EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS – A COMPREHENSIVE NARRATIVE REVIEW

EOZINOFILNA GRANULOMATOZA SA POLIANGIITISOM – SVEOBUHVATNI PREGLEDNI ČLANAK

Slobodan ŠAJINOVIĆ[1,2], Vladimir ĐUROVIĆ[1,2], Sonja GOLUBOVIĆ[1,2], Aleksandra BUKVIĆ ŠAJINOVIĆ[1], Dejan ĆELIĆ[1,2] and Milica POPOVIĆ[1,2]

ORCID NUMBER
Slobodan Šajinović – 0009-0004-0519-3400
Sonja Golubović – 0000-0003-3716-698X
Aleksandra Bukvić Šajinović – 0009-0003-5578-4412
Milica Popović – 0000-0002-0124-9444

University of Novi Sad, Faculty of Medicine Novi Sad[1]
University Clinical Center of Vojvodina, Novi Sad
Clinic for Nephrology and Clinical Immunology[2]

Review article
Pregledni članak
UDK 616-002.7-097-07/-08:615.357
https://doi.org/10.2298/MPNS2512270S

Abstract

Introduction. Eosinophilic granulomatosis with polyangiitis is a rare, systemic, immune-mediated vasculitis of small- to medium-sized blood vessels, characterised by eosinophil-rich inflammatory response, necrotising vasculitis, and granulomatous tissue reactions. **Pathogenesis.** The disease arises from a complex interplay of T helper 2- and T helper 1 cells mediated immunity, eosinophil activation, B-cell-autoantibody responses, and epithelial-derived alarmins. Anti-neutrophil cytoplasmic antibodies positive (predominantly myeloperoxidase) patients exhibit a vasculitic phenotype, whereas anti-neutrophil cytoplasmic antibodies-negative patients show eosinophil-driven organ involvement. Key laboratory features include marked peripheral eosinophilia, elevated inflammatory markers, increased immunoglobulin E levels, and raised immunoglobulin G4 level. **Clinical Presentation.** The disease evolves through overlapping prodromal, eosinophilic, and vasculitic phases, producing variable organ involvement and a relapsing-remitting course. Heterogeneous presentation may obscure diagnosis and affect prognosis. **Diagnosis and Differential Diagnosis.** Diagnosis integrates clinical features, laboratory findings, and histopathologicy analysis. Differential diagnoses include other anti-neutrophil cytoplasmic antibody-associated vasculitides, hypereosinophilic syndromes, eosinophilic lung disorders, drug-induced reactions, parasitic infections, and immunoglobulin G4-related disease. **Prognosis.** Despite limited evidence, overall survival is generally favourable. **Therapy.** Management is guided by severity and prognostic factors. Glucocorticoids remain foundational, while biologics targeting interleukin-5, interleukin-4/interleukin-13, anti-immunoglobulin E – as well as emerging approaches including B-cell depletion, alarmin inhibition, C5a receptor antagonism, and cellular therapies provide steroid-sparing options and improved disease control. **Conclusion.** Despite favorable survival, morbidity persists due to disease relapses, organ-specific complications, and long-term immunosuppression. Advances in immunogenetics, molecular profiling, and targeted therapies support a precision–medicine approach, multidisciplinary care and individualised management to optimise patient outcomes in eosinophilic granulomatosis with polyangiitis.

Key words: Granulomatosis with Polyangiitis; Eosinophilia; Vasculitis; Purpura; Asthma

Sažetak

Uvod. Eozinofilna granulomatoza sa poliangiitisom je retka sistemska imunoposredovana bolest koja zahvata male i srednje krvne sudove. Karakteriše se eozinofilnom infiltracijom tkiva praćenom nekrotizirajućim vaskulitisom i stvaranjem granuloma. **Patogeneza.** Bolest nastaje usled složene interakcije celularnog i humoralnog imuniteta, aktivacije eozinofila i alarmina epitelijalnog porekla. Pacijenti koji imaju pozitivna antineutrofilna citoplazmatska antitela pokazuju češće vaskulitisni oblik bolesti, dok pacijenti sa negativnim antitelima češće razvijaju eozinofilima posredovano oštećenje organa. **Klinička slika.** Bolest se razvija kroz tri faze (prodromalnu, eozinofilnu i vaskulitisnu) koje se često međusobno preklapaju. Zahvatanje organa je nespecifično, ali su najčešće zahvaćeni respiratorni i periferni nervni sistem i koža. Bolest ima relapsirajući karakter. Heterogena prezentacija može otežati dijagnozu i uticati na prognozu. **Dijagnoza i diferencijalna dijagnoza.** Dijagnoza se zasniva na kliničkim manifestacijama, laboratorijskim nalazima i histopatologiji. Diferencijalna dijagnoza obuhvata druge vaskulitise povezane sa pozitivnim antineutrofilnim citoplazmatskim antitelima, hipereozinofilne sindrome, eozinofilne plućne bolesti, reakcije na lekove, parazitske infekcije i imunoglobulin G4-povezanu bolest. **Prognoza** za ove pacijente je dobra. **Terapija.** Lečenje je uslovljeno težinom kliničke slike i prognostičkim faktorima. Kortikosterodi su i dalje osnova terapije, dok biološki lekovi usmereni protiv interleukina 5, interelukina 4 i 13, anti-imunoglobulina E i nove strategije poput B-limfocitne deplecije, blokade alarmina, antagonizma C5a receptora i ćelijskih terapija pružaju mogućnost smanjenja upotrebe kortikosteroida i bolje kontrole bolesti. **Zaključak.** Uprkos povoljnoj stopi preživljavanja, morbiditet i dalje postoji zbog relapsirajućeg karaktera bolesti, sistemskih komplikacija i posledice dugotrajne imunosupresivne terapije. Napredak u imunogenetici, molekularnom profilisanju i ciljanim terapijama podržava pristup terapije bez kortikosteroida, naglašavajući značaj multidisciplinarne nege i individualizovanog pristupa za optimizaciju ishoda bolesti.

