Azienda Ospedaliero Universitaria Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

**Decima Giornata Fiorentina dedicata ai pazienti con malattie mieloproliferative croniche**

**Sabato 18 maggio 2024**

# "Sindrome Ipereosinofila: diagnosi e gestione"

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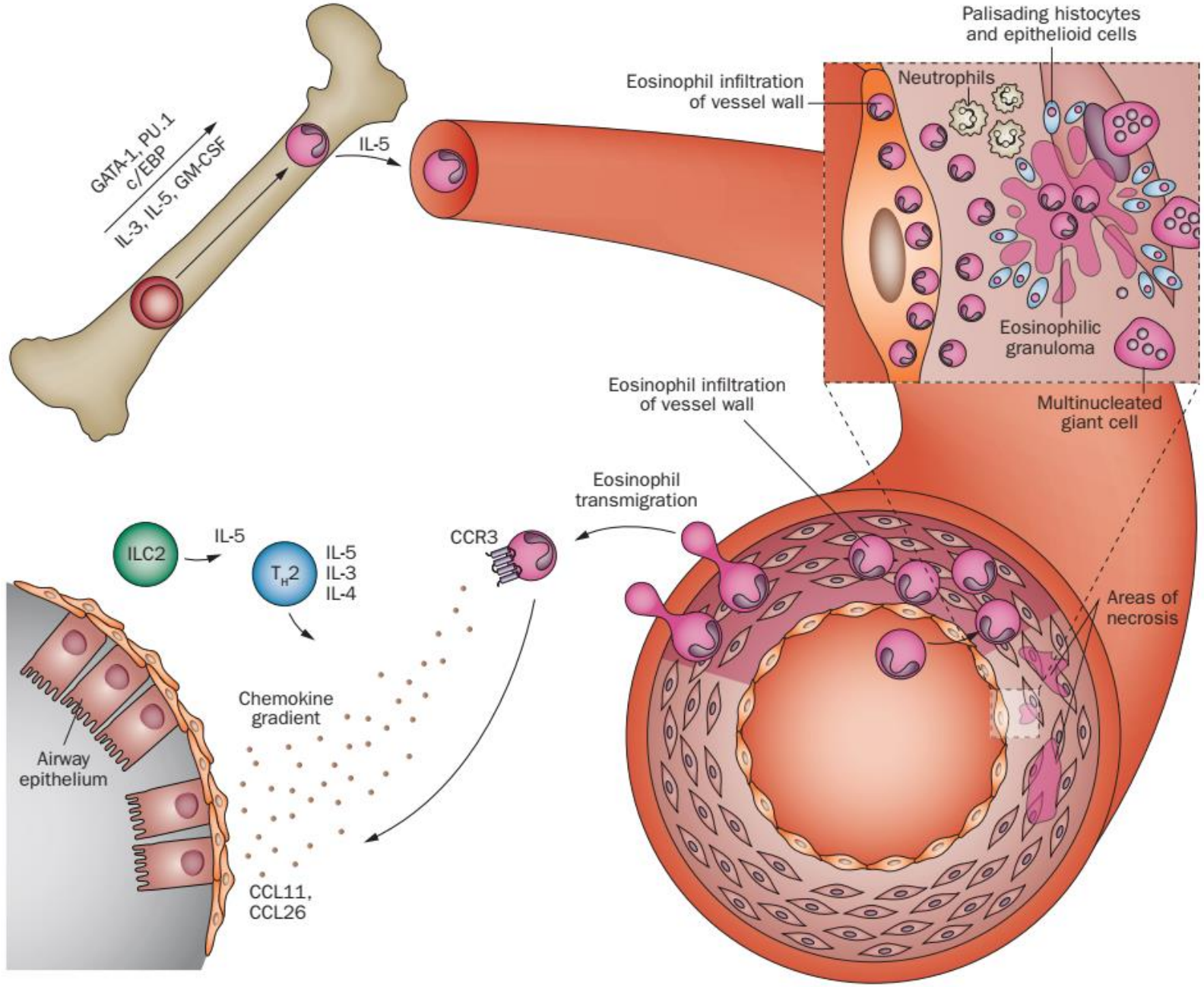
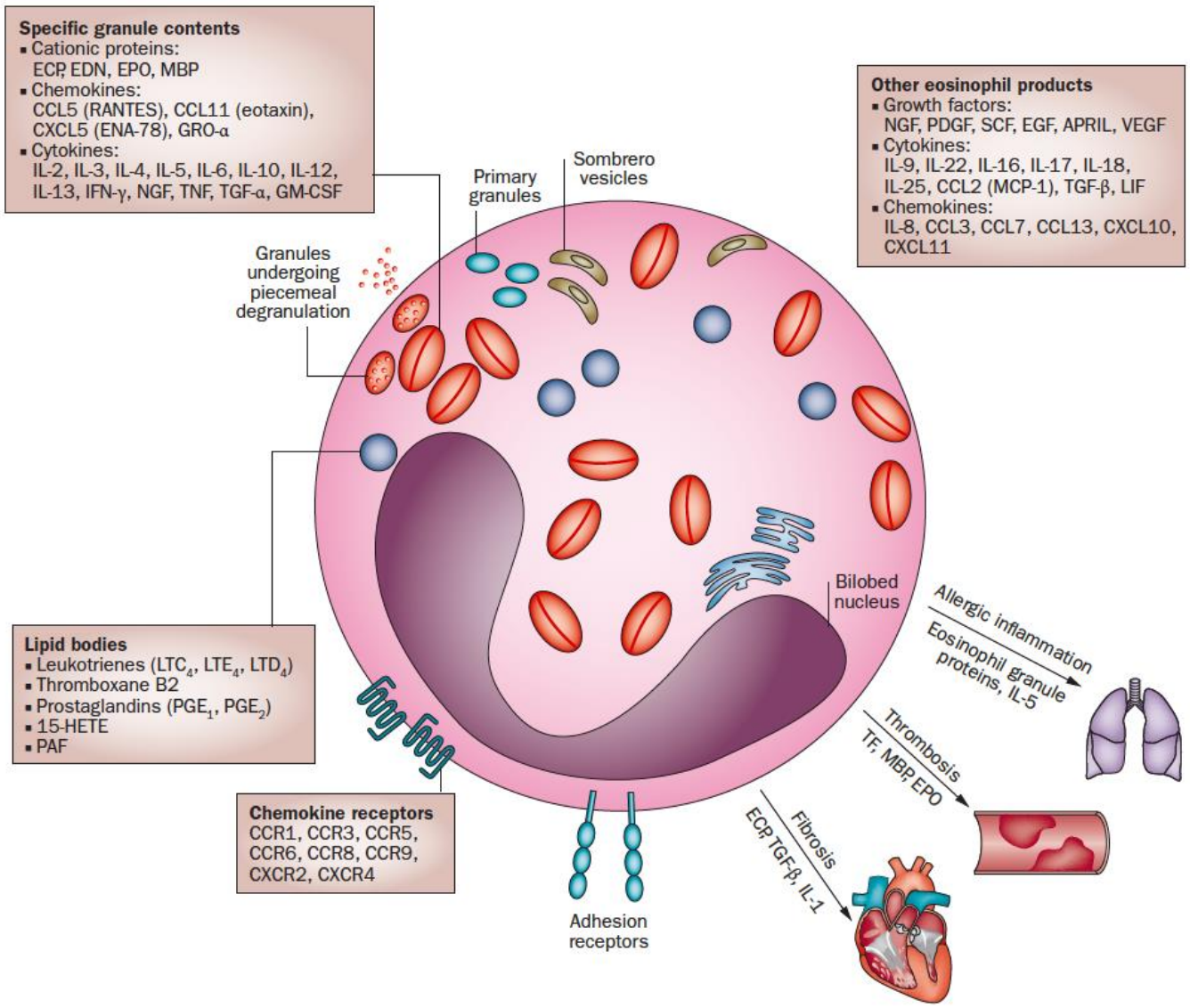
# Eosinophils’ biologic features




