Evidence-based Guidelines for the Diagnosis and Management of Eosinophilic Granulomatosis with Polyangiitis

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ABSTRACT

Eosinophilic Granulomatosis with Polyangiitis (EGPA) is a rare anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), characterised by asthma, eosinophilia and granulomatous or vasculitic involvement of several organs. The diagnosis and management of EGPA are often challenging and require an integrated, multidisciplinary approach. Current practice relies on the 2015 recommendations developed by an EGPA task force and on the 2016 EULAR/ERA-EDTA recommendations for AAV. In 2021, the ACR/Vasculitis Foundation guidelines for the management of AAV were developed. The 2016 and 2021 guidelines, however, focus on all AAV forms and are therefore not focussed on EGPA. In the past few years, new treatment options have become available for EGPA, and significant advances were made in understanding its pathogenesis, clinical subphenotypes and differential diagnosis. Herein, we developed evidence-based, cross-discipline guidelines for the diagnosis and management of EGPA. A panel of 30 European experts defined the items that drove literature search and voted the statements. Consensus was reached for 16 items and five overarching principles covering diagnosis and staging, treatment, outcome and follow-up of EGPA. The recommendations generated for each item were based on evidence from systematic literature reviews, as well as expert opinion, as appropriate. Level of evidence, grade of recommendation and level of agreement were assessed for each statement. These recommendations are primarily meant to be used by healthcare professionals, pharmaceutical industries and drug regulatory authorities, to guide clinical practice and decision-making in EGPA. These recommendations are not intended to limit access to medications by health care agencies, nor to impose a fixed order in medication use.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) is a rare small-vessel vasculitis that occurs in patients with asthma and eosinophilia, and is histologically characterised by tissue eosinophilia, necrotising vasculitis and eosinophil-rich granulomatous inflammation.(1, 2) The incidence of EGPA ranges between 0.5 and 4.2 cases/million/year, and its prevalence between 10 and 14 cases/million inhabitants.(3-5) The frequency of the disease is comparable in males and females, and the mean age at diagnosis is around 50 years.(6) Paediatric cases are extremely rare.(7)

EGPA usually evolves through three different phases, namely a prodromic ("allergic") phase, which may last for several years and is hallmarked by asthma and chronic rhinosinusitis, a eosinophilic phase, during which eosinophilia and end-organ involvement appear, and a vasculitic phase, characterised by clinical manifestations due to small-vessel vasculitis (*eg*, mononeuritis multiplex, glomerulonephritis). However, these phases often overlap, do not necessarily develop in the aforementioned sequence, and some patients do not manifest vasculitic complications.(2, 8) The clinical phenotype of EGPA is quite heterogeneous and the diagnosis is not always straightforward. Anti-neutrophil cytoplasmic antibodies (ANCA), usually against myeloperoxidase (MPO-ANCA), are detectable in ~40% of the cases and are associated with a different frequency of clinical manifestations: vasculitis features, particularly glomerulonephritis, peripheral neuropathy and purpura, occur more often in ANCA-positive patients, whereas the so-called eosinophilic features such as cardiac involvement and gastroenteritis are more frequent in ANCA-negative patients (**Figure 1, Table 1**).(6, 9-11) Asthma and ear-nose-throat (ENT) disease, which respectively occur in >90% and in 60-80% of the patients, are equally distributed in the two groups. From a histological standpoint, evidence of vasculitis on biopsy is more common in ANCA-positive patients, although EGPA lesions usually include eosinophilic infiltrates (with or without granulomas) along with necrotising vasculitis, and are therefore difficult to categorise as vasculitic or eosinophilic. (**Figure 2**)(12, 13)

The pathogenesis of EGPA is driven by genetic and environmental factors.(14-18) Genetic studies have highlighted associations between *HLA-DQ* and MPO-ANCA-positive EGPA, whereas ANCA-negative EGPA is mainly associated with gene variants involved in mucosal responses and eosinophil biology such as *GPA33* and *IL5*. Several other variants linked to asthma and eosinophil counts in the general population are associated with the whole EGPA spectrum.(14) Among environmental factors, exposure to silica, organic solvents and farming was associated with an increased risk of EGPA, while cigarette smoking with a lower risk.(17) How genetics and environment interact to shape the susceptibility to and the phenotype of EGPA is still unclear.

Several cell types participate in the immunopathogenesis of the disease. Eosinophils are clearly central and are likely to mediate tissue damage, a concept supported by the evidence that targeting IL-5 (*eg*, using mepolizumab), a survival factor for eosinophils, is an effective therapy for EGPA.(19, 20) CD4+ T-cells orchestrate the adaptive immune response and are polarised toward a Th2 phenotype, which enhances eosinophilic reactions; however, the Th1 and Th17 arms might also play a role, especially in vasculitis and granuloma formation.(2, 8, 21) In a mouse model of eosinophilic vasculitis, type 2 innate lymphoid cells were key in promoting vascular permeability and secretion of eotaxins,(22) which in turn induce tissue influx of eosinophils.(23) Humoral and B-cell responses are also dysregulated: in addition to the production of ANCA, enhanced production of IgG4 is a common feature of EGPA and probably results from Th2-skewed immunity.(24) The pathogenic relevance of B cells is also underlined by the good response to B-cell depleting agents (*eg*, rituximab) in a significant proportion of patients.(25, 26)

Given the rarity of the disease, its heterogeneous clinical presentation and the clinical overlap with other vasculitic or eosinophilic disorders, the diagnosis of EGPA is often challenging. Multiple disciplines are involved in the care of patients, which dictates an integrated and collaborative approach. To date, no systematically developed, evidence-based guidelines have been specifically dedicated to the diagnosis and management of EGPA, and current practice is mainly based on the 2015 recommendations for EGPA published by a consensus task force(12), and on the 2016 EULAR/ERA-EDTA recommendations for AAV.(27) More recently, the 2021 ACR/Vasculitis Foundation guidelines for the management of AAV were developed.(28) The 2016 and 2021 guidelines, however, focus on all AAV forms and are therefore not focussed on EGPA. In the last few years, significant advances have been made in EGPA research, particularly in the differential diagnosis, in understanding pathogenesis and clinical sub-phenotypes; additionally, new treatment options are available and long-term follow-up studies have allowed the definition of disease prognosis based on clinical presentation.(29) Herein, we developed comprehensive, evidence-based, cross-discipline recommendations for the diagnosis and management of EGPA, in order to contribute to the harmonisation of patient care, improve quality of care, and provide reliable instruments for patient education.

Methods

Overview of the guideline project

This guideline follows the RIGHT (Reporting Items for Practice Guidelines in Healthcare) Statement for Practice Guidelines.(30) To generate this evidence-based guideline, a core committee and a voting panel were assembled. The core committee included specialists in

immunology (G.E.), nephrology (A.V. and D.J.) and internal medicine (L.G.), and a methodologist (G.B.).

The voting committee included the core committee members and an additional 25 members with expertise in rheumatology, immunology, nephrology, internal medicine, pulmonology, cardiology, ENT surgery, and pathology, as well as two project fellows, healthcare professionals and representatives of EGPA and vasculitis patient advocacy organisations.

A Delphi approach was used to identify the questions driving the literature search and the guideline statements. Voting group members were asked, by means of an e-questionnaire, to provide a level of agreement on the importance of a set of 21 questions proposed by the core committee and discussed among all voting members (using a nine-point Likert scale, where 1 to 3 indicate “low importance”, 4 to 6 “uncertain importance”, and 7 to 9 “high importance”). After a first Delphi round, all questions were re-voted on the same scale on a second Delphi round, where some details were added to better explain unclear items. Only questions achieving positive consensus (>75% of respondents providing a positive score, *ie* 7-9 points on the Likert scale) in the second round were selected to drive literature search (**Supplementary Table 1**).

Developing the PICO questions

The questions that achieved consensus were then converted into PICO (P – Population; I – Intervention; C – Comparator; O – Outcome) questions, to be addressed in the literature search. Each PICO question represented the basis for a recommendation.

The *population* included patients with EGPA. With regards to *interventions* and *comparators*, evidence supporting the diagnostic (laboratory, imaging and procedures) and therapeutic interventions was retrieved on the basis of available literature studies. With regards to *outcomes*, not only disease-related but also treatment-related complications and comorbidities were considered. Where no specific study was available for EGPA, recommendations were based on evidence derived from other AAVs as well as on consensus reached among expert clinicians.

Literature search

A systematic literature search of the PubMed, Embase and Cochrane library databases was performed from 1980 until September 6th 2021. We considered all articles in English on humans, including prospective randomised controlled trials, uncontrolled or observational studies, registries, reviews (published after 2000) and case series. The search strategy used for the PubMed database was “(*EGPA OR churg-strauss OR "Eosinophilic Granulomatosis with Polyangiitis" OR "Churg-Strauss Syndrome"[Mesh])*”; this strategy was adapted for the Embase and Cochrane library databases.

Of the articles retrieved after the systematic literature review (SLR), we selected only those relevant to the diagnosis and management of EGPA (the selection was made by two independent investigators, A.B. and E.G., and discrepancies in their choices were resolved by consensus); pertinent articles, identified by manual search within the reference lists of the originally retrieved publications and by consultation with experts, were also included. Case reports or case series including five patients or less were excluded. Abstracts were considered for inclusion only if they provided novel data supporting the statements and were not yet published as full-length articles.

Grading system

We adopted the grading system from the Oxford Centre for Evidence-Based Medicine.(31) The level of evidence was graded based on the design and validity of the available studies, on a scale from 1a (systematic reviews of randomised controlled trials) to 5 (expert opinion); the grading of recommendations was judged based on a letter scale from A (highest, for consistent level 1 studies) to D (lowest, for level 5 evidence, or very inconsistent or inconclusive studies of any level), considering the total body of evidence. For each statement, members of the voting group were asked to rate the level of agreement on a 0–10 rating scale (which 0 being no agreement and 10 being full agreement), based on both the available literature evidence and their own expertise.

Results

After duplicate removal, the SLR retrieved 9,085 unique records. Of these, a total of 198 references were finally considered for the development of this guideline (**Supplementary Table 2**). Further details of the article selection flow are given in **Supplementary Figure 1.** We generated 16 recommendation statements, which are reported and discussed below, and five overarching principles (**Box 1**).

Statement 1

The diagnosis of EGPA should be considered in patients with asthma, chronic rhino-sinusitis and eosinophilia who develop end-organ involvement, particularly peripheral neuropathy, lung infiltrates, cardiomyopathy or other complications (*eg*, skin, gastrointestinal or kidney involvement). *(Level of evidence: 2b; Grade of recommendation: B)*

The vast majority (>90%) of EGPA patients suffer from asthma, which usually arises in adulthood, rarely shows seasonal exacerbations and tends to worsen over time.(32) Asthma is often accompanied by ENT symptoms, which include chronic rhinosinusitis with nasal polyps (where polyps commonly recur after surgical excision) and other manifestations such as otitis media.(33, 34) Eosinophilia (>10% or >1500 cells/μL) is also observed in almost all EGPA patients, although the use of systemic glucocorticoids can mask it.(21) The clinical suspicion of EGPA should be raised when patients with the above manifestations develop other complications. Lung infiltrates are common (40-50%), they are often multiple and migratory and respond to systemic glucocorticoids. Peripheral neuropathy occurs in 50-70% of the patients (35, 36), has a mononeuritis multiplex pattern, is usually sensory but may also cause motor deficits, and has an axonal damage pattern on nerve conduction studies. Skin lesions are also frequent but quite heterogeneous, with palpable purpura being the most vasculitis-specific lesion.(21, 37)

Other organ manifestations that contribute to shape the clinical phenotype of EGPA include myocarditis and pericarditis, gastroenteritis, renal disease (revealed by proteinuria, haematuria, and/or varying degrees of kidney failure) and systemic manifestations such as fatigue, weight loss, myalgia and arthralgia.(2)

Statement 2

There are no diagnostic criteria for EGPA. Classification criteria include the ACR 1990 and the 2022 ACR/European Alliance of Associations for Rheumatology ones, that have established sensitivity and specificity, and others (*eg*, MIRRA trial) that are based on expert opinion and require validation. EGPA should be diagnosed based on highly suggestive clinical features, objective evidence of vasculitis (*eg*, biopsy), and ANCA. *(Level of evidence: 2b; Grade of recommendation: B)*

Several sets of criteria have been generated for EGPA, but none of them has been validated for the diagnosis. In 1984, Lanham et al.(38) proposed that asthma, eosinophilia, and vasculitic involvement of two or more organs should be present to make a diagnosis of EGPA; these criteria are usually considered too stringent and were never validated. In 1990, the American College of Rheumatology (ACR) defined classification criteria to distinguish the different vasculitic syndromes and identified six criteria for EGPA, namely asthma, eosinophilia>10%, neuropathy, non-fixed lung infiltrates, paranasal sinus abnormalities and histological evidence of extravascular eosinophils. If four or more of these criteria are met, a patient with vasculitis can be classified as having EGPA with a sensitivity of 85% and a specificity of 99.7%.(39) In 1993, the Chapel Hill Consensus Conference (CHCC) provided

definitions for vasculitides, including EGPA, with a particular focus on histopathological aspects; in 2013, the revised CHCC nomenclature incorporated the concept that ANCA-positivity is associated with renal involvement in EGPA.(1) The CHCC criteria, however, are descriptive statements based on expert opinion. In 2017, the MIRRA trial (20) committee established eligibility criteria that could be used to define EGPA, but they still require validation. These criteria included asthma, eosinophilia, and at least two of the following: tissue evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration or eosinophil-rich granulomatous inflammation; neuropathy; pulmonary infiltrates; sinonasal abnormality; cardiomyopathy; glomerulonephritis; alveolar hemorrhage; palpable purpura; ANCA positivity. The MIRRA criteria were therefore the first to include ANCA as a potentially diagnostic tool.

