Title: CanVasc consensus recommendations for the management of antineutrophil cytoplasm antibody-associated vasculitis: 2020 update

Running head: CanVasc ANCA-associated vasculitis recommendations

Key Indexing Terms: Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis; Granulomatosis with Polyangiitis; Microscopic Polyangiitis; Eosinophilic Granulomatosis with Polyangiitis; Glomerulonephritis

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No grant or industrial support was received for this work.

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Conflicts of interest:

Dr. Mendel has nothing to disclose; Dr. Ennis has nothing to disclose; Dr. Go has nothing to disclose; Dr. Bakowsky reports advisory board attendance from Abbvie, Eli Lilly, and Jannsen, outside the submitted work; Dr Baldwin has nothing to disclose; Dr Benseler has nothing to disclose; Dr Cabral has nothing to disclose; Dr Carette has nothing to disclose; Dr. Clements-Baker has nothing to disclose; Dr. Alison Clifford reports other from Abbvie, personal fees from Hoffman La-Roche Limited, outside the submitted work; Dr Cohen Tervaert reports Chair of the Independent Data Monitoring Committee for InflaRx, outside the submitted work; Dr Gerard Cox has nothing to disclose; Dr Dehghan has nothing to disclose; Dr Dipchand has nothing to disclose; Dr. Dhindsa reports personal fees from Novartis, Sandoz and Amgen, outside the submitted work; Dr Famorca has nothing to disclose; Dr Fifi-Mah has nothing to disclose; Dr. Garner reports grants from Vasculitis Foundation and Roche, during the conduct of the submitted work; Dr. Girard has nothing to disclose; Dr Lessard has nothing to disclose; Dr. Liang reports grants from Roche, Amgen, Janssen, Abbvie, BMS, and Novartis, outside the submitted work; Dr Noone has nothing to disclose; Dr Makhzoum has nothing to disclose; Dr Milman has nothing to disclose; Dr Pineau has nothing to disclose; Dr Reich has nothing to disclose; Dr Rhéaume has nothing to disclose; Dr Robinson has nothing to disclose; Dr Rumsey has nothing to disclose; Dr Towheed has nothing to disclose; Dr. Trudeau reports personal fees from Hoffman-Laroche, personal fees from Medexus, other from Medpace, outside the submitted work; Dr Twilt has nothing to disclose; Dr Yacyshyn has nothing to disclose; Dr Yeung has nothing to disclose; Dr Barra reports honoraria from Roche, Bristol-Myers Squibb, Boehringer-Ingelheim, and Pfizer, outside the submitted work; Dr. Khalidi reports personal fees and non-financial support from Roche, non-financial support from Bristol Meyers Squibb, outside the submitted work; Dr. Christian Pagnoux reports grants and personal fees from Roche, personal fees from ChemoCentryx, grants and personal fees from GSK, personal fees from Sanofi, personal fees from InflaRx GmbH, outside the submitted work.

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 aimed 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-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 two-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 appendix 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.

Introduction

The anti-neutrophil 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)(1). 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(2) based on the expanding literature from the last 5 years. Full-length recommendations are contained within Data Supplement 1. Only new or revised recommendations from the original publication(2) are discussed. Data Supplement 2 contains treatment protocols and other practical guidance.

Methods

The full-length version of the article (Data Supplement 1) 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-September 2019, updated January and March 2020) included guidelines, randomized controlled trials (RCTs), systematic reviews and/or meta-analyses, 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 paediatric publications, and CP). The evidence and strength for revised and new recommendations were graded according to EULAR criteria (Table 2)(3). Through a modified Delphi consensus procedure, a 36-member working group voted on the inclusion, grading and wording of each recommendation. Disagreements were resolved in two rounds of

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

Results

I. Updated Diagnostic Recommendations

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 (Category 2A, Strength B)**.

Performance characteristics of antigen-specific immunoassays (first, second, third generation enzyme-linked immunosorbent assay [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 c-ANCA and p-ANCA, using a large cohort of untreated GPA or MPA patients and controls(4). Antigen-specific immunoassays had superior performance to the two IIF techniques (Areas Under Curve 0.92-0.95 vs 0.84 and 0.92)(4). High-quality antigen-specific immunoassays are now recommended for PR3- and MPO-ANCA detection in patients with suspected GPA or MPA(5). In selected patients with negative antigen-specific immunoassay testing but a high clinical suspicion of AAV, a second assay or IIF can improve sensitivity(5).

II. Updated Therapeutic Recommendations

A. Updated Recommendations for Induction Treatment of GPA and MPA

5 a. An initial dose of 1 mg/kg/day prednisone equivalent (no greater than 80 mg/day) is recommended for remission induction in adult patients with severe GPA or MPA. (Category 2A, Strength C).

While the optimal glucocorticoid starting dose in severe AAV is unknown, prednisone 1 mg/kg/day (not exceeding 80 mg/day) has been a common practice(6). Patients with non-severe/limited GPA can start at lower prednisone starting doses (e.g., 0.5 mg/kg/day)(7).

