American College of Rheumatology (ACR)
Vasculitis Guideline—ANCA-Associated Vasculitis

Project Plan – July 2018

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ORGANIZATIONAL LEADERSHIP AND SUPPORT

This project of the American College of Rheumatology (ACR) has the broad objective of developing an evidence-based clinical practice guideline related to the treatment and management of systemic vasculitis.

BACKGROUND

The ACR has previously not developed guidelines for the management of systemic vasculitis. The diagnosis, treatment, and monitoring of these diseases can be challenging given their rarity and the paucity of large, randomized clinical trials to guide therapy for some vasculitic diseases. Therefore, the ACR convened the Vasculitis Guideline core leadership team to develop evidence-based guidelines for the management of systemic vasculitis. The group was encouraged to scope broadly, without mandate to cover a specific type of vasculitis. It was recognized that one set of guidelines could not cover the entire spectrum of vasculitic diseases, and that vasculitides not addressed in this initial effort could be covered in future guidelines.

At the group’s first in-person meeting in June 2017, the Core Oversight Team, Voting Panel, and Expert Panel discussed the scope that should be covered in this initial guideline effort. The 2012 Revised International Chapel Hill Consensus Conference Nomenclature (1) was used as the basis for categorizing the vasculitides to be considered. For this initial effort, the vasculitides in the major categories—large, medium, and small vessel vasculitis—were prioritized given their prevalence compared to other categories of vasculitis. After discussion, the group members elected to first focus on large and medium vessel vasculitides, due to the scope of the project, need for clinical guidelines for these diseases and the available evidence upon which these guidelines could be based. The project plan presenting the committee’s work on large and medium vessel vasculitis was presented to the rheumatology community in March 2018. After development of that project plan, the committee began the current effort to develop guidelines for small vessel vasculitis. At this time, guidelines are being developed for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis due to the relative prevalence and availability of literature and therapeutic options. We recognize that management guidelines for other types of small vessel vasculitis such as IgA vasculitis, cryoglobulinemic vasculitis, hypocomplementemic urticarial vasculitis, and anti-glomerular basement membrane disease are also needed. Development of guidelines for these vasculitides may be addressed at a later time.

Using the Chapel Hill Consensus Conference nomenclature, the ANCA-associated vasculitides included in this effort are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic
OBJECTIVES

The objective of this project is to develop recommendations informing the use of laboratory testing, pharmacologic treatments, and non-pharmacologic interventions for the management of ANCA-associated vasculitis: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Specifically, we aim to:

1. Develop recommendations for the use of laboratory and imaging studies that inform the management of ANCA-associated vasculitis.

2. Develop recommendations for the use of glucocorticoids, non-glucocorticoid and biologic immunosuppressive agents, and non-pharmacologic interventions for the management of ANCA-associated vasculitis based on considerations of both efficacy and safety.

METHODS

Identification of Studies

Literature search strategies, based on PICO questions (Population/patients, Intervention, Comparator, and Outcomes; see Appendix A) will be developed by the principal investigators, systematic literature review leader, and a research librarian, with input from the Core Team. The search strategies will be peer reviewed by another medical librarian using Peer Review of Electronic Search Strategies (PRESS) (2). Searches will be performed in OVID Medline (1946 +), Embase (1974 +), the Cochrane Library, and PubMed (mid-1960s +).
The search strategies will be developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for OVID Medline, PubMed and Cochrane Library; and Emtree terms for Embase. Text words will also be used in OVID Medline, PubMed, and Embase, and keyword/title/abstract words in the Cochrane Library.

**Search Limits**

Only English language articles will be retrieved.

**Grey Literature**

The websites of appropriate agencies, such as the Agency for Healthcare Research and Quality (AHRQ), will be searched for peer-reviewed reports not indexed by electronic databases.

**Literature Search Update**

Literature searches will be updated just before the voting panel meeting to ensure completeness.

**Inclusion/Exclusion Criteria**

See PICO questions (*Appendix A*), which outline the defined patient population, interventions, comparators and outcomes.

