Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2026-B-129-z Benralizumab

Stand: Juli 2026

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Benralizumab
zur Behandlung des hypereosinophilen Syndroms

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung nach § 35a SGB V: • Mepolizumab (Beschluss vom 19.05.2022)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Benralizumab R03DX10 Fasenra	Fasenra ist angezeigt als Add-on-Therapie bei erwachsenen und jugendlichen Patienten im Alter von 12 Jahren und älter mit einem Körpergewicht von mindestens 35 kg mit unzureichend kontrolliertem hypereosinophilem Syndrom ohne eine erkennbare, nicht-hämatologische sekundäre Ursache (siehe Abschnitt 4.2 und 5.1).
Mepolizumab R03DX09 Nucala	<u>Hypereosinophiles Syndrom (HES)</u> Nucala ist angezeigt als Zusatzbehandlung bei erwachsenen Patienten mit unzureichend kontrolliertem hypereosinophilem Syndrom ohne eine erkennbare, nicht-hämatologische sekundäre Ursache (siehe Abschnitt 5.1). (Stand FI: Februar 2026)

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2026-B-129-z (Beratung nach § 35a SGB V) Benralizumab

Auftrag von:	Abt. AM
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Datum:	2. Juli 2026

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Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CBC	complete blood count
CCR4	C-C-Chemokinrezeptor Typ 4
CEREO	Centre de Référence des Syndromes Hyperéosinophiliques
ECRI	Emergency Care Research Institute
FGFR	Fibroblast growth factor receptor
FIP1L1	Factor interacting with PAPOLA and CPSF1
FISH	Fluorescence in situ hybridization
FLT	fms like tyrosine kinase
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HE	hypereosinophilia
HES	hypereosinophilic syndrome
HR	Hazard Ratio
HEUS	HE of undetermined significance
IL	Interleikin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
JAK	Janus kinase
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PDGFRA/B	Platelet-derived growth factor receptor A
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
STAT	Signal transducer and activator of transcription
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Zusatzbehandlung bei Erwachsenen und Jugendliche ab 12 Jahren mit unzureichend kontrolliertem hypereosinophilem Syndrom ohne erkennbare, nicht-hämatologische sekundäre Ursache.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *hypereosinophiles Syndrom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: *The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed*. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 05.06.2026 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 708 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Alle eingeschlossenen Referenzen wurden im Volltext beschafft. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen im Volltext gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Basierend darauf, wurden insgesamt 2 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnte kein CR identifiziert werden.

3.2 Systematische Reviews

Masood et al., 2025 [2].

Efficacy of anti-interleukin 5 therapy in hypereosinophilic syndrome: An updated systematic review and meta-analysis

Fragestellung

Given the central role of interleukin (IL) 5 in eosinophil development and survival, this study aimed to assess the efficacy and safety of anti–IL-5 therapies in patients with HES.

Methodik

Population:

- subjects aged 12 years or older, diagnosed with HES for at least 6 months
- documented failure of three or more standard therapies (corticosteroids, cytotoxic agents, immunomodulatory therapy, imatinib mesylate) at appropriate duration and dose
- blood eosinophil count >1500 cells/mL for ≥ 6 months and the absence of the FIP1L1–PDGFRA fusion gene

Intervention:

- mepolizumab or benralizumab

Komparator:

- nicht präspezifiziert

Endpunkte:

- Our primary outcomes included a reduction in the absolute eosinophil count (>50% from baseline).
- Secondary outcomes involved an incidence of flares

Recherche/Suchzeitraum:

- An extensive electronic data base search was conducted via PubMed and Google Scholar (Google LLC, California, United States), which encompassed articles from inception up to June 30, 2024

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool (RoB-2)

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs

Table 1 **Characteristics of the included studies**

Study	Year	Study Design	Intervention	Comparison	Route of Administration	Follow-up Time
Kuang *et al.*[13]	2019	Randomized controlled trial	Benralizumab	Placebo	Subcutaneous	48 weeks
Roufosse *et al.*[15]	2020	Randomized controlled trial	Mepolizumab	Placebo	Subcutaneous	40 weeks
Rothenberg *et al.*[14]	2008	Randomized controlled trial	Mepolizumab	Placebo	Intravenous	3 months
Kuang *et al.*[12]	2022	Randomized controlled trial	Benralizumab	Placebo	Subcutaneous	48 weeks

