International Journal of Clinical Dermatology
2026, Vol. 9, No. 1, pp. 47–59
https://doi.org/10.11648/j.ijcd.20260901.17

Review Article

Episodic Angioedema with Eosinophilia (Gleich Syndrome): Clinical Features, Diagnosis, and Management

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Abstract

Episodic angioedema with eosinophilia (EAE), also known as Gleich syndrome, is a rare immune-mediated disorder characterized by recurrent, self-limited episodes of non-urticarial angioedema accompanied by marked peripheral hypereosinophilia and systemic manifestations, including fever, myalgias, transient weight gain, and oliguria. The disease follows a cyclic course with symptom-free intervals and is typically associated with a favorable prognosis, lacking progressive end-organ damage, thereby distinguishing it from classical hypereosinophilic syndromes (HES). This review comprehensively evaluates current evidence regarding the clinical presentation, immunologic characteristics, and pathophysiological mechanisms of EAE. Available data support a central role of Th2-driven immune dysregulation, increased interleukin-5 (IL-5) production, and cyclic eosinophil activation and degranulation. In a subset of patients, aberrant or clonal T-cell populations have been identified, indicating partial pathogenetic overlap with the lymphocytic variant of HES, although EAE maintains a distinct and generally more benign clinical course. EAE remains a diagnosis of exclusion and requires structured evaluation, including assessment of C1 inhibitor and C4 levels to exclude bradykinin-mediated angioedema, and investigation for secondary causes of eosinophilia and myelo- or lymphoproliferative disorders through immunophenotyping, T-cell receptor gene rearrangement analysis, and molecular testing such as FIP1L1–PDGFRA screening. Acute episodes respond rapidly to systemic corticosteroids. In cases of frequent relapse or corticosteroid dependence, steroid-sparing strategies and targeted biologic therapies directed against IL-5 or its receptor represent promising options. Given the rarity of EAE and the absence of standardized algorithms, this review provides a clinically oriented synthesis of diagnostic principles, differential diagnostic considerations, and emerging targeted therapies to improve recognition and evidence-based management of this uncommon yet clinically significant disorder.

Keywords

Episodic Angioedema with Eosinophilia, Gleich Syndrome, Hypereosinophilia, Interleukin-5, Recurrent Angioedema, Hypereosinophilic Syndromes, Biologic Therapy

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Received: 19 February 2026; **Accepted:** 5 March 2026; **Published:** 19 March 2026

1. Introduction

Episodic angioedema with eosinophilia (EAE), also known as Gleich syndrome and angioedema recidivans cum eosinophilia, is a rare immune-mediated disorder first described in 1984 by Gerald J. Gleich and colleagues [1]. The condition is characterized by recurrent, self-limited episodes of non-urticarial angioedema accompanied by systemic manifestations, including fever, myalgias, oliguria, transient weight gain, marked peripheral eosinophilia, and elevated serum interleukin-5 (IL-5) levels during acute attacks.

The original description emphasized the cyclic nature of the disease, the absence of urticaria, and the lack of evidence for hereditary or bradykinin-mediated angioedema, thereby establishing its distinction from other forms of angioedema and eosinophilic disorders. Recognition of EAE as a distinct nosological entity is supported by its benign clinical course, excellent responsiveness to systemic corticosteroids, and the absence of progressive end-organ damage [1, 2].

EAE is considered exceptionally rare, and its precise incidence remains unknown due to the limited number of reported cases and the absence of large-scale epidemiologic studies. Despite its generally favorable prognosis, the syndrome is clinically relevant because of recurrent edema, associated functional impairment, reduced quality of life, and the need for long-term monitoring. Furthermore, the presence of marked eosinophilia and systemic manifestations necessitates comprehensive diagnostic evaluation to exclude myeloproliferative, lymphoproliferative, infectious, and autoimmune conditions [3, 4].

EAE occupies a distinctive position within the spectrum of eosinophilic disorders. In contrast to classical myeloproliferative and lymphocytic variants of hypereosinophilic syndrome (L-HES), EAE is characterized by intermittent rather than persistent eosinophilia, absence of progressive organ damage, and predominance of cutaneous manifestations. Current evidence supports a central role of T-cell–mediated immune dysregulation and IL-5 overproduction, placing EAE in close pathogenetic relationship with L-HES, yet with a clearly distinguishable clinical phenotype and significantly more favorable prognosis [2, 5].

The aim of this review is to synthesize the available evidence on EAE, addressing the historical evolution of the concept, current understanding of its pathophysiology, clinical characteristics, diagnostic approach, and contemporary therapeutic strategies. Particular emphasis is placed on targeted biologic therapies in refractory or corticosteroid-dependent cases, as well as on unresolved questions and future research directions concerning this rare but clinically significant dermatologic entity.