5. b. Pulse IV methylprednisolone (0.5-1 grams per 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(2). However, observational data suggest a lack of benefit and potential harm compared to high-dose GC without pulses.

Two retrospective studies of severe AAV patients (Cr >500 μmol/L or dialysis) found no difference in one-year overall survival or renal recovery(8, 9), and time to renal recovery or relapses(8) 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(8). Other

studies also found IV MP to be independently associated with severe infections(10, 11), and treatment-related damage(12).

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.

6.a. A GC tapering protocol should be initiated within 2 weeks of induction therapy in patients with severe GPA or MPA (Category 2A, Strength C). b. A reduced-dose GC tapering protocol can be considered in adult patients with severe GPA or MPA who are receiving cyclophosphamide (CYC) or rituximab (RTX) 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 RTX or CYC (Table S5, Data Supplement 2.3)(6, 13). The PEXIVAS trial(13) 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 non-inferior to a “standard” regimen reaching 15-25 mg/day by 3 months for the composite endpoint of death or end-stage renal disease (ESRD), and resulted in fewer serious infections(13). 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 recent meta-analysis of RAVE(6) and RITUXVAS(14) confirmed no difference between RTX and CYC for remission at 6-months, relapse at 12 months, death, or serious adverse events including infections(15). Post-hoc analyses of the RAVE trial found that subgroups with relapsing disease(16) and PR3-ANCA(17) achieved higher remission rates with RTX compared to CYC plus azathioprine. 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 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(18). Data Supplement 2 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(13). 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)(13). A meta-analysis assessing plasma exchange for the outcome of dialysis at one year (not including PEXIVAS data) found that plasma exchange reduced dialysis risk at 12 months (RR 0.45, 95% CI 0.29,0.72)(15). Meta-analyses 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)(15).

PEXIVAS included patients with pulmonary hemorrhage (27%) and creatinine ≥ 500 µmol/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(19) 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 anti-glomerular basement membrane (anti-GBM) antibodies(20), 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 (MMF) in combination with GC can be considered (Category 1B, Strength A).

Two recent open-label, multi-centre RCTs compared MMF to IV(21) or oral(22) CYC for induction, excluding patients with very severe disease. MYCYC(21) found non-inferiority for remission at 6 months (67% MMF and 61% CYC) and time to remission, but relapse-free survival was lower in the MMF group(21). 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 prednisone <10 mg at 6 months (62% vs 36%)(22). Patients in the highest tertile of disease severity were less likely to respond to MMF(22).

A meta-analysis including these 2 studies plus two prior RCTs from China (primarily MPO-ANCA positive patients with more severe renal disease(23, 24)), found no difference between MMF or CYC for remission, relapse, serious adverse events, or infection(25). 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(26) trial demonstrated long-term superiority of RTX over AZA for preventing major relapses after CYC induction(27). RITAZAREM was an open-label RCT comparing maintenance RTX (1 g every 4 months) to AZA (2mg/kg/day) among 170 patients with relapsing disease (72% PR3+) after RTX induction(28). At month 24, RTX showed superior relapse-free survival compared to AZA (HR 0.36, 95% CI 0.23-0.57), fewer serious adverse events (22% vs 36%), and no difference in infection rates(28). No RCTs have compared RTX to other maintenance therapies among non-relapsing 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(29). RTX biosimilars could thus be used for induction and maintenance of GPA and MPA if they receive approval.

15. a. "Tailored" RTX maintenance, with re-treatment based on ANCA titre rise, switch from negative to positive ANCA, or repopulation of CD19+ B cell subsets(30), 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 re-infusion if ANCA titres became positive, ELISA value rose two-fold, IIF titre increased ≥2 dilutions, or CD19 B cells rose above 0/mm^3, repeating ANCA and CD19 B cells at 3-month intervals)(30). 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(30).

A tailored regimen may reduce RTX cost, though 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.

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

Rising ANCA titre(31), return to ANCA positivity(32, 33), or persistently positive ANCA(27, 34) are associated with increased risk of relapse, while ANCA negative status is associated with decreased relapse risk(33, 35). While not all relapsing patients have detectable B cells(32, 36), relapse-free survival was lower among patients who repopulated B cells within 12 months(32). 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.

While 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.

16. In patients with GPA or MPA who received CYC or RTX induction therapy, azathioprine (AZA) or methotrexate (MTX) 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). b. 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 MTX maintenance(37). In a network meta-analysis of RCTs comparing MTX, AZA, LEF, and MMF for maintenance therapy, estimates for a superior agent were statistically inconclusive, but MMF was overall inferior(38). Observational data suggest that patients in stable remission who received MMF induction can continue MMF for maintenance(39).