Ključne reči: granulomatoza sa poliangitisom; eozinofilija; vaskulitis; purpura; astma

✉ Corresponding author: Slobodan Šajinović, E-mail: slobodan.sajinovic@mf.uns.ac.rs

Abbreviations

EGPA – eosinophilic granulomatosis with polyangiitis
ACR – American College of Rheumatology
Eular – European Alliance of Associations for Rheumatology
ANCA – antineutrophil cytoplasmic antibodies
anti-MPO – anti-myeloperoxidase antibodies
HIV – human immunodeficiency virus
IL – interleukin
IgG4 – immunoglobulin G4
Th1 – T helper type 1 cells, Treg – regulatory T cells
IFN-γ – interferon gamma
TNF-α – tumour necrosis factor alpha
WBC – white blood cells
Eos – eosinophils
CRP – C-reactive protein
ESR – erythrocyte sedimentation rate
GPA – granulomatosis with polyangiitis
MPA – microscopic polyangiitis
AZA – azathioprine
MTX – methotrexate
RTX – rituximab
CYC – cyclophosphamide
ENT – ear, nose, throat
TMP/SMX – trimethoprim-sulfamethoxazole
FFS – Five-Factor Score
GC – glucocorticoid
JAK – Janus kinase
Siglec-8 – sialic acid-binding immunoglobulin-like lectin

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare, immune-mediated disorder characterised by necrotising vasculitis of small- to medium-sized blood vessels accompanied by prominent eosinophilic infiltration and granulomatous tissue inflammation [1–5]. The condition was first described in the early 1950s by Churg and Strauss, who identified a group of patients presenting with asthma, marked eosinophilia, and multisystem involvement caused by necrotising, eosinophil-rich vasculitis and granulomatous inflammation. Based on these shared clinicopathological features, they proposed the entity initially termed *allergic granulomatosis* [6]. A few years later, comparative studies by Churg and Godman demonstrated that this syndrome, together with granulomatosis with polyangiitis and microscopic polyangiitis, constituted a distinct group of small-vessel *pauci-immune* vasculitides, separable from classic polyarteritis nodosa. This work laid the foundation for the modern classification of EGPA [7].

This narrative review provides a comprehensive overview of EGPA, focusing on its clinical manifestations, underlying immunopathological mechanisms, and current as well as emerging therapeutic strategies, while highlighting recent advances in diagnosis, risk stratification, and targeted therapy.

Incidence and Prevalence

The estimated annual incidence of EGPA ranges from 0.5 to 4.2 cases per million inhabitants, although reported figures vary considerably, largely due to differences in applied classification criteria [5,8,9]. The disease most commonly affects individuals between 40 and 60 years of age [10], with no significant difference between males and females [1,9]. Reported prevalence rates vary widely worldwide, ranging from approximately 2 cases per million in Germany to as high as 30 per million in Norway, with no consistent associations identified with temporal trends, geographic region, or specific diagnostic criteria [2].

Pathogenesis

The pathogenesis of EGPA is influenced by both genetic predisposition [2,11] and environmental exposures, including organic solvents, silica, and farming-related factors [12,13]. Accumulating evidence indicates that EGPA is a polygenic and heterogeneous disease composed of distinct antineutrophil cytoplasmic antibodies (ANCA)-defined endotypes, each characterised by unique genetic backgrounds, immune pathways, and clinical features.

Data from the European Vasculitis Genetics Consortium demonstrated that EGPA comprises two genetically distinct entities. The myeloperoxidase (MPO)-ANCA-positive form is associated with HLA-DQ alleles and exhibits a phenotype that overlaps with classical autoimmune vasculitides [14]. In contrast, ANCA-negative EGPA is associated with non-HLA genetic variants involved in epithelial barrier integrity and eosinophil regulation, supporting fundamentally divergent pathogenic mechanisms between these two subsets [14].