Finally, the Diagnosis and Classification criteria in Vasculitis (DCVAS) study recently defined the 2022 ACR/European Alliance of Associations for Rheumatology weighted criteria for the classification of small and medium-sized vessel vasculitis, also including EGPA. These comprised positively scored parameters, namely a maximum eosinophil count ≥1 × 10^9/L (+5 points), obstructive airway disease (+3), nasal polyps (+3), extravascular eosinophilic predominant inflammation (+2), mononeuritis multiplex/motor neuropathy not due to radiculopathy (+1), all of which make the diagnosis of EGPA more likely. Other parameters make the diagnosis of EGPA less likely and are therefore scored negatively; these include cytoplasmic-ANCA (C-ANCA) or anti-proteinase 3 (PR3)-ANCA positivity (-3), and hematuria (-1). If a cumulative score of six or more is reached, a patient with a diagnosis of small- and medium-sized vessel vasculitis can be classified as having EGPA with a sensitivity of 85% and a specificity of 99%.(40)

Given the absence of diagnostic criteria, the diagnosis of EGPA– as for other small-vessel vasculitides- should be based on objective evidence of vasculitis. The objective evidence of vasculitis should rely on histopathological findings. However, as a diagnostic biopsy is often lacking in EGPA patients, highly suggestive clinical features should be considered for the diagnosis. Examples of highly suggestive clinical features are those included in the classification criteria (*eg*, asthma, chronic rhinosinusitis with polyps, eosinophilia, neuropathy, lung infiltrates, eosinophilic cardiomyopathy or gastroenteritis, glomerulonephritis). ANCA are also to be considered for the diagnosis of EGPA.(41)

Statement 3

The diagnostic evaluation of patients suspected as having EGPA should always be multidisciplinary; it should rule out other eosinophilic and vasculitic disorders and investigate the main disease complications, particularly heart, respiratory, skin, renal

and nervous system involvement, along with ANCA and eosinophilia. Biopsy is recommended when feasible but is not essential to make the diagnosis. *(Level of evidence: 3b; Grade of recommendation: C)*

Patients suspected as having EGPA should undergo a multidisciplinary evaluation to confirm the diagnosis and investigate the involvement of the most common target organs. As shown in **Figure 3**, diagnostic tests can be grouped into “baseline investigations” and “investigations to be performed in selected cases”, which are clinically driven tests that can be ordered based on specific disease manifestations and/or the positivity of baseline screening tests. Biopsies from affected organs are encouraged because they can contribute to the diagnostic evaluation, exclude differential diagnoses and in certain instances, reflect the degree of activity/chronicity of the disease process.(42) Locations from which biopsies are taken include: kidney, skin, ENT-region, lung and gastrointestinal tract. Kidney biopsies typically show crescentic necrotising glomerulonephritis that may be accompanied by eosinophilic infiltrates, granulomatous changes and (eosinophil-rich) necrotising vasculitis of arterioles and arteries. Atypical renal presentations with other glomerulopathies such as membranous nephropathy, in particular in ANCA-negative patients, may also occur.(43) Skin biopsies in EGPA patients with palpable purpura invariably reveal necrotising vasculitis of small arteries that may be accompanied by extravascular granulomas. Tissue eosinophils may be distributed in a vascular, perivascular, or interstitial dermal pattern.(44) Biopsies of sino-nasal mucosa/polyps are often non-diagnostic,(33) in spite of attempts to use structured histopathological evaluation that have suggested certain lesions, *ie* neutrophil aggregates, to be more prevalent in EGPA than in chronic rhino-sinusitis.(45) Lung and gastrointestinal tract biopsies may reveal typical lesions(13) but are seldom performed in clinical practice.
The differential diagnosis of EGPA mainly includes other small-vessel vasculitides and eosinophilic disorders. The differential diagnosis with other small-vessel vasculitides such as granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) is often straightforward due to different phenotypes and histology, although GPA can sometimes present with peripheral or tissue eosinophilia, while a small proportion of EGPA patients present instead with PR3-ANCA and an associated granulomatous and eosinophilic phenotype.(46) Other small-vessel vasculitides (*eg,* IgA vasculitis, cryoglobulinemia) typically show immune deposits, which are absent in EGPA as in the other AAVs. Eosinophilic disorders are numerous and have different aetiologies, and range from allergic forms to haematologic conditions (*eg*, lymphocytic and myeloproliferative hypereosinophilic syndromes, the latter hallmarked by FIP1L1 fusion genes), parasitic infections, and hypersensitivity disorders such as allergic broncho-pulmonary aspergillosis. Other conditions

that only occasionally present with eosinophilia but may have overlapping features with EGPA (*eg*, HIV infection, IgG4-related disease) should also be considered.(2)

Statement 4

ANCA should be tested in all patients suspected as having EGPA. They are detectable in 30-40% of patients with EGPA and most test positive for MPO. MPO-ANCA positive patients frequently show vasculitis features, *ie* glomerulonephritis, neuropathy and purpura, while ANCA-negative patients more frequently manifest cardiomyopathy and lung involvement. *(Level of evidence: 2a; Grade of recommendation: B)*

ANCA can be detected by indirect immunofluorescence, which essentially shows cytoplasmic and perinuclear patterns (C- and P-ANCA), but ELISA for PR3- or MPO-ANCA is the reference test for AAVs. ANCA positivity is detectable in 30-40% of patients with EGPA and most of them test positive for P-ANCA and MPO-ANCA.(47). In patients with a compatible clinical phenotype (asthma, eosinophilia, rhinosinusitis, lung infiltrates), ANCA positivity supports the diagnosis of EGPA, with MPO-ANCA being considered more specific than P-ANCA for the diagnosis of vasculitis. In fact, an isolated P-ANCA positivity (with negative MPO-ANCA) can be found in other inflammatory, non-vasculitic conditions (*eg*, inflammatory bowel disease). ANCA are usually negative in primary eosinophilic disorders.(29)
MPO-ANCA positivity is associated with clinical manifestations such as peripheral neuropathy, renal involvement and purpura, while it confers a lower risk of having pulmonary infiltrates and cardiac manifestations.(14, 48) However, when considering the ANCA-positive and ANCA-negative phenotypes, the possibility of a significant overlap between the two should be taken in consideration and the clinical value of ANCA positivity should not be overestimated.(47) PR3 ANCA-positive EGPA patients are rare and differ from the MPO ANCA-positive or the ANCA-negative ones since they more frequently have lung nodules and skin manifestations, and less frequently active asthma, peripheral neuropathy, and hypereosinophilia.(46) Their phenotype seems therefore closer to that of GPA.
The ANCA status may have prognostic implications: overall survival seems worse in ANCA-negative patients,(6, 9) probably due to the higher frequency of cardiac involvement, whereas relapses tend to be more frequent in ANCA-positive patients, although some controversies still exist.(6, 49, 50) ANCA status itself is not useful in the choice of treatment.(51)

Statement 5

EGPA remission is defined as the absence of clinical signs or symptoms attributable to active disease, including asthma and ENT manifestations. The daily dose of glucocorticoids should also be considered for the definition of remission, and a maximum daily dose of 7.5mg of prednisone can be chosen as cut-off. *(Level of evidence: 5; Grade of recommendation: D)*

According to the EULAR recommendations, EGPA remission is defined as the absence of clinical signs or symptoms attributable to active disease, with a Birmingham Vasculitis Activity Score (BVAS) of zero on a maximum daily prednisone (or equivalent) dose of 7.5 mg.(52) This definition is currently used to assess efficacy outcomes in most observational studies and clinical trials on EGPA (20, 53-56) though more stringent definitions have also been adopted (*ie*, BVAS=0 on a maximum prednisone dose of 4mg/day).(20)
Based on current evidence,(20, 28, 52) we also recommend to define remission as a BVAS=0, on or off concomitant glucocorticoid and/or immunosuppressive therapy. In case of concomitant glucocorticoid treatment, the definition of remission could include a maximum prednisone (or equivalent) dose of 7.5 mg/day. This dose is arbitrarily fixed; considering the availability of new agents (*ie*, anti-IL5 biologics) which can allow steroid sparing also in patients with refractory respiratory manifestations, we conclude that a more stringent definition of remission, including a maximum prednisone dose of 4 mg/day, might be adopted. Future treatment strategies should definitely aim at further minimisation or withdrawal of glucocorticoids, therefore the definition of remission might entail a steroid-free therapy.
We also recommend to include the control of asthma and/or ENT manifestations in the definition of remission. Though it is commonly agreed upon that ENT manifestations and/or asthma flares do not necessarily reflect vasculitis activity, we believe that current evidence is insufficient to exclude these manifestations from the definition of EGPA remission. However, the BVAS has important limitations in the assessment of asthma and ENT disease: a BVAS of 0 does not preclude abnormal lung function tests,(57) while a normal lung function is an important objective in asthma treatment and contributes to asthma control definition. Therefore, disease scores that specifically address asthma and ENT disease, such as the Asthma Control Questionnaire (ACQ)(58) or the 22-item Sino-Nasal Outcome Test (SNOT-22)(59) could be combined with BVAS for a more comprehensive disease assessment in patients with EGPA.

Statement 6

Remission-induction treatment should be tailored on clinical manifestations with prognostic relevance. Organ-threatening manifestations included in the Five-Factor Score (renal insufficiency, proteinuria, cardiomyopathy, gastrointestinal tract and central nervous system involvement) as well peripheral neuropathy and other rare manifestations (*eg*, alveolar haemorrhage) should be considered when defining remission-induction strategies. *(Level of evidence: 2b; Grade of recommendation: B)*

The Five-Factor Score (FFS) predicts the mortality risk in patients with an established diagnosis of EGPA, as well as of polyarteritis nodosa (PAN), MPA or GPA. It includes five factors associated with shorter overall survival, namely renal insufficiency (serum creatinine >1.58 mg/dl), proteinuria >1g/day, cardiomyopathy, gastrointestinal and central nervous system (CNS) involvement.(60) The FFS considers clinical manifestations only at the time of diagnosis, hence the appearance of new manifestations during the follow-up should also be taken into account when establishing remission-induction regimens for disease flares.(60) The FFS has been subsequently revised,(61) by including age >65 years as a poor prognostic factor, and ENT involvement as a favourable prognostic factor, while CNS involvement was no longer included in the score. However, most studies considering the FFS for treatment decision refer to its original version.(60)
In addition to the items included in the FFS, other disease features influence remission-induction therapy. Peripheral neuropathy also required immunosuppression in large observational studies, and should thus be considered.(62-64) Evidence regarding the treatment of rare but severe complications such as alveolar haemorrhage or some forms of eye involvement (*eg*, central retinal artery or vein occlusion, ischemic optic neuropathy, orbital myositis, retinal vasculitis/infarcts/edema) (65) is scarce, but the clinical experience derived from the other AAVs suggests that they should also be treated aggressively.(66, 67)

Statement 7

For remission induction in patients with new-onset, active EGPA, glucocorticoids should be administered as initial therapy. In patients with severe disease (unfavourable prognostic factors discussed in Statement 6) cyclophosphamide or, as an alternative, rituximab, should be added. In patients with non-severe disease, glucocorticoids alone should be used. *(Level of evidence: 2b; Grade of recommendation: B)*

Remission-induction treatment should be stratified on disease severity, where severe disease is defined according to the presence of at least one adverse prognostic factor (*ie*, the

factors included in the FFS and those considered as manifestations of severe disease, such as peripheral neuropathy, alveolar haemorrhage, mesenteric ischemia, limb digital ischemia, eye disease). Patients with severe disease should be treated with intravenous glucocorticoid pulses (usually 3 daily methylprednisolone pulses of 500-1000 mg each, for a maximum total dose of 3g)- followed by high-dose oral glucocorticoids (*eg*, 0.75-1 mg/kg/day).

