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Original Article

Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management

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ABSTRACT

Objective: To develop disease-specific recommendations for the diagnosis and management of eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (EGPA).
Methods: The EGPA Consensus Task Force experts comprised 8 pulmonologists, 6 internists, 4 rheumatologists, 3 nephrologists, 1 pathologist and 1 allergist from 5 European countries and the USA. Using a modified Delphi process, a list of 40 questions was elaborated by 2 members and sent to all participants prior to the meeting. Concurrently, an extensive literature search was undertaken with publications assigned with a level of evidence according to accepted criteria. Drafts of the recommendations were circulated for review to all members until final consensus was reached.
Results: Twenty-two recommendations concerning the diagnosis, initial evaluation, treatment and monitoring of EGPA patients were established. The relevant published information on EGPA, antineutrophil-cytoplasm antibody-associated vasculitides, hypereosinophilic syndromes and eosinophilic asthma supporting these recommendations was also reviewed.
Discussion: These recommendations aim to give physicians tools for effective and individual management of EGPA patients, and to provide guidance for further targeted research.

Abbreviations: AAV, ANCA-associated vasculitides; ACR, American College of Rheumatology; ANCAs, antineutrophil cytoplasm antibodies; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; DVT, deep-vein thrombosis; ENT, ear, nose & throat; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss); ELISA, enzyme-linked immunosorbent assay; EULAR, European League Against Rheumatism; FFS, Five-Factor Score; GI, gastrointestinal; HE, hypereosinophilia; HES, hypereosinophilic syndromes; IL, interleukin; IV, intravenous; IVIg, IV immunoglobulins; LRA, leukotriene-receptor antagonists; MPO, myeloperoxidase; PR3, proteinase-3; SNV, systemic necrotizing vasculitis; VTEs, venous thromboembolic events.

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1. Introduction

Churg–Strauss syndrome, recently renamed eosinophilic granulomatosis with polyangiitis (EGPA) [1], is a systemic necrotizing vasculitis (SNV) that affects small-to-medium-sized vessels. In 2009, the European League Against Rheumatism (EULAR) published recommendations for the management of small- and medium-sized-vessel vasculitides [2] that continue to delineate the standard of care for EGPA patients. Much progress has been made over the past 30 years in understanding, redefining and treating SNV. Although EGPA belongs to the spectrum of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV), it differs from granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis because of its association with severe asthma, and blood and tissue eosinophilia. ANCA-positivity ranges from 30–70% of EGPA patients but is usually less frequently observed than in other AAV [3–7]. EGPA also shares some characteristics with hypereosinophilic syndromes (HES).

Despite the increasing number of high-quality clinical trials conducted on AAV and progress towards consensus approaches to treating HES [8], an unmet need remains for consensus guidelines for EGPA diagnosis and management. To address this need, the European Respiratory Society and the Foundation for the Development of Internal Medicine in Europe commissioned the EGPA Consensus Task Force to organize several meetings between 2009 and 2013 aimed at establishing recommendations for the definition, diagnosis, investigation and management of EGPA.

2. Methods

The Task Force, convened by JFC and LG, comprised 8 pulmonologists (EB, JFC, KD, MH, MW, RL, US, VC), 6 internists (AM, BD, CP, LG, LM, MG), 4 rheumatologists (CB, JH, WG, PM), 3 nephrologists (AV, DJ, RAS), 1 pathologist (CJ) and 1 allergist (PB) from 6 countries. MG was appointed to conduct the literature search and draft the manuscript. A list of 40 questions, based on a literature search for multiple terms referencing EGPA and elaborated by 2 committee members (CP, LG) and sent to all Task Force members prior to the final meeting held on 13 April 2013 in Paris, guided the meeting agenda (see Online Supplement). For each question, the Task Force members' answers and comments were collected and synthesized into a draft manuscript that was recirculated until consensus was reached.

Therapeutic intervention statements presented by the group were classified according to GRADE-method-defined levels of evidence [9] (Table 1). When evidence was low-grade and/or data contradictory, the recommendations were formed based on the opinions and practices of Task Force members.

Table 1
Level of evidence of the literature search, according to the Grading of Recommendations Assessment, Development and Assessment (GRADE) guidelines [9].

Code	Quality of evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect.
B	Moderate	• Several high-quality studies with consistent results • In special cases: one large, high-quality multi-center trial Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C	Low	• One high-quality study • Several studies with some limitations Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
D	Very Low	• One or more studies with severe limitations Any estimate of effect is very uncertain.
		• Expert opinion • One or more studies with very severe limitations • No direct research evidence

3. The 22 EGPA Consensus Task Force recommendations (Table 2) [evidence level]

Each entry is followed by the procedural approach for physicians.