At the immunological level, EGPA pathogenesis reflects the interaction between epithelial-derived alarmins, T helper 2 inflammation, eosinophil-mediated tissue injury, and B-cell/autoantibody production, with MPO-ANCA characterizing the vasculitic phenotype [15,16]. Environmental factors appear to further modulate disease susceptibility and clinical expression of ANCA-associated vasculitis (AAV), with the strongest evidence supporting roles for silica exposure, microbial triggers such as *Staphylococcus aureus*, farming, and certain medications, including penicillins, cephalosporins, phenytoin, and allopurinol [12]. Other proposed contributors – such as air pollution, seasonal variation, and viral infections - remain inconsistently supported across studies [13].

Immunological Pathways

EGPA is driven by dysregulation of T-cell responses, characterized by dominant T helper 2 (Th2) cytokine activity, including interleukin (IL)-3, IL-4, IL-5, IL-9, IL-10, IL-13, and IL-25, together with an antigen-driven T-cell repertoire. Additional immune imbalance arises from dysregulation of Th17/T regulatory (Treg) axis, which further amplifies inflammation through neutrophil recruitment. Increased interferon-γ (IFN-γ) production and activation of cytotoxic $CD8^+$ T cells reflect additional Th1-mediated vascular damage [17].

In ANCA-positive EGPA, B cells and neutrophils participate in a self-perpetuating inflammatory loop. Proinflammatory cytokines prime neutrophils to expose ANCA antigens, facilitating ANCA binding and subsequent neutrophil activation. This results in the release of reactive oxygen species (ROS), enzymes, and the formation of neutrophil extracellular traps (NETs), which in turn stimulate B cells to produce additional ANCA, perpetuating vascular injury [15–17].

Eosinophils, activated predominantly by IL-5, IL-4, and IL-13, migrate from the bone marrow to peripheral tissues, where they persist and contribute to EGPA through cytotoxic, inflammatory, and non-immunological mechanisms. Th2-derived cytokines establish a positive feedback loop that drives eosinophila rise [5,18]. Epithelial-derived alarmins – including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) – play a critical upstream role by promoting eosinophil differentiation and survival [5,17]. Collectively, these advances identify key pathways, including the IL-5-eosinophil axis, epithelial alarmins, and B-cell/IgG4 networks, providing biomarkers of disease activity and supporting the development of targeted biologic therapies [15,16].

Heterogeneous Clinical Presentation

The clinical presentation of EGPA is highly heterogeneous and frequently involves multiple organ systems. If left untreated, the disease may progress to severe or irreversible multiorgan damage [3–5]. EGPA typically follows a relapsing-remitting course, with more than one-third of patients experiencing relapse within five years of achieving initial remission [2].

Classically, EGPA evolves through prodromal, eosinophilic, and vasculitic phases, although these often coexist, contributing to diagnostic delay [18,19]. The **prodromal phase** is dominated by asthma, allergic rhinitis, and chronic sinusitis, and may persist for several years. The **eosinophilic phase** characterised by marked peripheral eosinophilia and eosinophilic infiltration of tissues, most commonly affecting the lungs, gastrointestinal tract, and heart [1, 5,20]. The **vasculitic phase** involves systemic necrotising small- to medium-sized vessels, resulting in organ-specific manifestations and constitutional symptoms, with ANCA positivity most frequently associated with this stage [1,2,5,15,20].

Approximately one-third of patients with EGPA are ANCA-positive, most commonly exhibiting MPO specificity [1,8]. Clinical manifestations vary according to ANCA status. ANCA-positive patients more frequently exhibit vasculitic features such as glomerulonephritis, peripheral neuropathy, and purpura [21,22]. In contrast, ANCA-negative patients tend to display predominantly eosinophilic manifestations, including cardiac involvement and gastroenteritis. Nonetheless, most patients demonstrate overlapping vasculitic and eosinophilic phenotypes [8,23,24].

Once diagnosed, EGPA may follow either mild, self-limiting course or progress to severe, multi-organ involvement associated with substantial morbidity and mortality [25]. Constitutional symptoms such as fever, weight loss, and fatigue are common and reflect systemic inflammation [4,8,18,26], often accompanied by cutaneous manifestations [24,27]. The severity and prognostic significance of organ involvement vary considerably, and some manifestations may remain underrecognised due to the absence of standardised diagnostic criteria [1,3,4]. **Table 1** summarizes organ involvement frequency, clinical manifestations, and ANCA positivity for each organ system in EGPA.