Khoury P, *Nat Rev Rheumatol* 2014




Khoury P, *Nat Rev Rheumatol* 2014

# Hypereosinophilia:
# definition, classification and clinical approach

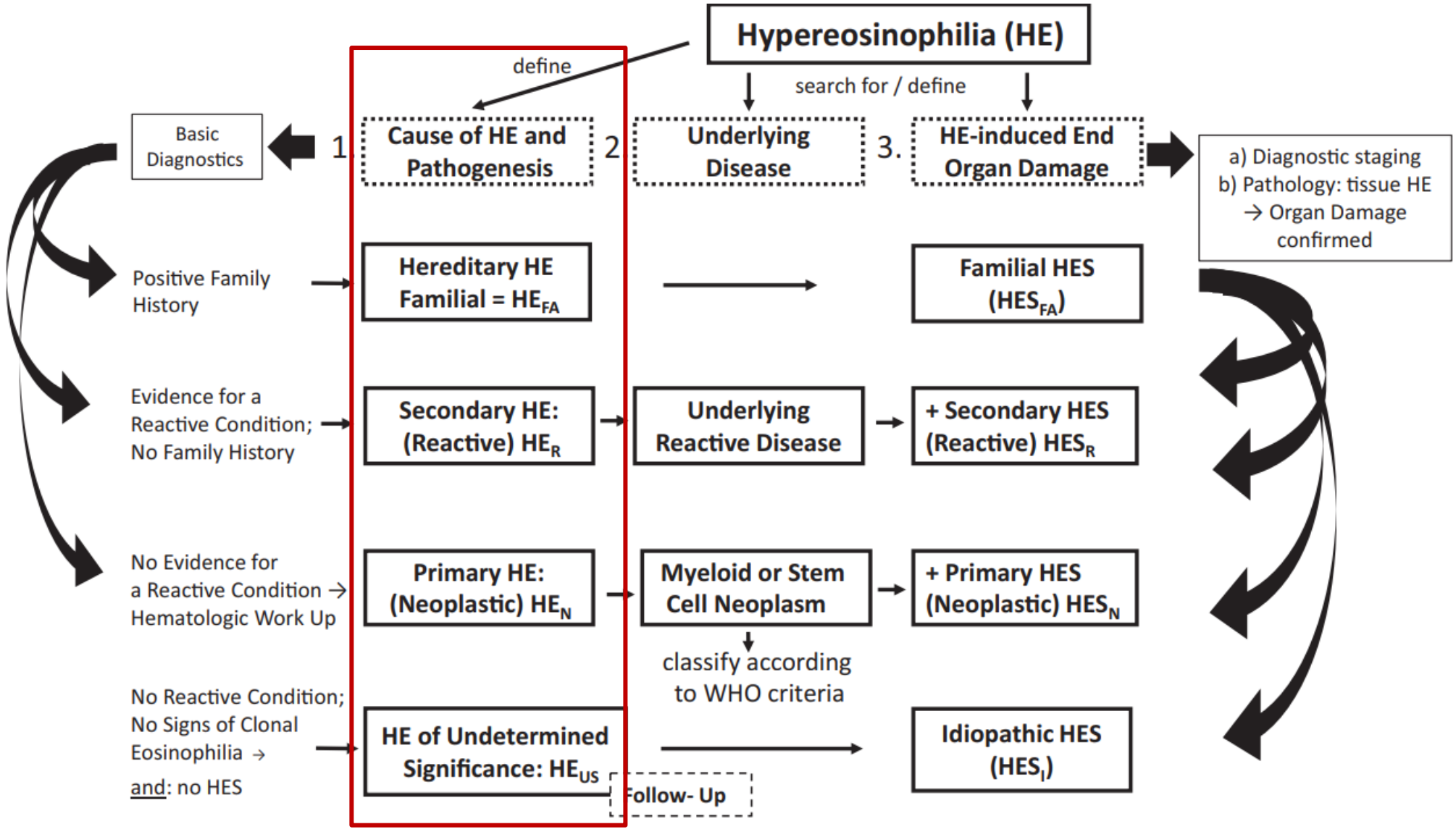
# Definition of (Hyper)eosinophilia and hypereosinophilic syndrome

