

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis.

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8 2021 08 7 2021 73 8 494881 1088 1105 05 08 2025 13 08 2025 13 08 2025 14 08 2025 This file is available for text mining. It may also be used consistent with the principles of fair use under the

copyright law. Objective: To provide evidence-based recommendations and expert guidance for the management of patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV): granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Clinical questions regarding the treatment and management of AAV were developed in the Patient population, Intervention, Comparator, and Outcome (PICO) format (47 for GPA/MPA, 34 for EGPA). Systematic literature reviews were conducted for each PICO question. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology to assess the quality of evidence and formulate recommendations. Each recommendation required consensus from at least 70% of the voting panel.

We present 26 recommendations and 5 ungraded position statements for GPA/MPA, and 15 recommendations and 5 ungraded position statements for EGPA. This guideline provides recommendations for remission induction and maintenance therapy, and adjunctive treatment strategies in GPA, MPA, and EGPA. These recommendations include the use of rituximab for remission induction and maintenance in severe GPA and MPA, and the use of mepolizumab in non-severe EGPA. All recommendations are conditional due in part to the lack of multiple randomized control trials and/or low-quality evidence supporting the recommendations

This guideline presents the first recommendations endorsed by the American College of Rheumatology and Vasculitis Foundation for the management of AAV and provides guidance to health care professionals on how to treat these diseases.

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are comprised of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss). These diseases affect small- and medium-sized vessels and are characterized by multisystem organ involvement.

GPA is characterized histologically by necrotizing granulomatous inflammation in addition to vasculitis. Common clinical manifestations include destructive sino-nasal lesions, pulmonary nodules, and pauci-immune glomerulonephritis. GPA is most commonly associated with cytoplasmic-staining ANCA and antibodies to proteinase 3. Among European populations, the prevalence ranges from 24 to 157 per million, with the highest prevalence reported in Sweden and the UK.[1]

MPA is characterized histologically by vasculitis without granulomatous inflammation. Common clinical manifestations include rapidly progressive pauci-immune glomerulonephritis and alveolar hemorrhage. MPA is most commonly associated with perinuclear staining ANCA and antibodies to myeloperoxidase. The prevalence of MPA ranges from 0 to 66 cases per million among European countries and 86 cases per million in Japan.[1 , 2]

EGPA is characterized histologically by eosinophilic tissue infiltration in addition to vasculitis. Common clinical manifestations include asthma, peripheral eosinophilia, and peripheral neuropathy. Only 40% of patients produce detectable ANCA. The overall prevalence of EGPA in European populations has been estimated to range from 2 to 38 cases per million.[1 , 3]

Prior to the use of alkylating agents, survival with these diseases was quite poor (e.g., median survival of patients with GPA at ~5 months).[4] Current treatment regimens have reversed this poor prognosis, but treatments are still associated with toxicity. Recent clinical trials have investigated the efficacy and toxicity of both biologic and non-biologic immunosuppressive agents for the treatment of AAV. Observational studies have provided additional insight regarding management strategies for these diseases. Therefore, this guideline was developed to provide evidence-based recommendations for the treatment and management of adults and children with GPA, MPA, and EGPA. Although this guideline may inform an international audience, these

recommendations are developed for health care providers within the United States.

This guideline follows the American College of Rheumatology (ACR) guideline development process (<https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines>) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations[5 , 6]. ACR policy guided the management of conflicts of interest and disclosures (<https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis>). Supplementary Appendix 1 presents a detailed description of the methods.

Briefly, the Literature Review team undertook systematic literature reviews for pre-specified questions addressing specific clinical populations, interventions, comparators, and outcomes (PICO). An in-person Patient Panel of 11 individuals with different types of vasculitis, moderated by a member of the Literature Review team, reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences. The patient panel included 4 patients with GPA, 1 patient with MPA, and 2 patients with EGPA. The Voting Panel, comprised of 14 physicians and 2 patients, reviewed the Literature Review team's evidence summaries and, bearing in mind the Patient Panel's deliberations, formulated and voted on recommendations. The voting panel was assembled for the ACR and Vasculitis Foundation's broad effort to develop recommendations for 7 forms of systemic vasculitis: giant cell arteritis, Takayasu arteritis, polyarteritis nodosa, Kawasaki disease, and the 3 AAV presented in this manuscript. The physicians on this panel included rheumatologists who could provide insight for all of these diseases, and did not to include other subspecialists who would not have experience with many of the other vasculitides addressed in this effort (e.g., pulmonologists who would not have experience with large- or medium-vessel vasculitis). The literature review team chair was a nephrologist. The patients on the voting panel presented the views of the patient panel, which consisted of patients with different types of vasculitis.