Diagnosis Criteria and Differential Diagnosis

The diagnosis of EGPA relies on an integrated assessment of characteristic clinical features, laboratory findings, and histopathological confirmation from tissue biopsy [5,8,20]. Key laboratory features include marked peripheral eosinophilia, typically exceeding 1.5×10^9/L or 10% of circulating leukocytes (often reaching 5,000–9,000/μL), elevated non-specific inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), increased serum IgE, and elevated IgG4 levels [5,10].

Although the complement system may contribute to disease pathogenesis in specific contexts [28], complement levels are not routinely considered clinically informative in EGPA [5]. In clinical practice and research settings, including clinical trials, diagnosis and classification commonly rely on the American College of Rheumatology (ACR) criteria and the European Alliance of Associations for Rheumatology (EULAR) recommendations [2,5,29] **(Table 2).**

The differential diagnosis of EGPA is broad and includes other small-vessel vasculitides as well as nu-

Table 1. Frequency and characteristics of organ involvement in EGPA

Organ/System	Frequency	Typical Manifestations	ANCA Association	References
Constitutional	Very common	Fever, fatigue, weight loss	Non-specific	[2,4,5,8,27]
Skin	Common	Palpable purpura, subcutaneous nodules, pruritus, ulcers, urticaria, splinter hemorrhages	Vasculitic features in ANCA-positive	[2,8,25,28]
Respiratory	Very common	Asthma (often severe, steroid-dependent), chronic rhinosinusitis, nasal polyps, recurrent pneumonia/bronchitis, eosinophilic pulmonary infiltrates, chronic cough, dyspnea, bronchiolitis	Both eosinophilic and vasculitic phenotypes	[5,8,27,31]
Gastrointestinal	Moderate	Abdominal pain, nausea, vomiting, diarrhea, systemic inflammation	ANCA-negative more likely eosinophilic involvement	[4,49]
Cardiac	Variable	Myocarditis, pericarditis, arrhythmias, heart failure, cardiac thrombi	Often eosinophilic and vasculitic phase	[3,4,5]
Neurologic	Common	Mononeuritis multiplex, distal polyneuropathy, paresthesia, cranial nerve deficits, CNS involvement (stroke, TIA, seizures)	ANCA-positive more vasculitic	[2,4,26]
Renal	Variable	Glomerulonephritis, hematuria, proteinuria, AKI/CKD, renal infarcts, eosinophilic infiltration	Mostly ANCA-positive	[47,50]
Musculoskeletal	Common	Arthralgia, myalgia, occasionally inflammatory arthritis	Non-specific	[28,36,39]
Hematologic	Very common	Peripheral eosinophilia, leukocytosis, thrombocytosis, mild anemia; rare hypercoagulability	Eosinophil-mediated	[11,20]
Ophthalmologic	Rare	Conjunctivitis, episcleritis, uveitis, orbital pseudotumor, optic neuritis	Small-vessel vasculitis or eosinophilic	[9,41]

CNS – central nervous system; TIA – transient ischemic attack; AKI – acute kidney injury; CKD – chronic kidney disease

merous eosinophilic disorders. Distinction from granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) is usually achievable based on clinical and histological features, although overlapping eosinophilia or PR3-ANCA positivity may complicate differentiation in rare cases [23]. Secondary causes of eosinophilia must be systematically excluded. Drug-indicted reactions and helminthic infections are key considerations, with serological testing for *Toxocara canis* and *Strongyloides stercoralis* particularly recommended [16]. EGPA also shares features with eosinophilic lung disorders, making differential diagnosis essential once peripheral eosinophilia is detected. Chronic eosinophilic pneumonia, frequently associated with asthma, is typically limited to pulmonary involvement and lacks the systemic vasculitic manifestations characteristic of EGPA [30]. Hypereosinophilic syndrome (HES) represents another important differential diagnosis, characterised by sustained eosinophilia and eosinophil-mediated organ damage. However, but asthma is neither required nor common in HES, and ANCA

Table 2. College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for EGPA

EGPA patients are classified after establishing the diagnosis of small- or medium-vessel vasculitis, provided that alternative conditions that may mimic vasculitis have been thoroughly excluded before applying the criteria.	
Clinical criteria	
Feature	Score
Obstructive airway disease	3
Nasal polyps	3
Mononeuritis multiplex	1
Laboratory and biopsy criteria	
Feature	Score
Blood eosinophil count ≥ 1×10^9/L	5
Extravascular eosinophilic-predominant inflammation on biopsy	2
Positive test for cytoplasmic ANCA [c-ANCA] or anti-PR3 antibodies	–3
Haematuria	–1
Sum the scores for all 7 items if present. EGPA classification requires a total score of ≥ 6	

positivity is typically absent [31]. In addition, non-myeloid malignancies can cause secondary hypereosinophilia and must be excluded [32,33]. Our previous work on HIV-associated lymphomas [34] demonstrated that delayed recognition of underlying pathology and advanced immune dysfunction significantly worsen outcomes, underscoring the importance of timely and accurate etiological diagnosis in patients presenting with eosinophilia.