2. Definition and Nomenclature

EAE is defined as a relapsing disorder characterized by recurrent non-urticarial angioedema temporally associated with episodic peripheral eosinophilia and spontaneous remission between attacks. The clinical presentation frequently includes systemic manifestations such as transient weight gain, fever, fatigue, and malaise. The disease follows a cyclic course with spontaneous remission between episodes.

The term episodic angioedema with eosinophilia is predominantly used in the English-language literature and has a descriptive character, emphasizing both the recurrent nature of the manifestations and their association with eosinophilia. The designation angioedema recidivans cum eosinophilia reflects traditional Latin nomenclature and underscores the relapsing course of angioedema; the synonym recurrent angioedema with eosinophilia is also encountered in published reports.

The eponym Gleich syndrome remains widely used and is generally regarded as synonymous with EAE. However, some contemporary authors favor descriptive terminology, given its greater clinical transparency and pathophysiological precision [2].

3. Epidemiology

3.1. Frequency

EAE is an exceptionally rare disorder. To date, fewer than 100 well-documented cases have been reported in the international literature. Its precise incidence and prevalence in the general population remain unknown due to the absence of large-scale epidemiologic studies, dedicated registries, and historically uniform diagnostic criteria. Most available data are derived from isolated case reports and small case series [2, 3].

3.2. Age and Sex Distribution

Disease onset most commonly occurs during the first three decades of life, with reported ages ranging from early childhood to approximately 30 years. However, EAE can manifest at virtually any age. Review articles indicate that in a substantial proportion of patients, initial episodes develop between 20 and 40 years of age, without a clearly defined age predominance [2, 5-7].

Most published series describe an approximately equal sex distribution. Although some reports suggest a slight female predominance, the limited number of documented cases precludes definitive conclusions regarding sex predilection [3, 6].

3.3. Geographic Distribution

Cases of EAE have been reported across diverse geographic regions, including North America, Europe, and Asia. A notable proportion of publications originate from Japan,

where several dozen patients with classical and variant forms of the disease have been described. This wide geographic distribution suggests that EAE is not restricted to a particular ethnic or regional population but represents a globally rare clinical entity [3, 5, 8].

3.4. Registry and Case Series Data

At present, no international or national registries specifically dedicated to EAE have been established. Available epidemiologic insights are derived primarily from retrospective analyses, case series, and systematic reviews of published reports [2]. One systematic review evaluated more than 30 publications involving patients with EAE, analyzing demographic characteristics, clinical course, and laboratory findings. Similar aggregative analyses have been conducted in the Japanese literature, where over 30 cases of classical and atypical presentations have been documented [7, 8].

The absence of registries and prospective cohort studies substantially limits accurate estimation of disease frequency, identification of potential risk factors, and assessment of possible genetic predispositions [3, 5, 9, 10].

4. Pathogenesis and Immunological Characteristics

The etiology and pathogenic mechanisms of EAE remain incompletely understood. Accumulating evidence indicates that the disorder represents an immune-mediated condition characterized by T-cell dysregulation, overproduction of Th2-associated cytokines—particularly IL-5—and cyclic eosinophil activation [1, 3, 5].

4.1. Early Pathogenetic Hypotheses

Initial observations by Gerald J. Gleich and colleagues demonstrated elevated serum levels of major basic protein (MBP) in patients with EAE, implicating eosinophil activation and degranulation in the development of angioedema [1]. The authors proposed the presence of an unidentified, periodically acting stimulus that induces eosinophil activation and migration to the skin, followed by degranulation, mast cell activation, and increased vascular permeability.

Subsequent investigations did not confirm the presence of an eosinophil colony-stimulating factor in vitro but identified eosinophil chemotactic activity in patient sera, although the precise cellular source and regulatory mechanisms remain undefined [11-13].

4.2. Immunological Mechanisms and T-Cell Dysregulation

Multiple studies have demonstrated the involvement of activated $CD4^+$ T-helper lymphocytes in disease pathogenesis. Immunophenotypic analyses revealed an increased Th/Tc ratio and predominance of HLA-DR–positive T cells in peripheral blood and dermal infiltrates, consistent with systemic and cutaneous T-cell activation [14-16]. Although not all investigations confirmed an elevated Th/Tc ratio, aberrant activation of T-helper cells has been consistently reported.

These findings support the hypothesis of a periodically recurring antigenic stimulus that activates the monocyte–macrophage system and T lymphocytes, initiating a downstream cytokine cascade.

4.3. Role of Interleukins

IL-5 represents the central cytokine in the pathogenesis of EAE. G. J. Gleich and K. M. Leiferman reported markedly elevated serum IL-5 levels during acute episodes, correlating with rapid increases in peripheral eosinophil counts and declining following corticosteroid therapy [11]. IL-5 promotes eosinophil proliferation, differentiation, survival, chemotaxis, and degranulation.

Additional cytokines appear to contribute to the inflammatory cascade. Elevated levels of soluble IL-2 receptor (sIL-2R), IL-1, and IL-6 have been described, reflecting systemic immune activation and potentially explaining constitutional symptoms such as fever, myalgias, and transient weight gain [17-19]. IL-1, produced by activated monocytes/macrophages, may play a role in amplifying the inflammatory response and subsequent T-cell activation. In isolated cases, increased levels of granulocyte–macrophage colony-stimulating factor (GM-CSF) and complement fragment C5a have also been reported, underscoring the immunological heterogeneity of EAE [20-22].

4.4. Clonal T-Cell Populations

In a subset of patients, clonal or oligoclonal IL-5–producing T-cell populations have been identified in the absence of overt malignant lymphoproliferation. This observation places EAE in close pathogenetic association with L-HES, albeit with a substantially more benign clinical course and prognosis [5, 12].

4.5. Role of Eosinophils

Eosinophils constitute the principal effector cells in EAE. Under the influence of IL-5, they migrate into tissues and undergo degranulation, releasing cytotoxic proteins such as MBP, eosinophil cationic protein, and eosinophil peroxidase. These mediators induce endothelial injury and increased vascular permeability, mechanisms considered central to the development of angioedema [1, 11].

Despite intense eosinophilic activation, permanent organ damage and fibrosis are exceedingly rare. This phenomenon may be explained by the intermittent rather than persistent nature of eosinophil activation and the absence of sustained

expression of early activation markers, such as CD69, on eosinophils [2, 9].

4.6. Triggering Factors

In most cases, no definitive precipitating factor can be identified. Isolated reports describe temporal associations with upper respiratory tract infections, medication exposure, or hormonal influences—particularly in women of reproductive age—but convincing evidence of a direct causal relationship remains lacking. Consequently, EAE is currently classified as a predominantly idiopathic immune-mediated disorder [5, 12, 19].

Collectively, current data support a model of cyclic, T-cell–driven immune dysregulation characterized by IL-5 overproduction and transient yet intense eosinophil activation, leading to reversible increases in vascular permeability without progressive tissue injury. A simplified pathogenetic Pathway of Episodic Angioedema with Eosinophilia is presented on Table 1.

Table 1. *A hypothetic pathogenetic pathway of EAE.*

Step	Pathophysiological Event	Mechanism	Clinical Consequence
1	Cyclic immune activation	Activation of $CD4^+$ Th2 cells	Initiation of acute episode
2	IL-5 overproduction	Increased IL-5 secretion	Eosinophil proliferation and survival
3	Peripheral hypereosinophilia	Bone marrow eosinophil expansion	Marked elevation of eosinophil count
4	Eosinophil tissue infiltration	Migration to dermis and activation	Local inflammatory response
5	Degranulation	Release of MBP, ECP, and other mediators	Endothelial activation
6	Increased vascular permeability	Barrier dysfunction ± complement activation	Non-urticarial angioedema, transient weight gain
7	Spontaneous resolution	Decline in IL-5 and eosinophils	Clinical remission without organ damage

5. Clinical Presentation

The clinical presentation of EAE is characterized by a relapsing, cyclic course in which cutaneous and systemic manifestations closely parallel fluctuations in peripheral eosinophil counts and serum IL-5 levels [1, 22]. Attacks are typically self-limited and separated by asymptomatic interepisodic intervals [1].

5.1. Dermatological Manifestations

The principal and most characteristic feature is recurrent angioedema, often occurring with an approximately monthly periodicity [1, 23]. The edema develops in the absence of urticaria and usually without significant pruritus; it is firm, non-pitting, and either painless or only mildly painful [1, 23]. Antihistamine therapy is generally ineffective, distinguishing EAE from histamine-mediated forms of angioedema [23]. In longstanding disease, edematous lichenification and transient erythematous macules or papules may be observed [23].

Angioedema most commonly affects the face, periorbital region, lips, and extremities, and less frequently the trunk [1, 23]. In contrast to hereditary angioedema, laryngeal involvement is exceedingly rare, and gastrointestinal manifestations are uncommon [1, 24]. Individual attacks typically last 3–14 days (mean duration approximately 7 days), with clinical improvement coinciding with normalization of eosinophil counts [1, 23]. Interepisodic intervals range from several weeks to months [1].

Non-episodic forms of angioedema with eosinophilia have also been described, most often in young women. These cases are characterized by persistent limb edema, absence of hyper-IgM, and favorable response to low-dose systemic corticosteroids [8]. Such presentations are considered a distinct clinical variant separate from classical EAE [8].

5.2. Systemic Manifestations

During acute attacks, a transient increase in body weight of approximately 5–15% is commonly observed, reflecting fluid retention secondary to increased vascular permeability [1, 24]. Marked oliguria (40–100 mL/24 h) has been reported and typically resolves approximately five days after peak disease activity [1].

Low-grade fever—or less commonly high-grade fever (rarely up to 39 ℃)—frequently accompanies acute episodes and is often associated with fatigue, generalized weakness, and malaise, reflecting systemic immune activation and eosinophil-mediated inflammation [23, 24]. Arthralgia or myalgia may occur, usually without objective evidence of inflammatory arthritis; these manifestations are transient and

parallel disease activity [23].

Transient generalized lymphadenopathy has been described in isolated cases and warrants careful differential diagnosis, particularly with lymphoproliferative disorders and other eosinophilic syndromes [23, 24].

5.3. Clinical Course

EAE follows a relapsing course, with patients remaining clinically asymptomatic during interepisodic periods [1, 23]. Both short-term and prolonged spontaneous remissions have been documented, potentially complicating assessment of therapeutic efficacy [23].

Overall prognosis is favorable, given the absence of persistent visceral involvement or life-threatening complications. Nevertheless, recurrent episodes may significantly impair quality of life and necessitate long-term monitoring and individualized management [1, 24].

6. Paraclinical Features and Biomarkers

The diagnosis of EAE is established on the basis of the characteristic clinical presentation in combination with recurrent hypereosinophilia and the systematic exclusion of alternative causes of angioedema and eosinophilia. Laboratory and specialized investigations are essential both for diagnostic confirmation and for differentiation from hypereosinophilic syndromes, lymphoproliferative disorders, and myeloproliferative diseases [1, 4, 23, 24].

6.1. Hematological Findings

Marked peripheral eosinophilia represents the hallmark laboratory abnormality. It typically coincides with acute episodes or may precede them by 2–3 days. The absolute eosinophil count frequently exceeds 1.5×10^9/L, with levels above 10×10^9/L reported in isolated cases. During interepisodic periods, eosinophil counts generally normalize or decline substantially [1, 23, 25].

Bone marrow examination demonstrates increased numbers of mature and immature eosinophils without evidence of dysplasia or malignant transformation [4, 24].

During active phases, moderate leukocytosis with eosinophil predominance may be observed, while other hematopoietic cell lines remain preserved. Anemia and thrombocytopenia are atypical findings and should prompt evaluation for alternative diagnoses, including myeloproliferative disorders or systemic inflammatory conditions [4, 24].

6.2. Biochemical and Immunological Parameters

Elevated serum IgE levels have been reported in a subset of patients; however, this finding is inconsistent and does not reliably correlate with disease severity. Increased IgM levels and, less frequently, IgG levels have also been described. Reduced C4 levels have been documented in isolated cases, necessitating differentiation from complement-mediated forms of angioedema [1, 8].

During acute episodes, laboratory abnormalities may include elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), alkaline phosphatase, total protein, globulins, and circulating immune complexes. These changes reflect systemic immune activation but lack disease specificity [22, 23].

6.3. Cytokine Profile and Markers of Eosinophil Activation

A defining feature of EAE is increased IL-5 production, which plays a central role in eosinophil proliferation, differentiation, activation, and survival. Serum IL-5 levels rise during acute episodes and decline during remission or following corticosteroid therapy, paralleling clinical activity [1, 25].

Elevated concentrations of other Th2-associated cytokines, including IL-4, IL-6, and IL-13, have also been reported in selected cases [25].

In addition, increased serum levels of eosinophil cationic protein (ECP) and other eosinophil degranulation products have been described, further supporting the active effector role of eosinophils in disease pathophysiology [22, 25].

6.4. Histopathological and Immunohistochemical Findings

Histopathological examination typically reveals an intact epidermis and pronounced dermal edema accompanied by a diffuse or perivascular mixed inflammatory infiltrate within the papillary dermis, which may focally extend into the deeper dermis. The infiltrate consists of lymphocytes, neutrophils, and histiocytes, with eosinophils constituting the predominant cell population. Evidence of vasculitis is generally absent [1, 23].

Immunofluorescence studies for MBP demonstrate cellular and extracellular granular and fibrillar deposition between collagen bundles, reflecting active eosinophil degranulation [26].

6.5. Immunophenotyping

Immunohistochemical analysis of the dermal infiltrate demonstrates predominance of $CD4^+$ T-helper lymphocytes, a substantial proportion of which express HLA-DR, indicating T-cell activation [8, 26].

6.6. T-Cell Phenotype and Molecular Genetic Studies

In a subset of patients, clonal or oligoclonal populations of

aberrant IL-5–producing T lymphocytes have been identified in the absence of overt malignant lymphoproliferative disease.

Analysis of T-cell receptor (TCR) gene rearrangement and flow cytometric immunophenotyping are particularly valuable when L-HES is suspected [4, 27].

Molecular testing for the FIP1L1–PDGFRA fusion gene and other myeloproliferative markers is required to exclude myeloproliferative variants of hypereosinophilic syndrome, which carry distinct prognostic and therapeutic implications [4, 24].

6.7. Imaging Studies

Imaging modalities, including ultrasonography and computed tomography, typically do not reveal disease-specific abnormalities. Nevertheless, they are useful in assessing lymphadenopathy or potential organ involvement during the differential diagnostic evaluation [23, 24].

7. Diagnostic Criteria and Diagnostic Approach

At present, no formally established international diagnostic criteria for EAE exist. The diagnosis is based on the combination of characteristic clinical, laboratory, and immunological findings together with the systematic exclusion of alternative causes of angioedema and eosinophilia [1, 2, 28-30]. Owing to the rarity of the condition and the absence of large prospective studies, the diagnostic approach relies primarily on published case series and narrative reviews [2, 30].

7.1. Proposed Diagnostic Criteria

Based on currently available evidence, the following diagnostic criteria may be proposed [1, 2, 29-31]:

Major criteria:

1) Recurrent non-urticarial angioedema, most commonly affecting the face and extremities;
2) Episodic peripheral eosinophilia, typically >1.5 $\times 10^9$/L, temporally associated with clinical episodes;
3) Spontaneous resolution of clinical manifestations and normalization (or marked reduction) of eosinophil counts during interepisodic periods.

Minor criteria:

1) Elevated serum IL-5 levels or other evidence of a Th2-skewed immune response;
2) Absence of persistent organ involvement characteristic of classical forms of hypereosinophilic syndrome (HES);
3) Rapid and favorable response to systemic corticosteroid therapy [1, 29, 32].

The presence of all major criteria and at least one minor criterion strongly supports the diagnosis, particularly after alternative etiologies have been carefully excluded.

7.2. Diagnosis of Exclusion

EAE remains a diagnosis of exclusion and requires systematic evaluation to eliminate other disorders presenting with angioedema and/or eosinophilia [2, 4, 30].

Hereditary and acquired angioedema should be excluded through quantitative and functional assessment of C1-inhibitor (C1-INH), as well as measurement of C4 and C1q levels [33].

Hypereosinophilic syndromes—particularly myeloproliferative and lymphocytic variants—should be

Eosinophilic dermatoses with distinct clinical and histopathological features should also be considered [35].

Secondary causes of eosinophilia, including allergic, parasitic, drug-induced, and infectious etiologies, must be carefully excluded through targeted history, laboratory investigations, and appropriate ancillary testing [4, 36].

7.3. Diagnostic Algorithm

The diagnostic evaluation of suspected EAE may be structured into sequential steps, as outlined below (Table 2) [2, 4, 29-31].

Table 2. *Proposed Diagnostic Algorithm for Suspected EAE.*

Step	Objective	Evaluation	Key Outcome / Decision
1. Clinical assessment	Recognition of a typical phenotype	Recurrent non-urticarial angioedema Episodic pattern with spontaneous remissions	If phenotype is suggestive → proceed to Step 2
2. Baseline laboratory investigations	Confirmation of eosinophilia and inflammatory activity	Complete blood count with differential Serum IgE CRP and ESR	If episodic eosinophilia ± inflammatory markers are present → proceed to Step 3
3. Exclusion of C1-INH deficiency	Exclusion of bradykinin-mediated angioedema	C4 Quantitative and functional C1-INH	If abnormal → evaluate for HAE/AAE; if normal → proceed to Step 4

Step	Objective	Evaluation	Key Outcome / Decision
4. Evaluation of hypereosinophilia	Exclusion of secondary causes	Parasitological investigations Detailed drug history Allergy testing when indicated	If a secondary cause is identified → treat accordingly; if not → proceed to Step 5
5. Specialized investigations	Assessment of Th2/IL-5 axis and exclusion of clonality	Serum cytokines (especially IL-5) Flow cytometry + TCR gene rearrangement Molecular testing (e.g., FIP1L1–PDGFRA)	If clonal/myeloproliferative markers are present → evaluate for HES variant; if findings are compatible with EAE → consider Step 6 if indicated
6. Histopathological assessment (when indicated)	Exclusion of vasculitis and other eosinophilic dermatoses	Skin biopsy (± immunohistochemistry)	Provides supportive findings and strengthens the diagnosis in cases of diagnostic uncertainty

8. Differential Diagnosis

The differential diagnosis of EAE encompasses a broad spectrum of conditions presenting with angioedema and/or eosinophilia. Accurate distinction is essential because of significant differences in pathogenesis, clinical course, prognosis, and therapeutic approach (Table 3).