Each recommendation required consensus from at least 70% of the voting panel.

How to interpret the recommendations: A strong recommendation is usually supported by moderate or high-quality evidence (e.g., multiple randomized controlled trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. In rare instances, a strong recommendation may be based on low or very low certainty evidence. For example, an intervention may be strongly recommended if it is considered benign, low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may be strongly recommended against if there is high certainty that the intervention leads to more harm than the comparison with low or very low certainty about its benefit [7].

A conditional recommendation is usually supported by lower quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of the patients, but the alternative is a reasonable consideration. Conditional recommendations always warrant a shared decision-making approach. We specify some conditions under which the alternative may be considered.

In some instances, the committee found that the evidence for a particular PICO question did not support a graded recommendation or did not favor one intervention over the other. However, the voting panel believed the PICO question addressed a commonly encountered clinical question and thus felt that providing guidance for this question was warranted. For these situations, we present 'ungraded position statements' which reflects general views of the voting panel.

In this evidence-based guideline, we explicitly use the best evidence available and present it for the clinician and reader[8]. In some instances, this includes randomized trials directly comparing the

interventions under consideration. The GRADE system rates evidence that comes exclusively from the collective experience of the Voting Panel and patient panel members as “very-low-quality” evidence.

For each recommendation, Supplementary Appendix 2 provides details regarding the PICO questions and GRADE evidence tables.

For the evidence report for GPA and MPA, 729 articles were reviewed to address 47 PICO questions. For the evidence report for EGPA, 190 articles were reviewed to address 34 PICO questions.

GPA and MPA are recognized as different diseases for which disease-specific management approaches exist. However, many recommendations and ungraded position statements consider GPA and MPA together because pivotal trials have enrolled both groups and presented results for these diseases together. Thus, we present recommendations and ungraded position statements applicable to both GPA and MPA as well as recommendations and ungraded position statements only applicable to GPA. All recommendations for GPA/MPA are conditional, due in part to a lack of multiple randomized control trials supporting the recommendations. The complete list of studies reviewed to form the recommendations is provided in the evidence report (Supplementary Appendix 2). Given that these diseases affect multiple organ systems, collaboration between rheumatologists, nephrologists, pulmonologists, and otolaryngologists can enhance the care of patients with GPA and MPA.

Table 1 presents the definitions for disease states described in the Recommendations and Ungraded Position Statements, including definitions of severe and non-severe disease, and the dosing regimens of medications used for remission induction and maintenance. Table 2 presents the PICO questions contributing to each Recommendation and Ungraded Position Statement and subsequent discussion, along with level of evidence. Figure 1 represents a flowchart of key recommendations for the treatment of GPA and MPA.

Both rituximab and cyclophosphamide, in combination with glucocorticoids, have been used for remission induction for GPA and MPA. Rituximab (RTX) has been shown to provide similar benefits to cyclophosphamide (CYC) for remission induction in a randomized controlled trial [9]. Although the current cumulative doses of CYC used are less than previous regimens, resulting in less toxicity per treatment course, RTX is still preferred. since RTX is considered less toxic than CYC..A single course of CYC can carry substantial risks such as neutropenia, bladder injury, and the small but present potential for infertility which can be devastating to a young patient. Risks of malignancy and infertility increase when repeated courses of CYC are used. RTX was also preferred by the patient panel. Retrospective studies suggest that the two remission induction regimens for rituximab used in adults, 375 mg/m² every week for 4 weeks (FDA-approved dosing schedule) and 1000 mg on days 1 and 15, are equally efficacious. The choice between these two regimens should be guided by patient preferences and values.

CYC (dosing provided in Table 1) may be used when RTX needs to be avoided or when patients have active disease despite use of RTX. It remains controversial whether CYC should be preferred for certain types of severe disease, such as acute renal failure (e.g., serum creatinine > 4.0 mg/dL). Clinicians can use either intravenous pulse or daily oral CYC [10 , 11]. For adults, the decision between these two options should be based on patient and physician preferences. In children, intravenous CYC may be preferred to facilitate compliance and limit toxicity. Data regarding the efficacy of combined CYC and RTX therapy for remission induction remains limited [12], and potential toxicity of this combination remains a concern.

The combination of RTX with CYC is not widely used in the US, and its efficacy compared to RTX or CYC alone is not established. This combination remains under study (Clinicaltrials.gov NCT03942887) at this time.

Plasma exchange should not be initiated for all patients with active glomerulonephritis but can be considered for patients at higher risk of progressing to end-stage kidney disease (ESKD) and accept a potential increased risk of infection.