Although elevated IgG4 levels are observed in a subset of EGPA patients, IgG4-related disease lacks the defining vasculitic features of EGPA [35]. When all secondary causes are excluded, idiopathic HES or other rare HES variants should be considered [32].

Therapy

The management of EGPA is primarily guided by disease severity and prognostic indicators, most commonly assessed using the Five-Factor Score (FFS) [5,17,36]. Patients presenting with non-severe disease (FFS = 0) are generally treated with glucocorticoid (GC) monotherapy. In the majority of cases, remission can be achieved; however, relapse is common, particularly during dose tapering [5,36].

In patients with relapsing or refractory non-severe disease, mepolizumab (300 mg administered subcutaneously once monthly) is recommended due to its proven efficacy in reducing relapse rates and its substantial steroid-sparing effect. Additional immunosuppressive agents, including azathioprine (AZA), methotrexate (MTX), mycophenolate, or rituximab (RTX), may be considered on an individual bases according to patient characteristics [2,5,8,36].

Patients with severe or organ- and life-threatening manifestations (FFS ≥1) require induction therapy with high-dose GC in combination with intravenous cyclophosphamide (CYC), preferably administered in pulsed regimens to limit cumulative toxicity [8,20,37]. RTX represents an effective alternative in situations where CYC is contraindicated, such as in patients requiring fertility preservation [36].

Maintenance therapy following induction typically avoids CYC use because of its long-term toxicity profile. Commonly employed agents include MTX, AZA, RTX, or mepolizumab. In relapsing patients without poor prognostic factors, mepolizumab is generally preferred [2,5,36].

The oral C5a receptor inhibitor avacopan has demonstrated efficacy in the management of severe GPA and MPA, enabling substantial reductions on glucocorticoid exposure while maintaining disease remission. Accordingly, avacopan has been incorporated into the 2024 KDIGO recommendations [38]. Tumour necrosis factor-α (TNF-α) inhibitors, such as etanercept, which are widely used in rheumatoid arthritis [39], are not recommended in EGPA due to the lack of demonstrated clinical benefit and concerns regarding safety in this patient population [40].

Biologic therapies now occupy a central role in the management of relapsing or refractory EGPA [41]. Mepolizumab has shown efficacy irrespective of ANCA status, whereas other IL-5-targeting agents (reslizumab, benralizumab) and anti-IgE therapy (omalizumab) are supported by more limited evidence and are generally reserved for selected cases [36,41]. Dupilumab may be beneficial in patients with prominent asthma or ENT involvement, although caution is warranted due to its potential to exacerbate eosinophilia [5,36]. The combination of dupilumab and mepolizumab may represent a safe and effective therapeutic strategy in selected patients with EGPA [42].

At present, no EGPA-specific protocol for GC tapering exists, and regimens used in GPA/MPA are frequently applied as guidance. Patients with persistent asthma or ENT involvement may require slower and more prolonged tapering, underscoring the importance of multidisciplinary management [36,43]. Follow-up should be guided by structured clinical assessment rather than reliance on laboratory findings alone. Although ANCA titers, eosinophil counts or CD19+ B-cell levels are routinely monitored, disease activity is best evaluated using validated clinical assessment instruments [17]. Among these, the Birmingham Vasculitis Activity Score and the Vasculitis Damage Index are widely recommended to distinguish active inflammation from irreversible organ damage [2,5]. Recent advances in the management of ANCA-associated vasculitis and EGPA have increasingly focused on minimizing GC exposure while maintaining durable disease control [38]. Infection prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX) is recommended for patients receiving RTX, CYC, or prolonged high-dose GC therapy to prevent *Pneumocystis jirovecii* and other opportunistic infections [44,45]. A systematic review suggests that intermittent TMP/SMX regimens are better tolerated than daily dosing while providing comparable prophylactic efficacy [45]. Alternative options include dapsone, atovaquone, or aerosolized pentamidine.

Vaccination strategies should adhere to current EULAR recommendations for patients with autoimmune diseases [46]. In addition, monitoring serum immunoglobulin levels prior to RTX therapy is essential to detect secondary hypogammaglobulinemia, which may develop in a substantial proportion of patients receiving long-term RTX or CYC [43].

Future Therapeutic Approaches

Systemic glucocorticoids continue to form the cornerstone of EGPA therapy. However, the introduction of biologics targeting IL-5 and IL-4/IL-13 pathways has markedly improved disease management. Ongoing research is increasingly focused on upstream targets within the inflammatory cascade, including epithelial-derived alarmin inhibition (tezepelumab), B-cell depletion approaches, and novel agents such as Janus kinase (JAK) and Siglec-8 inhibitors [15,38]. Furthermore, CD19-targeted chimeric antigen receptor (CAR) T–cell therapy has demonstrated promising results in refractory ANCA-associated vasculitis, leading to profound B–cell depletion and reduction in autoantibody levels [47,48]. Although clinical data in EGPA are not yet available, this approach may ultimately offer a therapeutic option for patients with severe, treatment-resistant disease.