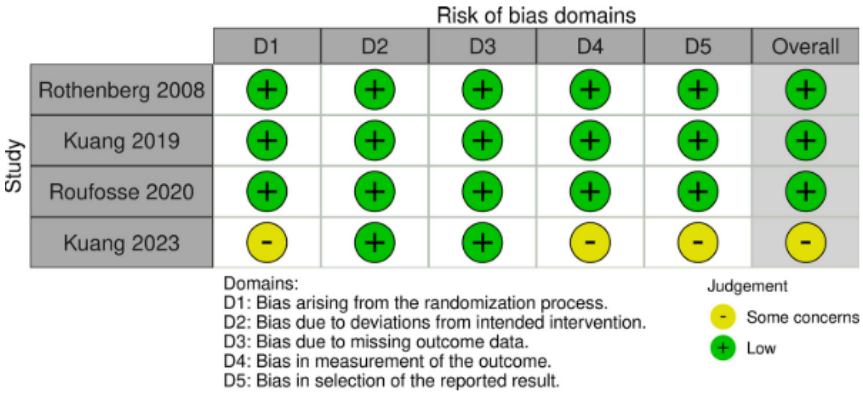
Charakteristika der Population/Studien:

Table 2 **Baseline characteristics of the population of included studies**

Study	Year	Gender, *n* (%)		Age, mean ± standard deviation		Population, *n* (%)		Variant of HES (*n*)
		Male	Female	Anti-IL-5	Placebo	Anti-IL-5	Placebo	Total
Kuang *et al.*[13]	2019	7 (35)	13 (65)	46.6 ± 13.2	45.2 ± 1.9	10 (50)	10 (50)	Myeloid variant (2); lymphoid variant (6); single-organ overlap (6); idiopathic (6)
Roufousse *et al.*[15]	2020	51 (47.22)	57 (52.88)	46.6	45.4	54 (50)	54 (50)	—
Rothenberg *et al.*[14]	2008	43 (51)	42 (49)	47 ± 6.2	49.1 ± 14.4	43 (51)	42 (49)	—
Kuang *et al.*[12]	2023	2 (28.5)	5 (71.5)	38.5 ± 10.8	36 ± 1	5 (71.5)	2 (28.5)	Lymphoid variant (2); single-organ overlap (5)

HES = Hypereosinophilic syndrome; IL = interleukin.

Qualität der Studien:



Studienergebnisse:

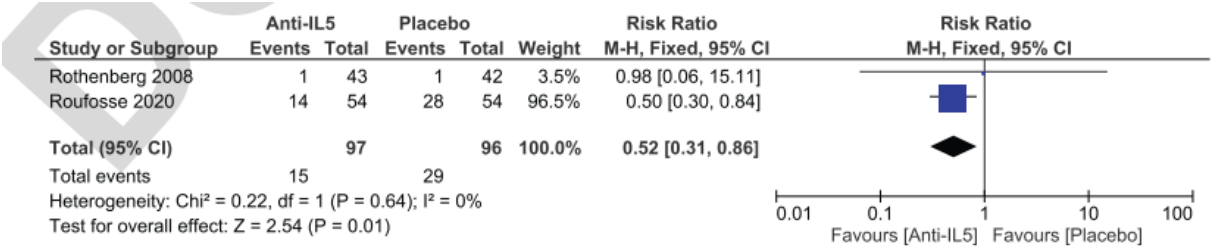
Primary outcome reduction in absolute eosinophil count

- Of the four included studies, three12–14 reported data on the reduction in the absolute eosinophil count (>50% from baseline). In the anti–IL5 therapy group, 55 of 58 participants showed a reduction in their absolute eosinophil count compared with 22 of 54 participants in the placebo group. A combined analysis of the data revealed that the difference between the two groups was statistically significant. Anti–IL-5 therapy treatment was linked to a greater reduction in absolute eosinophil count and to symptom resolution in patients compared with placebo (RR 2.32 [95% CI, 1.67–3.22]; p = <0.00001; I2 = 0%), as illustrated in Fig. 4.

Secondary Outcomes Flares

- Among the included studies, only two14,15 reported data on the incidence of flares, both used mepolizumab as an anti–IL-5 therapy. In the anti–IL-5 therapy arm, 15 of 97 participants experienced at least one flare, whereas 29 of 96 participants in the placebo

arm reported one or more flares. The difference between the two arms was statistically significant, which indicated that the patients who received anti– IL-5 therapy were less likely to experience an episode of flare compared with placebo. **(RR 0.50 [95% CI, 0.31–0.86]; p= 0.01; I2 = 0%)**, as depicted in Fig. 5.



Adverse Events

- Data on adverse events were provided by three13–15 of the four included studies. In the anti–IL-5 therapy group, 98 of 107 patients reported experiencing an adverse event (88 of 97 patients in the mepolizumab group and 10 of 10 patients in the benralizumab group), whereas, in the placebo group, 98 of 106 patients reported the same. The combined analysis showed no significant difference between the two groups, with the results being statistically insignificant (RR 0.99 [95% CI, 0.91–1.07]; p= 0.81; I2 = 0%).