Normal: <5%, < 500/mm$^3$

Eosinophilia: 500-1500/mm$^3$

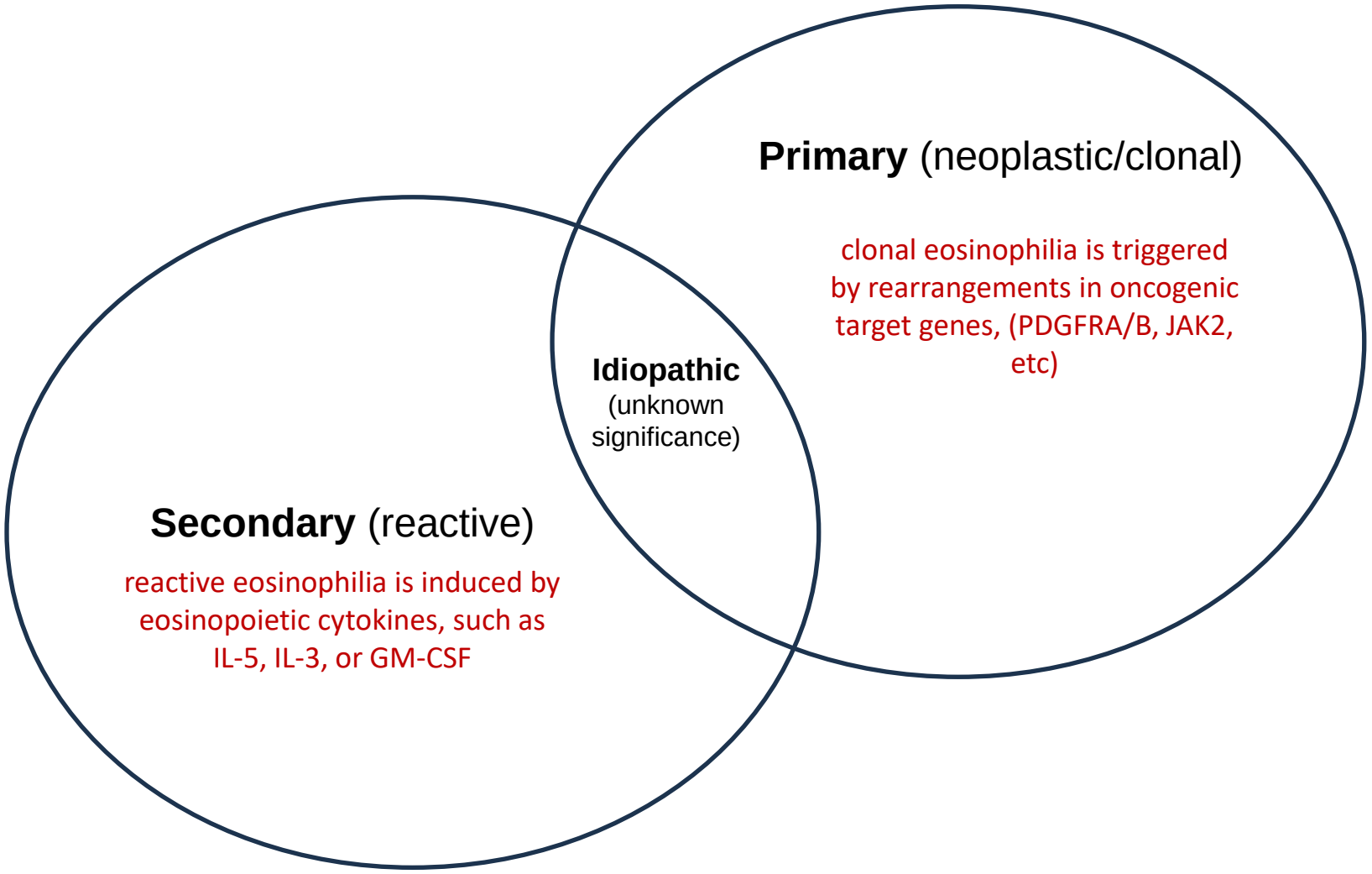
| Name/term | Abbreviation | Definition and criteria |
|---|---|---|
| Hypereosinophilia | HE | ≥1.5 eosinophils ×10$^9$/L peripheral blood on two examinations (interval ≥2 weeks).[a]<br>Tissue HE may or may not be detected. |
| Tissue hypereosinophilia | Tissue HE | One or more of the following applies:<br>a) the percentage of eosinophils in bone marrow section exceeds 20% of all nucleated cells, and/or<br>b) a pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or<br>c) marked deposition of eosinophil granule proteins is found (in the absence or presence of tissue infiltration by eosinophils) |
| Hypereosinophilic syndrome | HES | a) criteria for blood HE fulfilled and:<br>b) organ damage and/or dysfunction attributable to tissue HE[b] and:<br>c) exclusion of other disorders or condition as major reason for organ damage |
| Tissue-restricted HES[c] (organ-restricted HES) | | a) tissue HE but criteria for blood HE not fulfilled and:<br>b) organ damage and/or dysfunction attributable to tissue HE[b] and:<br>c) exclusion of other disorders or conditions as major reason for organ damage |

Modified from Valent P, et al. *Allergy*. 2023




Valent P, et al. *Allergy*. 2023

# Hypereosinophilia



# Hypereosinophilia

1. **Secondary** (reactive)

2. **Primary** (neoplastic/clonal)

3. **Idiopathic** (unknown significance)

# Hypereosinophilia

1. **Secondary** (reactive)
    - Allergic disorders

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# Hypereosinophilia

1. **Secondary** (reactive)
    - Allergic disorders
    - Non-allergic dermatological causes*