The recommendation is supported from data from the two largest trials of plasma exchange for the treatment of glomerulonephritis in AAV. The first trial, which required a serum creatinine ≥ 5.8 mg/dL for entry, showed that plasma exchange decreased the risk of ESKD but did not decrease mortality [13 , 14]. In a more recent randomized trial of plasma exchange in AAV [15], the addition of plasma exchange to conventional remission induction therapy did not improve the composite outcome of ESKD or death; a decrease in ESKD was observed but the result was not statistically significant (HR 0.81, 95% CI 0.57–1.13).

However, combined data from these two trials (see Supplemental Appendix 2) show that there is probably decreased ESKD in patients with glomerulonephritis who received PLEX compared to those who did not (HR 0.72 [95% CI 0.53– 0.98], moderate certainty). The benefit was most pronounced in patients at the highest risk of ESKD (118 fewer cases of ESKD per 1,000 cases of active glomerulonephritis [95% CI 217 fewer to 7 fewer]), although no difference in mortality was demonstrated (RR 1.15 [95% CI 0.78, 1.70], moderate certainty). Among four trials of plasma exchange in AAV, a higher risk of severe infection was observed with plasma exchange (RR 1.19 [95% CI 0.99, 1.42], moderate certainty).

These findings suggest that for patients with a low risk of progressing to ESKD, the risk of plasma exchange may outweigh the benefit while in patients at higher risk of progression to ESKD, the decrease in risk of progressing to ESKD could outweigh the increased risk of serious infection with plasma exchange. Thus, the voting panel does not recommend plasma exchange for all patients with active glomerulonephritis but favors consideration of plasma exchange for patients at higher risk of progression to ESKD. Factors that could influence whether plasma exchange is initiated include the patient's kidney function upon presentation, rate of loss of kidney function, response to remission induction therapies, and the patient's ability to tolerate serious infections.

Plasma exchange remains advisable in patients with GPA or MPA who also have anti-GBM disease.

Two trials evaluated the use of plasma exchange in patients presenting with alveolar hemorrhage, and no differences in mortality or remission rates were observed. Thus, plasma exchange does not have an established benefit for patients with alveolar hemorrhage, and is associated with an increased risk of serious infection (Recommendation 2). Plasma exchange may be considered for certain patients with active glomerulonephritis (Recommendation 2), or patients who are critically ill and whose disease is not responding to recommended remission induction therapies (i.e., plasma exchange as “salvage” or “rescue” therapy).

Plasma exchange remains advisable in patients with GPA or MPA who also have anti-GBM disease.

There are no trials comparing the efficacy of pulse intravenous to high dose oral glucocorticoids. Higher doses of glucocorticoids (such as pulse glucocorticoids) are generally used for patients with organ- or life-threatening disease manifestations but may be associated with an increased risk of infection [16].

A recent study [15] reported a reduced-dose glucocorticoid regimen provided similar benefit to a standard-dose regimen for the composite outcome of end-stage renal disease or death and was associated with a decreased risk of infection. Given the known toxicities associated with long-term glucocorticoid use, minimizing glucocorticoid exposure is critical to improving outcomes. Glucocorticoid dosing may be individualized for each patient. Of note, the reduced-dose regimen started with pulse methylprednisolone (3 daily pulses for maximum total dose of 3 g) and one week

of high-dose oral glucocorticoids. The standard and reduced-dose glucocorticoid regimen used in this study is provided in Supplementary Appendix 3 .

Non-severe GPA is defined as GPA without life- or organ-threatening manifestations (Table 1). Methotrexate (MTX[11]), RTX and CYC are effective at inducing remission in this patient group. However, like severe GPA, non-severe GPA can be a chronic disease that requires multiple courses of therapy. Thus, the voting panel favored using therapies with potentially less toxicity before utilizing therapies with potentially more toxicity. Therefore, MTX is preferred due to the greater toxicity of CYC. MTX is currently recommended over RTX because of the larger body of evidence and clinical experience with MTX use for this group of patients; a clinical trial is needed to compare their efficacy. RTX may be preferred in specific clinical situations, including patients with hepatic or renal dysfunction, recurrent relapses on MTX, or concerns regarding compliance.

MTX with glucocorticoids is recommended to minimize glucocorticoid exposure and toxicity. Overall, there are few clinical situations where treatment with glucocorticoids alone may be considered (e.g., arthralgias, or inability to tolerate other remission maintenance therapies), and close monitoring is needed should this treatment strategy be employed.

