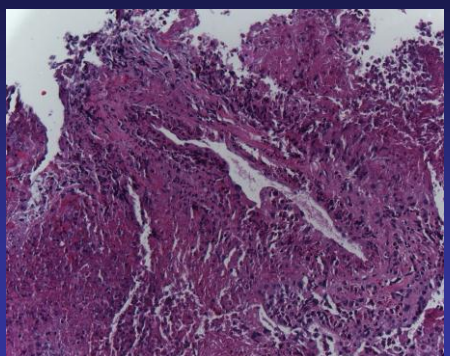
Nervous system - Mononeuritis multiplex, polyneuropathy, cerebral hemorrhage, stoke

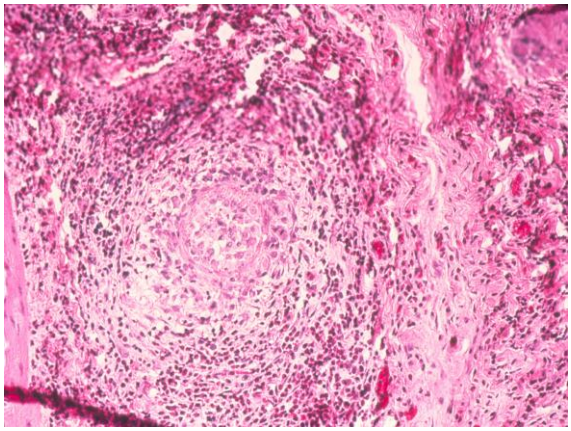
Skin - palpable purpura, skin nodules, urticaria, livedo

Heart - cardiomyopathy, myocarditis, heart failure, arrhythmia

Kidney - glomerulonephritis, renal insufficiency, renal infarct

GI tract - ischemic bowel, pancreatitis, cholecystitis





Diagnosis of Churg-Strauss Syndrome Historical Perspective

Churg and Strauss, 1951	1) Asthma 2) Necrotizing vasculitis of small and medium arteries and veins 3) Eosinophil infiltration around involved vessels and tissues 4) Extravascular granulomas 5) Fibrinoid necrosis of involved tissues
Lanham, 1984	1) Asthma 2) Eosinophilia >1.5 x 10^7 3) Systemic vasculitis involving 2 or more organs
American College of Rheumatology, 1990	1) Asthma 2) Eosinophilia >10% 3) Neuropathy 4) Pulmonary infiltrates 5) Paranasal sinus abnormality 6) Extravascular eosinophil infiltration on biopsy
Chapel Hill Criteria, 1994	1) Asthma 2) Eosinophilia 3) Eosinophil rich granulomatous inflammation involving the respiratory tract 4) Necrotizing vasculitis affecting small-to-medium sized vessels

Diagnosis of Churg Strauss Syndrome

- Asthma
  -Atopy
- Neuropathy
- Eosinophilia
  - Blood or Tissue
- Sinus Abnormalities
- Pulmonary Infiltrates/Vasculitis
- (Visceral Sx, Abnl LFT's, Hypertension)
  -Angio and CT for Nodose lesions, positive ANCA

Other Clinical Issues

- Forme Fruste of CSS - prodromal SX but not full blown CSS
- Major Differential Diagnosis:
  - HES
  - WG
  - PAN
  - MPA (SNV overlap)

Incidence of Common Vasculitis NHS, UK, 1998-1994

Vasculitis	Annual Incidence per million/GP
HV	31
WG	12
CSS	6
MPA	6
PAN	12

Watts et al. Seminar A&R 1995;25:28-34

Treatment of Systemic Vasculitis

Cyclophosphamide
Azathioprine
With or without Prednisone
Therapy continued for one year post-remission
Relapses treated as initial course
Long Term Remissions

Complications of Treatment of Systemic Vasculitis

- Decreased Marrow Reserve
- Hemorrhagic cystitis
- Nausea
- Herpes zoster
- Sterility
- Lymphoma