2. Primary (neoplastic/clonal)
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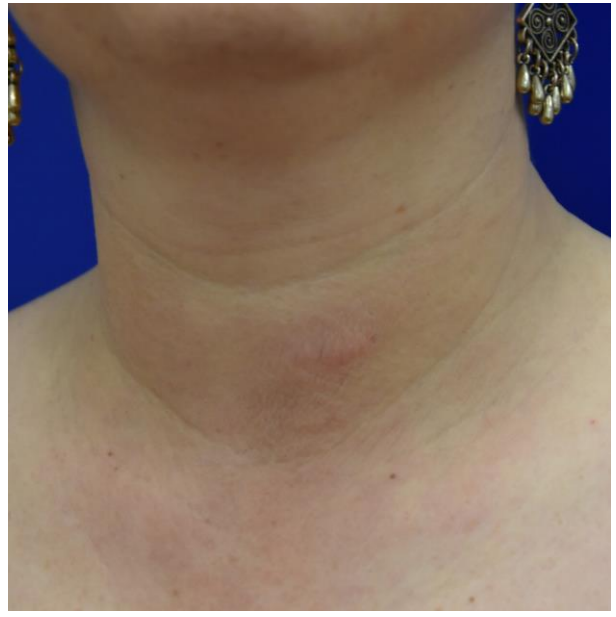
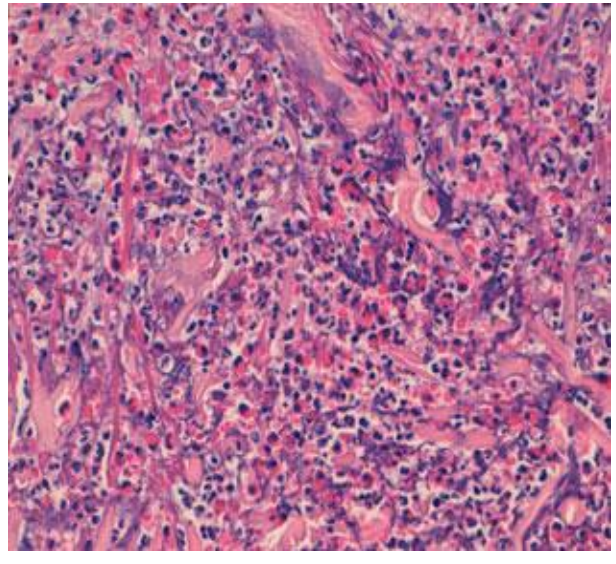
## Non-allergic dermatological causes*

**Wells syndrome** (eosinophilic cellulitis) is a recurring granulomatous dermatitis with eosinophilia (Wells, 1971) characterised by:

- sudden onset annular or circinate erythematous-oedematous patches that rapidly evolve to morphoea-like slate-blue plaques

- histological appearance characterized by the presence of ‘flame figures’





# Hypereosinophilia

1. **Secondary** (reactive)
    - Allergic disorders
    - Non-allergic dermatological causes*
    - Drug-induced eosinophilia**

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# Drug-induced eosinophilia**

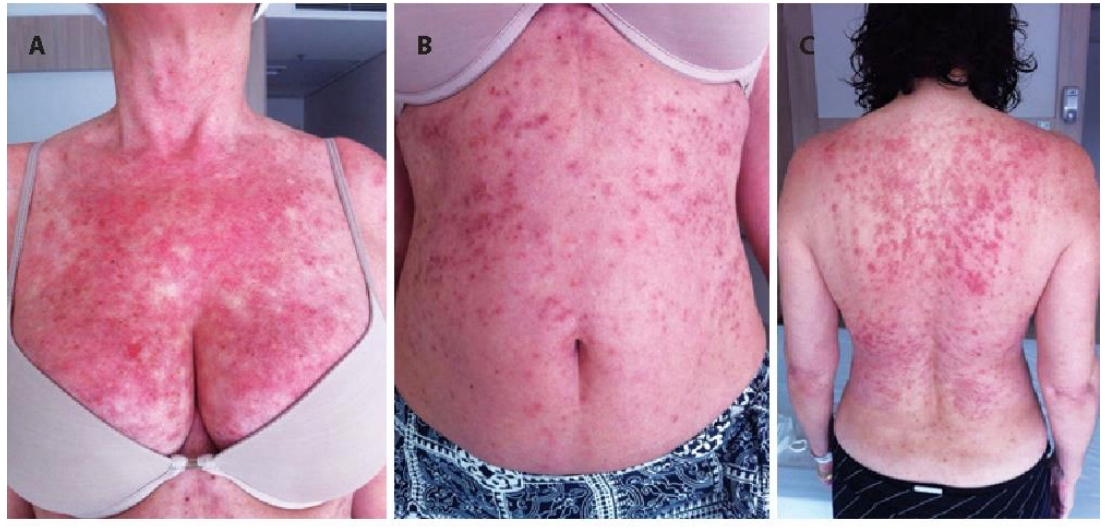
Drug reaction with eosinophilia and systemic symptoms (**DRESS syndrome**) occurs 3–6 weeks after the introduction of a new drug (antibiotics, anticovulsivants, allopurinol, etc).

This syndrome is characterised by a triad of a **skin eruption**, **fever** and **internal organ involvement** (lung, liver, kidneys, lymph nodes or heart).

**Drug-induced vasculitis and eosinophilia** is also reported, manifesting with purpura, arthralgia and myalgia with possible kidney and lung involvement.

| Category of drug | Drug name |
|---|---|
| Antimicrobial | Ampicillin, dapsone, isoniazid, linezolid, minocycline, rifampin, sulfasalazine, trimethoprim-sulfamethoxazole, vancomycin |
| Anticonvulsant | Carbamazepine, phenytoin, lamotrigine, phenobarbital |
| Antiviral | Abacavir, nevirapine |
| Antidepressant | Fluoxetine |
| Antihypertensive | Captopril |
| Others | Allopurinol, efalizumab, NSAID (celecoxib) |

NSAID: Nonsteroidal anti-inflammatory drug



# Hypereosinophilia

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    - Infectious diseases***

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## Infectious diseases***

**Parasitic infections**: Strongyloides, Filaria, Ascaria, Toxocara, Trichinella, Schistosoma

**Fungal infections**: Aspergillus fumigatus

*nb* In the presence of opportunistic or unusual infections, concomitant HIV infection should be considered

# Hypereosinophilia

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    - Gastrointestinal disorders****

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## Gastrointestinal disorders****

**Primary gastrointestinal eosinophilic disorders**
(1) Primary eosinophilic oesophagitis
(2) Primary eosinophilic gastritis
(3) Primary eosinophilic colitis

**Inflammatory bowel disease** (both ulcerative colitis and Crohn disease, ulcerative colitis with eosinophilia may be associated with a more severe clinical phenotype)

**Coeliac disease** (can be associated with eosinophilic oesophagitis)

**Chronic pancreatitis**

# Hypereosinophilia

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    - Inflammatory disorders (connettive tissue diseases/rheumatoid arthritis/IgG4RD)

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    - Inflammatory disorders (connettive tissue diseases/rheumatoid arthritis/IgG4RD)
    - Respiratory diseases*****

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## Respiratory diseases*****

- **Allergic bronchopulmonary aspergillosis** is caused by hypersensitivity to *Aspergillus fumigatus* and results in uncontrolled asthma and recurrent pulmonary infiltrates which can progress to bronchiectasis and pulmonary fibrosis