Anmerkung/Fazit der Autoren

This meta-analysis underscores the efficacy and safety of anti–IL-5 therapy in reducing flares and improving clinical outcomes in patients with HES. Based on the synthesized evidence from clinical trials, anti–IL-5 therapy represents a promising therapeutic strategy that should be integrated into treatment guidelines for HES, offering a targeted and effective approach to disease management.

Kommentare zum Review

EP “flares” wird für beide Studien berichtet, die Mepolizumab untersucht haben.

3.3 Leitlinien

Groh et al., 2023 [1].

French Healthcare Network for Rare Immune Hematological Diseases (MARIH)

French guidelines for the etiological workup of eosinophilia and the management of hypereosinophilic syndromes

Zielsetzung/Fragestellung

The aim of these recommendations established by national experts is to inform and assist health professionals in the diagnostic and/or therapeutic management of patients with hypereosinophilic syndrome (HES), including organ-specific eosinophilic disorders (excluding eosinophilic esophagitis, for which there are dedicated guidelines, and hypereosinophilic asthma).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz; unklar
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; unklar
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; trifft teilweise zu
- Regelmäßige Überprüfung der Aktualität gesichert; unklar

Recherche/Suchzeitraum:

- Pubmed 1975-2022
- Es wird jedoch auch eigenen Literaturrecherchen durch die Experten genannt
- 122 Referenzen eingeschlossen und gelistet

LoE/GoR

- Nicht formal angegeben
- Empfehlungen begründen sich teilweise auf Leitlinien, die aber bereits abgelaufen sind.

Sonstige methodische Hinweise

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Definitionen/Empfehlungen

Definition HES

Hypereosinophilic syndrome (HES) is defined as blood hypereosinophilia (HE) ≥ 1.5 x109/L and persistent tissue hypereosinophilia (>1 month) associated with tissue damage (of any kind) due to eosinophil toxicity.

It is a heterogeneous condition that includes:

- **Clonal (or neoplastic) HES**, including chronic eosinophilic leukemia associated with the 4q12 deletion responsible for the FIP1L1::PDGFRA (F/P) fusion.

- **Reactive (secondary) HES** caused by parasitic infections, medication or inflammatory or neoplastic diseases. Reactive HES also includes lymphocytic HES which is due to low-grade proliferation of T cells bearing an abnormal phenotype (usually CD3-CD4+).
- **Idiopathic HES.** Despite extensive investigations, the etiology of up to 3/4 of HES cases remains unknown.

The conditions covered include all types of HES, including single-organ eosinophilic disorders (except for eosinophilic esophagitis and hypereosinophilic asthma).

Condition	Definition
Blood eosinophilia	Eosinophil count between 0.5 and 1.5 × 10^9/L eosinophils
Hypereosinophilia (HE)	Eosinophil count > 1.5 × 10^9/L on two occasions one month apart and/or tissue eosinophilia (as defined in "Definition of HES-related organ involvement" section)
Hypereosinophilic syndrome (HES)	Blood HE AND
	Organ damage or dysfunction caused by tissue eosinophils (as defined in "Definition of HES-related organ involvement" Section), AND
	Exclusion of other possible causes of organ dysfunction
HES/organ-specific eosinophilic disease	Blood and/or tissue eosinophilia AND
	Single-organ/tract involvement

Behandlung

2. Therapeutic management

Therapeutic management is generally multidisciplinary and may be undertaken in partnership with a CEREO reference center and/or center of expertise.

The choice of treatment, treatment modalities (short-term vs. prolonged) and their goals (normalization of the complete blood count (CBC) vs. control of symptoms while tolerating a certain level of persistent eosinophilia) depends on the type of HES, the severity of the disease, the risk of relapse, and the patient's condition and risk factors (age, possible comorbidities). A general algorithm for the management of HES is provided in Figure 1.

The treatment of HES relies mainly on the following:

- For clonal HES: typically tyrosine kinase inhibitors (particularly imatinib) and hydroxycarbamide.
- For reactive and idiopathic HES: corticosteroids (topical and/or systemic), peginterferon alfa-2a, hydroxycarbamide and mepolizumab.

Following two clinical drug trials that demonstrated the superiority of mepolizumab (a humanized IgG1 kappa monoclonal antibody targeting IL-5) vs. placebo (both in terms of reduction of the number of clinical relapses and steroid sparing effect), this drug was approved by the EMA in November 2021 and by November 1rst 2022 is now reimbursed by the French National Health Insurance.