Use of MTX for remission induction in this patient group is supported by more data[11], but azathioprine (AZA) and mycophenolate mofetil (MMF) can be considered. Comparative effectiveness trials are needed to evaluate the efficacy of MTX, AZA, and MMF for remission induction in active non-severe GPA. Clinical factors may influence the medication selected. For example, MTX should be used with caution or avoided in patients with moderate to severe renal insufficiency. AZA is the preferred agent in pregnant patients or in patients who cannot tolerate MTX or MMF. MTX or MMF is indicated in patients with total thiopurine-S-methyltransferase deficiency or high risk TPMT and/or NUDT15 genotypes.

MTX is considered more effective than sulfamethoxazole/trimethoprim (SMX/TMP) for remission induction given previous experience suggesting MTX is more effective than SMX/TMP for remission maintenance[17]. Low-dose SMX/TMP may be given concurrently with immunosuppressive agents to prevent *Pneumocystis jirovecii* pneumonia (see GPA/MPA Recommendation 24).

RTX is associated with a lower relapse rate than AZA when used for remission maintenance after remission induction with CYC[18] MTX and AZA have comparable efficacy for remission maintenance.[19] Thus, RTX is favored over MTX or AZA. However, more long-term safety data is available for MTX and AZA, and cost and other factors may limit RTX use.

Different doses of RTX have been used for remission maintenance, including 500 mg IV every 6 months[18] (FDA-approved), 1000 mg IV every 4 months [20], and 1000 mg IV every 6 months [21]. No comparative trials have been conducted. Thus, the optimal dose of RTX for remission maintenance remains uncertain.

If MTX or AZA is being considered for remission maintenance, the patient's clinical situation, preferences, and values should guide selection between them, given their comparable efficacy.

In one randomized trial, patients who received RTX for remission maintenance based on changes in CD19 B cell counts and/or ANCA titers had similar rate of relapse as those receiving RTX on a scheduled dose. However, this study was limited by the small sample size and there were wide confidence intervals for the effect size[22]. This recommendation is based on part on the experience and expertise of the voting panel, which recognizes that flares can occur when patients are CD19 B-cell depleted and/or tests for ANCA are negative. Thus, CD19 B cell counts or ANCA titers may not accurately indicate the potential for a patient's disease to flare.

MTX and AZA are equally efficacious for remission maintenance [19]. AZA is favored over MMF because the relapse rate for MMF was higher than AZA when studied for remission maintenance[

23]. MMF may still be considered in those unable to tolerate or with contraindications to MTX, AZA, or rituximab (GPA/MPA Recommendation 9).

MTX or AZA is recommended over leflunomide due to the data supporting and clinical experience using MTX and AZA for remission maintenance. The data and clinical experience with leflunomide are more limited. In the one clinical trial comparing leflunomide to MTX[24], leflunomide use had a decreased rate of relapse but a higher rate of drug withdrawal. The trial used a leflunomide dose of 30 mg/day, which may have contributed to toxicity.

The voting panel strongly favored the use of MTX or AZA over SMX/TMP but this recommendation is conditional due to the lack of sufficient high-quality evidence comparing the two treatments.

SMX/TMP may have benefit for patients with sino-nasal involvement[25] but its use potentially increases toxicity (e.g., severe hypersensitivity reactions) and medication burden. SMX/TMP may still be indicated for prophylaxis against *Pneumocystis jirovecii* pneumonia (see GPA/MPA Recommendation 24). There is a potential drug interaction between MTX and SMX/TMP when SMX/TMP is dosed at 800 mg/160 mg twice a day. The SMX/TMP dose used for *Pneumocystis* prophylaxis is generally tolerated, but its use should be monitored when used in conjunction with methotrexate.

Immunoglobulin supplementation at replacement doses (e.g., 400–800 mg/kg/month) should be considered if patient has hypogammaglobulinemia and is experiencing recurrent infections. Immunoglobulin supplementation can also be considered for patients with hypogammaglobulinemia without recurrent infections but with impaired vaccine responses.[26] These considerations should be made in collaboration with an allergist/immunologist.

The optimal duration of remission maintenance therapy is not well-established. Although clinical trials have typically administered remission maintenance therapy for at least 18 months, patients may benefit from continuing remission maintenance therapy longer[27]. The patient panel favored remission maintenance therapy for at least 18 months, and potentially a longer duration depending on patient specific factors. Factors to be considered include previous relapse history, extent of organ involvement, and disease characteristics such as ANCA status (with PR3-ANCA positive patients more likely to relapse).[28]

The optimal duration of glucocorticoid therapy for GPA/MPA is not well established. The immunosuppressive effects of glucocorticoids contributing to disease control should be balanced with the toxicities associated with its use. Overall, patients expressed a desire to minimize the glucocorticoid dose as much as possible but recognize that some patients may require low dose glucocorticoid long-term. Screening for toxicities of glucocorticoid use (e.g., bone mineral density testing for osteoporosis) should be conducted.

RTX is more effective than oral CYC for re-induction of remission among patients who previously received CYC and then relapsed, based on subgroup analysis of a randomized controlled trial[9]. In addition, the cumulative toxicity of CYC raises concerns for repeated use of this agent.

Multiple factors can influence whether RTX or CYC (IV or oral) is used, such as time since last RTX infusion and cumulative CYC dose. CYC is recommended if the patient recently received RTX, while a remission induction dose of RTX may be effective if an extended period has passed since the last RTX infusion. As standard for remission induction, these agents should be used in conjunction with glucocorticoids.

Disease refractory to remission induction therapy is rare, and there is little data to guide treatment recommendations. Practitioners should evaluate whether other conditions such as infection could be mimicking vasculitis. However, if a patient's disease is refractory to one remission induction therapy, it is important to change the remission induction strategy. We recommend changing to the

other remission induction agent prior to using combination therapy.

Intravenous immunoglobulin (IVIg) should not be used routinely to treat GPA/MPA but can be considered at treatment doses (e.g., 2 g/kg) as adjunctive therapy for short term control while waiting for remission induction therapy (i.e., rituximab or cyclophosphamide) to become effective (per Recommendation 17)[29].

We suggest collaborating with an otolaryngologist with expertise in treating AAV to determine whether these interventions should be employed.

To optimize surgical outcomes, reconstructive surgery should be performed after a period of sustained remission by an otolaryngologist with expertise in treating GPA. [30 , 31]

Patients with subglottic or endobronchial stenoses should be managed with an otolaryngologist or pulmonologist, respectively, with expertise in management of these lesions. Immunosuppression is recommended for initial treatment of active inflammatory stenoses, and is usually comprised of glucocorticoids and other agents[32], and the degree of immunosuppression utilized may be based on the severity of other disease manifestations. Surgical dilation with intralesional glucocorticoid injection may be more appropriate for stenoses that are long-standing, fibrotic, or not responsive to immunosuppression. [32 – 34] Surgical dilation with intralesional glucocorticoid injection concurrent with medical treatment may also be considered as initial therapy for stenoses that require immediate intervention (e.g., critical narrowing).

Immunosuppression (with remission induction followed by remission maintenance) is almost always the initial treatment of choice for these lesions[35 , 36]. While these lesions tend to respond primarily to glucocorticoids, other agents are also usually used in hopes of having a glucocorticoid sparing effect. Debulking surgery may be considered if there is an urgent need for decompression, for example acute visual loss due to optic nerve compression or other life/organ-threatening compression.

Increases in ANCA titers/levels are only modestly informative as an indicator of disease activity[37] and are not reliable predictors of disease flares for individual patients. Increasing immunosuppression based on changes in ANCA titers/levels alone can result in unnecessary immunosuppression resulting in adverse events. Persistence of ANCA positivity does not necessarily indicate that continued immunosuppression is required. Instead, treatment decisions should be based on a patient's clinical symptoms in conjunction with diagnostic studies (e.g., laboratory, imaging, biopsy findings).

Prophylaxis to prevent *Pneumocystis jirovecii* pneumonia is routinely used with CYC treatment. [38] The prescribing information for RTX recommends prophylaxis for *Pneumocystis jirovecii* pneumonia for at least 6 months after the last RTX dose for patients with GPA or MPA. While many on the voting panel felt strongly that patients with GPA or MPA on CYC or RTX should receive prophylaxis against *Pneumocystis jirovecii* pneumonia, this recommendation is conditional given the lack of moderate or high-quality evidence directly addressing this question and the potential toxicity of the medications used for prophylaxis. Prophylaxis against *Pneumocystis jirovecii* pneumonia should also be considered for patients taking moderate-dose glucocorticoids (e.g., > 20 mg/day) or higher in combination with MTX, AZA, or MMF[38]. Prophylaxis is less commonly used in younger children receiving RTX but should be considered.

Outcomes of kidney transplantation in patients with ANCA associated vasculitis are similar to patients receiving transplants for other reasons, with relapses in the transplanted kidney being rare[39 , 40]. GPA and MPA in remission should not be considered a contraindication to kidney transplantation, but these patients should be monitored for relapse after transplantation.

IVIg should not be used routinely to treat GPA/MPA (GPA/MPA Recommendation 19). However, in the rare instances where patients with active disease may not be able to receive conventional immunosuppressive therapy (e.g., sepsis or pregnancy), IVIg can be used as a short-term intervention until conventional remission induction therapies can be used.[29]

AAV is associated with an increased risk of venous thrombotic events, including both deep vein thromboses and pulmonary emboli.[41 , 42] Venous thromboembolic events that occur in a patient with active disease and no other risk factors can be considered a provoked event with a transient risk factor (assuming subsequent disease control). Thus, short-term instead of life-long anticoagulation may be considered.

EGPA is characterized by diverse features, including asthma/allergic rhinitis, peripheral and tissue eosinophilia, and vasculitis. As these clinical features can potentially have differing responses to treatment, the management approach is typically based on a patient's disease features and their severity. The recommendations presented here focus primarily on the use of immunosuppressive medications to treat the vasculitic manifestations of EGPA. However, asthma and allergic manifestations are a significant component of EGPA, and measures directed towards these, including inhaled therapies and allergen avoidance, play an important role in management. Collaboration between rheumatologists, asthma/allergy specialists, and other medical disciplines can enhance the care of patients with EGPA.

In contrast to GPA/MPA, there have been very few randomized controlled trials conducted to date in EGPA. These recommendations/statements therefore reflect reliance on lower quality (i.e., indirect) evidence, including expert opinion.

Table 1 presents the definitions for the disease states and dosing regimens for medications described in the Recommendations and Ungraded Position Statements. Table 3 presents the PICO questions contributing to each Recommendation and Ungraded Position Statement and subsequent discussion, along with the level of evidence. Figure 2 represents a flowchart of key recommendations for the treatment of EGPA.

There are no data to support favoring either pulse intravenous or high-dose oral glucocorticoids over the other option in active, severe EGPA. Which approach to use should be influenced by individual patient factors. In either instance, glucocorticoids should be combined with a non-glucocorticoid immunosuppressive agent such as cyclophosphamide or rituximab (Ungraded Position Statement B).

CYC has been more commonly used for remission induction for patient with active severe EGPA given the experience with CYC with other forms of vasculitis.[43]. Increasing experience with RTX in GPA/MPA has also led more patients with EGPA to be treated with RTX, and case-series suggest that RTX may also have efficacy for active, severe disease.[44] Given the comparative effectiveness of CYC and RTX for EGPA is unknown, the voting panel felt both CYC and RTX could be considered for remission induction with active, severe EGPA. CYC would be preferred for patient with active cardiac involvement given the increased experience with CYC as cardiomyopathy has been found to be the main independent predictor of death in EGPA (25, 26). CYC can also be considered for patients who are ANCA negative and have severe neurologic or gastrointestinal manifestations. RTX may be considered in patients with a positive ANCA, active glomerulonephritis, prior CYC treatment, or at risk of gonadal toxicity from CYC.

The efficacy of mepolizumab in severe EGPA has not been established, as patients with active severe disease were excluded from the randomized trial[45]. CYC or RTX would be recommended over mepolizumab in this setting.

A range of immunosuppressive agents may be considered in the treatment of active, non-severe EGPA, all of which are used with glucocorticoids. The clinical profile of these non-severe EGPA

patients includes predominantly asthma, sinus disease, and non-severe vasculitis. While there is significant clinical experience with MTX, AZA, and MMF, there is limited data regarding their efficacy and these treatments have not been assessed in randomized clinical trials. The GRADE methodology used in the guideline development process weighs clinical trials more heavily than observational studies. Thus, mepolizumab is recommended as the first choice because it has been found to be efficacious for non-severe EGPA in a randomized trial[45]. All patients in this trial had relapsing or refractory disease with 55% receiving an additional non-glucocorticoid immunosuppressive agent at the time of enrollment. A large proportion of patients in this trial had asthmatic and eosinophilic features, for which mepolizumab has also been found to be effective in non-EGPA disease settings. Although patients with non-severe vasculitic manifestations were represented in this trial, questions remain about the effectiveness of mepolizumab for all aspects of non-severe vasculitis. Individual factors, including disease manifestations, may impact the decision to use mepolizumab, in which case MTX, AZA, or MMF may be used instead. There are insufficient data to favor one of these medications (MTX, AZA, MMF) over the others; therefore, the choice should be influenced by individual patient factors.

Patients should be treated with adjunctive MTX, AZA, or MMF rather than glucocorticoids alone to minimize glucocorticoid toxicity. One randomized trial that combined patients with EGPA, MPA, and polyarteritis nodosa without poor prognosis factors found the addition of AZA did not provide benefit beyond glucocorticoids alone.[46] Particularly in patients with asthma, this may impact the decision to use MTX, AZA, or MMF concurrently with glucocorticoids and could lead to consideration of mepolizumab. Glucocorticoid monotherapy may be appropriate for mild asthma, allergic symptoms, during pregnancy, or other individual patient situations.

While the comparative efficacy of MTX, AZA, MMF, and RTX is not well established, MTX, AZA, or MMF is favored given the longer experience with these agents in EGPA compared to RTX. However, RTX may be considered if other agents are not effective in controlling active non-severe disease, or the patient has non-severe vasculitis (which in some series included mononeuritis multiplex) and is positive for ANCA. CYC should be avoided in treating active non-severe disease due to its toxicity and is the least preferred option in this setting.

Typically, a maintenance agent would be used after remission induction of severe EGPA to reduce toxicity and the risk of relapse[47], although monophasic disease can occur[48]. AZA has been commonly used in published series of EGPA[46], but the lack of comparative evidence between AZA, MTX, or MMF in EGPA precludes recommending one agent over another.

Use of MTX, AZA, or MMF is recommended over RTX because there has been less experience with the use of RTX for remission maintenance in EGPA. RTX could be considered if remission was induced with rituximab, or if there are contraindications to other choices.

While there is limited data informing the use of remission maintenance therapy in EGPA, patients should be not continued on remission induction therapies (e.g., cyclophosphamide) indefinitely given the potential toxicity. Thus, MTX, AZA, or MMF can be considered for remission maintenance based on experience in GPA/MPA, expert opinion, and results from small studies [49]. The primary experience with mepolizumab is in refractory non-severe disease, and thus it is difficult to extrapolate its efficacy as a remission maintenance agent for severe disease.

There is insufficient published evidence to support a specific duration of glucocorticoid treatment and thus, the length of glucocorticoid therapy should be determined based on each patient's clinical circumstances. Many patients with EGPA require some amount of glucocorticoid, generally at a low-dose, to maintain control of asthma and allergic symptoms. The minimum effective dose should be prescribed to minimize glucocorticoid toxicity.

RTX is favored based on the general desire to avoid retreatment with CYC if possible, as well as an observational study of RTX in relapsing or refractory EGPA[50]. CYC may be considered in

instances of recurrent cardiac involvement due to its known association with mortality or with severe ANCA negative disease as discussed in Ungraded Position Statement B.

Re-induction with RTX is favored over CYC to minimize toxicity. However, the duration of remission prior to the onset of relapse should be examined. CYC should be considered if a severe relapse occurred quickly after use of RTX, or if cardiac involvement is present (see Ungraded Position Statement B and Recommendation 7).

For patients with EGPA with active asthma, inhaled therapies should be maximized prior to increasing systemic immunosuppression. Although no direct comparative data is available, mepolizumab was found efficacious in a randomized trial of patients specifically described in this recommendation: those with relapsing non-severe EGPA on immunosuppressive therapy.[45] It has also been independently proven to be effective in eosinophilic asthma.[51] Based on this evidence, mepolizumab is recommended to treat non-severe relapsing disease in patients receiving MTX, AZA, or MMF rather than switching to an alternative agent of that group.

Similar to the discussion for Recommendation 9, use of inhaled agents should be optimized in patients relapsing with asthma and/or sino-nasal disease. For patients on glucocorticoids alone, starting mepolizumab would be preferred over adding MTX, AZA, or MMF for patients with non-severe, relapsing EGPA given its proven efficacy for this population in a randomized trial.[45]

The published evidence with omalizumab, an anti-IgE antibody, in EGPA has been small. Thus, even in a patient with high serum IgE levels, mepolizumab is the preferred choice given the evidence from the randomized controlled trial.[45]

Following the introduction of leukotriene inhibitors, concerns were raised about a link with the development of EGPA. Subsequent retrospective studies have not concluded that there is a causal relationship between leukotriene inhibitors and EGPA.[52] Therefore, patients with newly diagnosed with EGPA should have the option to continue a leukotriene inhibitor if it is beneficial in the management of their asthma or sino-nasal disease.

Leukotriene inhibitors carry therapeutic indications for asthma and allergic rhinitis. As there has been no clear causal association with EGPA, a leukotriene inhibitor can be added to help manage asthma and sino-nasal disease. However, leukotriene inhibitors are one of many options and are not the only choice in this setting. Leukotriene inhibitors should not be used to treat manifestations aside from asthma and sino-nasal disease.

Cardiac involvement is the major cause of disease-related mortality in EGPA. [48] Echocardiography has minimal risk and can identify cardiac involvement, which if present, would impact treatment decisions. Not identifying cardiac involvement could negatively impact patient outcomes. Thus, we recommend obtaining an echocardiogram in all newly diagnosed patients with EGPA, even in the absence of cardiac symptoms.

