

# CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update

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**ABSTRACT. Objective.** In 2015, the Canadian Vasculitis Research Network (CanVasc) created recommendations for the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) in Canada. The current update aims to revise existing recommendations and create additional recommendations, as needed, based on a review of new available evidence.

**Methods.** A needs assessment survey of CanVasc members informed questions for an updated systematic literature review (publications spanning May 2014 to September 2019) using Medline, Embase, and Cochrane. New and revised recommendations were developed and categorized according to the level of evidence and strength of each recommendation. The CanVasc working group used a 2-step modified Delphi procedure to reach > 80% consensus on the inclusion, wording, and grading of each new and revised recommendation.

**Results.** Eleven new and 16 revised recommendations were created and 12 original (2015) recommendations were retained. New and revised recommendations are discussed in detail within this document. Five original recommendations were removed, of which 4 were incorporated into the explanatory text. The supplementary material for practical use was revised to reflect the updated recommendations.

**Conclusion.** The 2020 updated recommendations provide rheumatologists, nephrologists, and other specialists caring for patients with AAV in Canada with new management guidance, based on current evidence and consensus from Canadian experts.

**Key Indexing Terms:** antineutrophil cytoplasm antibody-associated vasculitis, eosinophilic granulomatosis with polyangiitis, glomerulonephritis, granulomatosis with polyangiitis, microscopic polyangiitis

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The antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are systemic necrotizing vasculitides, classified into granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA)<sup>1</sup>. Advances in the management of AAV have improved patient outcomes, but the burden of organ damage, treatment toxicity, and relapse risk remains high.

The Canadian Vasculitis Research Network (CanVasc) aimed to update the original (2015) AAV management recommendations<sup>2</sup> based on the expanding literature of the last 5 years. Full-length recommendations are contained within Supplementary Data 1 (available with the online version of this article). Only new or revised recommendations from the original publication<sup>2</sup> are discussed. Supplementary Data 2 contains treatment protocols and other practical guidance.

## MATERIALS AND METHODS

The full-length version of the article (Supplementary Data 1, available with the online version of this article) contains detailed methodology. Briefly, an electronic survey distributed to all 34 CanVasc Core members and main associates established 15 primary questions and 4 secondary topics to inform a systematic literature review (Table 1). The literature search (publications spanning May 2014 to September 2019, updated January and March 2020) included guidelines, randomized controlled trials (RCT), systematic reviews and/or metaanalyses, observational studies, and case series of  $\geq 15$  adult or pediatric patients (literature search and writing committee: AM, lead; DE for EGPA publications; EG for pediatric publications; and CP). The evidence and strength for revised and new recommendations were graded according to European League Against Rheumatism criteria (Table 2)<sup>3</sup>. Through a modified Delphi consensus procedure, a 36-member working group voted on the inclusion, grading, and wording of each

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recommendation. Disagreements were resolved in 2 rounds of teleconferences (January and March 2020). Each final recommendation achieved  $\geq 80\%$  approval. Reviewers from the Canadian Rheumatology Association Guidelines Committee, Canadian Thoracic Society, and Canadian Glomerulonephritis Registry provided feedback, as did 3 patients. Ethics approval was not required in accordance with the Tri-Council Policy Statement. Supplementary Data 3 contains author disclosures.

## RESULTS

### I. Updated Diagnostic Recommendations

1. A high-quality, antigen-specific immunoassay for proteinase 3-ANCA and myeloperoxidase-ANCA is the preferred method of ANCA detection for patients in whom there is clinical suspicion of ANCA-associated vasculitis (Category 2A, Strength B).

Performance characteristics of antigen-specific immunoassays (first, second, and third generation ELISA, chemiluminescent assay, fluorescence enzyme, and multiplex bead immunoassays, detecting IgG antibodies to proteinase-3 [PR3] and myeloperoxidase [MPO]) were compared to indirect immunofluorescence (IIF) detection of cytoplasmic staining ANCA and perinuclear staining ANCA, using a large cohort of untreated patients with GPA or MPA and controls<sup>4</sup>. Antigen-specific immunoassays had superior performance to the 2 IIF techniques (area under the curve [AUC] 0.92–0.95 vs 0.84–0.92)<sup>4</sup>. High-quality, antigen-specific immunoassays are now recommended for PR3- and MPO-ANCA detection in patients with suspected GPA or MPA<sup>5</sup>. In selected patients with negative antigen-specific immunoassay testing but a high clinical suspicion of AAV, a second assay or IIF can improve sensitivity<sup>5</sup>.

### II. Updated Therapeutic Recommendations

#### A. Updated recommendations for induction treatment of GPA and MPA

5a. An initial dose of 1 mg/kg/day prednisone equivalent (not exceeding 80 mg/day) is recommended for remission induction in adult patients with severe GPA or MPA. (Category 2A, Strength C). Whereas the optimal glucocorticoid (GC) starting dose in severe AAV is unknown, prednisone 1 mg/kg/day (not exceeding 80 mg/day) has been a common practice<sup>6</sup>. Patients with non-severe/limited GPA can start at lower prednisone doses (e.g., 0.5 mg/kg/day)<sup>7</sup>.

5b. Pulse intravenous methylprednisolone (0.5–1 g/day for 1–3 days) can be considered in severe, organ- or life-threatening GPA or MPA, but lacks proven efficacy and carries a potential risk of adverse effects (Category 3, Strength D).

Intravenous (IV) methylprednisolone (MP) pulses (500–1000 mg/day for 1–3 days) are often administered at the onset of induction therapy in patients with life-threatening AAV<sup>2</sup>. However, observational data suggest a lack of benefit and potential harm compared to high-dose GC without pulses.