1 *EGPA should be managed in collaboration with, or in, centers with established expertise in the management of small- and medium-sized-vessel vasculitides.*
EGPA is a rare disease. Its prevalence ranges from 10.7–13 cases/million inhabitants [10–12], with an annual incidence of 0.5–6.8 new cases/million inhabitants [13,14]. Although its incidence is higher among asthmatic patients [15,16], EGPA remains poorly understood and often goes unrecognized by most physicians. Thus, because inappropriate therapeutic decisions impact the prognosis of EGPA patients, disease-activity assessment and treatment should be managed in collaboration with, or in, centers with expertise in vasculitis management. Notably, in a 20-year retrospective study involving >100 EGPA patients, expert disease management was associated with increased life expectancy and less disease severity [17].

2 *As the minimal initial differential diagnosis work-up, we recommend serologic testing for toxocariasis and human immunodeficiency virus (HIV), specific IgE and IgG dosages for Aspergillus spp., search for Aspergillus spp. in sputum and/or bronchoalveolar lavage fluid, tryptase and vitamin B_{12} dosages, peripheral blood smear (looking for dysplastic eosinophils or blasts) and chest computed-tomography (CT) scan; additional investigations should be guided by patient-specific clinical findings and extensive search for causes of hypereosinophilia should be considered.*
When clinical manifestations include asthma, eosinophilia, pulmonary infiltrates and sinus disease, accompanied by extrapulmonary findings of vasculitis (e.g. purpura), and histologic evidence of vasculitis (and/or eosinophilic infiltration and/or granulomatous inflammation) [1], the EGPA diagnosis is usually straightforward. Indeed, the main differential diagnoses (i.e., other AAV and polyarteritis nodosa) are usually excluded, although eosinophilia occurs in vasculitides other than EGPA.
However, before the onset of vasculitis and/or asthma, particularly in ANCA-negative patients, EGPA manifestations may mimic other diseases (e.g., eosinophilic asthma, eosinophilic pneumonia or HES) and an individual step-by-step diagnostic work-up is recommended [18]. Notably, a recent multidisciplinary consensus report suggested a novel classification of eosinophilic disorders [19] and diagnostic evaluation could take this practical classification system into account.
A thorough investigation of the causes of reactive hypereosinophilia (HE) is mandatory. Familial HE is extremely rare and can easily be excluded. Prior symptoms and the use of databases (e.g. www.pneumotox.com) can usually exclude drug-induced eosinophilia. Also, because toxocariasis has a broad geographic distribution, is often asymptomatic and can cause severe eosinophilia [20], *Toxocara* serology is recommended. Further serologies for other helminthic infections should be guided by the patient's country of origin, travel history and dietary habits. Enzyme-linked immunosorbent assay (ELISA) screening for antibodies to *Strongyloides stercoralis* infection is recommended because this parasite can cause severe hyperinfestation syndromes in glucocorticoid-treated patients, even decades after infection [21]. HIV screening

Table 2
The 22 detailed recommendations for the diagnosis, follow-up and management of EGPA with corresponding levels of evidence.

The EGPA Consensus Task Force recommendations	Level of evidence
1. EGPA should be managed in collaboration with, or in, centers with established expertise in the management of small- and medium-sized-vessel vasculitides	NA
2. We recommend serologic testing for toxocariasis and HIV, specific IgE and IgG dosages for *Aspergillus* spp., search for *Aspergillus* spp. on a sputum and/or bronchoalveolar lavage fluid, tryptase and vitamin B_{12} dosages, peripheral blood smear (looking for dysplastic eosinophils or blasts) and chest CT scan as being the minimal initial differential diagnosis work-up; additional investigations should be guided by patient-specific clinical findings and extensive search for causes of hypereosinophilia should be considered	NA
3. Obtaining biopsies from patients with suspected EGPA is encouraged	NA
4. ANCA testing (with indirect immunofluorescence and ELISA) should be done for patients with suspected EGPA	NA
5. There is currently no reliable biomarker to measure EGPA activity	NA
6. Once EGPA is diagnosed, evaluating possible lung, kidney, heart, GI and/or peripheral nerve involvements is recommended	NA
7. Definition of EGPA remission: the absence of a clinical systemic manifestation (excluding asthma and/or ENT)	NA
8. Definition of EGPA relapse: the new appearance or recurrence or worsening of clinical EGPA manifestation(s) (excluding asthma and/or ENT) requiring the addition, change or dose increase of glucocorticoids and/or other immunosuppressants	NA
9. Use of glucocorticoids is appropriate to achieve EGPA remission; the dose prescribed should be ~1 mg/kg/day prednisone for patients with organ- or life-threatening manifestations	A
10. Patients with life and/or organ-threatening disease manifestations (i.e., heart, GI, central nervous system, severe peripheral neuropathy, severe ocular disease, alveolar hemorrhage and/or glomerulonephritis) should be treated with a remission-induction regimen combining glucocorticoids and an additional immunosuppressant (e.g. cyclophosphamide)	B
11. Maintenance therapy (with azathioprine or methotrexate) is recommended for patients with life- and/or organ-threatening disease manifestations a remission-induction therapeutic regimen	C
12. Glucocorticoids alone may be suitable for patients without life- and/or organ-threatening disease manifestations; additional immunosuppression can be considered for selected patients for whom the prednisone dose cannot be tapered to <7.5 mg/day after 3–4 months of therapy or patients with recurrent disease	C
13. Plasma exchanges are generally not effective in EGPA but can be considered for selected patients with ANCA and rapidly progressive glomerulonephritis or pulmonary–renal syndrome	D
14. Rituximab can be considered for selected ANCA-positive patients with renal involvement or refractory disease	C
15. IVIg can be considered a second-line therapy for patients on glucocorticoids (and/or other immunosuppressants) with EGPA flares refractory to other treatments or during pregnancy; in the context of drug-induced hypogammaglobulinemia with severe and/or recurrent infections, Ig-replacement may be considered	C
16. Interferon-alpha may be reserved as a second- or third-line drug for selected patients	C
17. LRA can be prescribed, if needed, for EGPA patients	B
18. Vaccinations with inactivated vaccines and against influenza and pneumococci should be encouraged; live-attenuated vaccines are contraindicated in patients taking immunosuppressants, and/or ≥20 mg/day of prednisone	D
19. Implementation of patient educational programs is encouraged	D
20. Patients with peripheral nerve involvement and motor deficit(s) should routinely be referred to a physiotherapist	D
21. Patients should be advised to avoid tobacco smoke and irritants	D
22. Venous thromboembolic events and pulmonary embolism should be treated according to general guidelines for the management of thromboembolic disease; it is unknown whether anticoagulation should be prolonged in selected patients with persistent or recurring disease activity	D

