Online supplement to: CanVasc Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitides: Short Version. *The Journal of Rheumatology.* doi:10.3899/jrheum.150376

ONLINE SUPPLEMENTARY DATA 1

ONLINE APPENDICES

Appendix 1. **Tests and investigations in ANCA-associated vasculitis**

Laboratory Investigations

We recommend the following tests be performed in all patients with suspected ANCA-associated vasculitis (AAV) at the time of diagnosis:

- Complete blood count (CBC)
- C-reactive protein, erythrocyte sedimentation rate (ESR)
- Liver function tests
- Renal function (creatinine, GFR)
- Dipstick urinalysis, and *if* urine dipstick positive for protein and/or blood:
    - 24hour urinary protein quantification
    - *or,* random urine protein: creatinine ratio.
    - Urine microscopic (for casts)
- ANCA, by indirect immunofluorescence and ELISA (both recommended for diagnosis).
- AntiGBM (glomerular basement membrane) antibody in patients with renal disease and/or alveolar hemorrhage

The following tests may be considered in patients with suspected AAV in order to rule out other causes of systemic vasculitis:

- Hepatitis B and C serologies
- Autoantibodies including Rheumatoid Factor, ANA (DNA binding antibodies and Extractable Nuclear Antigens (ENA) if ANA positive).
- Complement fractions C3 C4
- Cryoglobulins ± cryofibrinogen
- Serum immunoglobulins and protein electrophoresis (SPEP).

We recommend at each follow-up visit all patients have the following tested:

- Complete blood count (CBC)
- Renal function (creatinine, GFR)
- Liver function tests
- C-reactive protein and/or ESR
- Urine dipstick

Additional tests can be considered, depending on undergoing treatment and clinical status

- ANCA, by indirect immunofluorescence and ELISA (not more often than every 3 months – if only one possible, prefer ELISA for follow-up).
- B cell subsets if treated with Rituximab (CD19 B cell count)
- Immunoglobulin levels

Tissue Biopsy

The approximate diagnostic yield of biopsies of different tissue site in GPA is summarized below:

Tissue	**% 'positive' diagnostic yield**
Renal	85%[1]
Ear, Nose and Throat	24%[2]-68%[3]
Transbronchial lung (alveolar)	12%[3]
Open lung surgical biopsy/wedge lung biopsy	Up to 90%[4, 5]
Subglottic stenotic lesion	5-15%[6, 7]

Table S1. Diagnostic yield of tissue biopsy in GPA

Appendix 2. Disease severity in ANCA-associated vasculitis

Granulomatosis with Polyangiitis (GPA)

Study Group	Clinical Subgroup	Systemic Vasculitis outside ENT tract and lung	Threatened Vital Organ Function	Other definitions	Serum Creatinine (µmol/l)
EUVAS/EULAR[8]	Localized	No	No	No constitutional symptoms	< 120
	Early systemic	Yes	No	Constitutional symptoms present ANCA positive or negative	<120
	Generalized	Yes	Yes	ANCA positive	< 500
	Severe	Yes	Organ failure	ANCA positive	> 500
	Refractory	Yes	Yes	Refractory to standard therapy	Any
WGET Research Group/VCRC[9]	Limited	Allowed but not required	No	Not severe	< or = 124 but no red cell casts present
	Severe	Yes	Yes	Organ or life threatening disease implies need for remission induction with CYC	Any

Table S2. Definitions for disease stages used for sub classification of patients with granulomatosis with polyangiitis in clinical trials.

ANCA. Antineutrophil cytoplasmic antibody; CYC, cyclophosphamide; ENT, ear, nose and throat; EUVAS, European Vasculitis Study Group; VCRC, Vasculitis Clinical Research Consortium; WGET, Wegener's Granulomatosis in Etanercept Trial

Eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis: the Five Factor Score[10]

Five prognostic factors for EGPA and MPA (also for polyarteritis nodosa) include:

I. Central nervous system involvement
II. Severe gastrointestinal involvement
III. Proteinuria ≥ 1g/day
IV. Serum Creatinine > 1.58mg/dl (140 µmol/l)
V. Cardiomyopathy (diagnosed clinically and/or on echocardiography)

FFS	5-year Mortality rate (%)
0	11.9
1	25.9
2	45.95

Table S3. Five Factor Score (FFS) and mortality rates.