Prognosis and Outcomes

Despite the rarity of EGPA and the limited evidence, overall survival is generally favourable. White and Dubey reported – to 7-year survival rates of approximately 90-96%, although patients aged 65 years or older exhibited an increased risk of mortality [5]. Nonetheless, mortality rates remain heterogeneous across cohorts. Doline reported that EGPA-related mortality may exceed that of the general population, particularly among patients with relapsing or refractory disease or those requiring prolonged GC therapy [9]. An American cohort study reported an overall mortality of 4%, lower than historical estimates of 7–14%, likely reflecting improvements in early diagnosis and therapeutic strategies [26]. However, EGPA continues to impose a substantial chronic disease burden. Frequent hospital admissions, long-term corticosteroid dependence, and extensive healthcare utilisation negatively affect long-term outcomes and quality of life. Cardiac, renal, and gastrointestinal involvement remain well-established predictors of adverse prognosis [3,9,49,50].

Conclusion

Eosinophilic granulomatosis with polyangiitis represents a uniquely complex vasculitic disorder situated at the intersection of allergic inflammation, eosinophil-driven tissue injury, and pauci-immune autoimmunity. Accumulating evidence clearly establishes antineutrophil cytoplasmic antibodies-defined endotypes as biologically and clinically distinct entities. Although survival has improved substantially through earlier recognition, structured disease assessment, and the introduction of targeted biologic therapies, eosinophilic granulomatosis with polyangiitis continues to impose a significant long-term burden driven by relapsing disease, chronic glucocorticoid exposure, and organ-specific complications. Advances in understanding the IL-5–eosinophil axis, epithelial alarmins, B-cell and IgG4 networks, and the immunogenetic landscape have transformed both the conceptual framework and clinical management of this disease.

Emerging therapeutics – Including IL-5, IL-4/Il-13 blockade, alarmin inhibition, B-cell depletion strategies, Janus kinase and Siglec-8 inhibitors, C5a receptor antagonists, and early exploration of CD19-directed cellular therapies – signal a paradigm shift toward precision, steroid-sparing treatment algorithms. Nevertheless, significant unmet needs persist, including optimized glucocorticoid tapering strategies, risk stratification beyond the Five-Factor Score, reliable biomarkers distinguishing active disease from chronic damage, and evidence-based guidance for long-term follow-up.

Continued integration of immunogenetics, molecular profiling, and real-world outcomes is essential to refine prognostication, personalize therapy, and ultimately reduce the chronic morbidity associated with eosinophilic granulomatosis with polyangiitis. As the therapeutic landscape continues to evolve, multidisciplinary care, vigilant monitoring, and a sustained commitment to minimising treatment-related toxicity will remain central to improving quality of life and long-term outcomes for patients living with this rare but increasingly treatable vasculitis.

References

1. Jakes RW, Kwon N, Huynh L, Hwee J, Baylis L, Alfonso-Cristancho R, et al. Burden of eosinophilic granulomatosis with polyangiitis in Europe. ERJ Open Res. 2024;10(4):00912-2023.

2. Jakes RW, Kwon N, Nordstrom B, Goulding R, Fahrbach K, Tarpey J, et al. Burden of illness associated with eosinophilic granulomatosis with polyangiitis: a systematic literature review and meta-analysis. Clin Rheumatol. 2021;40(12):4829-36.

3. Srikantharajah M, Gopalan D, Wilson-Morkeh H, Siddiqui S, McAdoo SP, Youngstein T. Cardiac involvement in eosinophilic granulomatosis with polyangiitis. Curr Cardiol Rep. 2025;27(1):109.

4. Li R, Chen Y, Zhang S, Peng L, Zhou J, Fei Y, et al. Clinical characteristics and long-term outcome of patients with gastrointestinal involvement in eosinophilic granulomatosis with polyangiitis. Front Immunol. 2023;13:1099722.

5. White J, Dubey S. Eosinophilic granulomatosis with polyangiitis: a review. Autoimmun Rev. 2023;22(1):103219.

6. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol. 1951;27(2):277-301.

7. de Campos FPF, Geller SA. Churg-Strauss syndrome: a syndrome described on clinical observation and autopsy findings. Autops Case Rep. 2013;3(2):1-4.

8. Springer JM, Kalot MA, Husainat NM, Byram KW, Dua AB, James KE, et al. Eosinophilic granulomatosis with polyangiitis: a systematic review and meta-analysis of test accuracy and benefits and harms of common treatments. ACR Open Rheumatol. 2021;3(2):101-10.