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

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 non-biologic immunosuppressants following GC-CYC induction

Two RCTs(34, 41) compared “standard” to “extended” maintenance therapy among patients who received CYC induction. In a Dutch study(41), relapse-free survival was 52% among patients randomized to taper AZA after one year and 72% among those who continued for 4 years, although the difference was not statistically significant(41). In the REMAIN trial(34) 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(34). A meta-analysis 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(15).

In patients with a history of prior relapse, significant pre-existing 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, pre-existing damage, and patient preference.

17.2 Maintenance duration of RTX

MAINRITSAN 3(42) enrolled 97 patients in remission at month 28 from MAINRITSAN 2 (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 versus 74% in the placebo group (HR 7.5, 95% CI 1.7-33.7) with no difference in serious adverse events(42). 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 (Data Supplement 2.3).

C. Updated Recommendations for the Treatment of EGPA

20. An initial dose of 1 mg/kg/day prednisone equivalent (no greater than 80 mg/day) is recommended for remission induction in patients with severe EGPA (Category 2A Strength C). b. Pulse IV methylprednisolone 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-prognosis factors (ie, Five Factor Score [FFS] ≥ 1), IV MP pulses were given to 72% of patients(43). There are no studies comparing the efficacy of pulse versus 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(44) 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 ≥ 1, IV CYC pulses led to complete remission in 89%(43). Extrapolating from GPA and MPA data (34, 37, 38), CYC induction should be followed by either AZA or MTX maintenance (with LEF or MMF as alternatives) for a minimum of two years.

23. Patients with non-severe 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 non-severe (FFS=0), newly diagnosed EGPA (n=51), MPA (n=25), or polyarteritis nodosa (n=19)(45). Within the EGPA subset at 2 and 5 years, relapse-free survival did not differ between groups(46). 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(47). Until further data is 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 SC monthly can be considered in non-severe, glucocorticoid-dependent refractory or relapsing EGPA (Category 1B, Strength A).

MIRRA(48) compared mepolizumab (300mg subcutaneously [SC] 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 (BVAS=0) at week 36 and 48 occurred more often in the mepolizumab group (OR 16.74, 95% CI 3.6-77.6)(48). Relapse rates were reduced but remained high overall (56% vs 82% with placebo), with no difference in serious adverse events(48). However, MIRRA was unable to determine the efficacy of mepolizumab for acute vasculitic manifestations or myocarditis (48). As of yet, no anti-IL-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 centres of expertise (Category 4, Strength D).

Case series have suggested benefit of RTX for patients with relapsing or refractory EGPA(49, 50). Response or median time to remission may be better in ANCA positive patients(50). A retrospective study comparing 14 RTX-recipients to 14 CYC-recipients found similar remission (36% vs 29%) and relapse-free survival rates between groups(51). While two RCTs will evaluate RTX for EGPA induction (NCT02807103) and maintenance (NCT03164473), currently RTX should be reserved for patients who have failed conventional therapies and should be discussed with a centre 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 (SGS) occurs in 10-23% of GPA patients(52, 53) while bronchial stenosis is rarer(52). Cohort studies have demonstrated efficacy of dilatation procedures, often with intralesional corticosteroid injection, but recurrent stenosis is common, requiring repeated procedures(53, 54). 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)(55). Based on these limited data, patients with SGS and bronchial stenosis may benefit from peri-procedural 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, multi-centre, single-arm trial of RTX induction (375 mg/m^2 weekly for 4 doses) was conducted in 25 pediatric patients with new or relapsing GPA and MPA, excluding those with alveolar hemorrhage or hemodialysis(56). 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(56). This outcome is comparable to a cohort of 105 pediatric AAV patients who primarily received CYC(57). 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

36. a. 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).

b. Patients should be counselled on the increased risk of non-melanoma skin cancer after exposure to CYC and/or other conventional immunosuppressants (Category 3, Strength D).

AAV patients exposed to CYC have an increased risk of non-melanoma skin cancer (58-60) that may be accelerated by subsequent long-term AZA(59). Studies have demonstrated an increased risk of other malignancies with cumulative CYC exposure >25-36g(58-60), thus cumulative CYC

>25g should be avoided if possible. Patients exposed to CYC should undergo long-term urinalysis monitoring, and persistent unexplained hematuria evaluated with cystoscopy.

37. a. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis should be prescribed to prevent infection during induction therapy with CYC or RTX (Category 3, Strength C). b. 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 (PJP) 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 (Data Supplement 2.3). Furthermore, an RCT of therapeutic TMP-SMX in GPA(40) and a recent observational study of (primarily) prophylactic-dose TMP-SMX in RTX recipients(61) 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(6).

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 (VZV) subunit (non-live) 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 (PCV13) followed by 23-valent pneumococcal polysaccharide vaccine (PPV23) at least 8 weeks later (Data Supplement 2.4)(62, 63).