Two retrospective studies of patients with severe AAV (creatinine [Cr]  $> 500$   $\mu\text{mol/L}$  or dialysis) found no difference in 1-year overall survival or renal recovery<sup>8,9</sup> and time to renal recovery or relapses<sup>8</sup> among IV MP vs non-MP recipients. IV MP was associated with a nearly 3-fold higher risk of serious infection at 3 months, and a 6-fold higher risk of new-onset diabetes mellitus<sup>8</sup>.

Table 1. Questions informing the literature review for updated recommendations.

Question	Vote, n = 19
Which of indirect immunofluorescence and/or high-quality immunoassay should be recommended for ANCA detection in patients with suspected AAV?	100%
In patients undergoing induction therapy for severe AAV, does pulse methylprednisolone confer clinical benefit compared to no pulse?	100%
In patients undergoing induction therapy for GPA or MPA, can a “reduced dose” GC tapering protocol be used instead of a “standard” GC tapering protocol?	100%
In patients undergoing induction therapy for severe GPA and MPA, does plasma exchange confer clinical benefit compared to no plasma exchange?	100%
In patients undergoing induction therapy for GPA and MPA, does MMF have comparable clinical efficacy to CYC?	100%
In patients with severe AAV, which maintenance agents are effective?	100%
In patients with GPA and MPA, does extended maintenance therapy (48 months) lead to fewer relapses compared to standard (24 months) maintenance therapy?	100%
In patients with GPA and MPA, which RTX maintenance regimens are effective?	100%
In patients with GPA and MPA receiving RTX, should gamma globulins be monitored and how should hypogammaglobulinemia be managed?	100%
In patients with GPA and MPA receiving RTX, should B cells (CD19) be monitored to determine the risk of relapse?	95%
In patients with AAV, should ANCA be monitored to determine the risk of relapse?	100%
In patients with nonsevere EGPA or MPA (FFS = 0), does the addition of conventional immunosuppressants to GC improve remission or relapse rate?	95%
In patients with EGPA, is there a role for biological therapies for induction or maintenance?	95%
In patients receiving RTX or CYC for AAV, does TMP-SMX prophylaxis reduce severe infection risk?	95%
In patients with AAV, which vaccinations are safe, effective, and recommended?	95%
Additional topics of interest included in the literature search, suggested by ≥ 2 CanVasc members	
In patients with GPA or MPA, does the combination of RTX + CYC for induction confer clinical benefit?	
In patients with AAV, what is the optimal duration of low-dose GC during maintenance?	
In patients with AAV, is there a maximum recommended lifetime cumulative dose of CYC?	
In patients with GPA or MPA with subglottic stenosis, which medical treatments are effective?	
In patients with AAV, what is the efficacy of other biologic therapies or RTX biosimilars?	

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasm antibody; AZA: azathioprine; CD19: cluster of differentiation 19; CYC: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; FFS: Five Factor Score; GC: glucocorticoid; GPA: granulomatosis with polyangiitis; MMF: mycophenolate mofetil; MPA: microscopic polyangiitis; RTX: rituximab; TMP-SMX: trimethoprim-sulfamethoxazole.

Table 2. Level of evidence and grading of recommendations<sup>a</sup>.

Category of Evidence	Evidence Source
1A	From metaanalysis of randomized controlled trials
1B	From at least 1 randomized controlled trial
2A	From at least 1 controlled study without randomization
2B	From at least 1 quasi-experimental study
3	From descriptive studies, such as comparative studies, correlation studies, or case control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities
Strength	Directly Based on
A	Category 1 evidence
B	Category 2 evidence or extrapolated recommendations from category 1 evidence
C	Category 3 evidence or extrapolated recommendations from category 1 or 2 evidence
D	Category 4 evidence or extrapolated recommendations from category 2 or 3 evidence

<sup>a</sup> Following European League Against Rheumatism (EULAR) criteria.<sup>3</sup>

Other studies also found IV MP to be independently associated with severe infections<sup>10,11</sup> and treatment-related damage<sup>12</sup>.

IV MP pulses will remain a common practice in severe AAV, but caution should be exercised given the observed excess risk of adverse events and the lack of demonstrated benefit.

6a. A GC tapering protocol should be initiated within 2 weeks

of induction therapy in patients with severe GPA or MPA (Category 2A, Strength C).

6b. A reduced-dose GC tapering protocol can be considered in adult patients with severe GPA or MPA who are receiving cyclophosphamide or rituximab induction therapy, to reduce cumulative GC exposure and infection risk (Category 1B, Strength A).

In most patients, GC tapering can commence within 1–2 weeks of commencing induction therapy with rituximab (RTX) or cyclophosphamide (CYC; Supplementary Table 5 and Supplementary Data 2.3, available with the online version of this article)<sup>6,13</sup>. The PEXIVAS trial<sup>13</sup> found that a reduced-dose tapering protocol, which commenced tapering after 1 week and aimed for prednisone 7.5–12.5 mg/day by 3 months, was noninferior to a “standard” regimen reaching 15–25 mg/day by 3 months for the composite endpoint of death or endstage renal disease (ESRD), and resulted in fewer serious infections<sup>13</sup>. For certain PEXIVAS subgroups, particularly subjects who received RTX induction (15%), the safety and effectiveness of a reduced-dose GC regimen requires further study. GC tapering requires repeated clinical assessments, with modification of protocols according to the clinical status of the patient.