- *Diagnostic criteria include a history of asthma or cystic fibrosis, elevated aspergillus-specific IgE and IgG, elevated serum IgE, wheal-and-flare skin reaction to aspergillus antigen and blood eosinophilia*

- **Loeffler disease**: Loeffler first described this transient self-limiting pulmonary reaction with reticulonodular shadowing on chest radiology associated with a peripheral blood eosinophilia

- *Patients present with a low-grade fever and a cough for 7 – 10 days, which is usually due to an allergic reaction in the alveoli as a result of a parasitic infection or medications*

# Hypereosinophilia

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    - Infectious diseases***
    - Gastrointestinal disorders****
    - Inflammatory disorders (connettive tissue diseases/rheumatoid arthritis/IgG4RD) Respiratory diseases*****
    - Solid and hematologic tumors (eosinophilic leukemias, myeloproliferative neoplasms, acute myeloid leukemia, rare forms of myelodysplastic syndromes, advanced systemic mastocytosis, etc)

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    - Lymphocytic forms of hypereosinophilia

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# Lymphocytic forms of HESs

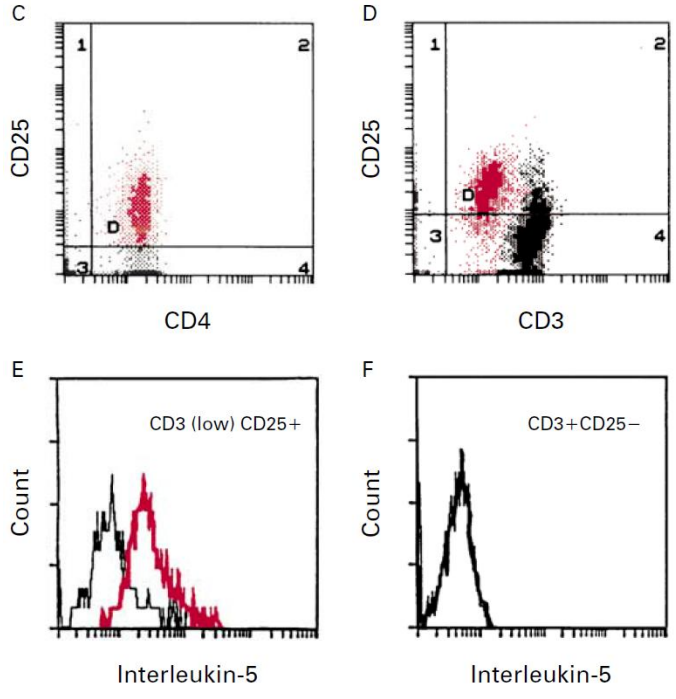
• 10-20% of HES
• Immunophenotypically abnormal (often clonal) subsets of circulating lymphocytes produce eosinophilopoietic cytokines (IL5, IL3, IL4, IL13)

• Different immunophenotypical abnormalities (low CD3, loss of CD7, double negative CD3+CD4-CD8-, etc.)
• demonstration of clonality by TCR rearrangement

• usually have cutaneous presentation and an indolent course, but may progress to T-cell lymphoma

• Serum levels of IgE and the chemokine TARC (CCL17) are usually elevated

• Episodic angioedema with eosinophilia (Gleich syndrome) is an unusual L-HES variant characterized by the monthly occurrence of eosinophilia, neutrophilia, lymphocytosis, angioedema, urticaria, and systemic symptoms that resolves spontaneously between episodes




Simon H-U, et al. *N Engl J Med* 1999

# Hypereosinophilia

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    - Allergic disorders
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    - Solid and hematologic tumors (eosinophilic leukemias, myeloproliferative neoplasms, acute myeloid leukemia, rare forms of myelodysplastic syndromes, advanced systemic mastocytosis, etc)
    - Systemic vasculitis (Eosinophilic granulomatosis with polyangitiis, EGPA)

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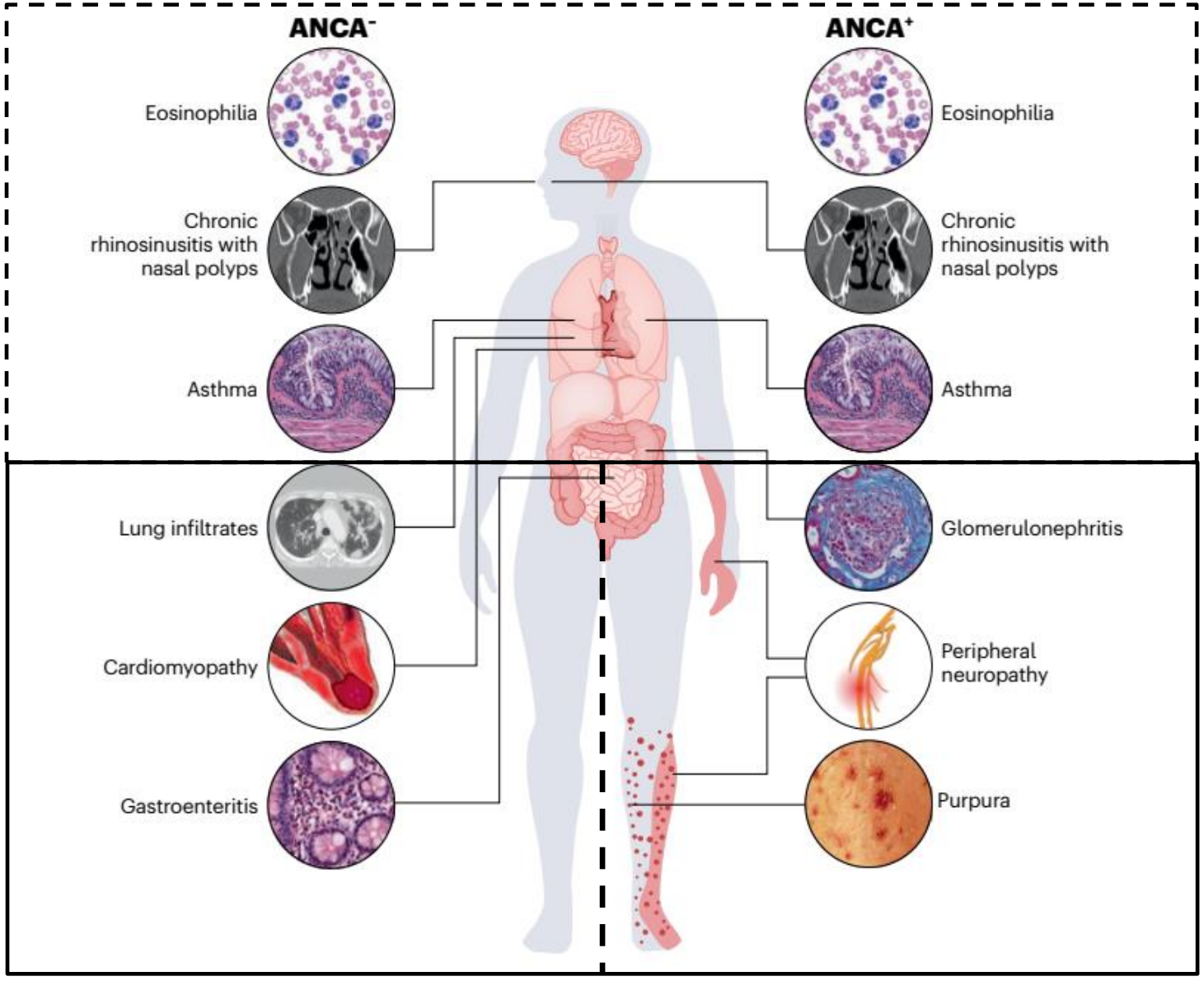



Emmi G, et al *Nat Rev Rheumatol* 2023

# EGPA disease phases

| ALLERGIC | EOSINOPHILIC | VASCULITIC |
|---|---|---|
| Several years | Months to Weeks | Weeks to Days |
| • Asthma<br>• Rhino-sinusitis (polyps)<br>• **(mild) peripheral eosinophilia** | • **Peripheral eosinophilia**<br>• Gastroenteritis<br>• Lung infiltrates<br>• Cardiomyopathy<br>• Skin lesions<br>• Thrombosis risk | • **Peripheral eosinophilia**<br>• Peripheral neuropathy<br>• Purpura<br>• Glomerulonephritis<br>• Alveolar haemorrhage<br>Thrombosis risk |

DIAGNOSIS

# Hypereosinophilia

1. **Secondary** (reactive)

2. **Primary*** (neoplastic/clonal)

3. **Idiopathic** (unknown significance)

# Myeloproliferative forms of HESs

***Clinical and lab work-up to exclude myeloid HES***

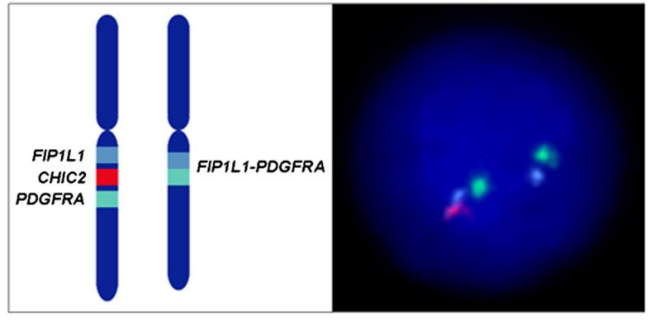
- hepatomegaly/splenomegaly
- Vit B12 levels
- Serum tryptase (eosinophil-to-tryptase ratio)
- Peripheral blood smear (blasts, dysplastic cells, monocytosis, anemia, thrombocytopenia)
- Test *FIP1L1-PDGFRA* gene fusion (RT-PCR or FISH)
- Selected molecular tests (BCR-ABL1, JAK2, KIT)

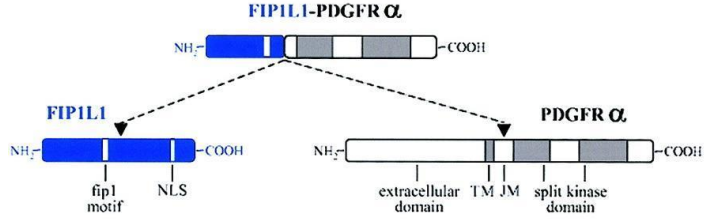
**FIP1L1-PDGFRA- related HES** (about 80%)

Almost all male

Gene fusion → constitutively activated PDGFRα-kinase sensitive to Tyr kinase inhibitor *imatinib*

Mutant kinases (PDGFRα, PDGFRβ, FGFR) share signaling pathways with IL5 and other eosinophilopoietins



# Hypereosinophilia

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# Hypereosinophilia

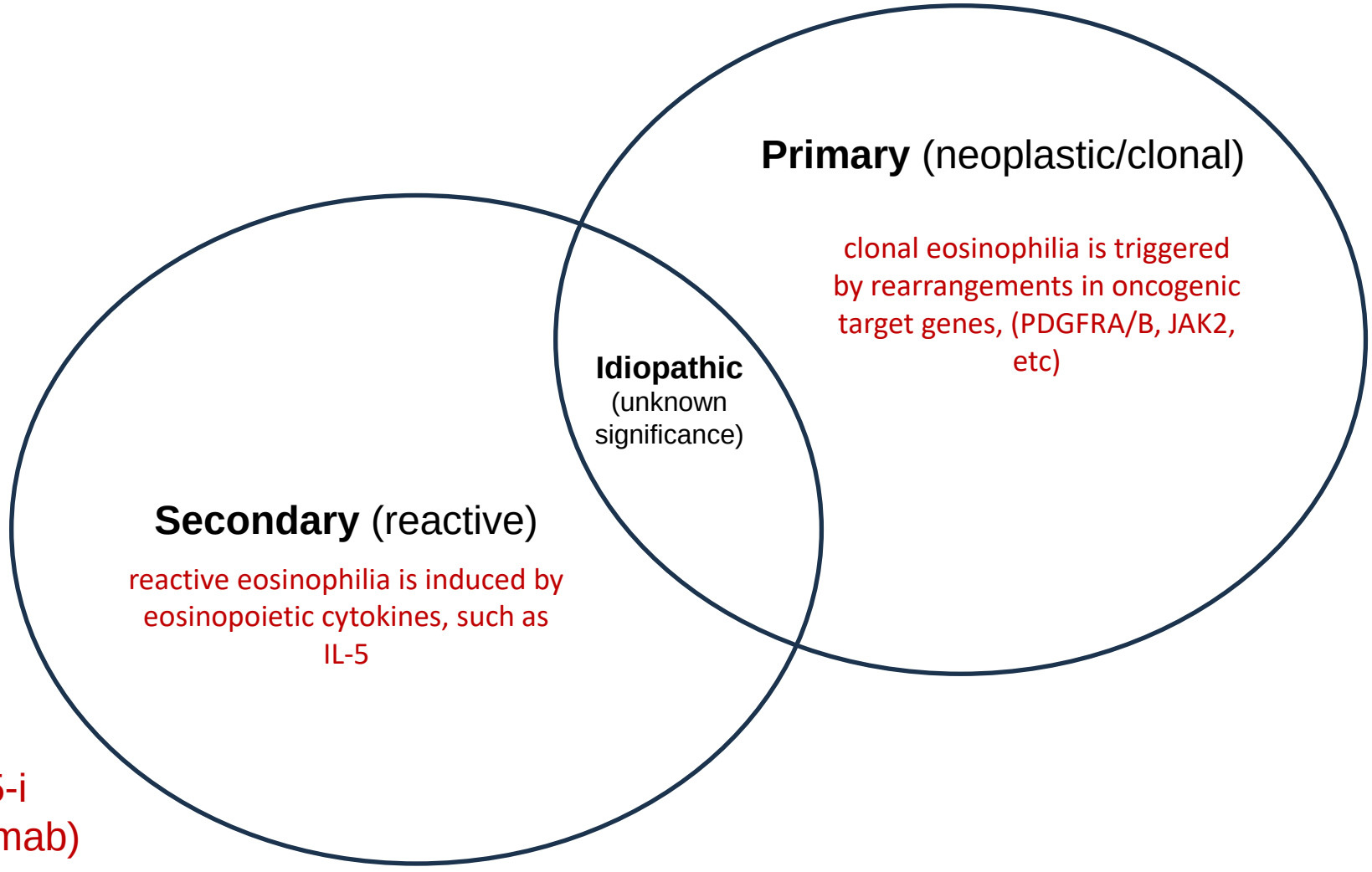
## **Idiopathic** (unknown significance)

- Idiopathic HE is a diagnosis of exclusion in patients who have been appropriately assessed with a detailed history, physical examination and thorough investigation without any cause being found

- Organ systems involved include the heart, lungs, skin, peripheral and central nervous systems and gastrointestinal tract. Thromboembolic complications are common.

# Treatments

# Hypereosinophilia




e.g TYK-i (imatinib)

e.g IL-5-i (mepolizumab)

# *FIP1L1-PDGFRA*+ HES: the imatinib experience

**Table 1.** Clinical and hematologic characteristics of study patients, according to *FIP1L1-PDGFRα* rearrangement.

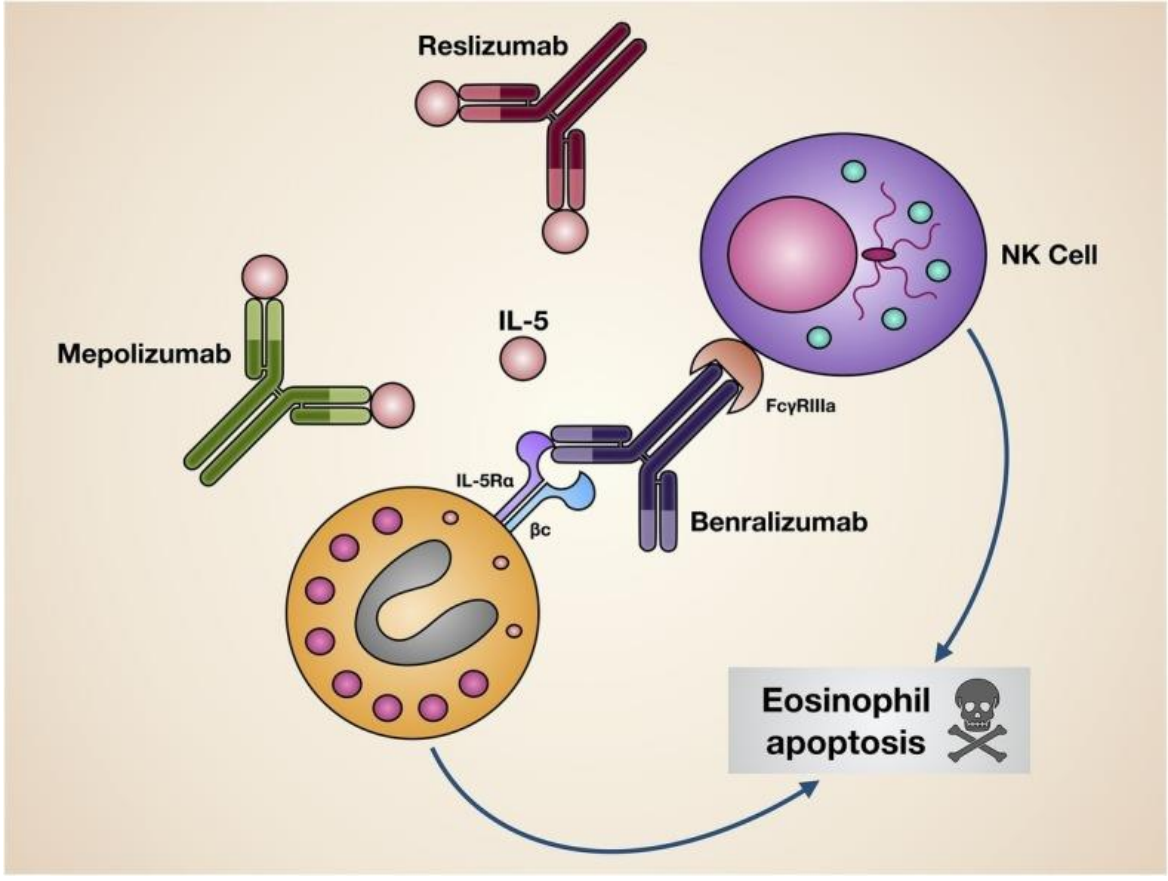
| | *FIP1L1-PDGFRα rearrangement* | *No FIP1L1-PDGFRα rearrangement* |
|---|---|---|
| No. of cases | 27 | 36 |
| Gender, Male/Female, no. of cases | 27/0 | 25/11 |
| Age, years, median (range) | 50 (17-75) | 58 (18-81) |
| Hemoglobin, g/L, median (range) | 137 (94-165) | 138 (84-180) |
| Platelet count, $\times 10^9$/L, median (range) | 191 (29-365) | 228 (27-668) |
| WBC count, $\times 10^9$/L, median (range) | 10.7 (1.8-57.5) | 12.2 (6.7-47.0) |
| Eosinophils %, median (range) | 43 (20-85) | 27 (13-38) |
| Eosinophil count $\times 10^9$/L, median (range) | 4.8 (1.6-16.5) | 3.4 (1.5-34.9) |
| Serum creatinine ≥20 mg/L, no. of cases | 1/27 | 1/37 |
| Serum uric acid ≥60 mg/L, no. of cases | 6/27 | 6/37 |
| Serum LDH ≥460 U/mL, no. of cases | 5/27 | 6/37 |
| Organ or tissue involvement, no. of cases | | |
| Lung | 5/27 | 10/37 |
| Spleen | 5/27 | 1/37 |
| Skin | 0/27 | 5/37 |
| Heart | 2/27 | 2/37 |
| Liver | 1/27 | 1/37 |
| Soft tissues | 2/27 | 0/37 |
| Waldeyer's ring | 0/27 | 1/37 |
| Intestine | 0/27 | 1/37 |
| Prior disease duration, months, median (range) | 16 (6-125) | 25 (6-209) |
| Prior treatment, % of cases | 66% | 66% |