**Management of Studies and Data**

References and abstracts will be imported into bibliographic management software (Reference Manager) (3), duplicates removed, and exported to Distiller SR, a web-based systematic review manager (4). Screening and data abstraction forms will be created in Distiller SR. Search results will be divided among reviewers, and two reviewers will screen each title/abstract, with disagreements at the title/abstract screening stage defaulting to inclusion for full manuscript review. Following the same dual review process, disagreements at the full manuscript screening stage will be discussed and adjudicated by the literature review leadership, if necessary.
Phases

1. A search for randomized controlled trials and observational studies about interventions aimed at the pharmacologic treatments and non-pharmacologic interventions for the management of ANCA-associated vasculitis (GPA, MPA, and EGPA) will be performed to determine existing studies covering outcomes of interest. Studies of renal limited ANCA-associated vasculitis will not be excluded. Subsequently, identified studies will be assessed using the RevMan (5) and GRADE Pro tools (6).

2. Chosen studies will be assessed for risk of bias using modified versions of the Cochrane Risk of Bias tool (7) and the Newcastle-Ottawa Scale (8).

3. Additionally, recently published systematic reviews covering outcomes of interest will also be sought and used for reference cross-checking.

GRADE Methodology

GRADE methodology (9) will be used in this project to grade available evidence and facilitate development of recommendations. The certainty in the evidence (also known as ‘quality’ of evidence) will be graded as high, moderate, low or very low. The strength of recommendations will be graded as strong or conditional. The strength of recommendations will not depend solely on the certainty in the evidence, but also on patient preferences and values, and the weight between benefits and harms. A series of articles that describe the GRADE methodology can be found on the GRADE working group’s website: www.gradeworkinggroup.org.

Analysis and Synthesis

The literature review team will analyze and synthesize data from included studies that address the PICO questions. An evidence profile, including a GRADE Summary of Findings table, will be prepared for each PICO question using Review Manager (RevMan) (3) and GRADEprofiler (GRADEpro) software (6). The Summary of Findings table contains the benefits and harms for each outcome across studies, the assumed and corresponding risk for comparators and interventions (95% CI), the absolute risk and relative effect (95% CI), the number of participants/number of studies, and the certainty in the evidence for each critical and important outcome (i.e., high, moderate, low or very low).

The evidence profile documents the overall certainty in the evidence for each critical and important outcome across studies and summarizes the rationale of the GRADE criteria for downgrading (risk of bias, inconsistency, indirectness, imprecision and publication bias), or upgrading the certainty in a body
Development of Recommendation Statements

PICO questions will be revised into drafted recommendation statements. Using the GRADE Evidence Profiles and Summaries of Findings tables, the voting panel, consisting of eight adult rheumatologists, four pediatric rheumatologists, and patient representatives, will consider the drafted recommendation statements in two stages. The first assessment will be done individually, and the results will be anonymous; this vote will only be used to determine where consensus might or might not already exist and develop the voting panel meeting agenda. At the face-to-face voting panel meeting, chaired by the principal investigator, the panelists will discuss the evidence in the context of their clinical experience and expertise to arrive at consensus on the final recommendations. The voting panel meeting discussions will be supported by the literature review leader, the GRADE expert, and selected members of the literature review team, who will attend the meeting to provide details about the evidence, as requested. Voting panel discussions and decisions will be informed by a separately convened patient panel, which will meet in the days before the voting panel meeting, to provide unique patient perspectives on the drafted recommendations based on their experiences and the available literature.

PLANNED APPENDICES (AT MINIMUM)

A. Final literature search strategies
B. GRADE evidence profiles and summary of findings tables for each PICO question

AUTHORSHIP

Authorship of the guideline will include: principal investigator, Dr. Sharon Chung, as the lead author and voting panel leader; Dr. Reem Mustafa, literature review leader; Drs. Gary Hoffman, Carol Langford, Mehrdad Maz, and Antoine Sreih, content experts; and Dr. Gordon Guyatt, GRADE expert. Members of the literature review team and voting panel will also be authors. The PI will determine final authorship, dependent on the efforts made by individuals throughout the guideline development process, using international authorship standards as guidance.
DISCLOSURES/CONFLICTS OF INTEREST

The ACR’s disclosure and COI policies for guideline development will be followed for this project. These can be found in the ACR Guideline Manual on this page of the ACR web site, under Policies & Procedures. See Appendix B for participant disclosures.