**7. In patients with severe, newly diagnosed GPA or MPA, we recommend GC plus either CYC or RTX for first-line remission induction therapy. RTX is preferred for remission induction in patients with severe GPA or MPA in whom CYC is contraindicated, including those with a risk of infertility (Category 1B, Strength A).**

A previous metaanalysis of RAVE<sup>6</sup> and RITUXVAS<sup>14</sup> confirmed no difference between RTX and CYC for remission at 6 months, relapse at 12 months, death, or serious adverse events (SAE) including infections<sup>15</sup>. Post-hoc analyses of the RAVE trial found that subgroups with relapsing disease<sup>16</sup> and PR3-ANCA<sup>17</sup> achieved higher remission rates with RTX compared to CYC plus azathioprine (AZA). In relapsing disease following initial CYC induction, RTX is the preferred induction agent (see Recommendation 13 in Table 3). Among patients with severe GPA and MPA who do not present an infertility risk or other contraindications to CYC, both CYC and RTX can be considered as first-line induction therapies. When CYC fails to induce remission, RTX should be used (and vice versa). Observational data suggest that RTX-treated patients with very severe renal disease have similar outcomes to those treated with CYC<sup>18</sup>. Supplementary Data 2 (available with the online version of this article) contains CYC administration, fertility, and monitoring guidance.

**9. Urgent plasma exchange is not recommended as part of initial induction therapy for most adult patients with severe GPA or MPA (Category 1B, Strength A).**

PEXIVAS compared plasma exchange to no plasma exchange along with standard treatment in 704 adults with severe AAV<sup>13</sup>. At a median of 2.9 years' follow-up, there was no difference in ESRD or death between groups (HR 0.86, 95% CI 0.65–1.13)<sup>13</sup>. A metaanalysis assessing plasma exchange for the outcome of dialysis at 1 year (not including PEXIVAS data) found that plasma exchange reduced dialysis risk at 12 months (risk ratio [RR] 0.45, 95% CI 0.29–0.72)<sup>15</sup>. Metaanalyses including data from PEXIVAS found no difference in sustained remission, total adverse events, or death at any time point, but found increased serious infections with plasma exchange (RR 1.26, 95% CI 1.03–1.54)<sup>15</sup>.

PEXIVAS included patients with pulmonary hemorrhage (27%) and Cr  $\geq$  500  $\mu$ mol/L or dialysis (29%), however some

may consider that the effect estimates for these disease subsets remain inconclusive. The possibility that plasma exchange could delay the short-term need for dialysis<sup>19</sup> requires further investigation. Although routine use of plasma exchange for induction is not recommended, it may still be considered in these subgroups, in consultation with vasculitis experts. Finally, plasma exchange is required in patients with antiglomerular basement membrane (anti-GBM) antibodies<sup>20</sup>, and in the absence of timely anti-GBM testing (serology or renal biopsy) initial empiric plasma exchange may be appropriate.

**11. In patients with GPA or MPA without life-threatening or extensive disease manifestations, remission induction with mycophenolate mofetil in combination with GC can be considered (Category 1B, Strength A).**

Two previous open-label, multicenter RCT compared mycophenolate mofetil (MMF) to IV<sup>21</sup> or oral<sup>22</sup> CYC for induction, excluding patients with very severe disease. The MYCYC trial<sup>21</sup> found noninferiority for remission at 6 months (67% MMF and 61% CYC) and time to remission, but relapse-free survival was lower in the MMF group<sup>21</sup>. In the second RCT including only relapsing patients (89% PR3–, ANCA+), 6-month remission rates and 2-year disease-free survival were not statistically different between CYC and MMF groups (81% vs 66% and 61% vs 43%, respectively), and more MMF recipients were taking < 10 mg of prednisone at 6 months (62% vs 36%)<sup>22</sup>. Patients in the highest tertile of disease severity were less likely to respond to MMF<sup>22</sup>.

A metaanalysis including these 2 studies plus 2 prior RCT from China (primarily MPO-ANCA+ patients with more severe renal disease)<sup>23,24</sup>, found no difference between MMF or CYC for remission, relapse, SAE, or infection<sup>25</sup>. In the absence of severe disease (e.g., patients with rash, mild neuropathy, or mild renal involvement), MMF can be used for remission induction in GPA or MPA.

## **B. Updated recommendations for remission maintenance in GPA and MPA**

**14. In patients with GPA or MPA who received CYC or RTX induction therapy, RTX (infusions every 4–6 months) is recommended as first-line maintenance therapy (Category 1B, Strength A).**

The MAINRITSAN<sup>26</sup> trial demonstrated long-term superiority of RTX over AZA for preventing major relapses after CYC induction<sup>27</sup>. RITAZAREM was an open-label RCT comparing maintenance RTX (1 g every 4 months) to AZA (2 mg/kg/day) among 170 patients with relapsing disease (72% PR3+) after RTX induction<sup>28</sup>. At month 24, RTX showed superior relapse-free survival compared to AZA (HR 0.36, 95% CI 0.23–0.57), fewer SAE (22% vs 36%), and no difference in infection rates<sup>28</sup>. No RCT have compared RTX to other maintenance therapies among nonrelapsing patients treated with RTX induction. RTX is not yet funded for GPA and MPA maintenance in every province.

Originator and biosimilar RTX have comparable efficacy and safety in rheumatoid arthritis<sup>29</sup>. RTX biosimilars could thus be used for induction and maintenance of GPA and MPA if they receive approval.

Table 3. Updated recommendations: executive summary.