9. Dolin P, Lucas S, Gamble A, Turner M, Rowell J. Systematic literature review and meta-analysis of the epidemiology and clinical burden of eosinophilic granulomatosis with polyangiitis. Modern Rheumatol. 2025;35(4):697-706.

10. Gioffredi A, Maritati F, Oliva E, Buzio C. Eosinophilic granulomatosis with polyangiitis: an overview. Front Immunol. 2014;5:549.

11. Lyons PA, Peters JE, Alberici F, Liley J, Coulson RMR, Astle W, et al. Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status. Nat Commun. 2019;10(1):5120.

12. Maritati F, Peyronel F, Fenaroli P, Pegoraro F, Lastrucci V, Benigno GD, et al. Occupational exposures and smoking in eosinophilic granulomatosis with polyangiitis: a case–control study. Arthritis Rheumatol. 2021;73(9):1694-702.

13. Katz G, Wallace ZS. Environmental triggers for vasculitis. Rheum Dis Clin North Am. 2022;48(4):875-90.

14. Holle JU, Vaglio A. Highlights from the plenary session: eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome. Rheumatology (Oxford). 2025;64(Suppl 1):i92-7.

15. López Paraja M, Starita Fajardo G, Donate Velasco I, Lucena López D, Iranzo Alcolea MP, Lirola Sánchez FJ, et al. Molecular pathogenesis and targeted therapies in eosinophilic granulomatosis with polyangiitis: an updated review. Int J Mol Sci. 2025;26(22):11141.

16. Fijolek J, Radzikowska E. Eosinophilic granulomatosis with polyangiitis – advances in pathogenesis, diagnosis, and treatment. Front Med (lausanne). 2023;10:1145257.

17. Kosałka-Węgiel J, Sebastian A. Dual pathogenesis and treatment approaches for eosinophilic granulomatosis with polyangiitis: a comprehensive review. Reumatologia. 2025;63(5):331-6.

18. Berti A, Boukhlal S, Groh M, Cornec D. Eosinophilic granulomatosis with polyangiitis: the multifaceted spectrum of clinical manifestations at different stages of the disease. Expert Rev Clin Immunol. 2020;16(1):51-61.

19. Trivioli G, Terrier B, Vaglio A. Eosinophilic granulomatosis with polyangiitis: understanding the disease and its management. Rheumatology (Oxford). 2020;59(Suppl 3):iii84-94.

20. Koike H, Nishi R, Ohyama K, Morozumi S, Kawagashira Y, Furukawa S, et al. ANCA-associated vasculitic neuropathies: a review. Neurol Ther. 2022;11(1):21-38.

21. Ljubicic B, Azasevac T, Popovic M, Zivkovic S, Bozic D, Celic D. Predictors of renal outcome in ANCA-associated glomerulonephritis. Vojnosanit Pregl. 2021;78(7):769-74.

22. Golubovic S, Veselinov V, Zivkovic S, Popovic M, Ilić T, Glogonjac N, et al. #2450 Predictors of disease activity in ANCA-associated vasculitis subtypes: a statistical and predictive analysis. Nephrol Dial Transplant. 2025;40(Suppl 3):gfaf116.0344.

23. Emmi G, Bettiol A, Gelain E, Bajema IM, Berti A, Burns S, et al. Evidence-Based Guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. Nat Rev Rheumatol. 2023;19(6):378-93.

24. Micheletti RG, Chiesa Fuxench Z, Craven A, Watts RA, Luqmani RA, Merkel PA, et al. Cutaneous manifestations of antineutrophil cytoplasmic antibody–associated vasculitis. Arthritis Rheumatol. 2020;72(10):1741-7.

25. Puéchal X, Pagnoux C, Baron G, Lifermann F, Geffray L, Quémeneur T, et al. Non-severe eosinophilic granulomatosis with polyangiitis: long-term outcomes after remission-induction trial. Rheumatology (Oxford). 2019;58(12):2107-16.

26. Doubelt I, Cuthbertson D, Carette S, Chung SA, Forbess LJ, Khalidi NA, et al. Clinical manifestations and long-term outcomes of eosinophilic granulomatosis with polyangiitis in North America. ACR Open Rheumatol. 2021;3(6):404-12.

27. Tabb ES, Duncan LM, Nazarian RM. Eosinophilic granulomatosis with polyangiitis: cutaneous clinical and histopathologic differential diagnosis. J Cutan Pathol. 2021;48(11):1379-86.

28. Trattner R, Iordanou M, Ohlsson S, Martin M, Segelmark M, Blom AM. Complement factors as biomarkers in ANCA-associated vasculitis in remission. Clin Exp Immunol. 2025;219(1):uxaf037.

29. Grayson PC, Ponte C, Suppiah R, Robson JC, Craven A, Judge A, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81(3):309-14.

30. Carbone RG, Puppo F, Mattar E, Roden AC, Hirani N. Acute and chronic eosinophilic pneumonia: an overview. Front Med. 2024;11:1355247.