AAV patients should also receive annual influenza vaccination and any available non-live vaccinations to other seasonal and/or pandemic viruses. In an RCT, trivalent influenza

immunogenicity among AAV patients in remission was acceptable (although attenuated compared controls)(64), and did not increase relapse risk(64). The high-dose influenza vaccine, which has greater immunogenicity in immunocompromised patients(65), requires study in AAV.

VZV infections are common in AAV(66). The recombinant zoster vaccine (RZV) 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(67). 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(66, 68). Risk factors for persistent or severe hypogammaglobulinemia include baseline low IgG(68), older age(68) and prior CYC(69). Immunoglobulin replacement (e.g. 0.4g/kg IVIg/month) is indicated if hypogammaglobulinemia is associated with “serious, persistent, unusual, or recurrent infections”(68-70).

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 immunoglobulin replacement if needed.

Conclusions

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 judgement 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 AAV patients in whom diagnostic or therapeutic uncertainty remains.

Acknowledgements:

CanVasc wishes to acknowledge the work of Brandon Lee, Renee Aklass, and Michael Wiensczyk, members of the Canadian Glomerulonephritis Registry and Canadian Rheumatology Association Guidelines Committee for their critical review of the updated recommendations.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1-11.
2. McGeoch L, Twilt M, Famorca L, Bakowsky V, Barra L, Benseler SM, et al. CanVasc Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitides. J Rheumatol 2016;43:97-120.
3. van der Heijde D, Aletaha D, Carmona L, Edwards CJ, Kvien TK, Kouloumas M, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Ann Rheum Dis 2015;74:8-13.
4. Damoiseaux J, Csernok E, Rasmussen N, Moosig F, van Paassen P, Baslund B, et al. Detection of antineutrophil cytoplasmic antibodies (ANCAs): a multicentre European Vasculitis Study Group (EUVAS) evaluation of the value of indirect immunofluorescence (IIF) versus antigen-specific immunoassays. Ann Rheum Dis 2017;76:647-53.
5. Bossuyt X, Cohen Tervaert JW, Arimura Y, Blockmans D, Flores-Suarez LF, Guillevin L, et al. Position paper: Revised 2017 international consensus on testing of

ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol 2017;13:683-92.
6. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.
7. Langford CA, Monach PA, Specks U, Seo P, Cuthbertson D, McAlear CA, et al. An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). Ann Rheum Dis 2014;73:1376-9.
8. Chanouzas D, McGregor JAG, Nightingale P, Salama AD, Szpirt WM, Basu N, et al. Intravenous pulse methylprednisolone for induction of remission in severe ANCA associated vasculitis: a multi-center retrospective cohort study. BMC Nephrol 2019;20:58.
9. Huang L, Zhong Y, Ooi JD, Zhou YO, Zuo X, Luo H, et al. The effect of pulse methylprednisolone induction therapy in Chinese patients with dialysis-dependent MPO-ANCA associated vasculitis. Int Immunopharmacol 2019;76:105883.
10. Yamaguchi M, Katsuno T, Iwagaitsu S, Nobata H, Kinashi H, Banno S, et al. Oral candidiasis is a significant predictor of subsequent severe infections during immunosuppressive therapy in anti-neutrophil cytoplasmic antibody-associated vasculitis. BMC Infect Dis 2019;19:664.
11. Sakai R, Tanaka E, Nishina H, Suzuki M, Yamanaka H, Harigai M. Risk of opportunistic infections in patients with antineutrophil cytoplasmic antibody-associated vasculitis, using a Japanese health insurance database. Int J Rheum Dis 2019.
12. Weiner M, Goh SM, Mohammad AJ, Hruskova Z, Tanna A, Sharp P, et al. Impact of treatment on damage and hospitalization in elderly patients with microscopic polyangiitis and granulomatosis with polyangiitis. J Rheumatol 2020;47:580-8.
13. Walsh M, Merkel PA, Peh CA, Szpirt W, Puechal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 2020;382:622-31.
14. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.
15. Walters GD, Willis NS, Cooper TE, Craig JC. Interventions for renal vasculitis in adults. Cochrane Database Syst Rev 2020;1:CD003232.
16. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417-27.
17. Unizony S, Villarreal M, Miloslavsky EM, Lu N, Merkel PA, Spiera R, et al. Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. Ann Rheum Dis 2016;75:1166-9.
18. Geetha D, Hruskova Z, Segelmark M, Hogan J, Morgan MD, Cavero T, et al. Rituximab for treatment of severe renal disease in ANCA associated vasculitis. J Nephrol 2016;29:195-201.
19. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180-8.