Recommendation <sup>a</sup>	Grading <sup>3</sup>
<b>Diagnosis</b>	
1. A high-quality, antigen-specific immunoassay for PR3-ANCA and MPO-ANCA is the preferred method of ANCA detection for patients in whom there is clinical suspicion of ANCA-associated vasculitis (AAV).	Category 2A, Strength B
2. Tissue biopsy should be considered in cases of suspected AAV to confirm diagnosis.	Category 4, Strength D
<b>Disease severity in AAV</b>	
3. Patients with newly diagnosed or relapsing AAV should be stratified according to the extent and severity of their disease, to allow therapy to be tailored accordingly.	Category 4, Strength D
<b>The role of vasculitis referral centers</b>	
4. Patients with AAV, particularly those with challenging disease, should be managed at, or in collaboration with, a referral center for vasculitis.	Category 4, Strength D
<b>Induction of GPA and MPA</b>	
5a. An initial dose of 1 mg/kg/day prednisone equivalent (not exceeding 80 mg/day) is recommended for remission induction in adult patients with severe GPA or MPA.	Category 2A, Strength C
5b. Pulse IV MP (0.5–1 g/day for 1–3 days) can be considered in severe, organ- or life-threatening GPA or MPA, but lacks proven efficacy and carries a potential risk of adverse effects.	Category 3, Strength D
6a. A GC tapering protocol should be initiated within 2 weeks of induction therapy in patients with severe GPA or MPA.	Category 2A, Strength C
6b. A reduced-dose GC tapering protocol can be considered in adult patients with severe GPA or MPA who are receiving CYC or RTX induction therapy, to reduce cumulative GC exposure and infection risk.	Category 1B, Strength A
7. In patients with severe, newly diagnosed GPA or MPA, we recommend GC plus either CYC or RTX for first-line remission induction therapy. RTX is preferred for remission induction in patients with severe GPA or MPA in whom CYC is contraindicated, including those with a risk of infertility.	Category 1B, Strength A
8. We recommend that the remission induction therapy with CYC, combined with GC, last a minimum of 3 to a maximum of 6 months. Once remission is achieved, CYC should be stopped and the patient switched to a different maintenance therapy.	Category 1B, Strength A
9. Urgent plasma exchange is not recommended as part of initial induction therapy for most adult patients with severe GPA or MPA.	Category 1B, Strength A
10. In patients with limited and/or nonsevere GPA (not life-threatening and without any major organ involvement), a remission induction regimen with MTX in combination with GC can be used.	Category 1B, Strength A
11. In patients with GPA or MPA without life-threatening or extensive disease manifestations, remission induction with MMF in combination with GC can be considered.	Category 1B, Strength A
<b>Treatment of GPA and MPA relapse</b>	
12. We recommend that relapses that are nonsevere (i.e., nonlife- and nonorgan-threatening) be treated with an increase in GC dose in addition to optimizing the patient's concurrent immunosuppressant agent.	Category 3, Strength C
13. We recommend remission induction of a major organ- or life-threatening relapse with either CYC or RTX in conjunction with GC. In patients who already received CYC for initial remission induction or a previous disease relapse, we recommend using RTX for remission reinduction.	Category 1B, Strength A
<b>Remission maintenance: GPA and MPA</b>	
14. In patients with GPA or MPA who received CYC or RTX induction therapy, RTX (infusions every 4–6 months) is recommended as first-line maintenance therapy.	Category 1B, Strength A
15a. "Tailored" RTX maintenance, with retreatment based on ANCA titer rise, switch from negative to positive ANCA, or repopulation of CD19+ B cell subsets <sup>30</sup> , can be an alternative maintenance strategy in adults with GPA or MPA who received CYC or RTX induction therapy.	Category 1B, Strength B
15b. Outside of "tailored" RTX maintenance, there is insufficient evidence to recommend escalating immunosuppressive therapy based on ANCA titer or CD19 B cell rise.	Category 4, Strength D
16a. In patients with GPA or MPA who received CYC (A) or RTX (B) induction therapy, AZA or MTX can be used for maintenance therapy when RTX maintenance cannot be used.	(A) Category 1B, Strength B for maintenance after CYC induction; (B) Category 3, Strength C for maintenance after RTX induction
16b. MMF (A) or LEF (B) can be considered as alternative maintenance therapies in patients with contraindications, poor tolerance, or lack of response to other agents.	(A) Category 3, Strength C for MMF; (B) Category 1B, Strength B for LEF
17. In patients with GPA or MPA, maintenance with RTX (or conventional immunosuppressants) should be continued for a minimum of 2 years; extended maintenance therapy can be considered, especially in high-risk clinical subgroups.	Category 1B, Strength B
18. Low-dose GC should be part of the initial remission maintenance therapy in GPA and MPA after remission is achieved; the optimal duration of low-dose GC for remission maintenance is not known.	Category 4, Strength D

Table 3. Continued.

Recommendation <sup>a</sup>	Grading <sup>3</sup>
19. Topical therapies may be considered, in combination with systemic therapy and in collaboration with ENT subspecialists, to alleviate the symptoms of upper airway and ENT disease.	Category 3, Strength C
<b>EGPA</b>	
20a. An initial dose of 1 mg/kg/day prednisone equivalent (not exceeding 80 mg/day) is recommended for remission induction in patients with severe EGPA.	Category 2A, Strength C
20b. Pulse IV MP can be considered in severe, organ- or life-threatening EGPA, but lacks proven efficacy and carries a potential risk of adverse effects.	Category 3, Strength D
21. A GC tapering protocol should be initiated within 2–4 weeks of induction therapy in EGPA.	Category 4, Strength D
22. We recommend remission induction therapy with a combination of GC and CYC in patients with severe, newly diagnosed EGPA.	Category 2A, Strength B
23. Patients with nonsevere EGPA without major organ involvement or poor prognostic factors may be treated with GC alone for initial induction therapy.	Category 1B, Strength A
24. MPB 300 mg SC monthly can be considered in nonsevere, GC-dependent refractory or relapsing EGPA.	Category 1B, Strength A
25. Consideration of other (off-label) therapies for EGPA should be made in collaboration with centers of expertise.	Category 4, Strength D
26. Patients with EGPA and persistent asthmatic symptoms, despite remission of their vasculitic manifestations, should be managed in collaboration with a physician subspecializing in asthma management.	Category 4, Strength D
<b>Refractory disease</b>	
27. Patients with refractory disease, and those in whom the aforementioned therapies are contraindicated or poorly tolerated, should be managed in a referral center for vasculitis in collaboration with subspecialists, for consideration of alternate, additional, and/or experimental therapies.	Category 4, Strength D
<b>Special patient groups</b>	
28. For patients with subglottic and/or bronchial stenosis, multidisciplinary management should be sought to optimize local interventions, and consideration should be given to systemic immunosuppressive therapy.	Category 3, Strength C
29. Women with AAV should not consider pregnancy earlier than 6 months after sustained remission of their disease has been achieved. Women with AAV planning pregnancy and those pregnant should be managed in close collaboration with an obstetrician with expertise in this field and/or in high-risk pregnancies.	Category 4, Strength D
<b>Pediatric AAV</b>	
30. Management of pediatric AAV should be provided by pediatric physicians at an academic healthcare center, in collaboration with referral centers for vasculitis and/or centers with special interest in pediatric vasculitis.	Category 4, Strength D
31. Children with newly diagnosed AAV should be treated according to adult recommendations for induction of remission and then maintenance, with medication doses adjusted for this specific population.	Category 4, Strength D
32. In children with newly diagnosed, severe GPA or MPA, we recommend GC plus either CYC or RTX for remission induction.	Category 3, Strength C
33. In children, severe, relapsing AAV or severe AAV refractory to the combination of CYC and GC (with major organ involvement or life-threatening manifestations) should be treated with RTX in combination with GC.	Category 4, Strength D
<b>Monitoring and prevention in AAV</b>	
General considerations	
34. Patients with AAV should be followed regularly for many years with full clinical assessment and routine laboratory work to assess disease course and track for disease activity and disease- or treatment-related damage.	Category 4, Strength D
35. As part of their lifelong annual follow-up, cardiovascular risk factors (including smoking status, diabetes, hypercholesterolemia, hypertension, and obesity) and risk for osteoporosis should be systematically assessed, with treatment as needed according to the current respective guidelines for each of these conditions.	Category 4, Strength D
CYC: safety considerations	
36a. All patients previously treated with CYC should have a urinalysis every 3–6 months as a lifelong means of screening for CYC-induced bladder malignancy. If micro- or macroscopic hematuria is present, in the absence of an alternate explanation, the patient should be referred for consideration of a cystoscopy.	Category 3, Strength D
36b. Patients should be counseled on the increased risk of nonmelanoma skin cancer after exposure to CYC and/or other conventional immunosuppressants.	Category 3, Strength D
Infection prevention	
37a. TMP-SMX prophylaxis should be prescribed to prevent infection during induction therapy with CYC or RTX.	Category 3, Strength C
37b. Prophylaxis should continue for at least 3 months following CYC cessation and 6 months following last RTX dose.	Category 4, Strength D
38. Pneumococcal vaccination (A) and annual influenza vaccination (B) are recommended in all patients with AAV receiving immunosuppression. Recombinant VZV subunit (nonlive) vaccine (C) can be offered to all adult patients at risk.	(A) Pneumococcal: Category 3, Strength D; (B) Influenza: Category 1B, Strength B; (C) VZV: Category 4, Strength D
39. Immunoglobulin levels should be checked in patients receiving RTX who experience serious or recurrent infections.	Category 4, Strength D

<sup>a</sup>New and revised recommendations in bold. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasm antibody; AZA: azathioprine; CYC: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear, nose, and throat (otolaryngologist); GC: glucocorticoid; GPA: granulomatosis with polyangiitis; IV: intravenous; LEF: leflunomide; MMF: mycophenolate mofetil; MP: methylprednisolone; MPA: microscopic polyangiitis; MPB: mepolizumab; MPO: myeloperoxidase; MTX: methotrexate; PR3: proteinase 3; RTX: rituximab; SC: subcutaneous; TMP-SMX: trimethoprim-sulfamethoxazole; VZV: varicella zoster virus.

15a. "Tailored" RTX maintenance, with retreatment based on ANCA titer rise, switch from negative to positive ANCA, or repopulation of CD19+ B cell subsets<sup>30</sup>, can be an alternative maintenance strategy in adults with GPA or MPA who received CYC or RTX induction therapy (Category 1B, Strength B).

MAINRITSAN2 was an open-label RCT comparing "fixed" maintenance (500 mg at Day 0 and 14, then every 6 months for 18 months) to "tailored" maintenance (500 mg at Day 0 with 500 mg reinfusion if ANCA titers became positive, ELISA value rose 2-fold, IIF titer increased  $\geq 2$  dilutions, or CD19 B cells rose above 0/mm<sup>3</sup>; repeating ANCA and CD19 B cells at 3-month intervals)<sup>30</sup>. Patients in the tailored regimen received fewer infusions with no difference in total or major relapses (17% vs 10% and 7% vs 4%, respectively) or relapse-free survival (84% vs 86%) at Month 28<sup>30</sup>.

A tailored regimen may reduce RTX cost, although the cost and availability of repeated CD19 B cell and ANCA measurements need to be considered. Tailored RTX maintenance may be useful for patients for whom systematic RTX infusions are not funded or according to patient preference, provided serial ANCA and CD19 B cell monitoring can be performed.

15b. Outside of "tailored" RTX maintenance, there is insufficient evidence to recommend escalating immunosuppressive therapy based on ANCA titer or CD 19 B cell rise (Category 4, Strength D).

Rising ANCA titer<sup>31</sup>, return to ANCA positivity<sup>32,33</sup>, or persistently positive ANCA<sup>27,34</sup> are associated with increased risk of relapse, whereas ANCA-negative status is associated with decreased relapse risk<sup>33,35</sup>. While not all relapsing patients have detectable B cells<sup>32,36</sup>, relapse-free survival was lower among patients who repopulated B cells within 12 months<sup>32</sup>. MAINRITSAN2, with a small number of total relapses (n = 22), was underpowered to analyze the predictive value of ANCA (rise, return) or B cell repopulation on relapses.

Whereas ANCA trajectory during remission maintenance likely adds predictive value for determining relapse risk, outside of the "tailored" RTX maintenance regimen, there is insufficient evidence that an ANCA rise alone should dictate therapy escalation. Nevertheless, ANCA testing can be useful in stratifying patients' future flare risk, to inform the frequency of clinical and laboratory follow-up.

16a. In patients with GPA or MPA who received CYC or RTX induction therapy, AZA or methotrexate can be used for maintenance therapy when RTX maintenance cannot be used (Category 1B, Strength B for maintenance after CYC induction; Category 3, Strength C for maintenance after RTX induction).

16b. MMF or leflunomide (LEF) can be considered as alternative maintenance therapies in patients with contraindications, poor tolerance, or lack of response to other agents (Category 1B, Strength B for LEF; Category 3, Strength C for MMF).

Ten-year follow-up from the WEGENT trial found no difference in relapse rates between AZA and methotrexate (MTX) maintenance<sup>37</sup>. In a network metaanalysis of RCT comparing MTX, AZA, LEF, and MMF for maintenance therapy, estimates for a superior agent were statistically inconclusive, but MMF

was overall inferior<sup>38</sup>. Observational data suggest that patients in stable remission who received MMF induction can continue MMF for maintenance<sup>39</sup>.

Full-dose trimethoprim-sulfamethoxazole (TMP-SMX; 800/160 mg once or twice daily) can be an adjunctive maintenance agent in selected GPA cases<sup>40</sup>.

17. In patients with GPA or MPA, maintenance with RTX (or conventional immunosuppressants) should be continued for a minimum of 2 years; extended maintenance therapy can be considered, especially in high-risk clinical subgroups (Category 1B, Strength B).

17.1. Maintenance duration of nonbiologic immunosuppressants following GC-CYC induction. Two RCT<sup>34,41</sup> compared "standard" to "extended" maintenance therapy among patients who received CYC induction. In a Dutch study<sup>41</sup>, relapse-free survival was 52% among patients randomized to taper AZA after 1 year and 72% among those who continued for 4 years, although the difference was not statistically significant<sup>41</sup>. In the REMAIN trial<sup>34</sup>, patients randomized to withdraw AZA and prednisone after a mean of 19 months had higher relapse rates (OR 5.96, 95% CI 2.58–13.77) and ESRD (7.8% vs 0%,  $P = 0.012$ ) compared to those who continued maintenance for an additional 24 months<sup>34</sup>. A metaanalysis of both studies found a reduced relapse risk with the extended maintenance (RR 0.41, 95% CI 0.26–0.64) with no difference in adverse events<sup>15</sup>.

In patients with a history of prior relapse, significant preexisting organ damage, or PR3-ANCA and/or persistent ANCA positivity, maintenance durations of at least 4 years should be considered. Beyond 4 years, clinicians should base further maintenance extension on history of relapses, preexisting damage, and patient preference.

17.2. Maintenance duration of RTX. MAINRITSAN3<sup>42</sup> enrolled 97 patients in remission at month 28 from MAINRITSAN2 (last possible maintenance RTX infusion at Month 18), who were randomized to receive RTX 500 mg every 6 months until 46 months, or placebo. At 56 months, relapse-free survival was 96% in the extended therapy vs 74% in the placebo group (HR 7.5, 95% CI 1.7–33.7) with no difference in SAE<sup>42</sup>. Hence, while the majority of patients may not require further RTX after 18 months, extended maintenance therapy reduces relapse risk further.

RTX maintenance should continue for 2 years minimum (last infusion at 18 months), but high-risk clinical characteristics (see 17.1 above) support continuing RTX maintenance for an additional 18 months (Supplementary Data 2.3, available with the online version of this article).

### C. Updated recommendations for the treatment of EGPA

20a. An initial dose of 1 mg/kg/day prednisone equivalent (not exceeding 80 mg/day) is recommended for remission induction in patients with severe EGPA (Category 2A, Strength C).

20b. Pulse IV MP can be considered in severe, organ- or life-threatening EGPA, but lacks proven efficacy and carries a potential risk of adverse effects (Category 3, Strength D).

In a trial of EGPA patients with poor prognostic factors [i.e.,

Five Factor Score (FFS)  $\geq 1$ ], IV MP pulses were given to 72% of patients<sup>43</sup>. There are no studies comparing the efficacy of pulse vs no pulse MP for induction of severe EGPA. Until such data are available, recommendations are extrapolated from GPA and MPA (Recommendation 5).

21. *A GC tapering protocol should be initiated within 2–4 weeks of induction therapy in EGPA (Category 4, Strength D).*

The EGPA Consensus Task Force<sup>44</sup> recommends tapering prednisone after 2–3 weeks, to approximately 20 mg/day by 3 months. Unlike in GPA and MPA, a reduced-dose GC taper has not been evaluated in EGPA.

22. *We recommend remission induction therapy with a combination of GC and CYC in patients with severe, newly diagnosed EGPA (Category 2A, Strength B).*

In a prospective trial of patients with EGPA and FFS  $\geq 1$ , IV CYC pulses led to complete remission in 89% of patients<sup>43</sup>. Extrapolating from GPA and MPA data<sup>34,37,38</sup>, CYC induction should be followed by either AZA or MTX maintenance (with LEF or MMF as alternatives) for a minimum of 2 years.

23. *Patients with nonsevere EGPA without major organ involvement or poor prognostic factors may be treated with GC alone for initial induction therapy (Category 1B, Strength A).*

CHUSPAN2 compared AZA plus GC to GC alone for induction in nonsevere (FFS = 0), newly diagnosed EGPA (n = 51), MPA (n = 25), or polyarteritis nodosa (n = 19)<sup>45</sup>. Within the EGPA subset at 2 and 5 years, relapse-free survival did not differ between groups<sup>46</sup>. Although there is no evidence that adding immunosuppressants to initial induction is superior to GC alone, conventional immunosuppressants are often justified if vasculitic disease manifestations, such as mononeuritis multiplex, progress<sup>47</sup>. Until further data are available, any of the conventional immunosuppressants (AZA, MTX, LEF, MMF, or even CYC in some cases) should be promptly added in patients with progressive vasculitic manifestations of EGPA for whom the FFS remains 0.

24. *Mepolizumab 300 mg subcutaneous monthly can be considered in nonsevere, GC-dependent refractory or relapsing EGPA (Category 1B, Strength A).*

MIRRA<sup>48</sup> compared mepolizumab (MPB; 300 mg subcutaneous every 4 weeks) to placebo in 136 patients with refractory, relapsing, or GC-dependent EGPA (new diagnosis and severe disease excluded). The primary endpoint of remission (Birmingham Vasculitis Activity Score = 0) at Weeks 36 and 48 occurred more often in the MPB group (OR 16.74, 95% CI 3.6–77.6)<sup>48</sup>. Relapse rates were reduced but remained high overall (56% vs 82% with placebo), with no difference in SAE<sup>48</sup>. However, MIRRA was unable to determine the efficacy of MPB for acute vasculitic manifestations or myocarditis<sup>48</sup>. As of yet, no anti-interleukin 5 studies have been completed in patients without relapsing or refractory, GC-dependent EGPA.

25. *Consideration of other (off-label) therapies for EGPA should be made in collaboration with centers of expertise (Category 4, Strength D).*

Case series have suggested benefit of RTX for patients with relapsing or refractory EGPA<sup>49,50</sup>. Response or median time to

remission may be better in ANCA-positive patients<sup>50</sup>. A retrospective study comparing 14 RTX recipients to 14 CYC recipients found similar remission (36% vs 29%) and relapse-free survival rates between groups<sup>51</sup>. While 2 RCT will evaluate RTX for EGPA induction (ClinicalTrials.gov: NCT02807103) and maintenance (ClinicalTrials.gov: NCT03164473), currently RTX should be reserved for patients who have failed conventional therapies and should be discussed with a center of expertise.

#### D. Updated recommendations for special treatment groups

28. *For patients with subglottic and/or bronchial stenosis, multidisciplinary management should be sought to optimize local interventions, and consideration should be given to systemic immunosuppressive therapy (Category 3, Strength C).*

Subglottic stenosis occurs in 10–23% of GPA patients<sup>52,53</sup> while bronchial stenosis is less common<sup>52</sup>. Cohort studies have demonstrated efficacy of dilatation procedures, often with intralesional corticosteroid injection, but recurrent stenosis is common, requiring repeated procedures<sup>53,54</sup>. Treatment with prednisone > 30 mg at the time of dilation was associated with a lower risk of restenosis (HR 0.53, 95% CI 0.31–0.89)<sup>55</sup>. Based on these limited data, patients with subglottic stenosis and bronchial stenosis may benefit from periprocedural escalation of GC (to > 30 mg/day for 3–5 days), and/or a trial of immunosuppressive therapy.

32. *In children with newly diagnosed, severe GPA or MPA, we recommend GC plus either CYC or RTX for remission induction (Category 3, Strength C).*

Although data on RTX remains limited in pediatric AAV, RTX may be preferred in children for whom CYC presents an excess risk of toxicity. A phase IIa, multicenter, single-arm trial of RTX induction (375 mg/m<sup>2</sup> weekly for 4 doses) was conducted in 25 pediatric patients with new or relapsing GPA and MPA, excluding those with alveolar hemorrhage or hemodialysis<sup>56</sup>. Remission (Pediatric Vasculitis Activity Score = 0 and prednisone  $\leq$  0.2 mg/kg/day) was 56% at 6 months and 100% at 18 months with no concerning adverse events<sup>56</sup>. This outcome is comparable to a cohort of 105 pediatric patients with AAV who primarily received CYC<sup>57</sup>. In patients with relapsing disease after CYC, RTX is the preferred agent (Table 3, Recommendation 33).

#### E. Updated recommendations for monitoring and prevention in AAV

36a. *All patients previously treated with CYC should have a urinalysis every 3–6 months as a lifelong means of screening for CYC-induced bladder malignancy. If micro- or macroscopic hematuria is present, in the absence of an alternate explanation, the patient should be referred for consideration of a cystoscopy (Category 3, Strength D).*

36b. *Patients should be counseled on the increased risk of nonmelanoma skin cancer after exposure to CYC and/or other conventional immunosuppressants (Category 3, Strength D).*

Patients with AAV and exposure to CYC have an increased risk of nonmelanoma skin cancer<sup>58,59,60</sup> that may be accelerated by subsequent long-term AZA<sup>59</sup>. Studies have demonstrated



Table 4. Clinical research questions of high importance.

1. Can induction with RTX and low-dose CYC in combination reduce the need for GC in AAV?
2. Can complement inhibitors replace the need for GC in AAV, and could such therapy be cost effective?
3. Is pulse IV MP beneficial in the induction of severe AAV?
4. What is the comparative effectiveness of RTX to conventional immunosuppressants in nonsevere GPA and MPA?
5. What is the optimal RTX maintenance dose, frequency, and duration?
6. What is the optimal duration of low-dose GC during remission maintenance?
7. Should duration of maintenance immunosuppression depend on PR3-ANCA and MPO-ANCA status?
8. Can serial ANCA testing be used in making therapeutic decisions (escalation or de-escalation)?
9. Is there equal access to evidence-based treatments for AAV in Canada and do inequities affect the survival and outcomes of Canadians with AAV?
10. Are there any variables to use to further individualize treatment in AAV patients (genetics, genomics)? Would such strategies be cost-effective?

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasm antibody; CYC: cyclophosphamide; GC: glucocorticoid; GPA: granulomatosis with polyangiitis; IV: intravenous; MP: methylprednisolone; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; RTX: rituximab.

an increased risk of other malignancies with cumulative CYC exposure > 25–36 g<sup>58,59,60</sup>, thus cumulative CYC > 25 g should be avoided if possible. Patients exposed to CYC should undergo long-term urinalysis monitoring, and persistent unexplained hematuria evaluated with cystoscopy.

37a. *TMP-SMX prophylaxis should be prescribed to prevent infection during induction therapy with CYC or RTX (Category 3, Strength C).*

37b. *Prophylaxis should continue for at least 3 months following CYC cessation and 6 months following last RTX dose (Category 4, Strength D).*

*Pneumocystis jirovecii* pneumonia prophylaxis with TMP-SMX is recommended in patients receiving CYC or RTX. In the presence of TMP-SMX intolerance or allergy, dapsone or atovaquone are alternatives (Supplementary Data 2.3, available with the online version of this article). Further, an RCT of therapeutic TMP-SMX in GPA<sup>40</sup> and a previous observational study of primarily prophylactic dose TMP-SMX in RTX recipients<sup>61</sup> found that TMP-SMX reduced overall infection risk in AAV. Although there is little evidence to inform prophylaxis duration, a recommended strategy is continued prophylaxis for 3 months following CYC cessation and 6 months following the last RTX infusion<sup>6</sup>.

38. *Pneumococcal vaccination (Category 3, Strength D) and annual influenza vaccination (Category 1B, Strength B) are recommended in all patients with AAV receiving immunosuppression. Recombinant varicella zoster virus subunit (nonlive) vaccine can be offered to all adult patients at risk (Category 4, Strength D).* Patients with AAV undergoing immunosuppression should receive the 13-valent pneumococcal conjugate vaccine followed by the 23-valent pneumococcal polysaccharide vaccine at least 8 weeks later (Supplementary Data 2.4, available with the online version of this article)<sup>62,63</sup>.

Patients with AAV should also receive annual influenza vaccination and any available nonlive vaccinations to other seasonal and/or pandemic viruses. In an RCT, trivalent influenza immunogenicity among patients with AAV in remission was acceptable (although attenuated compared to controls)<sup>64</sup>, and did not increase relapse risk<sup>64</sup>. The high-dose influenza vaccine, which has greater immunogenicity in immunocompromised patients<sup>65</sup>, requires study in AAV.

Varicella zoster virus (VZV) infections are common in AAV<sup>66</sup>. The recombinant zoster vaccine should be administered instead of the live, attenuated VZV vaccine in patients taking immunosuppression.

In patients receiving maintenance RTX, vaccines are ideally administered 5 months after the last infusion and 1 month before the upcoming infusion<sup>67</sup>. If such timing is not feasible, vaccination is still preferred, despite the lower likelihood of immunogenicity.

39. *Immunoglobulin levels should be checked in patients receiving RTX who experience serious or recurrent infections (Category 4, Strength D).*

Hypogammaglobulinemia secondary to RTX can be associated with severe infections<sup>66,68</sup>. Risk factors for persistent or severe hypogammaglobulinemia include baseline low IgG<sup>68</sup>, older age<sup>68</sup>, and prior CYC<sup>69</sup>. Ig replacement (e.g., 0.4 g/kg IV Ig/month) is indicated if hypogammaglobulinemia is associated with “serious, persistent, unusual, or recurrent infections”<sup>68,69,70</sup>.

Patients with hypogammaglobulinemia without recurrent infections can receive repeat RTX infusions with close monitoring. In the event of recurrent or severe infections, further RTX treatment should be individualized based on disease activity and relapse risk, with Ig replacement if needed.

In conclusion, these recommendations, which incorporate the expert consensus of more than 30 physicians with a wide breadth of experience from different Canadian healthcare contexts, provide a guide for applying new evidence to the care of Canadians with AAV, and must be used in conjunction with best clinical judgment in a given patient.

Table 4 lists current high-importance questions for AAV management in Canada. We continue to recommend collaborative multidisciplinary care, including referral to vasculitis centers, especially for patients with AAV in whom diagnostic or therapeutic uncertainty remains.

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## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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