31. Khoury P, Akuthota P, Kwon N, Steinfeld J, Roufosse F. HES and EGPA: two sides of the same coin. Mayo Clin Proc. 2023; 98(7):1054-70.

32. Helbig G, Klion AD. Hypereosinophilic syndromes – an enigmatic group of disorders with an intriguing clinical spectrum and challenging treatment. Blood Rev. 2021;49:100809.

33. Stella S, Massimino M, Manzella L, Pennisi MS, Tirrò E, Romano C, et al. Molecular pathogenesis and treatment perspectives for hypereosinophilia and hypereosinophilic syndromes. Int J Mol Sci. 2021;22(2):486.

34. Andric V, Turkulov V, Urosevic I, Salaj N, Boskovic N, Sajinovic S. Non-Hodgkin lymphoma in people living with human immunodeficiency syndrome. Med Pregl. 2020;73(1-2):37-42.

35. Kawashima H, Utsugi A, Shibamiya A, Iida K, Mimura N, Ohashi H, et al. Consideration concerning similarities and differences between ANCA-associated vasculitis and IgG-4-related diseases: case series and review of literature. Immunol Res. 2019;67(1):99-107.

36. Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis. 2024;83(1):30-47.

37. Golubović S, Ćelić D, Božić D, Milić B, Ljubićić B, Živković S, et al. Cyclophosphamide induced complication of primary glomerulonephritis-case reports. MD-Medical Data. 2020;12(2):101-5.

38. Francis L, Dhutia A, Pusey C, Jones RB. Highlights from the breakout session: optimising new treatments. Rheumatology (Oxford). 2025;64(Suppl 1):i117-9.

39. Ilić T, Milić B, Ćelić D, Vučković B, Mitić I. Etanercept therapy in rheumatoid arthritis: efficacy and safety. Srp Arh Celok Lek. 2013;141(7-8):495-502.

40. Torp CK, Brüner M, Keller KK, Brouwer E, Hauge EM, McGonagle D, et al. Vasculitis therapy refines vasculitis mechanistic classification. Autoimmun Rev. 2021;20(6):102829.

41. Pitlick MM, Li JT, Pongdee T. Current and emerging biologic therapies targeting eosinophilic disorders. World Allergy Organ J. 2022;15(8):100676.

42. Nakamura Y, Kikumoto N, Takeuchi H, Kimura T, Nakamori M, Fujiwara K. Combination biologic therapy with mepolizumab and dupilumab for severe eosinophilic granulomatosis with polyangiitis and chronic rhinosinusitis with nasal polyp. Yonago Acta Med. 2024;67(2):157-62.

43. Mendel A, Ennis D, Carette S, Pagnoux C. Assessment of glucocorticoid tapering in large vessel and anti-neutrophil cytoplasmic antibody-associated vasculitides. Clin Exp Rheumatol. 2021;39 Suppl 129(2):119-24.

44. Honda N, Tagashira Y, Kawai S, Kobayashi T, Yamamoto M, Shimada K, et al. Reduction of Pneumocystis jirovecii pneumonia and bloodstream infections by trimethoprim–sulfamethoxazole prophylaxis in patients with rheumatic diseases. Scand J Rheumatol. 2021;50(5):365-71.

45. Masaki T, Ishikawa K, Fujino T, Koyamada R, Kawai F, Ota E, et al. Intermittent versus daily trimethoprim/sulfamethoxazole regimens for Pneumocystis pneumonia prophylaxis: a systematic review and meta-analysis. Open Forum Infect Dis. 2024;11(9):ofae499.

46. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79(1):39-52.

47. Lodka D, Zschummel M, Bunse M, Rousselle A, Sonnemann J, Kettritz R, et al. CD19-targeting CAR T cells protect from ANCA-induced acute kidney injury. Ann Rheum Dis. 2024;83(4):499-507.

48. Ohno R, Nakamura A. Advancing autoimmune rheumatic disease treatment: CAR-T cell therapies - evidence, safety, and future directions. Semin Arthritis Rheum. 2024;67:152479.

49. Kawasaki K, Nakamura S, Esaki M, Kurahara K, Eizuka M, Okamoto Y, et al. Gastrointestinal involvement in patients with vasculitis: IgA vasculitis and eosinophilic granulomatosis with polyangiitis. Endosc Int Open. 2019;7(11):E1333-43.

50. Doreille A, Buob D, Bay P, Julien M, Riviere F, Rafat C. Renal involvement in eosinophilic granulomatosis with polyangiitis. Kidney Int Rep. 2021;6(10):2718-21.

Rad je primljen 4. XII 2025.
Recenziran 18. XII 2025.
Prihvaćen za štampu 18. XII 2025.
BIBLID.0025-8105:(2025):LXXVIII:9-12:270-277.