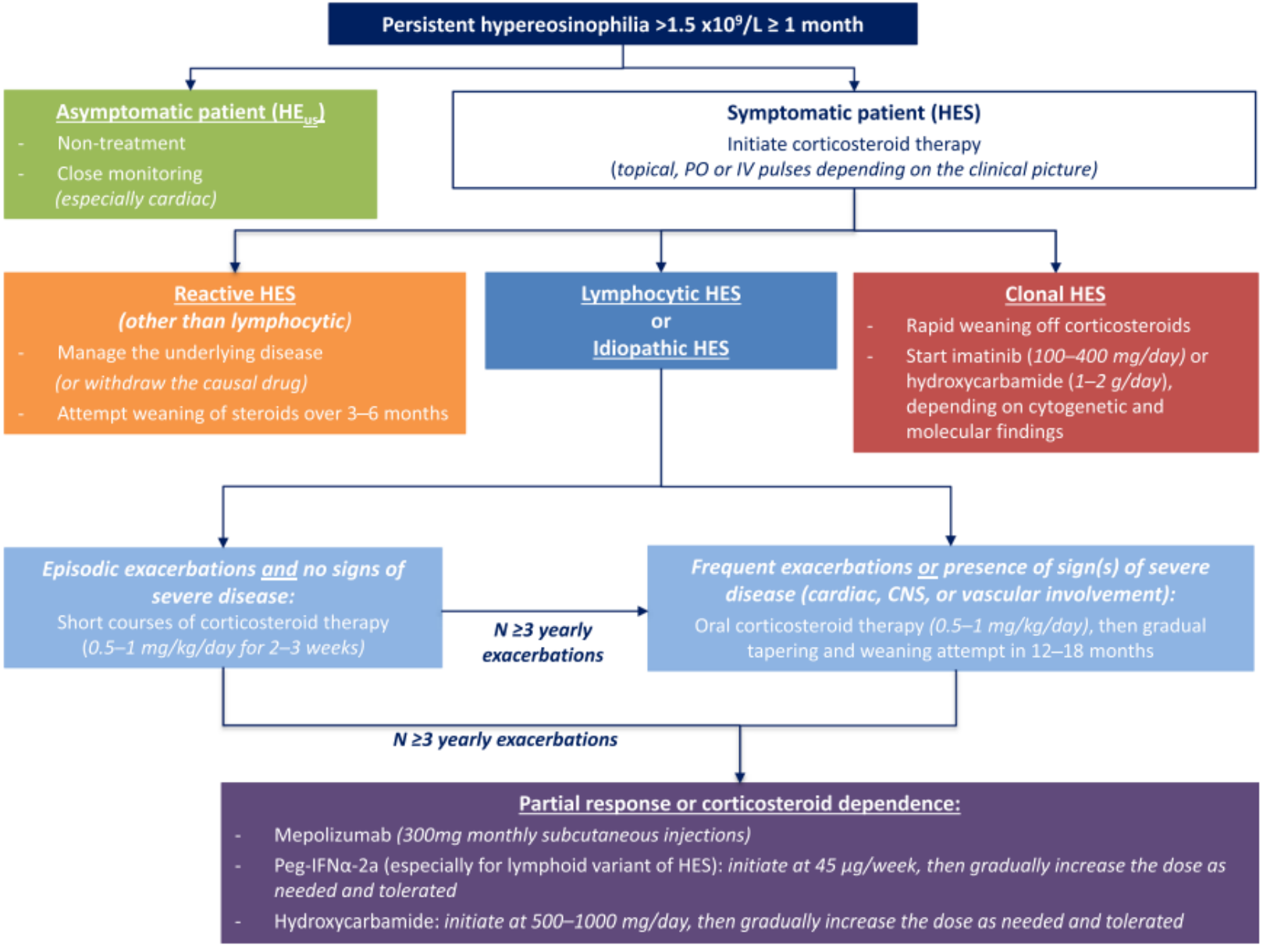
**Table 2.** Hematologic response to imatinib treatment.

| | *Complete hematologic response* | |
|---|---|---|
| *Time on treatment* | *FIP1L1-PDGFRα rearrangement (n=27)* | *No FIP1L1-PDGFRα rearrangement (n=36)* |
| 1 month | 27 (100%) | 4 (11%) |
| 3 months | 27 (100%) | 3 (8%) |
| 6 months | 27 (100%) | 3 (8%) |
| 12 months | 27 (100%) | 1 (3%) |
| Last contact | 27 (100%) | 0 – |

Baccarani M, et al. *Haematologica* 2007

# Mepolizumab and Benralizumab: mechanism of action






Groh M, et al. Orphanet J Rare Dis. 2023