EGPA: eosinophilic granulomatosis with polyangiitis (Churg–Strauss); ANCAs: anti-neutrophil cytoplasm antibodies; CT: computed tomography; EGPA: eosinophilic granulomatosis with polyangiitis (Churg–Strauss); ELISA: enzyme-linked immunosorbent assays; ENT: ear, nose & throat; HIV: human immunodeficiency virus; IVIg: intravenous immunoglobulins; LRA: leukotriene-receptor antagonists; NA: not applicable.

is now routine practice, even though eosinophilia in this infection is often mild. If the patient resides or has traveled in a region where human T-lymphocyte virus-1 is endemic, serologic testing for this retrovirus is recommended. When EGPA is suspected, IgE- and IgG-specific antibodies to *Aspergillus* species and *Aspergillus* species in sputum and/or bronchoalveolar lavage fluid should also be sought, especially when bronchiectasis is present. Notably, in untreated patients, normal serum IgE levels eliminate the diagnosis of allergic bronchopulmonary aspergillosis [22]. Paraneoplastic eosinophilia (namely in the setting of lung cancer, cervical cancer, Hodgkin's or non-Hodgkin's T-cell lymphoma) should also be investigated through patient and family history (tobacco smoking, colorectal cancer), physical examination, lactate dehydrogenase level, chest X-ray, abdominal ultrasound and, if necessary, high-resolution thoracoabdominal CT scan. Finally, patients with cutaneous lesions (e.g., skin rash and hives, eczema), hypergammaglobulinemia and/or cyclic recurrent angioedema (i.e., Gleich's syndrome) may have a lymphocytic variant reactive HE (formerly L-HES) [23]. In that specific population, lymphocyte immunophenotyping (to detect abnormal surface phenotypes including $CD3^-CD4^+$, $CD4^+CD7^-$ and $CD3^+CD4^-CD8^-$) and analysis of T-cell-receptor rearrangement are recommended, and should be performed in laboratories with appropriate expertise. Serum CCL17/TARC (thymus and activation-regulated cytokine) determination might also be useful in this setting but is not done routinely [24].

Hepatomegaly, splenomegaly, anemia, thrombocytopenia and/or the absence of response to glucocorticoids are suggestive of clonal (neoplastic) HE. The latter is a heterogeneous group comprising chronic eosinophilic leukemia (formerly the myeloproliferative variant of HES) and other myeloid neoplasms (e.g., chronic myeloid leukemia, systemic mastocytosis and myelodysplastic syndromes), which can be associated with HE [19]. Screening for serum vitamin B_{12} and tryptase levels is sensitive for neoplastic HE and is recommended for all patients [25,26]. When that diagnosis is suspected, testing for *PDGFRA*, *PDGFRB, FGFR1, BCR/ABL1* fusion genes and search for a Janus kinase-2 mutation could be helpful.

Idiopathic chronic eosinophilic pneumonia (formerly Carrington's disease) is also part of the differential diagnosis of EGPA because both entities may begin with chronic sinusitis, pulmonary infiltrates and peripheral blood HE. However, chronic eosinophilic pneumonia patients only rarely suffer from HE-associated systemic manifestations [27]. While the lung infiltrates of idiopathic chronic eosinophilic pneumonia may be located peripherally on chest imaging, this pattern is neither sensitive nor specific to chronic eosinophilic pneumonia and can also be observed in EGPA. The possible overlap of idiopathic chronic eosinophilic pneumonia and EGPA deserves further investigation, and these entities could be part of the same spectrum.

3 *Obtaining biopsies from patients with suspected EGPA is encouraged.*

While diagnostic criteria are lacking (a second Task Force paper addressing this topic is in preparation), diagnosing EGPA implies proven vasculitis or a strong clinical surrogate, but either can be difficult to obtain. Within the clinical context of asthma with eosinophilia, asthma with systemic manifestations or even eosinophilia with extrapulmonary disease, a biopsy demonstrating small- or medium-sized-vessel vasculitis (e.g., fibrinoid necrosis, leukocytoclasia or pauci-immune crescentic glomerulonephritis) and/or a strong clinical surrogate of vasculitis strongly supports a diagnosis of EGPA [28]. EGPA diagnosis implies a vasculitic feature but the selection of sites for biopsies depends on individual patient characteristics and the likelihood of safely obtaining tissue sample(s) that will be most definitive for a diagnosis. Skin, nerve and muscle are among the most common biopsied tissues, but endomyocardial, renal and gastrointestinal (GI) biopsies may also be useful.

4 *ANCA testing (with indirect immunofluorescence and ELISA) should be done for patients with suspected EGPA.*
A perinuclear immunofluorescent pattern with ELISA detecting antibodies to myeloperoxidase (MPO) is the most common EGPA ANCA-positivity finding. Together, positive immunofluorescence and ELISA are highly sensitive and specific for AAV diagnosis [29]. In the clinical context of asthma and eosinophilia, anti-MPO ANCA-positivity is highly suggestive of EGPA but, conversely, ANCA-negativity does not rule out its diagnosis. Importantly, a cytoplasmic ANCA-labeling pattern on immunofluorescence and ELISA detection of anti-proteinase-3 (PR3) antibodies have been reported in EGPA [4], but such results are quite unusual and, in this setting, an EGPA diagnosis should be reviewed critically.
ANCA-test results define EGPA-patient subgroups. Cohort-study findings suggest that ANCA status may reflect different EGPA phenotypes [4,5]. ANCA-positive patients are more likely to have a "vasculitic" phenotype with glomerulonephritis, mononeuritis multiplex and relapses. However, despite fewer relapses, the prognosis of ANCA-negative patients is poorer, possibly because of their high frequency of cardiomyopathy [30,31].

5 *There is currently no reliable biomarker to measure EGPA activity.*
Several groups have tried to assess the accuracy of biomarkers to define EGPA activity and predict relapses. Other than perhaps the total eosinophil count, common laboratory tests (e.g., serum IgE, erythrocyte sedimentation rate and C-reactive protein (CRP)) are not contributory [32]. IgE levels could be informative for patients with refractory asthma when contemplating omalizumab administration. Also, the eosinophil cationic protein was correlated with disease activity in small series [33,34] but longitudinal data are scarce [35].
Lastly, preliminary studies examined several novel biomarkers (e.g., CCCL17/TARC, IgG4 and CCL26/eotaxin-3) [36–39], but their routine determination is not yet recommended.

6 *Once EGPA is diagnosed, evaluating possible lung, kidney, heart, GI and/or peripheral nerve involvements is recommended.*
Asthma is almost always present at EGPA onset. However, some patients may develop asthma in the weeks following vasculitis onset. Thus, a complete pulmonary diagnostic evaluation, comprising baseline chest imaging (i.e., high-resolution CT scan which is more sensitive than plain radiography) and pulmonary function tests (at least spirometry) are recommended at the time of EGPA diagnosis. Complementary investigations should not delay treatment initiation for life-threatening manifestations. Any identified abnormalities in these investigations should subsequently be monitored according to the patients' clinical status [40].
Kidney, heart and/or GI involvements are associated with poor prognoses and mandate immunosuppressive therapy. Therefore, these organ manifestations should be diagnosed early and screened for regularly during follow-up [41].
Cardiac involvement is the leading cause of EGPA-patient deaths [3,31] and basic cardiac investigations (chest imaging, electrocardiography, transthoracic echocardiography, N-terminal pro-brain natriuretic peptide and troponin I measurements) are recommended. New cardiac imaging technique (e.g., cardiac magnetic resonance imaging and positron-emission-tomography scan) seem to be more sensitive than the above-mentioned investigations [42–46], but the clinical significance of abnormalities detected with those imaging modalities remains unclear. Asymptomatic MRI abnormalities are most likely heart involvement but should not yet engender treatment intensification (e.g. cyclophosphamide). Patients with symptoms suggestive of arrhythmia should undergo further investigation.
GI involvement, specifically ischemic disease, is predictive of poor outcomes. Patients with abdominal pain, nausea, vomiting, hematemesis, diarrhea, hematochezia and/or melena require radiologic and/or endoscopic investigations. However, because abdominal pain is almost always present in SNV-related GI involvement [47], routine screening of asymptomatic patients with abdominal imaging or endoscopy studies is not recommended.
Renal function tests and urinalysis (for examination of proteinuria and hematuria/casts) should be performed at disease onset and regularly during follow-up to screen for a renal disease flare, drug toxicity (e.g. cyclophosphamide) or help with drug–dose adjustments (cyclophosphamide and methotrexate). Ambulatory dipstick analysis of morning urine samples by the patient is encouraged, in addition to office or hospital-based renal function evaluations, urinalyses and protein/creatinine ratios.
Additional diagnostic procedures should be performed as indicated by symptoms or physical examination findings. Notably, electromyography and nerve-conduction studies should be ordered when clinically indicated (i.e., when myalgias, muscle weakness and/or peripheral neuropathy are present). Eye involvement is rare and systematic examination by an ophthalmologist at EGPA diagnosis is not mandatory.