Cyclophosphamide should be added to glucocorticoids for remission induction in patients with severe disease. The evidence on the use of cyclophosphamide is supported by a randomised trial performed in patients with FFS ≥1, which showed that relapse-free survival was longer after 12 than after 6 cyclophosphamide pulses (administered every two weeks for one month, then every four weeks, at a dose of 0.6 g/m^2/pulse).(68) However, the optimal duration of cyclophosphamide induction in severe EGPA remains to be established. In the routine clinical practice, we recommend cyclophosphamide induction be conducted until remission is achieved, usually within 6 months; longer induction periods (up to 9-12 months) can be reserved to patients who slowly improve but do not reach complete remission by month 6.

Observational studies have initially highlighted the potential role of rituximab for remission induction.(26, 69, 70) A randomised controlled trial (REOVAS), published in abstract form, recently showed that rituximab (1000 mg 2 weeks apart) is comparable to cyclophosphamide (9 iv pulses over 5 months) for induction of remission (defined as BVAS=0 and a prednisone dose ≤7.5 mg/day) in patients with FFS≥1. Adverse events and cumulative prednisone exposure were comparable between groups.(71) Unlike in previous observational studies, no significant differences in response to rituximab were found between ANCA-positive and ANCA-negative patients; likewise, no differences were found between new-onset and relapsing patients.

In patients with non-severe disease, glucocorticoids alone are usually sufficient to induce remission. In a prospective trial on 72 patients with FFS=0, the remission rate after glucocorticoid monotherapy was 93%.(72) However, a significant proportion of responding patients experienced early relapses (35% within the first year of treatment), mostly respiratory, and thus received immunosuppressants such as cyclophosphamide and azathioprine. Although the evidence supporting the use of traditional immunosuppressants for remission maintenance in non-severe EGPA is scarce, these agents are often used in routine clinical practice.

The randomised controlled MIRRA trial tested the efficacy and safety of mepolizumab vs placebo in achieving remission (BVAS=0 and prednisolone dose ≤4 mg/day) in patients with relapsing/refractory EGPA without organ- or life-threatening manifestations. Mepolizumab proved significantly more efficacious than placebo and had comparable toxicity. The ANCA status did not influence response, although the proportion of ANCA-positive patients included

in the trial was low (10%).(20) Therefore, the combination of mepolizumab and glucocorticoids for remission induction in non-severe EGPA should be considered.(19, 73). Further details on the MIRRA trial, the indications for mepolizumab in EGPA and the suggested dosage are discussed in Statement 13.

Overall, in both patients with severe and non-severe disease, remission-induction is centred on the use of high-dose glucocorticoids, which certainly contribute to short-term and long-term treatment-related toxicity. Treatment strategies (*eg*, mepolizumab) are already heading to glucocorticoid sparing, as demonstrated by the MIRRA trial, which however enrolled patients without organ- or life-threatening manifestations. It is advisable that remission induction in patients with severe disease aims at the same goal, as demonstrated in the other AAV by recent trials (*eg*, PEXIVAS).(74)

Statement 8

For remission-maintenance, in patients with severe EGPA, we recommend using rituximab, mepolizumab or traditional DMARDs in combination with glucocorticoids. In patients with non-severe EGPA, we suggest glucocorticoids, alone or in combination with mepolizumab. Glucocorticoids should be tapered to the minimum effective dosage to reduce toxicity. *(Level of evidence: 2b; Grade of recommendation: B)*

After remission induction, a maintenance treatment should be considered to reduce the risk of toxicity and that of relapse. Glucocorticoid-related toxicity is particularly relevant in patients with EGPA as they are often exposed to high cumulative glucocorticoid doses and only a small proportion of them can be weaned off glucocorticoids. Therefore, several efforts are being made to reduce glucocorticoid exposure without putting patients at risk of relapse. The available evidence on remission-maintenance therapies in EGPA is limited. We recommend adopting different remission-maintenance strategies based on the presence of unfavourable prognostic factors (as defined in Statement 6). In patients with severe disease, the maintenance approach is uncertain. Observational studies have reported the use of glucocorticoids combined with azathioprine, methotrexate and leflunomide to maintain remission,(55, 75) but none of these approaches demonstrated to prolong relapse-free survival (vs glucocorticoid monotherapy). Despite the absence of evidence from the literature, disease-modifying anti-rheumatic drugs (DMARDs) are routinely used in clinical practice for remission maintenance.(12, 28, 76, 77)

Rituximab has been proposed as an induction therapy for EGPA, but also seems to be effective for remission maintenance: in an observational study, scheduled rituximab maintenance (500mg/6 months) reduced relapse rate as compared to unscheduled treatment (*ie*, a single, 1g infusion, administered only in case of relapse).(25) In particular, all patients

receiving scheduled rituximab were able to maintain remission throughout the follow-up. In a recent retrospective study, rituximab maintenance also showed efficacy in reducing the median glucocorticoid dose for the control of asthma and systemic manifestations.(70) We recommend rituximab maintenance in patients with severe disease, particularly in those who achieved remission on rituximab.

Mepolizumab is commonly used during remission maintenance, mainly for the control of asthma and to reduce glucocorticoid exposure. However, some observational studies (19, 73) suggest that it might be effective also in major organ manifestations (*ie*, neuropathy, cardiomyopathy), therefore its use for remission-maintenance in patients with severe manifestations can be considered. In patients with non-severe disease, glucocorticoids combined with mepolizumab are often effective to maintain remission, as shown by the MIRRA trial in relapsing/refractory patients (20) and by observational studies.(19, 73)

Statement 9

EGPA relapse is defined as the recurrence of clinical signs or symptoms attributable to active disease following a period of remission. The need for an increase in the glucocorticoid dosage or the initiation or increase of an immunosuppressant should also be considered as a relapse. The relapse or new onset of systemic vasculitis (systemic relapse) should be differentiated from the isolated exacerbation of asthma and ENT manifestations (respiratory relapse). *(Level of evidence: 5; Grade of recommendation: D)*

EGPA relapse can be defined as the recurrence of clinical signs or symptoms attributable to active disease following a period of remission.(12, 28, 78) In line with recent trials,(20) we recommend considering as disease relapse the need for an increase in the daily glucocorticoid dosage or the initiation or increase of an immunosuppressive therapy. When defining relapse, we recommend distinguishing the relapse of systemic vasculitis (systemic relapse) from the isolated exacerbation of asthma and ENT manifestations (respiratory relapse). An increase in the eosinophil count without accompanying clinical manifestations should not be considered a relapse.

Systemic relapses can be distinguished into severe and non-severe, the former presenting with either manifestations included in the FFS or with life- or organ-threatening manifestations (Statement 6).(68) For example, relapsing peripheral neuropathy, glomerulonephritis, cardiomyopathy, or gastroenteritis are usually considered as severe relapses, while skin manifestations (*eg*, urticaria), arthralgia, or systemic symptoms (*eg*, fatigue, weight loss) are usually considered non-severe.

Statement 10

Relapses should be treated according to type (systemic vs respiratory) and severity. For severe systemic relapses, we recommend using rituximab or cyclophosphamide with glucocorticoids. For non-severe systemic and respiratory relapses, we recommend raising the dose of glucocorticoids and/or adding mepolizumab. *(Level of evidence: 2b; Grade of recommendation: C)*

The treatment of relapses depends primarily on their type (systemic vs. respiratory relapses) and severity (severe vs non-severe, for systemic relapses), but should also take into account previous treatments and the burden of chronic damage. For severe systemic relapses, rituximab or cyclophosphamide can be considered the main remission-induction agents. Rituximab can be preferred over cyclophosphamide especially when re-treatment with cyclophosphamide is to be avoided, in patients who previously achieved remission on rituximab or failed on cyclophosphamide. Cyclophosphamide may be considered in recurrent and severe cardiac disease, in other severe or life-threatening complications and/or in patients who previously failed on rituximab. These recommendations are essentially based on the results of observational studies (25, 26, 70, 77), since none of the published trials enrolled patients with severely relapsing disease. The REOVAS trial included relapsing patients as well as patients with new-onset disease, but the results on these two subgroups are still unavailable.(71)

For patients with non-severe systemic relapses, several options are available, and must be chosen on a patient-by-patient basis. Some minor relapses can be managed with optimisation of glucocorticoid therapy; mepolizumab can also be used on top of glucocorticoids to treat minor relapses. For respiratory relapses, a stepwise approach should be followed: first, topical therapies (*eg*, bronchodilators) should be optimised (Statement 14). Second, the dose of oral glucocorticoids can be raised and short courses of high-dose glucocorticoids (0.5-1 mg/kg/day for 5-7 days) can be given and stopped without tapering. Third, mepolizumab can be added. Functional endoscopic sinus surgery can be considered for relapsing ENT disease that does not adequately respond to the above approach.

Statement 11

Refractory EGPA is defined as unchanged or increased disease activity after four weeks of appropriate remission-induction therapy. The persistence/worsening of

systemic manifestations should be distinguished from that of respiratory manifestations. *(Level of evidence: 5; Grade of recommendation: D)*

Refractory EGPA denotes persisting or worsening disease despite an appropriate remission-induction therapy.(28, 52, 69) Refractory EGPA with severe manifestations is rare if patients are treated with cyclophosphamide as remission-induction regimen.(68) The minimum duration of remission-induction to define refractoriness has not been established, but four weeks can be considered a reasonable time frame, in analogy with the other AAVs.(52) EGPA can be defined as refractory only after addressing the following issues (52):

- the primary diagnosis should be re-evaluated, and it must be excluded that refractory manifestations are due to other aetiologies such as infections or malignancies
- the appropriateness of the remission-induction treatment (Statement 7) should be checked
- patients' compliance to the remission-induction regimen should be assessed
- persistently active manifestations should be distinguished from irreversible damage [a supporting tool is the Vasculitis Damage Index (VDI)].

Once refractory disease has been established, it must be ascertained whether this is due to persistence/worsening of systemic manifestations, asthma/ENT disease or both. For patients with refractory systemic EGPA despite remission-induction treatment with high-dose glucocorticoids plus cyclophosphamide, the use of rituximab is recommended, and vice versa.(69) For patients with refractory asthma/ENT disease (without systemic manifestations) despite high-dose glucocorticoids and optimised inhaled therapy, the addition of mepolizumab is recommended.(20) In patients not responding to these approaches, different therapeutic options can be considered, including other anti-IL5 agents (Statement 13), plasma exchange, and iv immunoglobulins; anti-IgE agents have also been tried but with unsatisfactory results.(73, 79-82) In selected patients, the use of interferon alpha (83) or mycophenolate mofetil can also be considered for remission induction (84). However, no solid evidence supports their use for maintenance.

Statement 12

We recommend the use of the IL-5 inhibitor mepolizumab combined with glucocorticoids to induce remission in patients with relapsing-refractory EGPA without organ- or life-threatening manifestations. Mepolizumab can also be used for remission maintenance, particularly in patients requiring a daily prednisone dose ≥7.5 mg for the control of their respiratory manifestations. *(Level of evidence: 2b; Grade of recommendation: B)*

IL-5 is a key cytokine for eosinophil maturation, differentiation and survival. Recently, there has been growing interest around the use of IL-5/IL-5 receptor (IL5R)-targeted therapies in EGPA. Among them, the monoclonal antibody mepolizumab was tested in observational studies (85-87) and subsequently in a randomised double-blind placebo-controlled phase III trial (MIRRA)(20) that included 136 EGPA patients with relapsing or refractory disease and without life- or organ-threatening manifestations. The results of this trial indicate that mepolizumab (300mg/4 weeks) is effective to induce and maintain remission, while improving lung function and allowing glucocorticoid sparing.(88)

However, recent cohort studies showed that a lower mepolizumab dosage (100mg/4 weeks) is also effective for EGPA, especially for the control of respiratory manifestations.(19, 73) In the largest of these studies,(19) the efficacy of 100 mg/4 weeks and 300 mg/4 weeks was comparable, although these findings resulted from a retrospective analysis.