In case of failure of standard treatments, cases can be referred for further discussion in the monthly national multidisciplinary meetings held by the CEREO team.

Depending on the clinical picture and the HES subtype, other treatments may also be considered. The latter may include:

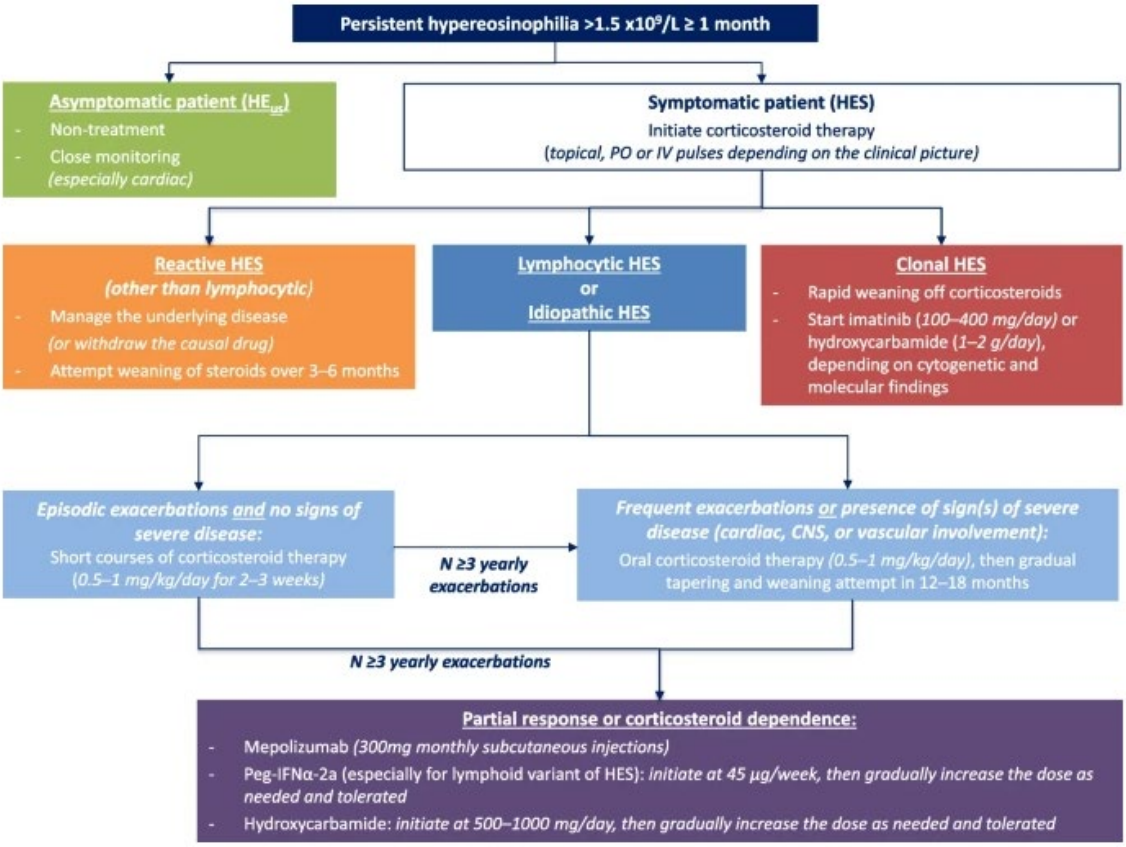
- Curative anticoagulant therapy in case of HE-related thromboembolism or cardiac disease at risk of embolism; preventive anticoagulant therapy.
- Prophylaxis of certain iatrogenic complications (including infections, glucocorticoid-induced osteoporosis).
- Surgical procedures (in case of advanced endomyocardial fibrosis, for example).

Some severe clinical manifestations, including cardiac (myocarditis, intracavitary thrombosis with peripheral or cerebral embolic events, coronary artery spasm), acute respiratory distress (severe acute asthma, hypoxic lung disease), or thrombotic events (venous or arterial) require urgent treatment with a combination of different drug classes

with anti-eosinophilic activity used sequentially (as detailed in Figure 3) before the findings of the etiological HE workup become available.

Information and therapeutic education of patients and their immediate relatives is also encouraged. Lastly, all health professionals and patients should be made aware of the existence of patient associations.

Fig. 1



Management of FIP1L1::PDGFRA–positive chronic eosinophilic leukemia

[…]

Management of non-F/P-associated clonal HES

The management of non-F/P-associated clonal HES is not standardized, and literature data are even sparser than those available for F/P + chronic eosinophilic leukemia [8, 91]. The therapeutic approach generally depends on the molecular/cytogenetic abnormality reported, and discussion in a multidisciplinary team meeting is recommended. Nonetheless, a few trends emerge.