7 *Definition of EGPA remission: the absence of a clinical systemic manifestation (excluding asthma and/or ear, nose & throat (ENT)).*
Systemic EGPA manifestations may have different clinical courses. ENT manifestations and/or asthma flares may not necessarily reflect vasculitis activity but are often part of the EGPA course [3,4]. Immunosuppressants other than glucocorticoids may control systemic EGPA features but not ENT manifestations and/or asthma. In accordance with some studies [3,4], the Task Force concluded that these symptoms be monitored separately. Most Task Force members concurred that the EGPA-remission definition excludes the control of asthma and/or non-specific ENT manifestations. Also, the experts were unable to define an upper eosinophil-count threshold during remission. The ideal definition of remission would be the absence of clinical symptoms and biologic abnormalities in patients weaned off glucocorticoids and immunosuppressants. Since such EGPA outcomes are rare (15.7% in one series (3)), the majority of Task Force members considered minimal prednisone and/or immunosuppressant dose(s) acceptable to define remission. The EULAR experts [2] concluded that the definition of remission could include a minimum prednisone dose of 7.5 mg/day to control systemic manifestations; however, that arbitrarily fixed dose is debatable.

8 *Definition of EGPA relapse: the new appearance or recurrence or worsening of clinical EGPA manifestation(s) (excluding asthma and/or ENT), requiring the addition, change or dose increase of glucocorticoids and/or other immunosuppressants.*
During the course of EGPA, asthma flares and/or ENT manifestations are frequent and multifactorial, and blood eosinophil counts may fluctuate. Isolated transient and fully reversible loss of asthma control with a clearly identified cause (e.g. viral infection), may occur in asthma of any cause, and should not be systematically considered an EGPA relapse. Most Task Force members considered that isolated asthma or sinusitis exacerbation with or without increased blood eosinophilia does not necessarily imply a relapse per se but, nonetheless, warrants therapy. These patients should be monitored closely because these symptoms may be early signs of a vasculitis flare.
Conversely, eosinophilia is not a mandatory criterion for diagnosing a flare. Indeed, glucocorticoids, which are the cornerstone of EGPA treatment, reduce the number of circulating eosinophils. In addition, eosinophilic activity may occasionally be organ-limited without blood eosinophilia.
The Task Force aimed to obtain a sharper definition of EGPA relapse but, given the lack of stringent criteria, this goal was not achieved.

9 *Use of glucocorticoids is appropriate to achieve EGPA remission; the dose prescribed should be ~1 mg/kg/day prednisone for patients with organ- or life-threatening manifestations [A].*

Glucocorticoids are the cornerstone of therapy for EGPA. In the presence of life-threatening symptoms, methylprednisolone pulses (7.5–15 mg/kg/day) should be administered. As induction therapy, we suggest starting prednisone at 1 mg/kg/day for 2–3 weeks, followed by gradual tapering (ideally down to 0.3 mg/kg/day after 3 months and 0.15 mg/kg/day after 6 months) to the minimal effective dose or, when possible, until withdrawal. The maintenance glucocorticoid dose should be adapted to tightly control each patient's needs to prevent relapses of systemic manifestations and control asthma. Optimally, this dose should be <7.5 mg/day to limit glucocorticoid-induced side effects [17]. However, in a recent series [3], approximately 85% of EGPA patients required long-term prednisone (mean dose 12.9 ± 12.5 mg/day) to control asthma, rhinitis and/or arthralgias, thereby highlighting the need for glucocorticoid-sparing therapies.

10 *Patients with life- and/or organ-threatening disease manifestations (i.e., heart, GI, central nervous system, severe peripheral neuropathy, severe ocular disease, alveolar hemorrhage and/or glomerulonephritis) should be prescribed a remission–induction regimen combining glucocorticoids and another immunosuppressant (e.g. cyclophosphamide) [B].*

The Five-Factor Score (FFS) is a prognostic tool that consists of 5 items, 4 of which [age >65 years, heart and GI (i.e., hemorrhage, infarction or pancreatitis), stabilized peak creatininemia >150 μmol/L, each accorded +1 point] are associated with poor prognoses, while the fifth (ENT manifestations) is associated with better outcomes and its absence is scored +1 [41]. Adjunctive cytotoxic drugs are recommended to treat FFS ≥ 1 high-risk EGPA patients. However, unlike other AAV for which several randomized–controlled trials have been conducted [48], no randomized–controlled-trial results are available to support this recommendation.