REFERENCES

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA; CHURG-STRAUSS)

Definitions:

A. Disease states
1. **Active disease**: new, persistent, or worsening clinical signs and/or symptoms attributed to eosinophilic granulomatosis with polyangiitis (Churg-Strauss; EGPA) and not related to prior damage
2. **Severe disease**: vasculitis with life/organ-threatening manifestations (e.g., glomerulonephritis, mononeuritis multiplex, diffuse alveolar hemorrhage, cardiac involvement, mesenteric ischemia, limb/digit ischemia)
3. **Non-severe disease**: vasculitis or non-vasculitis symptoms without life/organ-threatening manifestations (e.g. rhino-sinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)
4. **Remission**: absence of apparent clinical signs or symptoms attributed to EGPA on or off of immunosuppressive therapy
5. **Refractory**: persistent active disease (excluding rhinosinusitis and asthma) despite an appropriate course of immunosuppressive therapy
6. **Relapse**: recurrence of active disease following a period of remission

B. Therapy
1. **Pulse intravenous glucocorticoids**:
   - Adults: methylprednisolone 500-1000 mg given intravenously for 3-5 days or equivalent
   - Children: methylprednisolone 30 mg/kg/day (maximum 1000 mg/day) for 3-5 days or equivalent
2. **High dose oral glucocorticoids**:
   - Adults: prednisone 1 mg/kg/day (generally up to 80 mg/day) or equivalent
   - Children: prednisone 1-2 mg/kg/day (generally up to 60 mg/day) or equivalent
3. **Moderate dose oral glucocorticoids**:
   - Adults: prednisone 0.25-0.5 mg/kg/day (generally between 10-40 mg/day) or equivalent
   - Children: prednisone ~0.5 mg/kg/day (generally 10-30 mg/day) or equivalent
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4. **Low dose oral glucocorticoids:**
   - Adults: prednisone ≤ 10 mg/day or equivalent
   - Children: prednisone ≤ 0.2 mg/kg/day (maximum 10 mg/day) or equivalent

5. **Remission induction therapy:**
   - Cyclophosphamide (CYC)
     - Oral: up to 2 mg/kg/day
     - IV: 15 mg/kg q2 weeks x 3 doses, followed by 15 mg/kg q3 weeks for at least 3 doses
   - Rituximab (RTX): 375 mg/m² IV week x 4 doses or 1000 mg IV on days 1 and 15
   - Mepolizumab: 300 mg subcutaneous every 4 weeks

6. **Remission maintenance therapy:**
   - Azathioprine (AZA): up to 2 mg/kg/day
   - Methotrexate (MTX): up to 25 mg/week subcutaneous or po
   - Rituximab (RTX): 500 mg IV q6 months or 1 gm IV q4 months
   - Mycophenolate mofetil (MMF): up to 1500 mg po bid
     - Mycophenolic acid and mycophenolate sulfate also used
   - Mepolizumab: 300 mg subcutaneous every 4 weeks
   - Omalizumab: 300-600 mg subcutaneous every 2-4 weeks

7. **Pneumocystis prophylaxis:** SMZ/TMP, dapsone, atovaquone, aerosolized pentamidine

C. **Disease assessments**

1. **Clinical monitoring:** Assessing for clinical signs and symptoms of active disease and obtaining clinical labs including inflammatory markers, immunoglobulin E (IgE) levels and eosinophil count

2. **ANCA:** immunofluorescence testing for c-ANCA/p-ANCA and ELISA testing for MPO and PR3 antibodies

3. **Routine laboratory monitoring:** complete blood count, comprehensive metabolic panel, urinalysis with microscopy, erythrocyte sedimentation rate, C-reactive protein

4. **Cardiac imaging:** transthoracic echocardiogram or cardiac MRI

D. **Disease-related outcomes**

1. Activity as determined by the Birmingham Vasculitis Activity Score (BVAS), BVAS/WG, or study-specific disease activity assessment