Rearrangements involving PDGFRA (other than FIP1L1::PDGFRA)

Clonal forms of HES involving PDGFRA and a partner gene (such as BCR, ETV6, KIF5B, etc.) other than FIP1L1 are possible. Although exceedingly rare, and by analogy with F/P + chronic eosinophilic leukemia, they are also particularly sensitive to low dose imatinib (i.e., 100 mg daily), and their long-term prognosis seems to be excellent [8, 91].

Rearrangements involving PDGFRB

Rearrangements involving PDGFRB and other partners (about 30 to date) have been reported, including ETV6::PDGFRB, which may also be responsible for a chronic

myelomonocytic leukemia phenotype with HE due to t(5;12)(q32;p13). These cases are generally responsive to imatinib (MA), but initially at higher doses (400 mg daily) than those used to treat F/P + chronic eosinophilic leukemia [33, 91]. These dosages generally result in prolonged molecular remission with continued treatment. Once molecular remission is achieved, careful reduction of the doses to 100 mg imatinib may be suggested, subject to regular molecular monitoring.

JAK2 rearrangements

JAK2 rearrangements (including PCM1::JAK2 due to t(8;9)(p22;p24) and BCR::JAK2 due to t(9;22)(p24;q11)) are sensitive to JAK2 inhibitors, including ruxolitinib (off label). However, response to treatment may be transient and this therapeutic approach is usually a bridge to allogeneic bone marrow transplantation, which should be considered (depending on the patients' age and comorbidities) [91, 96].

FGFR1 rearrangements

FGFR1 rearrangements, including FGFR1::ZMYM2 due to t(8;13)(p11;q12), are associated with aggressive clinical phenotypes with, in the absence of treatment, constant and rapid progression (in one to two years) towards a high-grade hematological malignancy (acute myeloid leukemia, lymphoblastic lymphoma) resistant to standard TKIs (including ponatinib). In the FIGHT-203 study, a phase 2 multicenter trial assessing the safety and efficacy of pemigatinib (13.5 mg QD on a 21-day cycle with 2 weeks on and 1 week off)), complete hematological and cytological response rates reached 76% and 71%, respectively in 35 previously treated patients in both chronic and blast phase. Additionally, both treatment-naive patients on chronic phase achieved hematological and cytological responses, while one in three treatment-naive patients with blast phase disease achieved hematological and cytological responses. Overall, despite high rates of treatment-emergent adverse events (with hyperphosphatemia, alopecia, diarrhea and stomatitis being at the forefront), pemigatinib may offer a long-term treatment option for patients ineligible for hematopoietic stem cell transplantation, or may otherwise facilitate bridging to transplantation [97]. Of note, pemigatinib was approved by the FDA on August 2022 in this setting.

FLT3 rearrangements

Recently, FLT3 rearrangements have been included within the subgroup of "Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions" in the 2022 International Consensus Classification of myeloid neoplasms and acute leukemias [6]. Patients with FLT3 rearrangements generally have an aggressive phenotype resistant to the main TKI. Thus, as for rearrangements involving FGFR1, it seems appropriate to encourage enrollment in clinical trials assessing tyrosine kinase inhibitors showing in vitro activity against FLT3 (sorafenib, sunitinib, gilteritinib) either alone (in case of diagnosis at a chronic phase) or in combination with intensive multiagent chemotherapy, followed by early allogeneic bone marrow transplantation (when feasible) [91].

Chronic eosinophilic leukemia–not otherwise specified (CEL-NOS)

Although this is likely a heterogeneous condition (especially when the presumed clonality of eosinophils is based "only" on the presence of cytogenetic (karyotype / FISH) and/or molecular (NGS-based gene panel test) abnormalities, it appears to have a poor prognosis, with high rates of progression to acute myeloid leukemia in the main series reported to date. Thus, a case-by-case assessment considering the patient's cytogenetic and molecular findings is recommended. Case reports (and CEREO experience) have shown that probabilistic treatment with tyrosine kinase inhibitors (imatinib as well as second-

generation TKIs or JAK inhibitors) can sometimes elicit a complete hematologic response in this setting, including in patients with no overt molecular abnormality. Empirical (or even sequential, if first-line treatment with imatinib fails) use of these treatments may be considered. In young people, if this strategy fails (and/or if there is cytogenetic evidence of a poor prognosis), allogeneic bone marrow transplantation should also be considered. Cytoreductive therapy with hydroxycarbamide (off-label) is often administered to reduce blood HE (and possibly limit eosinophil toxicity) even though its effectiveness on the natural course of the blood disorder (including the risk of transformation to acute myeloid leukemia) has not been demonstrated. Finally, in the case of multiple documented molecular abnormalities with a significant allele frequency (≥ 5%) and/or a borderline form with a myelodysplastic syndrome, treatment with a hypomethylating agent (azacytidine, off-label) or allogeneic bone marrow transplantation may also be considered on a case-by-case basis [8, 98].