We recommend to consider mepolizumab for induction in patients with relapsing-refractory disease without organ- or life-threatening manifestations. Mepolizumab should also be considered for remission maintenance, mainly for the control of asthma and to reduce glucocorticoid exposure. The approved dosage for EGPA is 300mg/4 weeks. However, an initial lower dosage (100mg/4 weeks) can be considered, particularly in patients with limited respiratory manifestations; this dosage can subsequently be titrated up to 300 mg/4 week in non-responding patients.(19) The efficacy of other IL5/IL5R inhibitors (benralizumab, reslizumab) has been reported in case reports or case series;(89, 90) their use can therefore be considered in patients refractory to mepolizumab.

Statement 13

In EGPA patients with active asthma or ENT involvement, topical/inhaled therapy must be optimised. The approach to the management of these disease manifestations must involve specialists such as pulmonologists and otolaryngologists. *(Level of evidence: 5; Grade of recommendation: D)*

Asthma and ENT manifestations negatively impact the quality of life of patients with EGPA. Moreover, respiratory involvement is among the most frequently relapsing manifestations in EGPA, with a course mostly independent from systemic disease involvement.(75)

Although the use of systemic therapies (*ie*, glucocorticoids and mepolizumab) is the mainstay for the control of respiratory EGPA manifestations, combination with inhaled therapies should be considered as a supportive treatment for asthma control.(91) In particular, in patients with

asthmatic manifestations, the combination of high-dose inhaled glucocorticoids and long-acting beta2 agonists seems to be a valid option.(92) However, consultation with a pulmonologist is strongly recommended.

Patients with ENT involvement might also benefit from nasal rinses and other topical therapies (*eg,* antibiotics or lubricants), also for the long-term control of these symptoms. Consultation with an otolaryngologist is strongly encouraged in these patients.

Statement 14

We recommend that treatment decisions should be modified as necessary in special populations of patients such as children, elderly, women of child-bearing age and those with co-morbidities. There is still no evidence that different phenotypes (*eg*, ANCA-positive vs ANCA-negative) need different approaches. *(Level of evidence: 5; Grade of recommendation: D)*

Special populations should also be considered when defining the treatment approach. EGPA is extremely rare in children (7) therefore there is no guidance for treatment in this special population. Glucocorticoids and other traditional immunosuppressants remain the mainstay of therapy. However, as cyclophosphamide reduces the ovarian reserve and may affect male fertility, rituximab could be preferred in young patients. Also, mepolizumab can be considered an optimal therapy to spare glucocorticoids, and is approved for use in patients with EGPA of >6 years.(93)

In all patients with EGPA, we strongly recommend to taper glucocorticoids to the minimum effective dosage, to reduce long-term toxicity. Also, a reduction in the dose of immunosuppressants should be considered to limit the risk of complications, especially infections. These recommendations particularly apply to the elderly population (aged >65 years), considering their intrinsic fragility and higher burden of comorbidities. An open-label trial on 104 patients with systemic necrotising vasculitis (of whom 14 had EGPA) aged >65 years indicated that a dose reduction of cyclophosphamide (from 500mg/m2 to a fixed dose of 500mg) and a reduction in the duration of glucocorticoid treatment (from 26 to 9 months) is useful to lower the risk of adverse events and does not affect remission rates.(94)

Pregnant women should not discontinue treatment, as the risk of disease flare may have a negative impact on pregnancy outcomes; however, only glucocorticoids, intravenous immunoglobulins and azathioprine are considered to be safe during pregnancy.(95) Cyclophosphamide, mycophenolate mofetil and methotrexate are also contraindicated during pregnancy and should be stopped in women 3–6 months before conception. Rituximab and mepolizumab should also be avoided during pregnancy due to the lack of safety data.(93,

96) Considering that pregnancy loss can occur in up to 20% of EGPA patients, a dedicated obstetric management is advocated.(95)

Patients with EGPA can be subclassified according to the ANCA status (ANCA-positive vs ANCA-negative); preliminary evidence, mainly from observational studies, suggested that ANCA-positive and ANCA-negative patients have different sensitivity to treatments; in particular, ANCA-positive patients appeared more sensitive to rituximab than ANCA-negative patients.(26, 97) This view has been challenged by the results of the REOVAS trial, which did not reveal significant differences in the rates of response to rituximab between ANCA-positive and ANCA-negative patients.(56) The MIRRA trial also did not reveal any significant difference in response to mepolizumab between the two subgroups, although the ANCA-positive subgroup accounted for only 10% of the enrolled patients.(20) These results support the recent recommendation that ANCA status should not influence treatment,(51) although it denotes differences in clinical phenotype and genetic backgrounds.

Statement 15

Although some laboratory tests (*eg*, eosinophil count, ANCA) are commonly monitored, there are no reliable biomarkers to measure disease activity in EGPA. Disease activity should therefore be assessed on follow-up only using validated clinical tools. *(Level of evidence: 5; Grade of recommendation: D)*

During the follow-up, EGPA is usually monitored clinically, by detecting signs and symptoms of active disease and by means of appropriate imaging or functional studies (*eg*, pulmonary function tests, electromyography-electroneurography, echocardiography), and routine laboratory tests. However, no biomarker reliably correlates with disease activity or predicts relapse. The eosinophil count is routinely assessed in patients with EGPA as it is thought to mirror disease activity; however, despite eosinophil counts are markedly high in patients at diagnosis and drop during remission, relapses can also occur without an increase in the eosinophil count.(98) In a cohort study of 141 patients, the eosinophil count- as well as erythrocyte sedimentation rate, C-reactive protein and IgE- showed weak or no association with disease activity and disease flares. Therefore, the role of these parameters as longitudinal biomarkers seems limited.(99) Other biomarkers involved in eosinophil biology such as eosinophil cationic protein (ECP),(100) eotaxin-3 (23) and CCL17/TARC,(101) whose concentrations are high in patients at the time of diagnosis, do not follow disease activity during the follow-up and therefore are not used in clinical practice.

Although its use is still limited, monitoring of serum IgG4 levels might have some value for the assessment of disease activity. In an observational study on 72 AAV patients (of whom

46 had EGPA), 25 with atopic asthma and 20 healthy controls, serum IgG4 levels were found to be markedly increased in patients with active EGPA and correlated positively with BVAS and number of organs involved.(24) Nevertheless, these data are not yet confirmed and the use of IgG4 as disease activity biomarker is controversial.

The value of ANCA monitoring in EGPA is also debated, as ANCA positivity or titers are not clearly associated with disease activity or response to treatment.(19) However, serum ANCA monitoring is advisable in patients with MPO ANCA–positivity at disease onset, because persistence, rise, or reappearance of ANCA may justify more frequent clinical assessment.(51)

Statement 16

We recommend routine monitoring of EGPA-related manifestations, with particular reference to lung function, cardiovascular events, and neurological complications. Long-term monitoring of comorbidities (cancer, infections, osteoporosis) is also recommended. *(Level of evidence: 2b; Grade of recommendation: B)*

EGPA is associated with a consistent burden of morbidity and mortality. Among the most significant complications, persistent asthma negatively affects quality of life and life expectancy. Close monitoring of lung function is recommended, particularly in case of overweight patients, in those presenting with pulmonary infiltrates, in case of uncontrolled or severe asthma at diagnosis, and in patients with rhinosinusitis, as these features have been associated with a more severe asthma course.(32, 91)

Major vascular events (102, 103) and cardiac involvement (104) are frequent in EGPA and seem to be associated with a poorer survival.(105-107) Periodic echocardiography and electrocardiography is recommended in all patients (108) to early detect asymptomatic cardiac involvement. Cardiac magnetic resonance monitoring is recommended only in patients with overt cardiomyopathy, while its routine use in asymptomatic patients seems limited.(109, 110)

Another severe complication of EGPA is related to sequelae of neuropathy. Although neuropathy is not life-threatening, we strongly recommend an appropriate management of this complication, given the risk of disability due to muscle atrophy and neuropathic pain.(35, 64, 111) Consultation with a neurologist and a physiotherapist is strongly encouraged in these patients.

Some other complications should also be assessed and prevented. Patients with EGPA seem to have an increased risk of infections, also due to the immunosuppressive therapy.(108) We advocate prophylaxis against *Pneumocystis jirovecii* infection with

trimethoprim/sulfamethoxazole (800/160 mg on alternate days or 400/80 mg daily) in all patients treated with cyclophosphamide and/or rituximab.(27, 112) Screening for major chronic infections (HBV/HIV) is also strongly recommended before initiating cyclophosphamide or rituximab. Therapy with cyclophosphamide and rituximab has a negative impact on the humoral vaccine response and may lead to clinically relevant secondary hypogammaglobulinemia. Accordingly, timely vaccination according to current recommendations, passive immunization if necessary, and monitoring of quantitative IgG serum concentrations are recommended.

The risk of cancer should be carefully considered, especially in patients who received cyclophosphamide (113-115). All patients should undergo age-appropriate cancer screening; cyclophosphamide-treated patients should also be regularly screened for bladder cancer (*eg*, urine cytology examination), myeloid leukaemia (*eg*, peripheral blood cell count evaluation and/or haematological examination), and skin cancer (dermatologic surveillance). (113, 116, 117)

The risk of osteoporosis should also be assessed, particularly in patients under prolonged glucocorticoid treatment.(118) Periodic bone density assessment is recommended in all patients with EGPA, especially in those with a high cumulative glucocorticoid dose and in those with concomitant traditional risk factors for osteoporosis.

Despite only a subgroup of patients are allergic (30-40%),(119, 120) testing allergies, particularly perennial ones, through prick test and/or RAST is encouraged in EGPA patients, and appropriate anti-histaminic treatment should be considered in allergic patients, also to control ENT symptoms.(119)

Conclusions and future perspectives

EGPA is a rare vasculitis and has a complex phenotype. Clinicians face several challenges in the diagnosis and management of this condition, given the absence of diagnostic biomarkers and the paucity of controlled clinical trials. The management of the disease requires a multidisciplinary approach and is based on the use of glucocorticoids, traditional immunosuppressants and novel biologic agents. The evidence-based guidelines defined in this article provide guidance to diagnosis and to the best possible management strategies. Future research on EGPA will have to address several issues, such as better understanding its pathogenesis and the role of genetics. Defining diagnostic criteria and exploring biomarkers that can assist the differential diagnosis and the assessment of disease activity is also of utmost importance (**Box 2**). Management of comorbidities or disease-related complications such as cardiovascular disease is warranted. Finally, the indications for new treatment options need to be better defined.

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REFERENCES

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis and Rheumatism. 2013;65(1):1-11.
2. Vaglio A, Buzio C, Zwerina J. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. Allergy. 2013;68(3):261-73.
3. Mahr A, Guillevin L, Poissonnet M, Ayme S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis Rheum. 2004;51(1):92-9.
4. Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology (Oxford). 2009;48(12):1560-5.
5. Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? Best Pract Res Clin Rheumatol. 2005;19(2):191-207.
6. Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum. 2013;65(1):270-81.
7. Zwerina J, Eger G, Englbrecht M, Manger B, Schett G. Churg-Strauss syndrome in childhood: a systematic literature review and clinical comparison with adult patients. Semin Arthritis Rheum. 2009;39(2):108-15.
8. Mahr A, Moosig F, Neumann T, Szczeklik W, Taille C, Vaglio A, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolutions in classification, etiopathogenesis, assessment and management. Curr Opin Rheumatol. 2014;26(1):16-23.
9. Healy B, Bibby S, Steele R, Weatherall M, Nelson H, Beasley R. Antineutrophil cytoplasmic autoantibodies and myeloperoxidase autoantibodies in clinical expression of Churg-Strauss syndrome. Journal of Allergy and Clinical Immunology. 2013;131(2):571-6.e6.
10. Sablé-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Annals of Internal Medicine. 2005;143(9):632-8.
11. Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis and Rheumatism. 2005;52(9):2926-35.
12. Groh M, Pagnoux C, Baldini C, Bel E, Bottero P, Cottin V, et al. Eosinophilic granulomatosis with polyangiitis (churg-strauss) (EGPA) consensus task force recommendations for evaluation and management. Nephron. 2015;129:158.
13. Vaglio A, Corradi D, Ronda N, Garini G, Buzio C. Large bowel obstruction heralding Churg-Strauss syndrome. Am J Gastroenterol. 2004;99(3):562-3.
14. 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.
15. Martorana D, Bonatti F, Alberici F, Gioffredi A, Reina M, Urban ML, et al. Fcγ-receptor 3B (FCGR3B) copy number variations in patients with eosinophilic granulomatosis with polyangiitis. Journal of Allergy and Clinical Immunology. 2016;137(5):1597-9.e8.
16. Vaglio A, Martorana D, Maggiore U, Grasselli C, Zanetti A, Pesci A, et al. HLA-DRB4 as a genetic risk factor for Churg-Strauss syndrome. Arthritis Rheum. 2007;56(9):3159-66.
17. Maritati F, Peyronel F, Fenaroli P, Pegoraro F, Lastrucci V, Benigno G, et al. Occupational Exposures and Smoking in Eosinophilic Granulomatosis With Polyangiitis: A Case–Control Study. Arthritis and Rheumatology. 2021;73(9):1694-702.
18. Fagni F, Bello F, Emmi G. Eosinophilic Granulomatosis With Polyangiitis: Dissecting the Pathophysiology. Front Med (Lausanne). 2021;8:627776.
19. Bettiol A, Urban ML, Dagna L, Cottin V, Franceschini F, Del Giacco S, et al. Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis (EGPA): a European multicenter observational study. Arthritis & rheumatology (Hoboken, NJ). 2021.

20. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. New England Journal of Medicine. 2017;376(20):1921-32.
21. Vaglio A, Casazza I, Grasselli C, Corradi D, Sinico RA, Buzio C. Churg-Strauss syndrome. Kidney Int. 2009;76(9):1006-11.
22. Kotas ME, Dion J, Van Dyken S, Ricardo-Gonzalez RR, Danel CJ, Taille C, et al. A role for IL-33-activated ILC2s in eosinophilic vasculitis. JCI Insight. 2021;6(12).
23. Zwerina J, Bach C, Martorana D, Jatzwauk M, Hegasy G, Moosig F, et al. Eotaxin-3 in Churg-Strauss syndrome: A clinical and immunogenetic study. Rheumatology. 2011;50(10):1823-7.
24. Vaglio A, Strehl JD, Manger B, Maritati F, Alberici F, Beyer C, et al. IgG4 immune response in Churg-Strauss syndrome. Ann Rheum Dis. 2012;71(3):390-3.
25. Emmi G, Rossi GM, Urban ML, Silvestri E, Prisco D, Goldoni M, et al. Scheduled rituximab maintenance reduces relapse rate in eosinophilic granulomatosis with polyangiitis. Annals of the Rheumatic Diseases. 2018;77(6):952-4.
26. Mohammad AJ, Hot A, Arndt F, Moosig F, Guerry MJ, Amudala N, et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Ann Rheum Dis. 2016;75(2):396-401.
27. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016;75(9):1583-94.
28. Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. Arthritis Care and Research. 2021;73(8):1088-105.
29. Trivioli G, Terrier B, Vaglio A. Eosinophilic granulomatosis with polyangiitis: understanding the disease and its management. Rheumatology (Oxford). 2020;59(Suppl 3):iii84-iii94.
30. Chen Y, Yang K, Marusic A, Qaseem A, Meerpohl JJ, Flottorp S, et al. A Reporting Tool for Practice Guidelines in Health Care: The RIGHT Statement. Ann Intern Med. 2017;166(2):128-32.
31. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009.
32. Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, et al. Respiratory manifestations of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). European Respiratory Journal. 2016;48(5):1429-41.
33. Bacciu A, Bacciu S, Mercante G, Ingegnoli F, Grasselli C, Vaglio A, et al. Ear, nose and throat manifestations of Churg-Strauss syndrome. Acta Oto-Laryngologica. 2006;126(5):503-9.
34. Bacciu A, Buzio C, Giordano D, Pasanisi E, Vincenti V, Mercante G, et al. Nasal polyposis in Churg-Strauss syndrome. Laryngoscope. 2008;118(2):325-9.
35. Cho HJ, Yune S, Seok JM, Cho EB, Min JH, Seo YL, et al. Clinical Characteristics and Treatment Response of Peripheral Neuropathy in the Presence of Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome): Experience at a Single Tertiary Center. J Clin Neurol. 2017;13(1):77-83.
36. Padoan R, Marconato M, Felicetti M, Cinetto F, Cerchiaro M, Rizzo F, et al. Overall Disability Sum Score for Clinical Assessment of Neurological Involvement in Eosinophilic Granulomatosis With Polyangiitis. J Clin Rheumatol. 2018;24(4):197-202.
37. Micheletti RG, Chiesa Fuxench Z, Craven A, Watts RA, Luqmani RA, Merkel PA. Cutaneous Manifestations of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol. 2020;72(10):1741-7.
38. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore). 1984;63(2):65-81.
39. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990;33(8):1094-100.
40. 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. Arthritis Rheumatol. 2022;74(3):386-92.
41. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Annals of the Rheumatic Diseases. 2007;66(2):222-7.
42. Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, et al. Revisiting the systemic vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): A study of 157 patients by the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and the European Respiratory Society Taskforce on eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Autoimmunity Reviews. 2017;16(1):1-9.
43. Durel C, Sinico RA, Teixeira V, Jayne D, Belenfant X, March, et al. Renal involvement in eosinophilic granulomatosis with polyangiitis (EGPA): A multicentric retrospective study of 63 biopsy-proven cases. Rheumatology (United Kingdom). 2021;60(1):359-65.
44. Tabb ES, Duncan LM, Nazarian RM. Eosinophilic granulomatosis with polyangiitis: Cutaneous clinical and histopathologic differential diagnosis. J Cutan Pathol. 2021;48(11):1379-86.
45. Contro G, Brescia G, Alessandrini L, Barion U, Padoan R, Frigo AC, et al. Neutrophil infiltrates and eosinophil aggregates in chronic rhinosinusitis with nasal polyps and EGPA. Clin Rheumatol. 2021;40(5):1949-57.
46. Papo M, Sinico RA, Teixeira V, Venhoff N, Urban ML, Iudici M, et al. Significance of PR3-ANCA positivity in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Rheumatology (Oxford). 2021;60(9):4355-60.
47. Moiseev S, Kronbichler A, Makarov E, Bulanov N, Crnogorac M, Direskeneli H, et al. Association of venous thromboembolic events with skin, pulmonary and kidney involvement in ANCA-associated vasculitis: a multinational study. Rheumatology (Oxford, England). 2021.
48. Chang HC, Chou PC, Lai CY, Tsai HH. Antineutrophil Cytoplasmic Antibodies and Organ-Specific Manifestations in Eosinophilic Granulomatosis with Polyangiitis: A Systematic Review and Meta-Analysis. Journal of Allergy and Clinical Immunology: In Practice. 2021;9(1):445-52.e6.
49. Samson M, Puéchal X, Devilliers H, Ribi C, Cohen P, Stern M, et al. Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. Journal of Autoimmunity. 2013;43:60-9.
50. Sokolowska BM, Szczeklik WK, Wludarczyk AA, Kuczia PP, Jakiela BA, Gasior JA, et al. ANCA-positive and ANCA-negative phenotypes of eosinophilic granulomatosis with polyangiitis (EGPA): outcome and long-term follow-up of 50 patients from a single Polish center. Clin Exp Rheumatol. 2014;32(3):S41-7.
51. Moiseev S, Bossuyt X, Arimura Y, Blockmans D, Csernok E, Damoiseaux J, et al. International consensus on antineutrophil cytoplasm antibodies testing in eosinophilic granulomatosis with polyangiitis. American Journal of Respiratory and Critical Care Medicine. 2020;202(10):1360-72.
52. Yates M, Watts R, Bajema I, Cid M, Crestani B, Hauser T, et al. Validation of the EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis by disease content experts. RMD Open. 2017;3(1).
53. MAINRITSEG trial [Available from: https://clinicaltrials.gov/ct2/show/NCT03164473.
54. MANDARA trial [Available from: https://clinicaltrials.gov/ct2/show/NCT04157348.
55. Moosig F, Bremer JP, Hellmich B, Holle JU, Holl-Ulrich K, Laudien M, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): Monocentric experiences in 150 patients. Annals of the Rheumatic Diseases. 2013;72(6):1011-7.
56. Vega Villanueva KL, Espinoza LR. Eosinophilic Vasculitis. Curr Rheumatol Rep. 2020;22(1):5.
57. Suppiah R, Mukhtyar C, Flossmann O, Alberici F, Baslund B, Batra R, et al. A cross-sectional study of the Birmingham Vasculitis Activity Score version 3 in systemic vasculitis. Rheumatology (Oxford). 2011;50(5):899-905.
58. Santino TA, Chaves GS, Freitas DA, Fregonezi GA, Mendonca KM. Breathing exercises for adults with asthma. Cochrane Database Syst Rev. 2020;3:CD001277.

59. Cai S, Xu S, Lou H, Zhang L. Comparison of Different Biologics for Treating Chronic Rhinosinusitis with Nasal Polyps: A Network Analysis. J Allergy Clin Immunol Pract. 2022.
60. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis Nodosa and Churg-Strauss syndrome: A prospective study in 342 patients. Medicine. 1996;75(1):17-28.
61. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Toumelin PL. The five-factor score revisited: Assessment of prognoses of systemic necrotizing vasculitides based on the french vasculitis study group (FVSG) cohort. Medicine. 2011;90(1):19-27.
62. Samson M, Puéchal X, Devilliers H, Ribi C, Cohen P, Bienvenu B, et al. Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors. Autoimmunity Reviews. 2014;13(9):945-53.
63. Hattori N, Ichimura M, Nagamatsu M, Li M, Yamamoto K, Kumazawa K, et al. Clinicopathological features of Churg-Strauss syndrome-associated neuropathy. Brain. 1999;122(3):427-39.
64. Hattori N, Mori K, Misu K, Koike H, Ichimura M, Sobue G. Mortality and morbidity in peripheral neuropathy associated Churg-Strauss syndrome and microscopic polyangiitis. Journal of Rheumatology. 2002;29(7):1408-14.
65. Akella SS, Schlachter DM, Black EH, Barmettler A. Ophthalmic Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss Syndrome): A Systematic Review of the Literature. Ophthalmic Plast Reconstr Surg. 2019;35(1):7-16.
66. Perez-Jacoiste Asin MA, Charles P, Rothschild PR, Terrier B, Brezin A, Mouthon L, et al. Ocular involvement in granulomatosis with polyangiitis: A single-center cohort study on 63 patients. Autoimmun Rev. 2019;18(5):493-500.
67. Abe Y, Kusaoi M, Tada K, Yamaji K, Tamura N. Efficacy of plasma exchange therapy for diffuse alveolar hemorrhage in patients with microscopic polyangiitis. Ther Apher Dial. 2022.
68. Cohen P, Pagnoux C, Mahr A, Arène JP, Mouthon L, Le Guern V, et al. Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Care and Research. 2007;57(4):686-93.
69. Thiel J, Troilo A, Salzer U, Schleyer T, Halmschlag K, Rizzi M, et al. Rituximab as Induction Therapy in Eosinophilic Granulomatosis with Polyangiitis Refractory to Conventional Immunosuppressive Treatment: A 36-Month Follow-Up Analysis. Journal of Allergy and Clinical Immunology: In Practice. 2017;5(6):1556-63.
70. Casal Moura M, Berti A, Keogh KA, Volcheck GW, Specks U, Baqir M. Asthma control in eosinophilic granulomatosis with polyangiitis treated with rituximab. Clinical Rheumatology. 2020;39(5):1581-90.
71. Terrier B PG, de Moreuil C, Bonnotte B, Benhamou Y, Diot E, Chauveau D, Duffau P, Limal N, Neel A, Urbanski G, Jourde-Chiche N, Martin-Silva N, Maurier F, Mekinian A, Schleinitz N, Ackermann F, Fauchais A, Froissart A, Le Gallou T, Uzunhan Y, Viallard J, Berezne A, Chiche L, Crestani B, Direz G, Durel C, Godmer P, Kahn J, Lambert M, Quemeneur T, Cadranel J, Charles P, Dossier A, Jilet L, Guillevin L, Abdoul H, Puechal X. Rituximab versus Conventional Therapeutic Strategy for Remission Induction in Eosinophilic Granulomatosis with Polyangiitis: A Double-blind, Randomized, Controlled Trial [abstract]. Arthritis Rheumatol. 2021;73
72. Ribi C, Cohen P, Pagnoux C, Mahr A, Arène JP, Lauque D, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors: A multicenter, prospective, randomized, open-label study of seventy-two patients. Arthritis and Rheumatism. 2008;58(2):586-94.
73. Canzian A, Venhoff N, Urban ML, Sartorelli S, Ruppert AM, Groh M, et al. Use of Biologics to Treat Relapsing and/or Refractory Eosinophilic Granulomatosis With Polyangiitis: Data From a European Collaborative Study. Arthritis and Rheumatology. 2021;73(3):498-503.
74. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puechal X, Fujimoto S, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med. 2020;382(7):622-31.
75. 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.
76. Terrier B, Charles P, Aumaître O, Belot A, Bonnotte B, Crabol Y, et al. ANCA-associated vasculitides: Recommendations of the French Vasculitis Study Group on the use of