Table 3. *Differential Diagnostic Approach in EAE.*

Diagnosis	Distinguishing Features Compared with EAE (Gleich Syndrome)	Key Investigations / Evidence	Ref.
Hereditary angioedema (HAE)	Bradykinin-mediated; absence of eosinophilia; frequent gastrointestinal and laryngeal attacks; no response to corticosteroids; persistently reduced C4	Serum C4; quantitative and functional C1-INH; family history; clinical phenotype	[37, 38]
Acquired angioedema (AAE)	Later age at onset; association with lymphoproliferative or autoimmune disorders; absence of eosinophilia; no cyclic pattern or spontaneous remissions	Reduced C1-INH; decreased C1q and C4; evaluation for underlying disease	[33, 37]
Hypereosinophilic syndrome (HES)	Persistent (non-episodic) eosinophilia; organ involvement (cardiac, pulmonary, neurologic); angioedema not predominant; frequently clonal or myeloproliferative features	Persistent AEC >1.5 $\times 10^9$/L; organ assessment; FIP1L1–PDGFRA and other molecular tests; immunophenotyping/TCR analysis	[4, 5, 39]
Wells syndrome (eosinophilic cellulitis)	Erythematous, infiltrated "cellulitis-like" plaques rather than true angioedema; presence of "flame figures"; limited systemic symptoms	Skin biopsy demonstrating flame figures; clinical correlation	[40]
Eosinophilic pustular folliculitis (Ofuji disease)	Pruritic sterile follicular papulopustules; predilection for seborrheic areas; absence of angioedema and cyclic eosinophilia	Skin biopsy showing eosinophilic folliculitis; clinical correlation	[41]
Eosinophilic fasciitis (Shulman syndrome)	Deep fascial and subcutaneous induration; skin tightening and contractures; absence of angioedema; prominent musculoskeletal manifestations	MRI or soft-tissue ultrasonography; fascial biopsy; inflammatory markers	[42]
Eosinophilia–myalgia syndrome (EMS)	Association with L-tryptophan exposure; progressive multisystem involvement; potentially severe complications; eosinophilia may be transient or absent	History of L-tryptophan use; clinical evaluation; laboratory and organ assessment	[43]
Recurrent cutaneous necrotizing eosinophilic vasculitis	Palpable purpura; histologic evidence of necrotizing vasculitis with fibrinoid necrosis; possible systemic involvement	Skin biopsy demonstrating necrotizing vasculitis; ± immunofluorescence	[44]

Diagnosis	Distinguishing Features Compared with EAE (Gleich Syndrome)	Key Investigations / Evidence	Ref.
Aspirin-exacerbated respiratory disease (AERD; Samter's triad)	Asthma, chronic rhinosinusitis with nasal polyps, intolerance to aspirin/NSAIDs; absence of typical cyclic pattern; predominantly respiratory manifestations	History of aspirin/NSAID reactions; ENT and pulmonary evaluation	[45]
Systemic capillary leak syndrome (Clarkson disease)	Episodes of severe hypotension; hemoconcentration and hypoalbuminemia; absence of eosinophilia; potentially life-threatening	Elevated hemoglobin/hematocrit; low albumin; hemodynamic assessment; exclusion of other causes	[46]
Drug-induced angioedema	Temporal association with ACE inhibitors, NSAIDs, or antibiotics; typically no episodic eosinophilic peaks; resolution after drug withdrawal	Detailed drug history; clinical follow-up after discontinuation; complement testing when indicated	[37]
Parasitic infections	Common cause of secondary eosinophilia; angioedema not a predominant feature; absence of characteristic cyclic pattern	Stool parasitology; serologic testing guided by epidemiologic risk and travel history	[4]

Among these conditions, hypereosinophilic syndromes and bradykinin-mediated angioedema warrant particular attention, given their distinct therapeutic implications and their potential for significant or life-threatening organ involvement.

9. Treatment

Therapeutic management of EAE aims at rapid control of acute episodes, reduction of peripheral eosinophilia, and prevention of recurrences. Although the overall disease course is generally benign, its chronic-relapsing nature often necessitates prolonged therapy and an individualized treatment strategy.

9.1. Management of Acute Episodes

9.1.1. First-line Therapy

Systemic corticosteroids represent first-line therapy. Prednisolone at a dose of 0.5–1 mg/kg/day typically leads to rapid clinical improvement and a marked decline in peripheral eosinophil counts, usually within 24–72 hours. A characteristic feature of EAE is the high propensity for relapse following rapid dose reduction or abrupt discontinuation of corticosteroids, necessitating gradual tapering and careful clinical monitoring [1, 2, 24].

9.1.2. Symptomatic Treatment

Antihistamines have limited or no efficacy, as the angioedema in EAE is not primarily histamine-mediated. Although they may provide partial symptomatic relief, they are not recommended as monotherapy and do not influence the frequency or severity of disease episodes [2].

9.2. Long-term Therapy and Prevention of Recurrences

9.2.1. Steroid-sparing Strategies

In patients with recurrent episodes or corticosteroid dependence, steroid-sparing approaches may be considered. Favorable outcomes have been reported with hydroxyurea, interferon-α, and methotrexate. The available evidence is largely limited to case reports and small case series; however, these agents may offer benefit in carefully selected patients, particularly those with frequent relapses or steroid-related adverse effects [4, 24, 34].

9.2.2. Immunomodulatory Therapies

In cases characterized by T-cell dysregulation or clonal T-cell populations, immunomodulatory strategies targeting aberrant IL-5 production and eosinophil activation may be considered. Such approaches are conceptually aligned with the proposed pathogenic role of Th2-skewed immune responses in EAE [4, 5].

9.2.3. Targeted Biologic Therapies

Monoclonal antibodies directed against IL-5, including mepolizumab and reslizumab, have been shown to reduce peripheral eosinophilia and decrease episode frequency, while facilitating corticosteroid dose reduction or discontinuation in steroid-dependent patients [5, 11, 47, 48, 55-57].

Benralizumab (anti–IL-5Rα) induces rapid and near-complete eosinophil depletion through antibody-dependent cell-mediated cytotoxicity. Although data specific to EAE remain limited, successful use has been reported in refractory forms of hypereosinophilic syndromes, supporting its potential role

in selected severe or treatment-refractory cases [58].

9.2.4. Emerging and Investigational Approaches

Ongoing research focuses on therapeutic strategies targeting the Th2 immune axis, combination biologic regimens, and personalized approaches guided by immunologic and molecular profiling in patients with severe, relapsing, or treatment-refractory disease [5, 29].

10. Prognosis and Monitoring

EAE is generally associated with a favorable long-term prognosis, particularly in comparison with other eosinophilic disorders [1, 2, 4]. Despite its chronic-relapsing course, severe or persistent organ damage is rare [1, 2].

Most published case series and review articles describe a benign clinical trajectory characterized by prolonged remission periods between episodes [1, 24]. Although recurrences may persist for years, they typically do not result in progressive organ damage, are controllable with low- to moderate-dose systemic corticosteroids or targeted biologic therapies, and are not associated with increased overall mortality [2, 4, 24].

In contrast to classical hypereosinophilic syndrome (HES), there is no evidence of cumulative eosinophil-mediated tissue injury during long-term follow-up in patients with EAE [4, 5].

Systemic organ involvement in EAE is exceedingly uncommon. Reported manifestations include transient arthralgia or myalgia, mild and reversible lymphadenopathy, and minimal cardiopulmonary findings without evidence of structural damage or progression [1, 2, 5]. There is no convincing evidence for the development of eosinophilic cardiomyopathy, thromboembolic complications, or transformation into hematologic malignancy, further distinguishing EAE from myeloproliferative variants of HES [4, 5].

Notwithstanding the overall favorable prognosis, regular and long-term follow-up is recommended to ensure early detection of atypical features, assessment of therapeutic response, and timely differentiation from other eosinophilic syndromes [2, 4, 5]. The recommended components of follow-up are summarized in Table 4.

Table 4. *Recommended Monitoring in Patients with EAE.*

Aspect of Follow-up	Parameters Assessed	Timing / Frequency	Purpose	Ref.
Hematologic monitoring	Complete blood count with differential, with emphasis on absolute eosinophil count	During acute episodes Periodically during remission	Assessment of disease activity and eosinophil dynamics	[4, 5, 24]
Clinical assessment	Systemic symptoms and signs of organ involvement	At each follow-up visit	Early detection of systemic manifestations or atypical disease course	[2, 5]
Treatment safety monitoring	Adverse effects related to corticosteroids or biologic agents	Periodically, according to therapy	Risk minimization and treatment adjustment	[4, 5, 24]
Evaluation for progression to HES	Persistent or uncontrolled eosinophilia; emergence of new systemic findings	Upon changes in clinical course or laboratory parameters	Early differentiation from HES	[4, 5, 24]
Individualization of follow-up	Frequency and scope of assessments	According to disease severity, recurrence rate, and therapeutic modality	Personalized monitoring strategy	[2, 5]

Overall, the absence of progressive organ damage and the favorable response to targeted therapy distinguish EAE from other hypereosinophilic conditions and support its classification as a benign, albeit chronic, immune-mediated disorder.

11. Special Considerations

11.1. Immunologic and Prognostic Aspects

Accumulating evidence indicates that a subset of patients with EAE exhibit T-cell dysregulation, including clonal populations of aberrant $CD3^{-}CD4^{+}$ T lymphocytes producing IL-5 [2, 4, 5]. These findings position EAE within the immunologic spectrum of L-HES [4, 29].

Despite these immunologic features, long-term observational data suggest that progression to overt lymphoproliferative or malignant hematologic disease is exceedingly rare [2, 49, 50]. The clinical course typically remains stable and is not associated with organ-destructive complications or cumulative eosinophil-mediated tissue injury [1, 30].

Nevertheless, prolonged follow-up is recommended, particularly in patients presenting with persistent eosinophilia, lymphadenopathy, or documented T-cell clonality, in order to ensure early detection of atypical evolution or diagnostic reclassification [4, 29].

Collectively, these observations support the concept of EAE as a borderline entity situated between benign reactive eosinophilic conditions and lymphocyte-driven forms of HES within the broader spectrum of eosinophilic disorders [2, 29].

11.2. Special Considerations in Specific Populations

11.2.1. Pregnancy

Data regarding the course of EAE during pregnancy are limited and derive primarily from isolated case reports and small case series [31, 51]. Available evidence suggests that pregnancy does not necessarily exacerbate disease activity [31]. In some patients, a reduction in the frequency and severity of episodes has been observed, possibly related to physiological immunologic adaptations and the predominance of a Th2-skewed immune milieu during gestation [5, 51].

Therapeutic management in pregnant patients should be strictly individualized. When treatment is required, systemic corticosteroids remain the preferred option. The use of biologic agents, including anti–IL-5 therapies, necessitates careful risk–benefit assessment due to the limited safety data available in this population [5, 30].

11.2.2. Pediatric Cases

EAE is exceedingly rare in childhood; however, pediatric cases with a clinical presentation comparable to that observed in adults have been reported [7, 52]. In children, recurrent episodes of angioedema are likewise associated with episodic peripheral eosinophilia. The clinical course is generally benign, with no evidence of severe systemic organ involvement or impairment of long-term physical or psychomotor development [7].

Pediatric patients require particularly comprehensive diagnostic evaluation to exclude parasitic infections, primary immunodeficiencies, hereditary forms of angioedema, and other rare eosinophilic syndromes that are more prevalent in this age group [4, 52].

12. Conclusion

EAE is a rare yet clinically well-defined immune-mediated disorder characterized by recurrent non-urticarial angioedema, episodic hypereosinophilia, and systemic manifestations following a cyclic course [1, 2, 11, 23, 28, 34]. Accumulating clinical and immunologic evidence supports a central pathogenic role of Th2-skewed immune responses, IL-5 overproduction, and aberrant T-cell activation, leading to eosinophil expansion and increased vascular permeability [3, 29]. Despite the often striking manifestations during acute episodes, the disease generally follows a benign clinical trajectory with spontaneous remissions and a favorable long-term prognosis [1, 28].

Early recognition of EAE is essential in patients presenting with recurrent angioedema accompanied by eosinophilia. Accurate differentiation from hereditary and acquired forms of angioedema, as well as from classical variants of HES, is critical to avoid unnecessary investigations and inappropriate therapeutic interventions [53, 54]. In this context, biologic agents targeting IL-5 and its receptor have expanded the therapeutic armamentarium and provide effective steroid-sparing options in patients with frequent relapses or corticosteroid dependence [47].

In clinical practice, EAE should be considered in cases of episodic angioedema associated with transient eosinophilia and systemic symptoms such as weight gain, fever, and arthralgia [1, 3]. A structured diagnostic approach, combined with longitudinal follow-up, is recommended to exclude alternative causes and to ensure timely recognition of atypical evolution or lymphocyte-mediated disease. Therapeutic management should be individualized: short courses of systemic corticosteroids remain the standard for acute control, whereas targeted biologic therapy may be considered in relapsing or treatment-refractory disease within a personalized treatment strategy [47].

Abbreviations

AAE	Acquired Angioedema
AEC	Absolute Eosinophil Count
ARCE	Angioedema Recidivans Cum Eosinophilia
C1-INH	C1 Inhibitor
$CD3^{-}CD4^{+}$ T cells	CD3-negative, CD4-Positive T Lymphocytes
CRP	C-Reactive Protein
EAE	Episodic Angioedema with Eosinophilia
ECP	Eosinophil Cationic Protein
ESR	Erythrocyte Sedimentation Rate
FIP1L1–PDGFRA	FIP1-Like 1–Platelet-Derived Growth Factor Receptor Alpha Fusion Gene
GM-CSF	Granulocyte–Macrophage Colony-Stimulating Factor
HAE	Hereditary Angioedema
HES	Hypereosinophilic Syndrome
IgE	Immunoglobulin E
IL-5	Interleukin-5
JAK–STAT	Janus Kinase–Signal Transducer and Activator of Transcription Pathway
LDH	Lactate Dehydrogenase

L-HES	Lymphocytic Variant of Hypereosinophilic Syndrome
MBP	Major Basic Protein
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
sIL-2R	Soluble Interleukin-2 Receptor
TCR	T-cell Receptor
Th2	T Helper Type 2 (Th2) Cells

Acknowledgments

The authors thank the clinical teams involved in the management of patients with eosinophilic disorders.

Author Contributions

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Conflicts of Interest

The authors declare no conflicts of interest.

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