Management of idiopathic HES (whether single-organ or systemic)

First-line treatment: topical and/or systemic corticosteroid therapy

Corticosteroid therapy is generally the first-line treatment for idiopathic HES, and rapid response (complete or partial) is the norm.

Depending on the clinical manifestations, the use of locally active steroids (topical corticosteroids, orodispersible budesonide for esophagitis, gastro-resistant budesonide for lower GI manifestations and inhaled corticosteroid therapy or nasal spray) is encouraged to reduce the use of systemic corticosteroids.

When organs not accessible (or resistant) to topical corticosteroids are involved, systemic corticosteroids are the first-line treatment for idiopathic HES. The loading dose (0.5–1 mg/kg/day prednisone (off-label)), possibly preceded by pulses of methylprednisolone (15 mg/kg/day for 1–3 days) in case of organ- or life-threatening manifestations, should be tailored to the severity of symptoms before gradual tapering. Overall, the minimum effective dose should be used, and weaning should always be discussed: in acute forms, cessation of corticosteroid therapy may be attempted after a few weeks of treatment; in the case of chronic disease, a treatment period of approximately 12 months seems advisable before considering cessation.

Second-line treatments

To minimize the potential adverse reactions of systemic corticosteroid therapy, steroid-sparing treatment may be considered in patients with high dose corticosteroid dependence, considering the patient's specific comorbidities).

To date, being the only drug having been assessed in prospective randomized controlled trials, we currently recommend mepolizumab (300 mg subcutaneous monthly) as the first-line steroid-sparing agent. Contrariwise, all other compounds are prescribed off-label based essentially on the available retrospective data.

Following two clinical trials that demonstrated the superiority of mepolizumab, an IgG1 kappa monoclonal antibody targeting IL-5, vs. placebo in terms of reduction of the number of clinical relapses and steroid-sparing effect, mepolizumab was approved by the FDA in September 2020, by the EMA in November 2021 [99, 100]. Conversely, although preliminary data suggest that mepolizumab could remain efficacious even at lower “asthma” doses (i.e. 100 mg subcutaneous monthly) in other eosinophil-associated diseases (e.g. EGPA or idiopathic chronic eosinophilic pneumonia), it should be emphasized that, to date, standard treatment of HES relies on a full dose regimen i.e. 300 mg mepolizumab subcutaneous monthly [101].

Specifically, we suggest using mepolizumab in the following settings:

- Chronic AND idiopathic AND oral-corticosteroid-dependent HES (meaning that the efficacy of oral corticosteroids has previously been established, and that an attempt to withdraw oral corticosteroids has been followed by both a clinical AND a hematological relapse)
- Relapsing (either single-organ OR systemic) HES with at least 3 yearly flares requiring short courses of oral costicosteroids.

Under treatment with mepolizumab, once that sustained clinical and hematological remission have been achieved, the tapering (or even withdrawal) of both oral corticosteroids and other cytotoxic-immunosuppressive drugs is strongly encouraged.

Contrariwise, it should also be emphasized that there is to date no rationale for the prescription of mepolizumab either as first-line therapy (even in the setting of organ or life-threatening HES—where systemic corticosteroids, along with antiparasitic treatments and anticoagulants are usually effective, as detailed in "Follow-up of F/P + HE/HES" Section). Likewise, in patients under low dose oral corticosteroids and with no treatment-related side effect, maintenance treatment with low dose oral corticosteroids monotherapy is acceptable.