immunosuppressants and biotherapies for remission induction and maintenance. Presse Medicale. 2020;49(3).
77. Maritati F, Alberici F, Oliva E, Urban ML, Palmisano A, Santarsia F, et al. Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: a randomised trial. PloS one. 2017;12(10).
78. Terrier B, Darbon R, Durel CA, Hachulla E, Karras A, Maillard H, et al. French recommendations for the management of systemic necrotizing vasculitides (polyarteritis nodosa and ANCA-associated vasculitides). Orphanet journal of rare diseases. 2020;15:351.
79. Celebi Sozener Z, Gorgulu B, Mungan D, Sin BA, Misirligil Z, Aydin O, et al. Omalizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA): Single-center experience in 18 cases. Allergy: European Journal of Allergy and Clinical Immunology. 2019;74:450.
80. Jachiet M, Samson M, Cottin V, Kahn JE, Le Guenno G, Bonniaud P, et al. Anti-IgE Monoclonal Antibody (Omalizumab) in Refractory and Relapsing Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss): Data on Seventeen Patients. Arthritis and Rheumatology. 2016;68(9):2274-82.
81. Yamada Y, Harada M, Hara Y, Iwabuchi R, Hashimoto K, Yamamoto S, et al. Efficacy of plasma exchange for antineutrophil cytoplasmic antibody-associated systemic vasculitis: a systematic review and meta-analysis. Arthritis Res Ther. 2021;23(1):28.
82. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Genereau T, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. Arthritis Rheum. 1995;38(11):1638-45.
83. Metzler C, Schnabel A, Gross WL, Hellmich B. A phase II study of interferon-alpha for the treatment of refractory Churg-Strauss syndrome. Clinical and Experimental Rheumatology. 2008;26(3):S35-S40.
84. Philobos M, Perkins A, Karabayas M, Dospinescu P, Fluck N, Kidder D, et al. A real-world assessment of mycophenolate mofetil for remission induction in eosinophilic granulomatosis with polyangiitis. Rheumatology International. 2021.
85. Kahn JE, Grandpeix-Guyodo C, Marroun I, Catherinot E, Mellot F, Roufosse F, et al. Sustained response to mepolizumab in refractory Churg-Strauss syndrome. J Allergy Clin Immunol. 2010;125(1):267-70.
86. Kim S, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. J Allergy Clin Immunol. 2010;125(6):1336-43.
87. Moosig F, Gross WL, Herrmann K, Bremer JP, Hellmich B. Targeting interleukin-5 in refractory and relapsing Churg-Strauss syndrome. Ann Intern Med. 2011;155(5):341-3.
88. Steinfeld J, Bradford ES, Brown J, Mallett S, Yancey SW, Akuthota P, et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol. 2019;143(6):2170-7.
89. Manka LA, Guntur VP, Denson JL, Dunn RM, Dollin YT, Strand MJ, et al. Efficacy and safety of reslizumab in the treatment of eosinophilic granulomatosis with polyangiitis. Ann Allergy Asthma Immunol. 2021;126(6):696-701 e1.
90. Koga Y, Aoki-Saito H, Kamide Y, Sato M, Tsurumaki H, Yatomi M, et al. Perspectives on the Efficacy of Benralizumab for Treatment of Eosinophilic Granulomatosis With Polyangiitis. Front Pharmacol. 2022;13:865318.
91. Berti A, Cornec D, Casal Moura M, Smyth RJ, Dagna L, Specks U, et al. Eosinophilic Granulomatosis With Polyangiitis: Clinical Predictors of Long-term Asthma Severity. Chest. 2020;157(5):1086-99.
92. Latorre M, Baldini C, Seccia V, Pepe P, Novelli F, Celi A, et al. Asthma Control and Airway Inflammation in Patients with Eosinophilic Granulomatosis with Polyangiitis. Journal of Allergy and Clinical Immunology: In Practice. 2016;4(3):512-9.
93. NUCALA-EMA.
94. Pagnoux C, Quéméneur T, Ninet J, Diot E, Kyndt X, De Wazières B, et al. Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: Results of a

multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. Arthritis and Rheumatology. 2015;67(4):1117-27.
95. Pagnoux C, Mahendira D, Laskin CA. Fertility and pregnancy in vasculitis. Best Pract Res Clin Rheumatol. 2013;27(1):79-94.
96. MABTHERA-EMA.
97. Teixeira V, Mohammad AJ, Jones RB, Smith R, Jayne D. Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis. RMD Open. 2019;5(1):e000905.
98. Dejaco C, Oppl B, Monach P, Cuthbertson D, Carette S, Hoffman G, et al. Serum biomarkers in patients with relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss). PLoS One. 2015;10(3):e0121737.
99. Grayson PC, Monach PA, Pagnoux C, Cuthbertson D, Carette S, Hoffman GS, et al. Value of commonly measured laboratory tests as biomarkers of disease activity and predictors of relapse in eosinophilic granulomatosis with polyangiitis. Rheumatology (United Kingdom). 2015;54(8):1351-9.
100. Guilpain P, Auclair JF, Tamby MC, Servettaz A, Mahr A, Weill B, et al. Serum eosinophil cationic protein: A marker of disease activity in Churg-Strauss syndrome. 2007. p. 392-9.
101. Dallos T, Heil, GR, Strehl J, Karonitsch T, Gross WL, et al. CCL17/thymus and activation-related chemokine in Churg-Strauss syndrome. Arthritis Rheum.62(11):3496-503.
102. Bettiol A, Sinico RA, Schiavon F, Monti S, Bozzolo EP, Franceschini F, et al. Risk of acute arterial and venous thromboembolic events in eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome). European Respiratory Journal. 2021;57(5).
103. Allenbach Y, Seror R, Pagnoux C, Teixeira L, Guilpain P, Guillevin L. High frequency of venous thromboembolic events in Churg-Strauss syndrome, Wegener's granulomatosis and microscopic polyangiitis but not polyarteritis nodosa: A systematic Retrospective Study on 1130 patients. Annals of the Rheumatic Diseases. 2009;68(4):564-7.
104. Cereda AF, Pedrotti P, De Capitani L, Giannattasio C, Roghi A. Comprehensive evaluation of cardiac involvement in eosinophilic granulomatosis with polyangiitis (EGPA) with cardiac magnetic resonance. European Journal of Internal Medicine. 2017;39:51-6.
105. Bourgarit A, Le Toumelin P, Pagnoux C, Cohen P, Mahr A, Le Guern V, et al. Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: A retrospective analysis of causes and factors predictive of mortality based on 595 patients. Medicine. 2005;84(5):323-30.
106. Hazebroek MR, Kemna MJ, Schalla S, Sanders-Van Wijk S, Gerretsen SC, Dennert R, et al. Prevalence and prognostic relevance of cardiac involvement in ANCA-associated vasculitis: Eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis. International Journal of Cardiology. 2015;199:170-9.
107. Hasegawa W, Yamauchi Y, Yasunaga H, Sunohara M, Jo T, Matsui H, et al. Factors that predict in-hospital mortality in eosinophilic granulomatosis with polyangiitis. Allergy: European Journal of Allergy and Clinical Immunology. 2015;70(5):585-90.
108. Garcia-Vives E, Segarra-Medrano A, Martinez-Valle F, Agraz I, Solans-Laque R. Prevalence and risk factors for major infections in patients with antineutrophil cytoplasmic antibody-associated vasculitis: Influence on the disease outcome. Journal of Rheumatology. 2020;47(3):407-14.
109. Dunogué B, Terrier B, Cohen P, Marmursztejn J, Legmann P, Mouthon L, et al. Impact of cardiac magnetic resonance imaging on eosinophilic granulomatosis with polyangiitis outcomes: A long-term retrospective study on 42 patients. Autoimmunity Reviews. 2015;14(9):774-80.
110. Drosos GC, Vedder D, Houben E, Boekel L, Atzeni F, Badreh S, et al. EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome. Ann Rheum Dis. 2022.
111. Cattaneo L, Chierici E, Pavone L, Grasselli C, Manganelli P, Buzio C, et al. Peripheral neuropathy in Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis. Journal of Neurology, Neurosurgery and Psychiatry. 2007;78(10):1119-23.
112. Kronbichler A, Kerschbaum J, Gopaluni S, Tieu J, Alberici F, Jones RB, et al. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2018;77(10):1440-7.

113. Choi ST, Ahn SV, Lee PH, Moon CM. The cancer risk according to three subtypes of ANCA-associated vasculitis: A propensity score-matched analysis of a nationwide study: Cancer risk in AAV three subtypes. Seminars in Arthritis and Rheumatism. 2021;51(4):692-9.
114. Ahn SS, Han M, Yoo J, Jung SM, Song JJ, Park YB, et al. Risk of cancers in antineutrophil cytoplasmic antibody-associated vasculitis: Results from the korea national health insurance claims database 2010–2018. Journal of Clinical Medicine. 2019;8(11).
115. Yoo J, Ahn SS, Jung SM, Song JJ, Park YB, Lee SW. Cancer development in Korean patients with ANCA-associated vasculitis: A single centre study. Clinical and Experimental Rheumatology. 2018;36:S73-S7.
116. Calatroni M, Buzio C, Vaglio A. The evolving paradigm of cancer risk related to cyclophosphamide therapy in granulomatosis with polyangiitis. Rheumatology (Oxford). 2015;54(8):1339-41.
117. Faurschou M, Mellemkjaer L, Voss A, Keller KK, Hansen IT, Baslund B. Prolonged risk of specific malignancies following cyclophosphamide therapy among patients with granulomatosis with polyangiitis. Rheumatology (Oxford). 2015;54(8):1345-50.
118. Box CD, Cronin O, Hauser B. The Impact of High Dose Glucocorticoids on Bone Health and Fracture Risk in Systemic Vasculitides. Front Endocrinol (Lausanne). 2022;13:806361.
119. Bottero P, Bonini M, Vecchio F, Grittini A, Patruno GM, Colombo B, et al. The common allergens in the Churg-Strauss syndrome. Allergy: European Journal of Allergy and Clinical Immunology. 2007;62(11):1288-94.
120. Bello F, Maritati F, Radice A, Sinico RA, Emmi G, Vaglio A. Microarray evaluation of allergen-specific IgE in eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis. 2021;80(9):1247-8.

Box 1. *Overarching principles*

- Patients with EGPA should be offered the best care through the management at or in association with centres of expertise
- EGPA is best managed by interdisciplinary care, with decisions being shared by patients and physicians, and considering safety, efficacy and costs
- Patients with EGPA should be educated and made aware of the risks associated with the disease
- Improvement of quality of life of patients with EGPA is an important goal to be achieved, together with clinical outcomes such as survival, long-term preservation of organ function and prevention of disease flares
- Patients with EGPA should be screened for treatment-related and cardiovascular comorbidities. Prophylaxis and life-style advices should be given to reduce cardiovascular risk and treatment-related complications

Box 2. *Research agenda*

- Diagnostic criteria for EGPA
- Identification of diagnostic and disease activity-related biomarkers for EGPA
- Adequately powered genetic studies
- Improved assessment of cardiovascular disease activity and damage
- Role of IL-5 targeting agents in severe organ manifestations
- Other biologics for the treatment of EGPA
- Differential efficacy of biologics in EGPA subsets

FIGURE LEGENDS

Figure 1. *Main clinical characteristics of EGPA based on ANCA status*

The clinical manifestations of EGPA are quite heterogeneous and their frequencies differ on the basis of the ANCA status. Specifically, vasculitic features (*eg*, glomerulonephritis, peripheral neuropathy purpura), occur more often in ANCA-positive patients, whereas eosinophilic features (*eg*, cardiac involvement, gastroenteritis) are more frequent in ANCA-negative patients. The vasculitic and eosinophilic phenotypes, however, are not clearly separated, as most patients manifest an overlap between vasculitic and eosinophilic features.