Furthermore, severe alveolar hemorrhage, eye involvement (albeit rare in EGPA) and fulminant mononeuritis multiplex can be life-threatening and/or carry poor functional prognoses. Thus, although they are not part of the FFS [41], immunosuppressant (including cyclophosphamide) use for these symptoms should be considered [31].

Cyclophosphamide may be equally effective as continuous oral therapy (2 mg/kg/day) or intravenous (IV) pulses. If pulse administration is chosen, the first 3 infusions (15 mg/kg or 0.6 g/m^2) should be given every 2 weeks, with a maximum of 1.2 g per infusion. Pulses 3–6 at 15 mg/kg or 0.7 g/m^2 can then be infused every 3 weeks. Cyclophosphamide doses should be adjusted to renal function. While pulse administration may be associated with more relapses [49], it might favor compliance and decrease long-term morbidity and mortality [50], but prospective data are scarce. As suggested by the preliminary CORTAGE trial results, patients ≥ 65 years with or without poor-prognosis factors might also benefit from lower immunosuppressant doses to avoid drug-related side effects [51].

Because serious side effects of cyclophosphamide may occur, physicians should strive to prevent them. Because of gonadal toxicity, semen cryopreservation and GnRH-analog treatment for women is recommended [52]. By analogy with granulomatosis with polyangiitis (Wegener's), *Pneumocystis jiroveci* pneumonia prophylaxis with co-trimoxazole (400 mg/day or 800 mg thrice weekly) should be considered [53,54]. Lastly, regular screening for drug-induced neutropenia is necessary.

11 *Maintenance therapy (with azathioprine or methotrexate) is recommended for patients with life- and/or organ-threatening disease manifestations after a remission–induction therapeutic regimen [C].*

In a prospective study assessing the benefits of glucocorticoid-&-cyclophosphamide induction for high-risk EGPA patients, overall survival without maintenance therapy reached 97% and 92% at 5 and 8 years, respectively [55]. However, relapse rates were also high, 73.8% or 85.7% respectively, depending on whether patients had received 6 or 12 cyclophosphamide pulses [55]. These observations suggested that, as with other AAV, EGPA patients would also benefit from maintenance therapy to avoid relapses and allow glucocorticoid tapering.

Maintenance therapy with an immunosuppressant can be started 2–3 weeks after the last cyclophosphamide pulse or a few days after oral cyclophosphamide. Unlike other AAV [56–58], no study has compared immunosuppressants for EGPA maintenance therapy. Since the CYCAZAREM trial (which did not include EGPA patients) demonstrated that azathioprine (2 mg/kg/day) was as effective as cyclophosphamide for preventing relapses, cyclophosphamide is now used to induce vasculitis remission but not for longer-term remission maintenance [56]. Other than azathioprine, methotrexate (10–30 mg/week, along with folic acid replacement, 10–30 mg/week) has also been used as a potent remission-maintenance agent for AAV [58]. The optimal duration of maintenance therapy remains unknown; 18–24 months following remission induction could be recommended. A recent study established that ANCA-positivity, cutaneous manifestations and a low eosinophil count at the time of EGPA diagnosis were predictive of relapse [3].

12 *Glucocorticoids alone may be suitable for patients without life- and/or organ-threatening disease manifestations; additional immunosuppression can be considered for selected patients for whom the prednisone dose cannot be tapered to <7.5 mg/day after 3–4 months of therapy or for patients with recurrent disease [C].*

In the CHUSPAN study, treatment of FFS = 0 EGPA and polyarteritis nodosa patients with glucocorticoids alone was effective, achieving a 5-year survival rate of 96.8%. However, one-third of the patients (especially those with peripheral neuropathy) eventually required a cytotoxic agent, suggesting that more patients might also benefit from early prescription of additional immunosuppression [31].

A recent retrospective study on FFS = 0 EGPA patients, who could not have their prednisone dose lowered to <7.5 mg/day after 3 months due to systemic manifestations and/or refractory asthma and who received additional immunosuppressants, suggested that these patients had low relapse rates and did not develop more serious infectious events than patients from previous series [17]. However, whether cytotoxic drugs should be added to regimens for patients unable to taper prednisone for asthma and/or ENT manifestations remains unclear. The CHUSPAN 2 trial (ClinicalTrials.gov NCT00647166) is currently evaluating the effectiveness of adjunctive azathioprine for FFS = 0 EGPA patients. Until additional data become available, immunosuppressant prescription for this purpose should be discussed on an individual basis.