In case of failure of mepolizumab, further-line steroid-sparing treatments include:

- Interferon alfa-2a, an immunomodulatory agent acting on both eosinophilia and Th2-polarized T cells [102]. Currently, only the pegylated form is available (Pegasys®). Although the reported efficacy is relatively high, its safety profile can be a barrier to its use and long-term maintenance [103]. It is therefore standard practice to start with the lowest possible dosage (e.g., 45 µg pegylated interferon alfa-2a weekly by subcutaneous injection) and to increase it gradually monthly if necessary, depending on tolerability. The practicalities of prescribing pegylated interferon alfa-2a are detailed in Box 9.
- Hydroxycarbamide, a non-specific myelotoxic agent with anti-eosinophilic activity. In practice, it is usually started at a low dosage (1 g/day in a single dose) and then increased if necessary (up to 2 g/day in a single dose) depending on effectiveness and tolerability [8]. The practicalities of prescribing hydroxycarbamide are detailed in Box 10.
- Although its primary indication is clonal HES (specifically F/P + chronic eosinophilic leukemia), imatinib (400 mg/day) may also be used empirically (and off label) in patients with laboratory and clinical findings suggestive of underlying myeloid malignancies (although by definition, idiopathic HES does not show the cytogenetic or molecular abnormalities characteristic of clonal HES) e.g. splenomegaly, elevated vitamin B12 or tryptase, presence of other CBC abnormalities, nonresponse to corticosteroid therapy (or corticosteroid dependence on more than 10 mg/day prednisone) [104]. In the absence of response at 1 month after initiation of imatinib, the latter should be discontinued and replaced by another steroid-sparing drug.
- Conventional immunosuppressive agents (cyclosporine, methotrexate, and mycophenolate mofetil): limited data are available regarding their benefit in HES. For the time being, their use in this indication is limited.
- Recent preliminary data suggest that benralizumab (a monoclonal antibody targeting the alpha subunit of IL-5 receptor, IL-5Rα) could be a promising treatment for HES [105], and a prospective randomized placebo-controlled trial is underway.

In daily practice, pegylated interferon alfa-2a is often favored in young patients because of the theoretical long-term leukemogenic risk of hydroxycarbamide, and the need for male and female contraception during treatment and up to 3–6 months after cessation. However, the indications for treatment with pegylated interferon alfa-2a must be assessed

on a case-by-case basis, particularly in patients with a significant psychiatric history, liver disease and/or a history of concurrent underlying autoimmune disease (particularly lupus).

Therapeutic management of lymphocytic HES

First-line treatments

In general, lymphocytic HES is highly responsive to corticosteroids.

Topical corticosteroids can be effective on localized inflammatory lesions, keeping in mind the cumulative dose.

Inhaled corticosteroids are recommended for recurrent and/or persistent moderate respiratory manifestations.

Oral corticosteroid therapy is the usual first-line treatment of lymphocytic HES. The loading dose (0.5–1 mg/kg/day prednisone) should be tailored to the severity of the symptoms related to eosinophilia, before gradual tapering. Overall, the lowest effective dose should be used and weaning attempted as early as possible.

Second-line treatments

Mirroring the fact that lymphocytic HES is usually highly sensitive to systemic corticosteroids, high-dose steroid dependence is also common (possibly due to high levels of serum IL-5 and/or persistent underlying T-cell lymphoproliferative disease). To minimize the potential adverse reactions of systemic corticosteroids, steroid-sparing treatment may be considered in steroid-dependent patients.

Currently mepolizumab and interferon alfa-2a are the preferred first-line steroid-sparing treatments for lymphocytic-HES patients with high-dose corticosteroid dependency.

- Interferon alfa-2a, an immunomodulatory agent acting on both eosinophils and Th2-polarized T cells. Retrospective of both series Both Belgian, Canadian, and French retrospective showed marked clinical and hematological efficacy [10, 11, 106]. Nevertheless, the drug tolerability can be a barrier to its use and long-term maintenance. In daily practice, to minimize potential side effects and to promote adherence to treatment, we suggest starting at the lowest possible dose of the pegylated form (e.g., weekly subcutaneous injections 45 µg pegylated interferon alfa-2a) and to increase it gradually based on tolerability.
- Mepolizumab has also showed efficacy and steroid-sparing effect in lymphocytic HES, with a presumed better safety profile than interferon [107]. Yet persistent symptoms (despite normal absolute eosinophil counts) have also been reported [11].

In case of failure of both mepolizumab and interferon, further-line steroid-sparing drugs may be discussed in expert centers. These include:

- A few cases of successful treatment of refractory lymphocytic HES with romidepsin have been reported [108]. However, the small number of cases ($n < 5$) and short follow-up do not currently make it possible to clearly define the place of this compound in the therapeutic arsenal against lymphoid variant of HES, the indication of which may be discussed in a multidisciplinary team meeting.
- The membrane expression of CCR4 by clonal T cells suggests that mogamulizumab may be of interest, but its relevance remains to be determined.
- Following the identification of acquired abnormalities in factors affecting the JAK-STAT signaling pathway (including gain-of-function mutations of STAT3) in lymphocytic HES [108, 109], the potential effectiveness of JAK inhibitors (ruxolitinib and tofacitinib) has been suggested in small case series, surprisingly even in the absence of gene mutations of the JAK/STAT pathway [110, 111].