Figure 2. *Key imaging and histopathological aspects of EGPA*

(A) Computed tomography (CT, coronal view) of the paranasal sinuses showing signs of diffuse rhinosinusitis (arrow); (B) high-resolution CT scan (axial view) showing patchy bilateral lung infiltrates; (C) cardiac magnetic resonance: phase sensitive inversion recovery (PSIR) image showing a hypointense, small apical mass suggestive for intraventricular thrombus (arrow); (D) purpura of the lower limbs; (E) biopsy of a nasal polyp showing a dense, eosinophil-rich infiltrate within the submucosa (haematoxylin and eosin, original magnification x20); (F) eosinophilic vasculitis in a biopsy of the airway mucosa (haematoxylin and eosin, original magnification x20); (G) eosinophil-rich granuloma in a biopsy of the airway mucosa (haematoxylin and eosin, original magnification x20); (G) skin biopsy in a patient with purpura showing perivascular inflammation of dermal vessels (arrows); (haematoxylin and eosin, original magnification x10)

Figure 3. *Diagnostic evaluation of EGPA*

The figure shows the main investigations performed in patients suspected as having EGPA. In the left-hand column, “baseline investigations” indicate laboratory and imaging tests or procedures that are usually non-invasive and should be performed in all patients; the procedures listed in the right-hand column should be performed only in the presence of specific clinical manifestations. The investigations reported in parentheses are indicated only in selected cases. *urinary protein excretion >1g/day, glomerular haematuria

Abbreviations used in the figure: ABPA: allergic bronchopulmonary aspergillosis; ANCA: anti-neutrophil cytoplasmic antibodies; AV: arterial and venous; BAL: broncho-alveolar lavage; BNP: brain natriuretic peptide; CNS: central nervous system; CSF: cerebro-spinal fluid; CT: computed tomography; CV: cardiovascular; EKG: electrocardiogram; EMG-ENG: electromyography-electroneurography; ENT: ear-nose-throat; FESS: functional endoscopic sinus surgery; GI: gastrointestinal; HIV: human immunodeficiency virus; HRCT: high-resolution computed tomography; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging

Figure 4. *Proposed treatment algorithm for EGPA*

Abbreviations used in the figure: GCs: glucocorticoids; DMARDs: disease-modifying anti-rheumatic drugs; FFS: five-factor score

Table 1. *Main clinical features of EGPA in three large cohorts*

	Comarmond et al. (2013)[6]			Sinico et al. (2005)[11]			Healy et al. (2013)[9]		
	ANCA+ (n=108)	**ANCA-** (n=240)	**p value**	**ANCA+** (n=35)	**ANCA-** (n=58)	**p value**	**MPO ANCA+** (n=15)	**ANCA-** (n=55)	**p value**
Asthma	93%	91%	ns	97%	95%	ns	100%	100%	ns
Sinusitis	52%	38%	0.02	77%	78%	ns	60%	64%	ns
Lung involvement, *all kinds*	93%	91%	ns	34%	60%	0.02	40%	76%	<0.01
Alveolar haemorrhage	7%	3%	ns	20%	0	0.001	na	na	na
Heart involvement	8%*	19%*	0.01*	6%	22%	<0.01	0	38%	<0.01
Gastrointestinal involvement	22%	23%	ns	20%	22%	ns	0	14%	0.03
Skin involvement, *all kinds*	45%	36%	ns	60%	48%	ns	67%	62%	ns
Purpura	29%	20%	ns	26%	7%	0.02	53%	40%	ns
Peripheral neuropathy, *all kinds*	63%	44%	<0.01	71%	60%	ns	73%	42%	0.02
Mononeuritis multiplex	55%	39%	<0.01	51%	24%	0.01	na	na	na
CNS involvement	7%	4%	ns	17%	12%	ns	20%	13%	ns
Renal involvement	27%	16%	0.02	51%	12%	<0.001	33%	16%	ns
Vasculitis on biopsy	na	na	na	76%	32%	<0.001	81%	61%	ns

*In Comarmond et al, the % refers to “cardiomyopathy” rather than to heart involvement of any kind

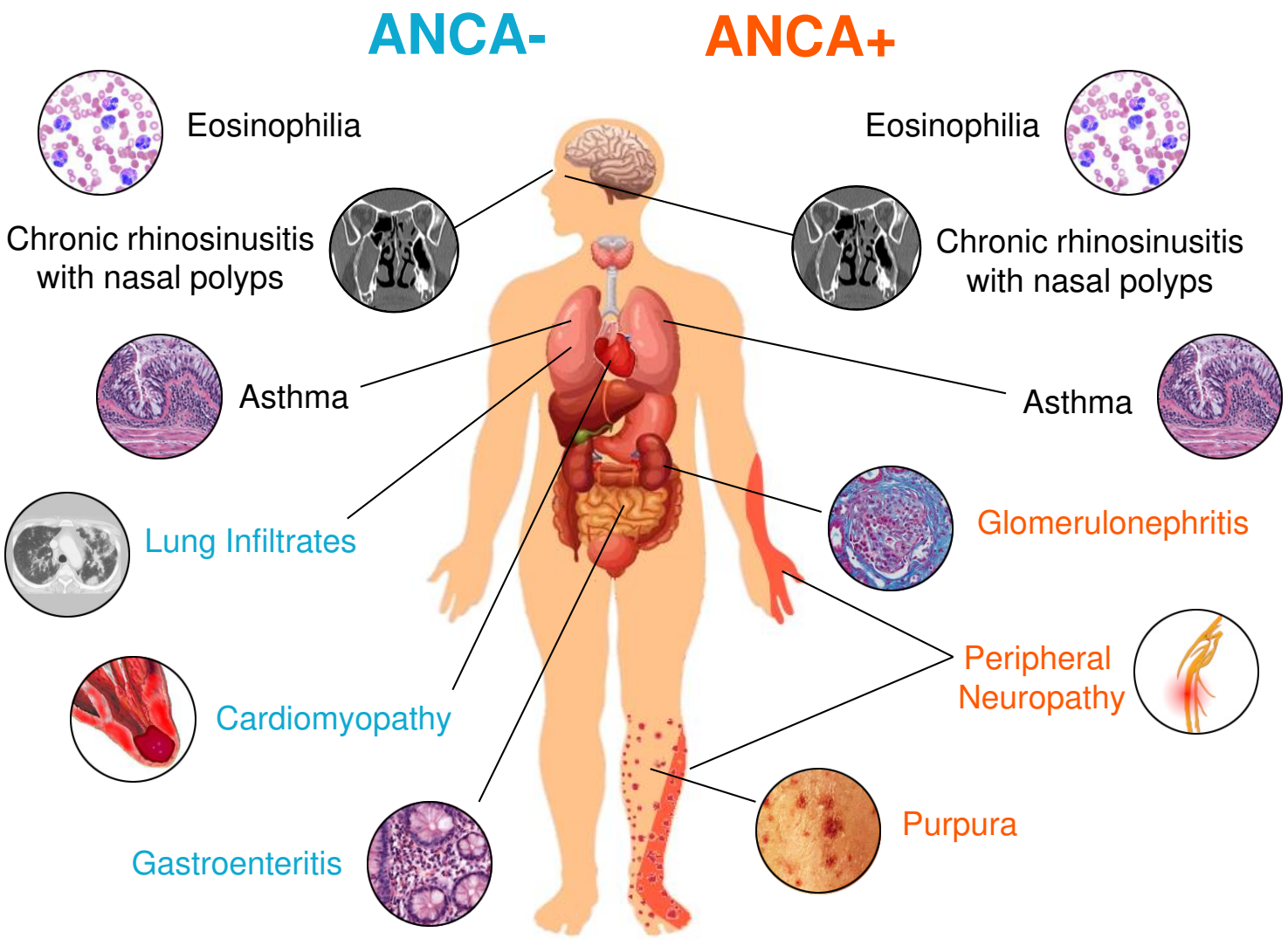
Abbreviations used in the table: ANCA: anti-neutrophil cytoplasmic antibodies; ns: not significant; na: not available; CNS: central nervous system

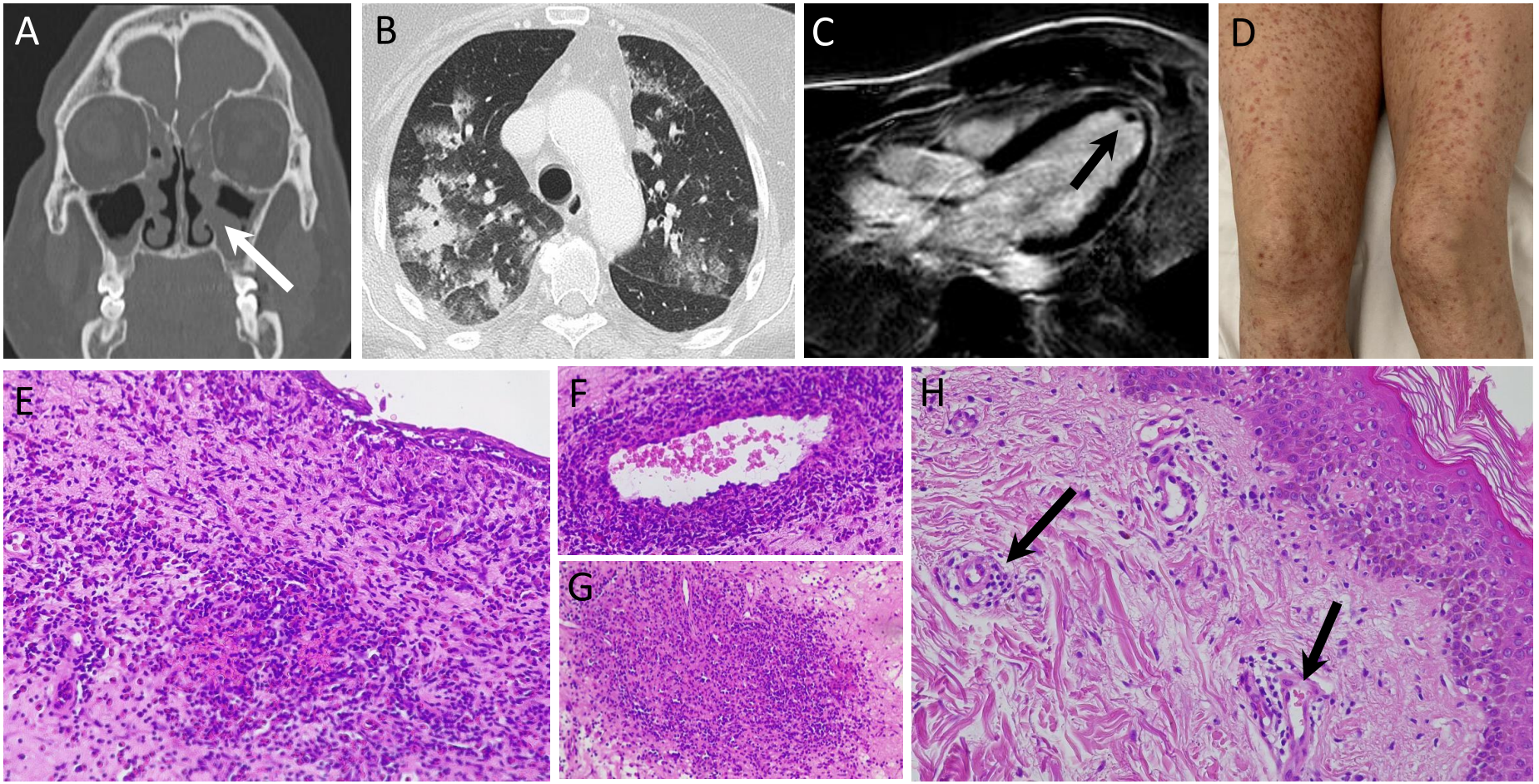
Table 2. *Recommendation statements, levels of evidence, grade of recommendation and level of agreement*

Statement	Level of evidence	Grade of recommendation	Level of agreement *mean (SD)*
1. The diagnosis of EGPA should be considered in patients with asthma, chronic rhino-sinusitis and eosinophilia who develop end-organ involvement, particularly peripheral neuropathy, lung infiltrates, cardiomyopathy or other complications (*eg*, skin, gastrointestinal or kidney involvement).	2b	B	9.9 (0.4)
2. There are no diagnostic criteria for EGPA. Classification criteria include the ACR 1990 and the 2022 ACR/European Alliance of Associations for Rheumatology ones, that have established sensitivity and specificity, and others (*eg*, MIRRA trial) that are based on expert opinion and require validation. EGPA should be diagnosed based on highly suggestive clinical features, objective evidence of vasculitis (*eg*, biopsy), and ANCA.	2b	B	9.2 (1.4)
3. The diagnostic evaluation of patients suspected as having EGPA should always be multidisciplinary; it should rule out other eosinophilic and vasculitic disorders and investigate the main disease complications, particularly heart, respiratory, skin, renal and nervous system involvement, along with ANCA and eosinophilia. Biopsy is recommended when feasible but is not essential to make the diagnosis.	3b	C	9.5 (0.9)
4. ANCA should be tested in all patients suspected as having EGPA. They are detectable in 30-40% of patients with EGPA and most test positive for MPO. MPO-ANCA positive patients frequently show vasculitis features, *ie* glomerulonephritis, neuropathy and purpura, while ANCA-negative patients more frequently manifest cardiomyopathy and lung involvement.	2a	B	9.7 (0.7)
5. EGPA remission is defined as the absence of clinical signs or symptoms attributable to active disease, including asthma and ENT manifestations. The daily dose of glucocorticoids should also be considered for the definition of remission, and a maximum daily dose of 7.5mg of prednisone can be chosen as cut-off.	5	D	8.9 (1.2)
6. Remission-induction treatment should be tailored on clinical manifestations with prognostic relevance. Organ-threatening manifestations included in the Five-Factor	2b	B	9.5 (0.9)

Score (renal insufficiency, proteinuria, cardiomyopathy, gastrointestinal tract and central nervous system involvement) as well peripheral neuropathy and other rare manifestations (*eg*, alveolar haemorrhage) should be considered when defining remission-induction strategies.			
7. For remission induction in patients with new-onset, active EGPA, glucocorticoids should be administered as initial therapy. In patients with severe disease (unfavourable prognostic factors discussed in Statement 6) cyclophosphamide or, as an alternative, rituximab, should be added. In patients with non-severe disease, glucocorticoids alone should be used.	2b	B	8.4 (1.6)
8. For remission-maintenance, in patients with severe EGPA, we recommend using rituximab, mepolizumab or traditional DMARDs in combination with glucocorticoids. In patients with non-severe EGPA, we suggest glucocorticoids, alone or in combination with mepolizumab. Glucocorticoids should be tapered to the minimum effective dosage to reduce toxicity.	2b	B	8.2 (1.8)
9. EGPA relapse is defined as the recurrence of clinical signs or symptoms attributable to active disease following a period of remission. The need for an increase in the glucocorticoid dosage or the initiation or increase of an immunosuppressant should also be considered as a relapse. The relapse or new onset of systemic vasculitis (systemic relapse) should be differentiated from the isolated exacerbation of asthma and ENT manifestations (respiratory relapse).	5	D	9.4 (1.0)
10. Relapses should be treated according to type (systemic vs respiratory) and severity. For severe systemic relapses, we recommend using rituximab or cyclophosphamide with glucocorticoids. For non-severe systemic and respiratory relapses, we recommend raising the dose of glucocorticoids and/or adding mepolizumab.	2b	C	8.9 (1.5)

11. Refractory EGPA is defined as unchanged or increased disease activity after four weeks of appropriate remission-induction therapy. The persistence/worsening of systemic manifestations should be distinguished from that of respiratory manifestations.	5	D	9.1 (1.0)
12. We recommend the use of the IL-5 inhibitor mepolizumab combined with glucocorticoids to induce remission in patients with relapsing-refractory EGPA without organ- or life-threatening manifestations. Mepolizumab can also be used for remission maintenance, particularly in patients requiring a daily prednisone dose ≥7.5 mg for the control of their respiratory manifestations.	2b	B	9.3 (1.4)
13. In EGPA patients with active asthma or ENT involvement, topical/inhaled therapy must be optimised. The approach to the management of these disease manifestations must involve specialists such as pulmonologists and otolaryngologists.	5	D	9.8 (1.0)
14. We recommend that treatment decisions should be modified as necessary in special populations of patients such as children, elderly, women of child-bearing age and those with co-morbidities. There is still no evidence that different phenotypes (*eg*, ANCA-positive vs ANCA-negative) need different approaches.	5	D	9.7 (0.7)
15. Although some laboratory tests (*eg*, eosinophil count, ANCA) are commonly monitored, there are no reliable biomarkers to measure disease activity in EGPA. Disease activity should therefore be assessed on follow-up only using validated clinical tools.	5	D	9.4 (1.1)
16. We recommend routine monitoring of EGPA-related manifestations, with particular reference to lung function, cardiovascular events, and neurological complications. Long-term monitoring of comorbidities (cancer, infections, osteoporosis) is also recommended.	2b	B	9.7 (0.6)


ANCA-
ANCA+
Eosinophilia
Eosinophilia
Chronic rhinosinusitis with nasal polyps
Chronic rhinosinusitis with nasal polyps
Asthma
Asthma
Lung Infiltrates
Glomerulonephritis
Peripheral Neuropathy
Cardiomyopathy
Purpura
Gastroenteritis

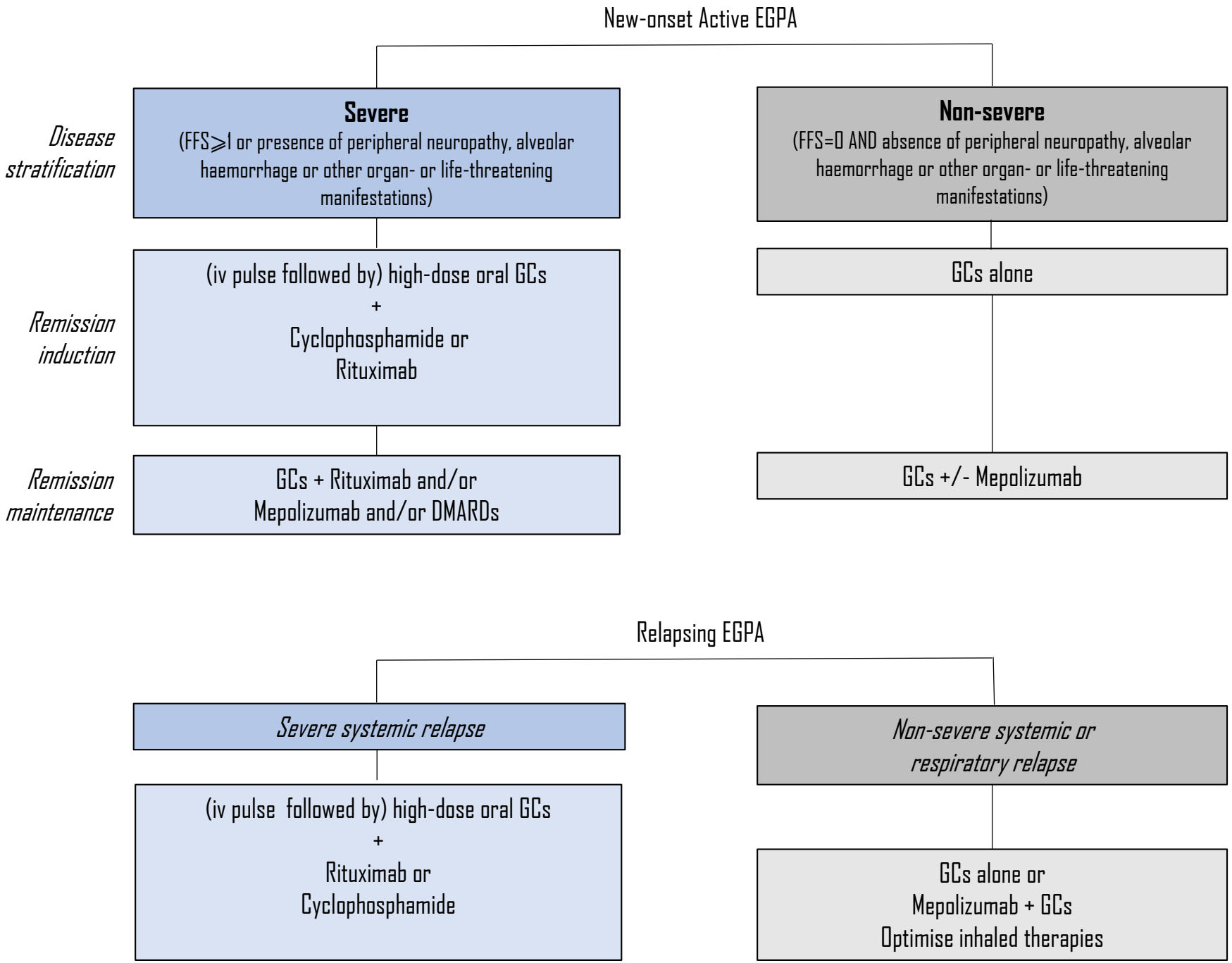

A
B
C
D
E
F
G
H

EGPA diagnostic work-up

Baseline investigations	Screening/diagnostic aims
Routine laboratory investigations **a**. Routine blood tests **b**. Complete blood count with differential **c**. urinalysis, 24h proteinuria or urinary protein-to-creatinine ratio **d**. Sputum culture (where available) **e**. D-dimer, Troponin, BNP **f.** Faecal occult blood **g**. C-reactive protein **h**. LDH, tryptase, vitamin B12	a,b. General/haematologic assessment c. Kidney involvement screening d, g. Infectious disease screening e. Cardiac involvement screening f. Intestinal involvement screening g. Disease activity assessment h. Screening for myeloproliferative forms
Immunological/allergic tests ANCA, IgG IgA IgM IgE, IgG4	EGPA-related immune parameters
Infectious tests Stool cultures for parasites (*eg*, *Strongyloides stercoralis*) Toxocara serology HIV serology	Screening for parasitic and viral infections
Haematologic tests Blood smear (dysplastic eosinophils or blasts) FIP1-L1-fusion proteins	Screening for haematologic forms of hypereosinophilia
Imaging studies/other procedures **a**. Chest X ray and/or HRCT **b**. Pulmonary function tests **c**. ENT consultation (with nasal endoscopy) **d**. EKG, Echocardiography **e**. Abdominal ultrasound	a, b. Lung involvement screening c. ENT involvement d. Cardiac involvement screening e. General assessment, screening for hepato-splenomegaly (haematologic hypereosinophilia)

Investigations to be performed in selected cases

Indications	*Procedures*
Peripheral neuropathy	EMG-ENG (Sural nerve biopsy)
Renal function impairment, urinary abnormalities*	Kidney biopsy
GI symptoms and/or bleeding	Endoscopy
ENT abnormalities (e.g. polyps, sino-nasal obstruction symptoms, hearing loss)	Audiometry Sinus CT scan FESS
Lung infiltrates/pleural effusions	BAL, pleural puncture, lung biopsy
Clinical signs of ABPA	*Aspergillus*-specific IgE/IgG Sputum (or BAL) cultures for *Aspergillus spp*.
Purpura	Skin biopsy
Clinical/EKG/echo signs of cardiomyopathy	Cardiac MRI (Endomyocardial biopsy)
Vascular events and/or high CV risk	AV Doppler ultrasound
CNS manifestations	Brain/spinal cord MRI (CSF analysis)
Miscellaneous/haematologic	T-cell immunophenotyping Bone marrow biopsy


New-onset Active EGPA
Disease stratification
Severe
(FFS⩾1 or presence of peripheral neuropathy, alveolar haemorrhage or other organ- or life-threatening manifestations)
Non-severe
(FFS=0 AND absence of peripheral neuropathy, alveolar haemorrhage or other organ- or life-threatening manifestations)
Remission induction
(iv pulse followed by) high-dose oral GCs
+
Cyclophosphamide or
Rituximab
GCs alone
Remission maintenance
GCs + Rituximab and/or
Mepolizumab and/or DMARDs
GCs +/- Mepolizumab
Relapsing EGPA
Severe systemic relapse
Non-severe systemic or respiratory relapse
(iv pulse followed by) high-dose oral GCs
+
Rituximab or
Cyclophosphamide
GCs alone or
Mepolizumab + GCs
Optimise inhaled therapies