2. Damage as determined by the Vasculitis Damage Index (VDI), ANCA-Vasculitis Damage Index (AVID) or study-specific disease damage measure
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3. Clinical symptoms and organ damage attributable to disease
4. Relapse
5. Death
6. Patient-Reported Outcomes
   a. SF36 (Short Form Health Survey), EQ-5D (EuroQol), or CHQ (Child Health Questionnaire)
   b. If above not available: Patient Global Assessment, PROMIS, RAPID3, or MDHAQ

E. Treatment-related adverse events
1. Serious adverse events
2. Infection
3. Malignancy
4. Glucocorticoid Toxicity Index
5. Any toxicity leading to drug dose reduction or treatment discontinuation
6. Complications of surgical procedures

PICO Questions:

Diagnostic/prognostic tools

Role of FFS:
1. In patients with EGPA, what is the impact of using the Five Factor Score vs. intuitive assessment of patient’s status to guide therapy on disease-related outcomes and treatment-related adverse events?

Cardiac imaging:
2. In patients with EGPA, what is the impact of performing cardiac imaging at time of diagnosis and yearly vs. not performing cardiac imaging on disease-related outcomes and treatment-related adverse events?

Treatment: Remission Induction

Pulse vs. high dose prednisone:
3. In patients with active severe EGPA, what is the impact of using pulse intravenous vs. high-dose oral glucocorticoids on disease-related outcomes and treatment-related adverse events?
Rituximab vs. CYC:

4. In patients with active severe EGPA, what is the impact of using rituximab vs. cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse events?

4a. How does the impact vary by ANCA status?

Role of mepolizumab:

5. In patients with active severe EGPA, what is the impact of using mepolizumab plus glucocorticoids vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

6. In patients with active severe EGPA, what is the impact of using mepolizumab vs. rituximab for remission induction on disease-related outcomes and treatment-related adverse events?

7. In patients with active severe EGPA, what is the impact of using mepolizumab vs. cyclophosphamide for remission induction in disease-related outcomes and treatment-related adverse events?

Non-severe disease:

8. In patients with active non-severe EGPA, what is the impact of initiating treatment with azathioprine + glucocorticoids vs. methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?

9. In patients with active non-severe EGPA, what is the impact of initiating treatment with azathioprine + glucocorticoids vs. MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?

10. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate + glucocorticoids vs. MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?

11. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. rituximab + glucocorticoids on disease-related outcomes and treatment-related adverse events?

12. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. cyclophosphamide + glucocorticoids on disease-related outcomes and treatment-related adverse events?

13. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
Treatment: Remission Maintenance

CYC, MTX/AZA, RTX, MMF:

14. In patients with severe EGPA who have entered remission, what is the impact of using methotrexate vs. azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

15. In patients with severe EGPA who have entered remission, what is the impact of using methotrexate vs. MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?

16. In patients with severe EGPA who have entered remission, what is the impact of using azathioprine vs. MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?

17. In patients with severe EGPA who have entered remission, what is the impact of using rituximab vs. methotrexate/azathioprine/MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?

18. In patients with severe EGPA who have entered remission with mepolizumab therapy, what is the impact of using methotrexate/azathioprine/MMF vs. continuing mepolizumab for remission maintenance on disease-related outcomes and treatment-related adverse events?

Duration of remission maintenance therapy:

19. In patients with severe EGPA on remission maintenance therapy not using prednisone, what is the impact of continuing remission maintenance therapy for > 18 months vs. stopping remission maintenance therapy at or prior to 18 months on disease related outcomes and treatment related adverse events?

20. In patients with severe EGPA on remission maintenance therapy and prednisone, what is the impact of continuing remission maintenance therapy for > 18 months with prednisone vs. stopping remission maintenance therapy at or prior to 18 months and continuing prednisone on disease related outcomes and treatment-related adverse events?

21. In patients with severe EGPA on remission maintenance therapy, what is the impact of using oral glucocorticoids for 6 months versus more than 6 months on disease-related outcomes and treatment-related adverse events?