- Despite an attractive rationale for their use, limited data are available on immunosuppressive agents that can target T cells, such as cyclosporine, methotrexate, and mycophenolate mofetil.

Therapeutic management of reactive HES (other than lymphocytic)

As a general rule, when an underlying factor is identified as the cause of HE/HES, its management is based on the etiological treatment of the underlying disorder (discontinuation of the causal drug/antiparasitic treatment/chemotherapy).

In addition, in the event of organ involvement related to eosinophil toxicity, oral corticosteroid therapy may be recommended at the acute phase, pending the effects of the etiological treatment, and with the aim of weaning the patient from systemic steroids within than three months, if possible.

Management of HE of undetermined significance

The management of HEUS is not standardized. Some teams have reported prolonged follow-up (several years) in patients with significant HE (sometimes > 5.0 × 109/L in the absence of any treatment [12]. However, the time between the onset of HE and the first related clinical manifestation can also be prolonged. The therapeutic approach should therefore be discussed with patients on a case-by-case basis, depending on their possible comorbidities, their understanding of the situation and their compliance with follow-up. Although there is no strict correlation between the levels of blood HE and tissue HE, it is conceivable not to initiate treatment in patients with asymptomatic HE < 5.0 × 109/L but to continue long-term monitoring as described in “Follow-up” section. In asymptomatic clonal (or presumed clonal) HE, a multidisciplinary team meeting on whether treatment is indicated should be considered.

Specific settings

[…]

Children

Some specific factors also need to be considered in this population. Physical growth and pubertal development should be monitored, as well as the psychological impact of the disease and its treatment. Attempts should be made to reduce corticosteroid exposure as much as possible to limit potential steroids-related side-effects e.g., by not exceeding the maximum dose of 2 mg/kg/day of prednisone or equivalent, by trying to reduce the dose whenever the clinical situation and laboratory results allow so, or by considering a rapid switch to a second-line steroid-sparing treatment. In addition, peginterferon alfa-2a, mepolizumab and benralizumab have not been assessed in children under 3, 6, and 12 years of age, respectively. For imatinib, the dose should be adjusted based on body surface area, and close monitoring of physical growth in treated children is recommended (there have been reports of stunted growth in children and preadolescents receiving imatinib). Although not currently published, real-life data suggest that ciclosporin or JAK inhibitors (e.g., ruxolitinib) may also be useful in the context of pediatric HES. In adolescence, early contact with adult medical care teams, as well as collaborative management, is advisable to facilitate the transition to adulthood.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 06 of 12, June 2026) am 02.06.2026

#	Suchschritt
1	MeSH descriptor: [Hypereosinophilic Syndrome] explode all trees
2	(hypereosinophil* OR (hyper NEXT eosinophil*)):ti,ab,kw
3	(loeffler* OR loffler*):ti,ab,kw
4	MeSH descriptor: [Eosinophilia] this term only
5	(eosinophili*):ti,ab,kw
6	#1 OR #2 OR #3 OR #4 OR #5
7	#6 with Cochrane Library publication date from Jun 2021 to present, in Cochrane Reviews
8	#7 with Cochrane Library publication date from Jun 2024 to present

Leitlinien und systematische Reviews in PubMed am 02.06.2026

verwendeter Suchfilter für Leitlinien ohne Änderung:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 20.03.2026.

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 01.01.2026.

#	Suchschritt
	Leitlinien
1	"Hypereosinophilic Syndrome"[Mesh]
2	hypereosinophil*[tiab] OR hyper-eosinophil*[tiab]
3	loeffler*[tiab] OR loffler*[tiab]
4	"Eosinophilia"[Mesh:NoExp]
5	eosinophili*[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[pt] OR Practice Guideline[pt] OR Consensus Statement [pt] OR Consensus Development Conference, NIH[pt] OR guideline*[ti] OR recommendation*[ti] OR ((consensus[ti] OR position[ti]) AND (expert[ti] OR delphi[ti] OR statement*[ti] OR paper*[ti] OR document*[ti] OR report*[ti])))
8	(#7) AND ("2021/06/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])

#	Suchschritt
	systematische Reviews
10	(#6) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
11	(#10) AND ("2021/06/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT "The Cochrane database of systematic reviews"[Journal]
13	(#12) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
14	(#13) NOT (#9)
15	(#14) AND ("2024/06/01"[PDAT] : "3000"[PDAT])
16	#14 NOT #15

Iterative Handsuche nach grauer Literatur, abgeschlossen am 05.06.2026

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI) (*derzeit nicht durchsuchbar*)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO