Description of Hypereosinophilic syndrome (HES) and subtypes in the literature

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Aims

- Hypereosinophilic syndrome (HES) is a group of rare hematologic disorders in which eosinophils are overproduced for prolonged periods of time resulting in organ damage[1]. Different subtypes of HES have been identified but little is known about their similarities or differences[2]. This review aimed to describe clinical characteristics of HES types based on reported cases in the literature.

Methods

- A PubMed search focused on different types of HES (idiopathic I-HES; lymphocyte variant L-HES; myeloproliferative variant M-HES; and chronic eosinophilic leukemia, not otherwise specified CEL-NOS), was performed on March 2020, from January 2000, for articles only in English. Search strings of HES terms; organ damage; HES types; and HES markers were combined to yield 513 unique hits. From the selected articles (**Figure 1**) the following information was collected:
  - Author, country and year of publication
  - Age, gender, HES subtype and blood eosinophilic count at diagnosis
  - Organ affected, symptoms/diagnosis at presentation
  - Treatment, maintenance therapy, follow-up time and mortality
- Only individual data from 170 publications is presented here.

Key inclusion criteria

- I-HES: persistently elevated eosinophil counts without any underlying causes and with presence of end-organ damage
- L-HES: with abnormal T-cell immunophenotype and clonal T-cell receptor gene rearrangement
- M-HES: myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2
- CEL-NOS: with clonal cytogenetic/molecular abnormalities and/or increase marrow blasts (5-19%)

Key exclusion criteria

- Animal studies
- Pre-clinical studies
- Secondary HES
- Associated / reactive HES
- Overlap / single organ HES
- Familial HES
- No relevant data
- No specific data by HES subtype
- Duplicate data
- Full text article not available
- Article not written in English

Results

Figure 1. PRISMA flow chart

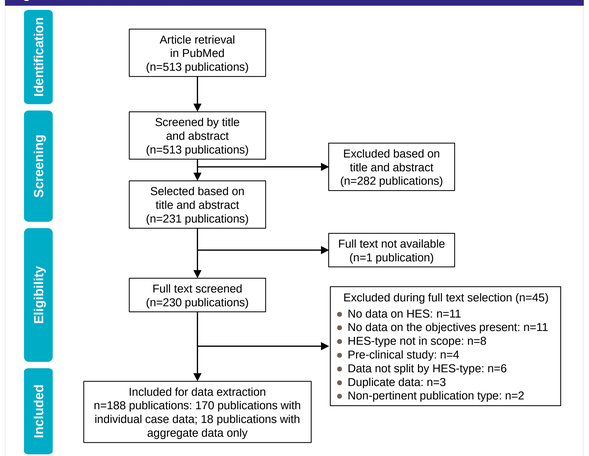

Table 1. Age, gender and eosinophilic count at diagnosis by HES subtype

HES type	Age, years mean (range)	Male n (%)	AEC, cells/µL Median (range)
I-HES (N=152)	46.1 (1 – 88)	91 (59.9)	6074 (410 – 215700)
M-HES (N=121)	42.5 (2 – 80)	109 (90.1)	9400 (55.5 – 200000)
L-HES (N=62)	46.5 (5 – 81)	32 (54.8)	5700 (1040 – 82960)
CEL-NOS (N=12)	47.9 (19 – 82)	11 (91.7)	12000 (1300 – 46300)

*AEC=Absolute Eosinophil Count; I-HES- idiopathic HES; M-HES- myeloproliferative HES; L-HES-lymphocyte variant; CEL, NOS-chronic eosinophilic leukaemia, not otherwise specified

Figure 2. Organ involvement by HES subtype

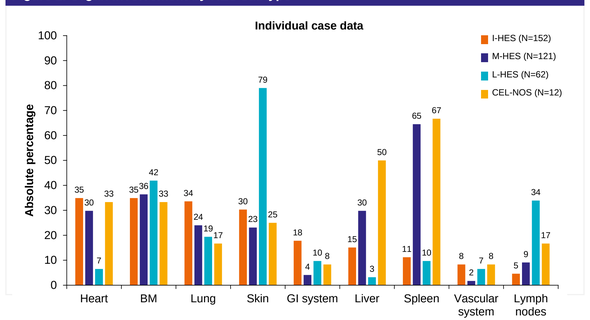

Table 2. Five most commonly reported signs and/or symptoms*

I-HES (N=152)	M-HES (N=121)	L-HES (N=62)	CEL-NOS (N=12)
Cardiac#: **22%**	Splenomegaly: **40%**	Pruritus/Itch: **34%**	Splenomegaly: **67%**
Dyspnea: **21%**	Bone marrow involvement: **23%**	Bone marrow involvement: **32%**	Fatigue; hepatosplenomegaly: **33%**
Bone marrow involvement: **19%**	Cardiac#: **15%**	Skin lesions: **31%**	Lymphadenopathy: **25%**
Fever: **17%**	Cough: **14%**	Edema/anasarca: **19%**	Cardiac#; dyspnea; skin lesions; anemia; weight loss: **17%**
Cough: **15%**	Fatigue; skin lesions: **13%**	Eczema: **16%**	-

*Signs and/or symptoms are presented as reported in the articles, and categories are not mutually exclusive
#Left ventricular abnormalities, murmur, thrombus

Conclusions

HES is a rare disease with heterogeneous manifestations involving different medical specialties such as allergy/immunology, dermatology, pulmonary, haematology, oncology and onco-haematology. Given the heterogeneity of HES, differentiating subtypes is important for optimal management.

Table 3. Main treatment reported

	I-HES (N=152)	M-HES (N=121)	L-HES (N=62)	CEL-NOS (N=12)
Any corticosteroid (CS)	84.9%	50.4%	64.5%	83.3%
Hydroxyurea / hydroxycarbamide	37.5%	38.0%	11.3%	41.7%
Imatinib	22.4%	81.0%	11.3%	58.3%
Interferon alpha	7.2%	17.4%	12.9%	41.7%
Cyclosporine	3.9%	2.5%	6.5%	-
Vincristine	3.3%	2.5%	3.2%	-
Methotrexate	1.3%	-	14.5%	-
Mepolizumab	1.3%	-	9.7%	-
Alemtuzumab	1.3%	-	3.2%	-

Findings summary

- The most common type of HES reported is idiopathic.
- There is a male predominance of HES particularly for the M-HES/CEL-NOS subtypes.
- Cases with M-HES/CEL-NOS presented higher AEC compared to the other types.
- Skin is the organ most affected by L-HES patients; spleen is the organ most affected by M-HES/CEL-NOS patients; whereas for I-HES, heart, lungs and skin are affected in a similar way.
- Mortality was similar between subgroups except for CEL-NOS, which was higher.
- Majority of I-HES, L-HES and CEL-NOS patients received CS, whereas most of M-HES received imatinib.

References

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2. Shomali W & Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. *American journal of hematology* 2019;94:1149–1167. doi:10.1002/ajh.25617.

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