Treatment: Refractory/Smoldering Disease

Refractory disease:

22. In patients with severe EGPA who have not entered remission with cyclophosphamide or rituximab therapy, what is the impact of adding mepolizumab vs. continued...
rituximab/cyclophosphamide therapy on disease-related outcomes and treatment-related adverse events?

### Treatment: Relapse

#### Severe Relapse:

23. In patients with EGPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab and on either non-rituximab maintenance therapy or no maintenance therapy, what is the impact of using the same agent vs. switching to the other agent for remission re-induction on disease-related outcomes and treatment-related adverse events?

#### Non-severe relapse with asthma and sino-nasal disease only:

24. In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of adding mepolizumab versus switching to another agent on disease-related outcomes and treatment-related adverse events?

25. In patients with EGPA and high IgE levels who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of adding omalizumab versus switching to another agent on disease-related outcomes and treatment-related adverse events?

26. In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on low dose glucocorticoids and no other therapy, what is the impact of increasing the dose of glucocorticoids versus adding methotrexate/azathioprine/MMF/mepolizumab on disease-related outcomes and treatment-related adverse events?

#### Other

#### Role of continued prednisone use:

27. In patients with EGPA in remission and currently only on prednisone, what is the impact of continuing with low dose prednisone long-term (e.g., > 18 months) vs. stopping low dose prednisone on disease-related outcomes and treatment related adverse events?

28. In patients with EGPA in remission on remission maintenance therapy and prednisone, what is the impact of continuing low dose prednisone long-term (e.g., > 18 months) vs. stopping low dose prednisone and continuing remission maintenance therapy on disease-related outcomes and treatment related adverse events?
Role of nasal rinses:
29. In patients with sino-nasal involvement in EGPA, what is the impact of using nasal rinses vs. not using nasal rinses on disease related outcomes and treatment-related adverse events?

Pneumocystis prophylaxis:
30. In patients with EGPA on cyclophosphamide or rituximab, what is the impact of using Pneumocystis prophylaxis vs. not using Pneumocystis prophylaxis on Pneumocystis infection and treatment-related adverse events?

Role of leukotriene inhibitors:
31. In patients with newly diagnosed EGPA and on leukotriene inhibitors, what is the impact of discontinuing leukotriene inhibitors versus continuing leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?
32. In patients with EGPA and active asthma and/or sino-nasal disease what is the impact of adding leukotriene inhibitors versus not adding leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?

GRANULOMATOSIS WITH POLYANGIITIS (GPA) and MICROSCOPIC POLYANGIITIS (MPA)

Definitions:

A. Disease states
1. **Severe disease**: vasculitis with life/organ-threatening manifestations (e.g., alveolar hemorrhage, rapidly progressive glomerulonephritis)
2. **Non-severe disease**: vasculitis without life/organ-threatening manifestations (e.g. sinusitis)
3. **Active disease**: new, persistent, or worsening clinical signs and/or symptoms attributed to GPA/MPA and not related to prior damage
4. **Remission**: absence of clinical signs or symptoms attributed to GPA/MPA, on or off of immunosuppressive therapy
5. **Refractory**: persistent active disease despite an appropriate course of immunosuppressive therapy
6. **Relapse**: recurrence of active disease following a period of remission

B. Therapy
1. **Pulse intravenous glucocorticoids**:
   - Adults: methylprednisolone 500-1000 mg given intravenously for 3-5 days or equivalent
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- Children: methylprednisolone 30 mg/kg/day (maximum 1000 mg/day) for 3-5 days or equivalent

2. **High dose oral glucocorticoids**:
   - Adults: prednisone 1 mg/kg/day (generally up to 80 mg/day) or equivalent
   - Children: prednisone 1-2 mg/kg/day (generally up to 60 mg/day) or equivalent

3. **Moderate dose oral glucocorticoids**:
   - Adults: prednisone 0.25-0.5 mg/kg/day (generally between 10-40 mg/day) or equivalent
   - Children: prednisone ~0.5 mg/kg/day (generally 10-30 mg/day) or equivalent

4. **Low dose oral glucocorticoids**:
   - Adults: prednisone ≤ 10 mg/day or equivalent
   - Children: prednisone ≤ 0.2 mg/kg/day (maximum 10 mg/day) or equivalent