20. Kaewput W, Thongprayoon C, Boonpheng B, Ungprasert P, Bathini T, Chewcharat A, et al. Inpatient burden and mortality of Goodpasture's syndrome in the United States: nationwide inpatient sample 2003-2014. J Clin Med 2020;9.
21. Jones RB, Hiemstra TF, Ballarin J, Blockmans DE, Brogan P, Bruchfeld A, et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. Ann Rheum Dis 2019.
22. Tuin J, Stassen PM, Bogdan DI, Broekroelofs J, van Paassen P, Cohen Tervaert JW, et al. Mycophenolate mofetil versus cyclophosphamide for the induction of remission in nonlife-threatening relapses of antineutrophil cytoplasmic antibody-associated vasculitis: randomized, controlled trial. Clin J Am Soc Nephrol 2019;14:1021-8.
23. Hu W, Liu C, Xie H, Chen H, Liu Z, Li L. Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement. Nephrol Dial Transplant 2008;23:1307-12.
24. Han F, Liu G, Zhang X, Li X, He Q, He X, et al. Effects of mycophenolate mofetil combined with corticosteroids for induction therapy of microscopic polyangiitis. Am J Nephrol 2011;33:185-92.
25. Song GG, Lee YH. Comparative efficacy and safety of mycophenolate mofetil versus cyclophosphamide in patients with active antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis of randomized trials. Z Rheumatol 2020.
26. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771-80.
27. Terrier B, Pagnoux C, Perrodeau E, Karras A, Khouatra C, Aumaitre O, et al. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. Ann Rheum Dis 2018;77:1150-6.
28. Smith R, Jayne D, Merkel PA. A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients wtih ANCA-associated vasculitis and relapsing disease [abstract]. Arthritis Rheum 2019;71.
29. Smolen JS, Cohen SB, Tony HP, Scheinberg M, Kivitz A, Balanescu A, et al. A randomised, double-blind trial to demonstrate bioequivalence of GP2013 and reference rituximab combined with methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 2017;76:1598-602.
30. Charles P, Terrier B, Perrodeau E, Cohen P, Faguer S, Huart A, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77:1143-9.
31. Fussner LA, Hummel AM, Schroeder DR, Silva F, Cartin-Ceba R, Snyder MR, et al. Factors determining the clinical utility of serial measurements of antineutrophil cytoplasmic antibodies targeting proteinase 3. Arthritis Rheumatol 2016;68:1700-10.
32. Alberici F, Smith RM, Jones RB, Roberts DM, Willcocks LC, Chaudhry A, et al. Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. Rheumatology (Oxford) 2015;54:1153-60.
33. Watanabe H, Sada KE, Matsumoto Y, Harigai M, Amano K, Dobashi H, et al. Association between reappearance of myeloperoxidase-antineutrophil cytoplasmic antibody and relapse in antineutrophil cytoplasmic antibody-associated vasculitis:

Subgroup analysis of nationwide prospective cohort studies. Arthritis Rheumatol 2018;70:1626-33.
34. Karras A, Pagnoux C, Haubitz M, Groot K, Puechal X, Tervaert JWC, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. Ann Rheum Dis 2017;76:1662-8.
35. McClure ME, Wason J, Gopaluni S, Tieu J, Smith RM, Jayne DR, et al. Evaluation of PR3-ANCA status after rituximab for ANCA-associated vasculitis. J Clin Rheumatol 2019.
36. Puechal X, Iudici M, Calich AL, Vivot A, Terrier B, Regent A, et al. Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: a single-centre cohort study on 114 patients. Rheumatology (Oxford) 2019;58:401-9.
37. Puechal X, Pagnoux C, Perrodeau E, Hamidou M, Boffa JJ, Kyndt X, et al. Long-term outcomes among participants in the WEGENT trial of remission-maintenance therapy for granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis. Arthritis Rheumatol 2016;68:690-701.
38. Hazlewood GS, Metzler C, Tomlinson GA, Gross WL, Feldman BM, Guillevin L, et al. Non-biologic remission maintenance therapy in adult patients with ANCA-associated vasculitis: a systematic review and network meta-analysis. Joint Bone Spine 2014;81:337-41.
39. Draibe J, Poveda R, Fulladosa X, Vidaller A, Zulberti C, Goma M, et al. Use of mycophenolate in ANCA-associated renal vasculitis: 13 years of experience at a university hospital. Nephrol Dial Transplant 2015;30 Suppl 1:i132-7.
40. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med 1996;335:16-20.
41. Sanders JS, de Joode AA, DeSevaux RG, Broekroelofs J, Voskuyl AE, van Paassen P, et al. Extended versus standard azathioprine maintenance therapy in newly diagnosed proteinase-3 anti-neutrophil cytoplasmic antibody-associated vasculitis patients who remain cytoplasmic anti-neutrophil cytoplasmic antibody-positive after induction of remission: a randomized clinical trial. Nephrol Dial Transplant 2016;31:1453-9.
42. Charles P, Perrodeau E, Samson M, Bonnotte B, Neel A, Agard C, et al. Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Trial. Ann Intern Med 2020.
43. Samson M, Puechal X, Devilliers H, Ribi C, Cohen P, Stern M, et al. Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. J Autoimmun 2013;43:60-9.
44. Groh M, Pagnoux C, Baldini C, Bel E, Bottero P, Cottin V, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med 2015;26:545-53.
45. Puechal X, Pagnoux C, Baron G, Quemeneur T, Neel A, Agard C, et al. Adding azathioprine to remission-induction glucocorticoids for eosinophilic granulomatosis with polyangiitis (Churg-Strauss), microscopic polyangiitis, or polyarteritis nodosa without poor prognosis factors: a randomized, controlled trial. Arthritis Rheumatol 2017;69:2175-86.

46. Puechal X, Pagnoux C, Baron G, Lifermann F, Geffray L, Quemeneur T, et al. Non-severe eosinophilic granulomatosis with polyangiitis: long-term outcomes after remission-induction trial. Rheumatology (Oxford) 2019.
47. Doubelt I, Pulenzas N, Carette S, Pagnoux C, Network CVR. Efficacy of conventional immunosuppressants in relapsing or refractory eosinophilic granulomatosis with polyangiitis: evidence from a Canadian single-centre cohort. Clin Exp Rheumatol 2020.
48. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med 2017;376:1921-32.
49. Mohammad AJ, Hot A, Arndt F, Moosig F, Guerry MJ, Amudala N, et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Ann Rheum Dis 2016;75:396-401.
50. Teixeira V, Mohammad AJ, Jones RB, Smith R, Jayne D. Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis. RMD Open 2019;5:e000905.
51. Thiel J, Troilo A, Salzer U, Schleyer T, Halmschlag K, Rizzi M, et al. Rituximab as induction therapy in eosinophilic granulomatosis with polyangiitis refractory to conventional immunosuppressive treatment: a 36-month follow-up analysis. J Allergy Clin Immunol Pract 2017;5:1556-63.
52. Quinn KA, Gelbard A, Sibley C, Sirajuddin A, Ferrada MA, Chen M, et al. Subglottic stenosis and endobronchial disease in granulomatosis with polyangiitis. Rheumatology (Oxford) 2019.
53. Fijolek J, Wiatr E, Gawryluk D, Martusewicz-Boros MM, Orlowski TM, Dziedzic D, et al. Intratracheal dilation-injection technique in the treatment of granulomatosis with polyangiitis patients with subglottic stenosis. J Rheumatol 2016;43:2042-8.
54. Girard C, Charles P, Terrier B, Bussonne G, Cohen P, Pagnoux C, et al. Tracheobronchial stenoses in granulomatosis with polyangiitis (Wegener's): a report on 26 cases. Medicine (Baltimore) 2015;94:e1088.
55. Terrier B, Dechartres A, Girard C, Jouneau S, Kahn JE, Dhote R, et al. Granulomatosis with polyangiitis: endoscopic management of tracheobronchial stenosis: results from a multicentre experience. Rheumatology (Oxford) 2015;54:1852-7.
56. Brogan P, Cleary G, O. HA, Kasapcopur O, Rangaraj S, Yeung R, et al. Pediatric open-label clinical study of rituximab for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) [abstract]. Arthritis Rheum 2018;70.
57. Morishita KA, Moorthy LN, Lubieniecka JM, Twilt M, Yeung RSM, Toth MB, et al. Early outcomes in children with antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2017;69:1470-9.
58. Faurschou M, Mellemkjaer L, Voss A, Keller KK, Hansen IT, Baslund B. Prolonged risk of specific malignancies following cyclophosphamide therapy among patients with granulomatosis with polyangiitis. Rheumatology (Oxford) 2015;54:1345-50.
59. Rahmattulla C, Berden AE, Wakker SC, Reinders ME, Hagen EC, Wolterbeek R, et al. Incidence of malignancies in patients with antineutrophil cytoplasmic antibody-

associated vasculitis diagnosed between 1991 and 2013. Arthritis Rheumatol 2015;67:3270-8.
60. van Daalen EE, Rizzo R, Kronbichler A, Wolterbeek R, Bruijn JA, Jayne DR, et al. Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis. Ann Rheum Dis 2017;76:1064-9.
61. Kronbichler A, Kerschbaum J, Gopaluni S, Tieu J, Alberici F, Jones RB, et al. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2018;77:1440-7.
62. Centers for Disease C, Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012;61:816-9.
63. Groh M, Puechal X, Terrier B, Le Jeunne C, Batteux F, Launay O. Failure of pneumococcal immunization during remission induction treatment of ANCA-associated vasculitis: The Pneumovas Pilot 1 study. Joint Bone Spine 2017;84:643-4.
64. Jeffs LS, Peh CA, Jose MD, Lange K, Hurtado PR. Randomized trial investigating the safety and efficacy of influenza vaccination in patients with antineutrophil cytoplasmic antibody-associated vasculitis. Nephrology (Carlton) 2015;20:343-51.
65. Lai JJ, Lin C, Ho CL, Chen PH, Lee CH. Alternative-dose versus standard-dose trivalent influenza vaccines for immunocompromised patients: a meta-analysis of randomised control trials. J Clin Med 2019;8.
66. Shah S, Jaggi K, Greenberg K, Geetha D. Immunoglobulin levels and infection risk with rituximab induction for anti-neutrophil cytoplasmic antibody-associated vasculitis. Clin Kidney J 2017;10:470-4.
67. Papp KA, Haraoui B, Kumar D, Marshall JK, Bissonnette R, Bitton A, et al. Vaccination guidelines for patients with immune-mediated disorders taking immunosuppressive therapies: executive summary. J Rheumatol 2019;46:751-4.
68. Cortazar FB, Pendergraft WF, 3rd, Wenger J, Owens CT, Laliberte K, Niles JL. Effect of continuous B cell depletion with rituximab on pathogenic autoantibodies and total IgG levels in antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2017;69:1045-53.
69. Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun 2015;57:60-5.
70. Wijetilleka S, Mukhtyar C, Jayne D, Ala A, Bright P, Chinoy H, et al. Immunoglobulin replacement for secondary immunodeficiency after B-cell targeted therapies in autoimmune rheumatic disease: Systematic literature review. Autoimmun Rev 2019.

Table 1: Questions informing the literature review for updated recommendations

Question	Vote (n=19)
1. Which of indirect immunofluorescence and/or high-quality immunoassay should be recommended for ANCA detection in patients with suspected ANCA-associated vasculitis?	100%
2. In patients undergoing induction therapy for severe AAV, does pulse methylprednisolone confer clinical benefit compared to no pulse?	100%
3. 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%
4. In patients undergoing induction therapy for severe GPA and MPA, does plasma exchange confer clinical benefit compared to no plasma exchange?	100%
5. In patients undergoing induction therapy for GPA and MPA, does MMF have comparable clinical efficacy to CYC?	100%
6. In patients with severe AAV, which maintenance agents are effective?	100%
7. In patients with GPA and MPA, does extended maintenance therapy (48 months) lead to fewer relapses compared to standard (24 months) maintenance therapy?	100%
8. In patients with GPA and MPA, which RTX maintenance regimens are effective?	100%
9. In patients with GPA and MPA receiving RTX, should gamma globulins be monitored and how should hypogammaglobulinemia be managed?	100%
10. In patients with GPA and MPA receiving RTX, should B cells (CD19) be monitored to determine the risk of relapse?	95%
11. In patients with AAV, should ANCAs be monitored to determine the risk of relapse?	100%
12. In patients with non-severe EGPA or MPA (FFS=0), does the addition of conventional immunosuppressants to GC improve remission or relapse rate?	95%
13. In patients with EGPA, is there a role for biological therapies for induction or maintenance?	95%

14. In patients receiving RTX or CYC for AAV, does trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis reduce severe infection risk?	95%
15. In patients with AAV, which vaccinations are safe, effective, and recommended?	95%
Additional topics of interest included in the literature search based on CanVasc member feedback:	
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 AAV of reproductive age requiring treatment with CYC, how can fertility be preserved? In patients with GPA or MPA with subglottic stenosis, which medical treatments are effective? In patients with AAV, what is the efficacy other biologics or RTX biosimilars?	

Legend: AAV, ANCA-associated vasculitis; GC, glucocorticoids; MMF, mycophenolate mofetil; CYC, cyclophosphamide; RTX, rituximab, EGPA, eosinophilic granulomatosis with polyangiitis; MPA, microscopic polyangiitis; FFS, Five Factor Score; AZA, azathioprine; MTX, methotrexate; TMP-SMX, trimethoprim sulfamethoxazole; GPA, granulomatosis with polyangiitis

Table 2. Level of evidence and grading of recommendations*

Category of evidence	Evidence source
1A	From meta-analysis 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 of recommendation based on level of evidence	
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

*Following European League Against Rheumatism (EULAR) criteria[3]

Table 3. Updated Recommendations: executive summary (new and revised recommendations in bold)

Recommendation	Grading[3]
Diagnosis	
1. A high-quality antigen specific-immunoassay for PR3-ANCA and MPO-ANCA is the preferred method of ANCA detection in patients in whom there is clinical suspicion of ANCA-associated vasculitis	**Category 2A, Strength B**
2. Tissue biopsy should be considered in cases of suspected AAV to confirm diagnosis	Category 4, Strength D
Disease severity in AAV	
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
The role of vasculitis referral centres	
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
Induction of GPA and MPA	
5. a. An initial dose of 1 mg/kg/day prednisone equivalent (no greater than 80 mg/day) is recommended for remission induction in adult patients with severe GPA or MPA. **b. Pulse IV methylprednisolone (0.5-1g per 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.**	**5a. Category 2A, Strength C** **5b. Category 3, Strength D**
6 a. A glucocorticoid (GC) tapering protocol should be initiated within 2 weeks of induction therapy in patients with severe GPA or MPA.	**6a Category 2A, Strength C**

b. A reduced-dose GC tapering protocol can be considered in adult patients with severe GPA or MPA who are receiving cyclophosphamide (CYC) or rituximab (RTX) induction therapy, to reduce cumulative GC exposure and infection risk.	**6b. 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 methotrexate (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 mycophenolate mofetil (MMF) in combination with GC can be considered.	**Category 1B, Strength A**
Treatment of GPA and MPA relapse	
12. We recommend that relapses that are nonsevere, i.e., nonlife- and nonorgan-threatening, be treated with an increase in GC dose in	Category 3, Strength C

addition to optimizing the patient's concurrent immunosuppressant agent	
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
Remission maintenance - 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**
15. a. "Tailored" RTX maintenance, with re-treatment based on ANCA titre rise, switch from negative to positive ANCA, or repopulation of CD19+ B cell subsets can be an alternative maintenance strategy in adults with GPA or MPA who received CYC or RTX induction therapy **b. Outside of "tailored" RTX maintenance, there is insufficient evidence to recommend escalating immunosuppressive therapy based on ANCA titre or CD 19 B cell rise.**	**a. Category 1B, Strength B** **b. Category 4, Strength D**
16. a. In patients with GPA or MPA who received CYC or RTX induction therapy, azathioprine (AZA) or MTX can be used for maintenance therapy when RTX maintenance cannot be used **b. MMF or leflunomide (LEF) can be considered as alternative maintenance therapies in patients with contraindications, poor tolerance, or lack of response to other agents**	**a. Category 1B, Strength B for maintenance after CYC induction; Category 3, Strength C for maintenance after RTX induction**

	b. Category 1B, Strength B for LEF; Category 3, Strength C for MMF
17. In patients with GPA/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
19. Topical therapies may be considered, in combination with the systemic therapy and in collaboration with ENT subspecialists, to alleviate the symptoms of upper airway and ENT disease	Category 3, Strength C
EGPA	
20. a. An initial dose of 1 mg/kg/day prednisone equivalent (no greater than 80 mg/day) is recommended for remission induction in patients with severe EGPA. b. Pulse IV methylprednisolone can be considered in severe, organ or life-threatening EGPA, but lacks proven efficacy and carries a potential risk of adverse effects.	**Category 2A, Strength C** **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 non-severe EGPA without major organ involvement or poor prognostic factors may be treated with GC alone for initial induction therapy	**Category 1B, Strength A**
24. Mepolizumab 300 mg SC monthly can be considered in non-severe, glucocorticoid-dependent refractory or relapsing EGPA	**Category 1B, Strength A**
25. Consideration of other (off-label) therapies for EGPA should be made in collaboration with centres 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
Refractory disease	
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
Special patient 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**
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

Pediatric ANCA-associated vasculitis	
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 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
Monitoring and Prevention in AAV	
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
Cyclophosphamide - safety considerations	

36. a. 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. b. Patients should be counselled on the increased risk of non-melanoma skin cancer after exposure to CYC and/or other conventional immunosuppressants.	**Category 3, Strength D.**
Infection prevention	
37. a. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis should prescribed to prevent infection during induction therapy with CYC or RTX **b. Prophylaxis should continue for at least 3 months following CYC cessation and 6 months following last RTX dose**	**a. Category 3, Strength C** **b. Category 4, Strength D**
38. Pneumococcal vaccination and annual influenza vaccination are recommended in all patients with AAV receiving immunosuppression. Recombinant varicella zoster virus (VZV) subunit vaccine (non-live) can be offered all adult patients at risk	***Pneumococcal*: Category 3, Strength D** ***Influenza*: Category 1B, Strength B** ***VZV*: Category 4, Strength D**
39. Immunoglobulin levels should be checked in patients receiving RTX who experience serious or recurrent infections	**Category 3, Strength D**

Legend: MPO, myeloperoxidase; PR3, proteinase-3; ANCA, anti-neutrophil cytoplasm antibody; AAV, anti-neutrophil cytoplasm antibody associated vasculitis; mg, milligrams; kg, kilograms; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; IV, intravenous; GC, glucocorticoid(s); CYC, cyclophosphamide; RTX, rituximab; MTX, methotrexate; MMF, mycophenolate mofetil; CD19, cluster of differentiation 19; AZA, azathioprine; LEF, leflunomide; ENT, ear-nose-throat (otolaryngologist); EGPA, eosinophilic granulomatosis with polyangiitis; SC, subcutaneously; TMP-SMX, trimethoprim sulfamethoxazole; VZV, varicella zoster virus.

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 non-severe 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 to making therapeutic decisions (escalation or de-escalation)?
9. Is there equal access to evidence-based treatments for AAV in Canada and do inequities impact the survival and outcomes of Canadians with AAV?
10. Are there any parameters to use to further individualize treatment in AAV patients (genetics, genomics)? Would such strategies be cost-effective?

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