13 *Plasma exchanges are generally not effective in EGPA but can be considered for selected ANCA-positive patients with rapidly progressive glomerulonephritis or pulmonary–renal syndrome [D].*

Two randomized–controlled trials published in the mid-1990s that enrolled EGPA patients with or without factors predicting increased mortality risk failed to demonstrate that plasma exchange adjunction to standard therapy improved survival [59,60]. However, whether plasma exchanges could be beneficial for selected patients remains unknown. Currently available data do not support their routine use. They should only be considered for patients with severe diffuse alveolar hemorrhage [61] and rapidly progressive, severe renal insufficiency. In this setting, among patients with AAV, but not EGPA, plasma exchanges attenuated end-stage renal disease and enhanced renal recovery 12 months after a flare [62], but long-term benefits are unclear [63]. The use of plasma exchanges for severe AAV remains under active investigation [64].

14 *Rituximab can be considered for selected ANCA-positive patients with renal involvement or refractory disease [C].*
Rituximab, a chimeric monoclonal antibody directed against the B-lymphocyte, cell-surface CD20 protein, has been shown to be as effective as cyclophosphamide at inducing remission of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis [65,66]. For maintenance, a prospective study's results showed that rituximab was superior to azathioprine as maintenance therapy [67]. However, those 3 trials did not include EGPA patients. Data on rituximab use for EGPA, limited to case reports [68,69] and case series [70–72], suggest that it is effective and safe. Remission rates seemed to be higher for ANCA-positive than ANCA-negative patients [72]. However, despite concomitant administration of IV glucocorticoids, severe bronchospasms immediately after the first infusion have been reported [73]. In addition to B-cell depletion, rituximab might have other mechanisms of action. Notably, it was shown to diminish T-cell interleukin (IL)-5 production [74]. More information is needed regarding rituximab use for EGPA. Until then, although not licensed for EGPA, using rituximab seems reasonable for ANCA-positive patients with renal involvement or severe refractory disease, despite conventional therapy, for whom traditional cytotoxic agents are contraindicated or undesirable (e.g., to prevent cyclophosphamide-induced gonadal toxicity in younger patients and/or urinary bladder toxicity in those who have already received high cumulative cyclophosphamide doses).

15 *IV immunoglobulins (IVIg) can be considered a second-line therapy for patients on glucocorticoids (and/or other immunosuppressants) with EGPA flares refractory to other treatments or during pregnancy; in the context of drug-induced hypogammaglobulinemia with severe and/or recurrent infections, Ig-replacement may be considered [C].*
Several case reports demonstrated the efficacy of high-dose IVIg (i.e., 2 g/kg for 2–5-day cycles which can be repeated every 3–4 weeks) in naïve and previously treated EGPA patients [75,76]. In a small Japanese case series, EGPA-related heart involvement and peripheral neuropathy seemed to respond well to this therapeutic strategy [77]. IVIg were also effective during pregnancy, when glucocorticoids and azathioprine are the only authorized immunosuppressants [78]. A small study on 9 patients suggested that, when added to conventional therapy, synchronized monthly plasma exchange followed by IVIg cycles of could be beneficial [79]. Furthermore, although no strong data support this recommendation, Ig replacement may be considered for patients with severe and/or recurrent infections and drug-related hypogammaglobulinemia.

16 *Interferon-alpha may be reserved as a second- or third-line therapy for selected patients [C].*
Although interferon-alpha achieved acceptable remission rates in a small, prospective, open-label study [80], its effect was transient and relapses were frequent after its discontinuation [81]. Because of numerous side effects and development of new promising biologics, interferon-alpha should be considered a second- or third-line drug.

17 *Leukotriene-receptor antagonists (LRA) can be prescribed, if needed, for EGPA patients [B].*
Several early series suggested that LRA could have triggered or caused EGPA [82,83]. That attribution remains controversial and review of available evidence suggests that LRA do not directly cause EGPA [84], and that EGPA onset after starting an LRA might be coincidental to EGPA worsening or as a result of glucocorticoid-tapering unmasking symptoms [85,86].
Whether LRA can be safely prescribed to EGPA patients remains controversial but can be tried, if necessary, to treat asthma, with close monitoring. Further prospective studies are needed to address this issue.

18 *Vaccination with inactivated vaccines and against influenza and pneumococci should be encouraged; live-attenuated vaccines are contraindicated in patients taking immunosuppressants and/or ≥20 mg/day of prednisone [D].*

Table 3
Research topics.

Genetic studies on EGPA
Development of animal models
Identification of markers for early identification of patients with late-onset asthma who will develop EGPA
Identification of reliable diagnostic biomarkers to differentiate eosinophilic asthma vs. HES vs. vasculitis
Identification of reliable biomarkers to differentiate asthma flares from vasculitis flares
Development of tools that specifically address clinical aspects of EGPA
Improving maintenance treatment to prevent relapses and reduce the glucocorticoid burden
Optimize treatment(s) for patients with persistent asthma (mepolizumab vs. omalizumab vs. lebrikizumab)
Development of an alternative to cyclophosphamide for patients with FFS ≥ 1 EGPA
Investigations of other drugs that are used to treat some forms of HES (e.g. tyrosine-kinase inhibitors)
Determine the place of ANCA monitoring
Optimize the diagnostic strategy for and treatment of EGPA-related heart involvement
Implementation of an international registry of EGPA patients

ANCAs: anti-neutrophil cytoplasm antibodies; EGPA: eosinophilic granulomatosis with polyangiitis (Churg–Strauss); FFS: Five-Factor Score; HES: hypereosinophilic syndromes.