5. **Remission induction therapy**:
   - Cyclophosphamide (CYC)
     - Oral: up to 2 mg/kg/day
     - IV: 15 mg/kg q2 weeks x 3 doses, followed by 15 mg/kg q3 weeks for at least 3 doses
   - Rituximab (RTX): 375 mg/m2 IV a week x 4 doses or 1000 mg IV on days 1 and 15
   - Methotrexate (MTX): up to 25 mg/week po or subq

6. **Remission maintenance therapy**:
   - Azathioprine (AZA): up to 2 mg/kg/day
   - Methotrexate (MTX): up to 25 mg/week subq or po
   - Rituximab (RTX): 500 mg IV q6 months or 1 gm IV q4 months
   - Mycophenolate mofetil (MMF): up to 1500 mg po bid
     - Mycophenolic acid and mycophenolate sulfate also used
   - Leflunomide (LEF): up to 30 mg/day
   - Sulfamethoxazole/trimethoprim (SMZ/TMP): up to 1 DS tablet po bid

7. **Pneumocystis prophylaxis**: low dose SMZ/TMP, dapsone, atovaquone, aerosolized pentamidine

C. **Disease assessments**

1. **Clinical monitoring**: Assessing for clinical signs and symptoms of active disease and obtaining clinical labs including inflammatory markers
2. **ANCA**: immunofluorescence testing for c-ANCA/p-ANCA and ELISA testing for MPO and PR3 antibodies
3. **Routine laboratory monitoring:** Complete blood count, Comprehensive metabolic panel, Urinalysis with microscopy, Erythrocyte sedimentation rate, C-reactive protein

4. **Non-invasive imaging:** volumetric chest CT

D. **Disease-related outcomes**
1. Activity as determined by the Birmingham Vasculitis Activity Score (BVAS), Birmingham Vasculitis Activity Score for Wegener’s granulomatosis (BVAS/WG), or other study-specific disease activity assessment
2. Damage as determined by the ANCA-Vasculitis Index of Damage (AVID), Vasculitis Damage Index (VDI) or other study-specific disease damage measure
3. Clinical symptoms and organ damage attributable to disease
4. Relapse (up to 24 months of follow-up)
5. Death
6. **Patient-Reported Outcomes**
   a. SF36 (Short Form Health Survey), EQ-5D (Euroqol), or CHQ (Child Health Questionnaire)
   b. If above not available: Patient Global Assessment, PROMIS, RAPID3, or MDHAQ

E. **Treatment-related adverse events**
1. Serious adverse events
2. Infection
3. Malignancy
4. Any toxicity leading to drug dose adjustment or treatment discontinuation
5. Complications of surgical procedures

**PICO Questions (GPA/MPA = GPA or MPA):**

**Diagnostic Testing**

**Role of following ANCA titers in assessing disease activity:**
1. In patients with GPA/MPA, what is the impact of obtaining ANCA levels/titers at fixed intervals vs. not obtaining ANCA levels/titers on disease-related outcomes and treatment-related adverse events?

**Treatment: Remission Induction**

**Prednisone dosing:**
2. In patients with active severe GPA/MPA, what is the impact of using pulse intravenous vs. high-dose oral glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?

3. In patients with active severe GPA/MPA, what is the impact of using high-dose vs. moderate dose oral glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?

**Rituximab vs. CYC:**

4. In patients with active severe GPA/MPA, what is the impact of using rituximab vs. cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse events?

4a. How does the impact differ between those who are ANCA positive vs. ANCA negative?

**IV vs. po CYC:**

5. In patients with active severe GPA/MPA, what is the impact of using IV CYC vs. po CYC for remission induction on disease-related outcomes and treatment-related adverse events?

**Different rituximab regimens:**

6. In patients with active severe GPA/MPA, what is the impact of initiating treatment with rituximab 1000 mg IV days 1 and 15 vs. rituximab 375 mg/m² qweek x 4 weeks on disease-related outcomes and treatment-related adverse events?

**Avacopan:**

7. In patients with active severe GPA/MPA, what is the impact of using avacopan + cyclophosphamide/rituximab vs. cyclophosphamide/rituximab + glucocorticoids on disease-related outcomes and treatment-related adverse events?

**Non-severe disease:**

8. In patients with active non-severe GPA, what is the impact of initiating treatment with azathioprine + glucocorticoids vs. methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?

9. In patients with active non-severe GPA, what is the impact of initiating treatment with azathioprine + glucocorticoids vs. MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?

10. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate + glucocorticoids vs. MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?

11. In patients with active non-severe GPA, what is the impact of initiating treatment with glucocorticoids + SMZ/TMP vs. glucocorticoids + methotrexate or azathioprine on disease related outcomes and treatment-related adverse events?
12. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine vs. rituximab on disease-related outcomes and treatment-related adverse events?

13. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine vs. cyclophosphamide on disease-related outcomes and treatment-related adverse events?

14. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine vs. glucocorticoids on disease-related outcomes and treatment-related adverse events?

Treatment: Remission Maintenance

15. In patients with severe GPA/MPA who have entered remission with cyclophosphamide therapy, what is the impact of using methotrexate or azathioprine vs. continuing cyclophosphamide for remission maintenance on disease-related outcomes and treatment-related adverse events?

16. In patients with severe GPA/MPA who have entered remission, what is the impact of using methotrexate vs. azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

17. In patients with severe GPA/MPA who have entered remission with cyclophosphamide therapy, what is the impact of using rituximab vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

18. In patients with severe GPA/MPA who have entered remission with rituximab therapy, what is the impact of using rituximab vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

19. In patients with severe GPA/MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using MMF for remission maintenance vs. methotrexate or azathioprine on disease-related outcomes or treatment-related adverse events?

20. In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using leflunomide for remission maintenance vs. methotrexate or azathioprine on disease-related outcomes or treatment-related adverse events?
SMZ/TMP (sulfamethoxazole/trimethoprim):

21. In patients with non-severe GPA who have entered remission, what is the impact of using SMZ/TMP vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

22. In patients with severe GPA who have entered remission, what is the impact of using SMZ/TMP vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes or treatment-related adverse events?

CD19/ANCA titers with rituximab remission maintenance:

23. In patients with GPA/MPA on rituximab for remission maintenance therapy, what is the impact of using CD19 counts to guide re-dosing of rituximab vs. scheduled re-dosing of rituximab on disease-related outcomes or treatment-related adverse events?

24. In patients with GPA/MPA on rituximab for remission maintenance therapy, what is the impact of using ANCA titers to guide re-dosing of rituximab vs. scheduled re-dosing of rituximab on disease-related outcomes or treatment-related adverse events?

Duration of remission maintenance therapy:

25. In a patient with severe GPA/MPA using remission maintenance therapy, what is the impact of continuing remission maintenance therapy for > 18 months vs. stopping remission maintenance therapy at or prior to 18 months on disease-related outcomes and treatment-related adverse events?

25a. How does this impact change in the presence of concomitant prednisone?

26. In patients with severe GPA/MPA starting remission maintenance therapy that includes prednisone, what is the impact of treatment with prednisone for 6 months or less vs. 6-18 months vs. longer than 18 months during remission maintenance on disease-related outcomes and treatment-related adverse events?

Treatment: Relapse

Therapy for remission induction following remission and relapse:

27. In patients with GPA/MPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab and on either non-rituximab maintenance therapy or no maintenance therapy, what is the impact of using the same agent vs. switching to the other agent for remission induction on disease-related outcomes and treatment-related adverse events?

Relapse treatment if on rituximab:

28. In patients with GPA/MPA who have relapsed with severe disease manifestations while on rituximab for remission maintenance, what is the impact of continuing rituximab at a higher
dose vs. switching to cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse effects?

Other

Role of continued prednisone use:
29. In patients with GPA/MPA in remission and currently only on prednisone, what is the impact of continuing with low dose prednisone long-term (e.g., > 18 months) vs. stopping low dose prednisone on disease-related outcomes and treatment related adverse events?

Role of plasma exchange in severe disease:
30. In patients with GPA/MPA with active glomerulonephritis, what is the impact of adding plasma exchange to cyclophosphamide or rituximab vs. not adding plasma exchange on disease-related outcomes and treatment-related adverse events?
31. In patients with GPA/MPA with active alveolar hemorrhage, what is the impact of adding plasma exchange to cyclophosphamide or rituximab vs. not adding plasma exchange on disease-related outcomes and treatment-related adverse events?

Role of nasal rinses/topical nasal therapy:
32. In patients with sino-nasal involvement in GPA, what is the impact of using nasal rinses vs. not using nasal rinses on disease related outcomes and treatment-related adverse events?
33. In patients with sino-nasal involvement in GPA, what is the impact of using nasal antibiotics vs. not using nasal antibiotics on disease related outcomes and treatment-related adverse events?
34. In patients with chronic sino-nasal disease and mucosal damage, what is the impact of topical nasal lubricants (e.g., oils, ointments, or hyaluronic acid spray) on disease-related outcomes and treatment-related adverse events?
35. In patients with chronic sino-nasal disease and mucosal inflammation, what is the impact of topical corticosteroid therapies on disease-related outcomes and treatment-related adverse events?

Role of immunosuppression for subglottic and/or endobronchial stenosis:
36. In patients with GPA and subglottic and/or endobronchial stenosis, what is the impact of treatment with immunosuppression vs. surgical dilation with intralesional glucocorticoid injection on disease-related outcomes and treatment related adverse events?

Role of immunosuppression for orbital pseudotumor and mass lesions:
37. In patients with GPA and orbital pseudotumor, what is the impact of treatment with immunosuppression vs. surgical removal of pseudotumor tissue on disease-related outcomes, ocular symptoms (e.g. ocular/orbital pain, diplopia, and vision loss) and treatment-related adverse events?
38. In patients with GPA and mass lesions aside from orbital pseudotumor (e.g., lung, brain, parotid gland, kidney, prostate gland), what is the impact of treatment with immunosuppression vs.
surgical removal of the mass lesion on disease-related outcomes and treatment-related adverse events?

Pneumocystis prophylaxis
39. In patients with GPA/MPA on cyclophosphamide or rituximab, what is the impact of using Pneumocystis prophylaxis vs. not using Pneumocystis prophylaxis on the development of Pneumocystis pneumonia and treatment-related adverse events?

Infection prophylaxis
40. In patients with GPA/MPA on remission maintenance therapy with rituximab who have hypogammaglobulinemia (e.g., IgG < 3 g/L), what is the impact of IVIG supplementation vs. no IVIG supplementation on the development of infections and treatment-related adverse events?

Cosmetic surgery
41. In patients with GPA/MPA in remission and nasal bridge collapse/nasal fistulas, what is the impact of cosmetic surgery vs. no surgery on disease-related outcomes and treatment-related adverse events?

Kidney transplant in ESRD
42. In patients with GPA/MPA in remission and chronic kidney disease stage V, what is the impact of renal transplantation vs. no renal transplantation on disease-related outcomes and treatment-related adverse events?

Duration of anticoagulation in patients with GPA/MPA and venous thromboembolism
43. In patients with GPA/MPA and venous thromboembolism what is the impact of anticoagulation for 6 months vs. anticoagulation for 6-18 months vs. anticoagulation > 18 months on the development of recurrent venous thromboembolic events and treatment-related side effects?
APPENDIX B – Participant Disclosures

In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College’s integrity be maintained. The cornerstone of the ACR’s Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts. The purpose of the ACR’s Disclosure Policy is identification of relationships which may pose actual or potential conflicts. These actual or potential conflicts can then be evaluated by the College so that adjustments can be made that will avoid any undue influence. This policy is based on the principle that, in many cases, full disclosure of the actual or potentially conflicting relationship will of itself suffice to protect the integrity of the College and its interests.

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<tr>
<th>Participants</th>
<th>Role</th>
<th>Primary Employer</th>
<th>Sources of Financial Income (only information from primary employers is required)</th>
<th>Research Grants/Contracts</th>
<th>Financial Interests to Include Medical Industry and Pharmaceutical Industry</th>
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