Eosinophilic granulomatosis with polyangiitis (EGPA), microscopic Polyangiitis (MPA) and Granulomatosis with Polyangiitis (GPA): The Revised 2009 Five Factor Score[11]

Revised five prognostic factors for EGPA, MPA and GPA (also for polyarteritis nodosa) include:

1. Age > 65 years.
2. Renal insufficiency (creatinine ≥150µmol/l).
3. Gastrointestinal involvement
4. Cardiac symptoms
5. Absence of ENT involvement (applies to EGPA and GPA only).

Revised FFS	5-year Mortality rate (%)
0	9
1	21
≥2	40

Table S4. Revised Five Factor Score (FFS) and mortality rates.

Appendix 3. Drug Prescribing in ANCA-associated vasculitis

GLUCOCORTICOIDS

Possible glucocorticoid regimens for the treatment of severe ANCA-associated vasculitis:

RITUXVAS prednisone tapering regimen

Time (weeks)	Prednisone dose (mg/kg/day)	Prednisone dose (mg/day) for 60kg patient
0 week	1 (maximum 80mg/day)*	60
1 week	0.75	45
2 weeks	0.5	30
3 weeks	0.4	25
6 weeks	0.33	20
8 weeks	0.25	15
	Prednisone dosage (mg/day)	
at end of month 3	12.5	12.5
at end of month 4	10	10
at end of month 5	7.5	7.5
at end of month 6	5	5
18- 24 months	Reduce from 5 to 0	

Table S7. Prednisone regimen used in RITUXVAS[12]

CYCLOPS/CYCAZAREM prednisone tapering regimen

Time from entry	Prednisone dosage mg/kg/day	Prednisone dosage (mg/day) for 60 kg patient
0 week	1 (maximum 80mg/day)	60
1 week	0.75	45
2 weeks	0.5	30
3 weeks	0.4	25
4 weeks	0.4	25
6 weeks	0.33	20
8 weeks	0.25	15
	Prednisone dosage (mg/day)	
12 weeks	15	15
16 weeks	12.5	12.5
6 months	10	10
During months 12–15	7.5	7.5
During months 15–18	5	5

Table S8. Prednisone regimen used in CYCLOPS and CYCAZAREM studies[13-15]

RAVE prednisone tapering regimen[16]

Initial dose: prednisone orally, 1 mg/kg/day, not to exceed 80 mg/day and rounded to the nearest 5 (following completion of intravenous glucocorticoids).

Prednisone Tapering: Physicians should reduce the prednisone dose to 40 mg/day by the end of month 1 (i.e., 1 month from the first day of rituximab or cyclophosphamide). Once a participant's dose has been decreased to 40 mg/day, the physicians will continue prednisone tapering as follows:

- Patients will maintain the dose of 40 mg/day for 2 weeks.
- Subsequently, they will reduce the dose in a stepwise fashion every 2 weeks to 30 mg/d, 20 mg/d, 15 mg/d, 10 mg/d, 7.5 mg/d, 5 mg/d, 2.5 mg/d, until the participant is completely off prednisone. The entire tapering process will require 20 weeks from the first day of rituximab or cyclophosphamide.

Patients who develop symptoms of adrenal insufficiency at <10 mg of prednisone/day may decrease their prednisone doses in 1 mg decrements weekly. Patients with documented pituitary insufficiency resulting from their AAV (damage) may continue their required replacement dose of prednisone (usually between 5 and 10 mg/day).

WGET prednisone tapering regimen[17]

• Initial treatment with 1 mg/kg/day of prednisone for the first 28 days, up to a maximum of 80 mg/day. Patients with fulminant disease may receive intravenous methylprednisone (1 g/day x 3 days) at the start of treatment. For patients with limited disease, the initial dose of prednisone may be lower than 1 mg/kg/day.