Exogenous factors might trigger EGPA. A few case reports, but no case–control study, described EPGA onset after vaccination [87,88] or allergic desensitization [89]. Infections are a burden in systemic AAV [90] and represent approximately 25% of the causes of deaths during the first year after their onset [91]. In a large population of vasculitis (including EGPA) patients, vaccination against A/H1N1 influenza with a non-adjuvant vaccine was effective and well-tolerated. No patient relapsed following vaccination [92,93] but some patients' eosinophil counts rose. To date, the benefit/risk ratio seems to favor vaccination of vasculitis patients. Other than live-attenuated vaccines, which are contraindicated in patients taking immunosuppressants and/or ≥20 mg/day of prednisone [94], the Task Force recommends that EGPA patients be vaccinated in the same manner as the general population, except possibly patients who had an EGPA flare after a vaccination. In addition, vaccination against pneumococci and yearly vaccination against influenza should be encouraged.

19 *Implementation of patient educational programs is encouraged [D].*
In a vasculitis referral center, educational programs have been effective at improving patients' knowledge of their disease [95]. Thus, such programs may favor earlier diagnoses of flares and treatment side effects, and contribute to better outcomes.

20 *Patients with peripheral nerve involvement and motor deficit(s) should routinely be referred to a physiotherapist [D].*
Although no specific data are available on physiotherapy and vasculitis, the Task Force recommends, based on experience with other acquired peripheral neuropathies [96,97], that patients with peripheral nerve involvement and motor deficit(s) be routinely referred to a physiotherapist.

21 *Patients should be advised to avoid tobacco smoke and irritants [D].*
Consistent with the guidelines for asthma diagnosis and management [98], we recommend that EGPA patients avoid tobacco smoke and irritants, which may trigger asthma flares and reduce pulmonary function.

22 *Venous thromboembolic events (VTE) and pulmonary embolism should be treated according to general guidelines for the management of thromboembolic disease; it is unknown whether anticoagulation should be prolonged in selected patients with persistent or recurring disease activity [D].*
AAV are associated with an increased risk of VTEs, which occur mainly during active-disease phases [99]. In the largest published EGPA-patient cohort [3], no VTE-frequency difference was observed between ANCA-negative and ANCA-positive patients (20% vs. 8%, respectively, $P = 0.77$). No specific guidelines are available for VTEs and/or pulmonary

embolus treatment in AAV patients. The European Society of Cardiology guidelines for the management of pulmonary embolism and deep-vein thromboses recommend 3–6 months of anticoagulation after a VTE [100]. By analogy with HES [101], and in light of the thrombotic pathophysiologic mechanisms involved in EGPA, it remains unknown whether anticoagulation duration should be prolonged in selected patients with persistent or recurrent disease activity.

4. Discussion

The Task Force members acknowledge that some of their recommendations have low evidence levels because they were derived from existing data on EGPA-related diseases, rather than EGPA itself, and/or are opinion-based. Thus, future (especially prospective) EGPA-specific studies are needed.

First, mepolizumab, a humanized monoclonal antibody targeting IL5, the major eosinophil-survival factor, is effective against eosinophilic asthma [102,103] and, thus, holds promise for EGPA [104]. To date, the results of only 2 pilot studies showed that mepolizumab successfully treated refractory EGPA, thereby achieving glucocorticoid-sparing [105], and maintained remission without further conventional immunosuppression [106]. An international randomized placebo-controlled trial on EGPA is ongoing (ClinicalTrials NCT02020889); its results are eagerly awaited.

Next, whether ANCA-negative and ANCA-positive EGPA patients indeed represent the same disease entity and whether these subgroups would benefit from distinct therapeutic strategies are debatable. Future studies and updated recommendations should address these issues.

Lastly, these recommendations should not be considered definitive guidelines but rather as consensus statements derived from up-to-date data on EGPA. They are intended to give physicians tools for effective, individualized management of EGPA patients and to serve as a starting point for future EGPA-targeted research. We identified 13 high-priority research topics (Table 3) and regular updates will be necessary to maintain recommendation accuracy.

Over the past several decades, much has been achieved and good progress made in understanding EGPA. Nevertheless, these recommendations and the data supporting them also reveal that more research is needed to continue to improve management of patients with this complex disease.

5. Conflict of interests

Matthieu Groh: congress registration funded by LFB.

Chiara Baldini: fees paid to the institution by GSK for being an investigator in a clinical trial on mepolizumab for EGPA.

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