Newer Approaches to Therapy of Systemic Vasculitis

TM/Sulfa
Pulse Cyclophosphamide
Methotrexate, Azathioprine
Mycophenylate mesylate (Cellcept)
IVIG
Interferon-α-2b, Anti-IgE(Xolair)-CSS
Enbrel, Remicade
Rituxan

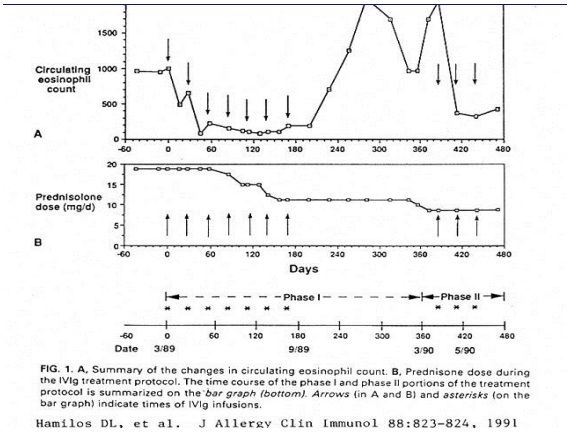


FIG. 1. A, Summary of the changes in circulating eosinophil count. B, Prednisone dose during the IVIg treatment protocol. The time course of the phase I and phase II portions of the treatment protocol is summarized on the *bar graph (bottom). Arrows* (in A and B) and *asterisks* (on the bar graph) indicate times of IVIg infusions.

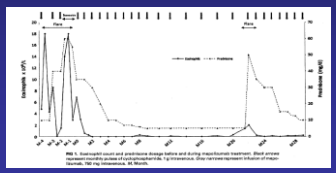
Hamilos DL, et al. J Allergy Clin Immunol 88:823-824, 1991

IL-5 pathway inhibition in the treatment of asthma and Churg-Strauss syndrome

TABLE I. Promising anti–IL-5 drugs, anti–IL-5Rα drugs, or both

Drug	Target	Mode of action	Recent results	References
Mepolizumab	IL-5	Neutralizing	Steroid sparing and reduction of exacerbations in eosinophilic asthma; steroid sparing in patients with CSS and HES	1-4, 8
Reslizumab	IL-5	Neutralizing	Steroid sparing and reduction of exacerbations	9
MEDI-563	IL-5Rα	Cytotoxic and neutralizing	Reduction of eosinophilia	6, 7

HES, Hypereosinophilic syndrome.



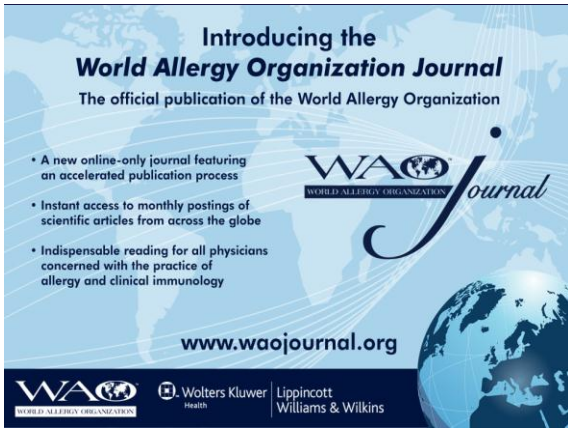
J ALLERGY IMMUNOL 2010 APR

Table 5. Clinical outcome of 94 patients with CSS

Clinical Outcome	No.(%)
Remission of Vasculitis	86/94 (91.5)
Relaye of Vasculitis	22/86 (25.6)
Treatment Failure	8/94 (8.5)
Death during follow-up	23 (24.5)

Guillevin L, et. Al. Medicine 78:26-37, 1999

"It's a very rare disease—it doesn't have a cure. It doesn't even have a spokesperson."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