The Five Factor Score (FFS) first published in 1996[53] was based on 342 patients with either polyarteritis nodosa (PAN), as it was then defined, or EGPA. These five factors include proteinuria greater than > 1 gram/day, renal insufficiency with serum creatinine above 1.58 mg/dL, GI tract involvement, cardiomyopathy, and central nervous system involvement. The FFS is primarily a prognostic tool in which higher scores have been associated with a worse outcome.[53] It has been used to guide treatment[43] but its applicability to newer therapies is unknown. The FFS was revisited in 2011 in a population of 1108 patients with GPA, MPA, EGPA, or PAN.[54] The 2011 derivation included ENT parameters and age above 65. The 1996 FFS remains more commonly used and may be helpful in identifying organ-specific parameters associated with severe disease and guiding treatment. Although the definitions of severe and non-severe EGPA used in this guideline were not based on FFS, the FFS was felt to be useful to clinicians in making treatment decisions. The components of the FFS can serve as markers of severe disease that warrant more

aggressive treatment.

Allergic rhinitis and sino-nasal disease are frequent clinical features of EGPA. Although the efficacy of nasal rinses and topical therapies in EGPA is not well-established, select patients may benefit. Where possible, consultation with an otolaryngologist who has expertise in treating AAV should be obtained to guide the use and choice of these agents. These interventions can continue to be beneficial even when symptoms have improved or resolved.

Prophylaxis to prevent *Pneumocystis jirovecii* pneumonia is discussed in GPA/MPA Recommendation 24. The same considerations regarding prophylaxis to prevent *Pneumocystis jirovecii* for patients with GPA/MPA also apply to patients with EGPA.

In this guideline, we present the first ACR/Vasculitis Foundation recommendations for the management of GPA, MPA, and EGPA. Although these recommendations provide a general guide for disease management, patients' clinical condition, preferences, and values should influence their treatment. Overall, these recommendations reflect the evolving management of these diseases, including the new roles for biologic therapies and aggressive strategies to minimize glucocorticoid toxicity. The recommendations for GPA/MPA are supported by a greater number of randomized trials than are currently available in EGPA. All of the recommendations made for these three diseases are conditional, reflecting that there are settings in which the evidence is not strong or an alternative is a reasonable consideration. These recommendations should not be used by any agency to restrict access to therapy or to require that certain therapies be utilized prior to other therapies.

The physicians on the voting panel were primarily rheumatologists because the recommendations were being developed for rheumatologists in the US. Since the AAV are multi-system diseases, patients with AAV often receive care from other medical subspecialists (e.g., nephrologists, pulmonologists, and/or otolaryngologists). While the recommendations presented in this guideline are driven by the published data, other medical subspecialists may favor a different management strategy. We encourage rheumatologists to discuss treatment plans and coordinate care with other subspecialists as needed.

Recently, a clinical trial of avacopan in patients with GPA and MPA was published.[55] This guideline development effort did not include consideration of avacopan since the guidelines consider therapies that were approved by the US Food and Drug Administration (FDA) for use for any indication at the time of the last literature search. Therapies that are approved by the FDA after that date will be considered for inclusion in future updates to this guideline.

This guideline highlights gaps in our knowledge for the treatment of AAV. Most glaring is the lack of biomarkers or other non-invasive diagnostic testing with minimal toxicity that can accurately assess disease activity and predict outcomes. In addition, while we have evidence from randomized clinical trials to support recommendations regarding initial remission induction and maintenance therapy, critical questions remain unanswered, such as the optimal duration of therapy.

These gaps in knowledge reinforce the need for ongoing research in these diseases. Specific areas to investigate include: Biomarker studies to identify more specific, reliable indicators of disease activity that can guide treatment decisions

Trials to clarify how best to use the medications currently available (e.g., dosing, duration, effective combinations, and in which population to use which drugs)

Trials to identify novel, targeted, and/or glucocorticoid-sparing agents with minimal toxicity

Long-term studies to understand the course of disease and safety of current therapies

We hope significant progress will be made in these areas such that future recommendations provide a more tailored approach to disease management, minimize treatment toxicity, and prevent organ damage in these patients.

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Key recommendations for the treatment of eosinophilic granulomatosis with polyangiitis.

Definitions for the disease states specified in the recommendations and ungraded position statements for granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Recommendations/Statements for the management of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

PICO= Population Intervention Comparator Outcome question used in GRADE methodology. Please refer to Supplementary Appendix 2 for the PICO questions developed for GPA/MPA.

Recommendations/Statements for management of eosinophilic granulomatosis with polyangiitis (EGPA).

PICO= Population Intervention Comparator Outcome question used in GRADE methodology. Please refer to Supplementary Appendix 2 for the PICO questions developed for EGPA.