• After 28 days, prednisone is tapered by 10 mg/week (The goal: to achieve a dose of 20 mg/day by the end of 8–10 weeks of therapy)

• Then: 20 mg/day for 2 weeks
• Then: reduce dose by 2.5 mg/week until a dose of 10 mg/day is reached
• Then: reduce dose by 1 mg/week until off

Additional guidance for glucocorticoid prescribing:

- Above regime may be preceded by daily pulse of intravenous methylprednisolone (0.5-1g total dose per pulse) given for 1 to 3 consecutive days in patients with life threatening disease or when rapid onset of action deemed necessary.
- In children (<15 years old), the initial dose of oral prednisone is 1 to 2 mg/kg/day with a maximum of 60 mg/day. Some centers use initially divided doses of oral prednisone (e.g., 30mg twice per day).
- Daily calcium (500 to 1000mg) and vitamin D (1000 iU) supplementation is recommended

Osteoporosis prophylaxis

The long-term use of glucocorticoids increases the risk of osteoporosis. The prevention of osteoporosis should rely on the last, updated and available Canadian guidelines[18-20] (available at http://www.osteoporosis.ca). The presence of renal impairment in AAV patient adds a level of complexity in the therapeutic decisions for the prevention of osteoporosis. Referral to a centre specialized in the prevention and management of osteoporosis should be considered for these latter patients, as well as for women of child-bearing age and children.

The *2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada*[18] suggests:

- For patients undergoing long-term glucocorticoid therapy, the appropriate duration of osteoporosis treatment is unknown.
- For individuals over age 50 who are on long-term glucocorticoid therapy (≥ three months cumulative therapy during the preceding year at a prednisone-equivalent dose ≥ 7.5 mg daily), a bisphosphonate (alendronate, risedronate, zoledronic acid) should be initiated at the outset and should be continued for at least the duration of the glucocorticoid therapy [grade A].

- Teriparatide should be considered for those at high risk for fracture who are taking glucocorticoids (≥ three months cumulative therapy during the preceding year at a prednisone-equivalent dose ≥ 7.5 mg daily) [grade A].
- For long-term glucocorticoid users who are intolerant of first-line therapies, [calcitonin or – *removed from the Canadian market*] etidronate may be considered for preventing loss of bone mineral density [grade B].

BSR 2014 guidelines similar state that "Prophylaxis against osteoporosis should be considered in patients receiving corticosteroids. The need for treatment and fracture risk should be assessed following national guidance."[21]

CYCLOPHOSPHAMIDE

Oral preparation

- ***Dose***: 2 mg/kg/day, maximum dose 200 mg/day (same dosage in children).
- ***Additional guidance***:
  - Adequate oral hydration pre- and post-dose (approximately 2-3 l/day).
  - Oral mesna may be considered (no standardized regimen – 1 dose per day, of 40-50% that of the CYC daily dose [~1mg/kg], ideally taken 1 to 2 hours before the daily dose of cyclophosphamide OR 3 doses per day, each of 20% the CYC daily dose and taken 1-2 hours before CYC, then 4 and 8 hours later) – *evidence for mesna to effectiveness in preventing cystitis remains limited and there is no direct evidence for its effectiveness in preventing bladder cancer in humans.*
  - For patients receiving plasma exchange or dialysis, the CYC dose should be given after the plasma exchange or dialysis session.
- ***Recommended monitoring***:
  - Weekly CBC and renal function for the first month, every 2 weeks for the second and third month and then monthly thereafter.
  - Adjust dose if leucopenia develops:
    - if white cell count (WBC) <4 x 10^9/l or neutrophils <2 x 10^9/l, withhold and restart at reduced dose by at least 25 mg when WBC have recovered, thereafter monitor weekly for 4 weeks.
    - if severe (WBC <1x109/l, neutrophils <0.5x109/l) or prolonged for >2 weeks, then stop oral cyclophosphamide and restart it at 50 mg/day when WBC and neutrophil counts have recovered, increasing to target dose weekly, WBC permitting.
  - Renal function should be measured alongside WBC monitoring and adjustments to cyclophosphamide dose should be made accordingly.

- ***Oral cyclophosphamide dose adjustments for age***
    - According to CYCLOPS, the oral cyclophosphamide dose should be reduced by 25% for persons older than 60 years and 50% for those older than 70 years.
    - The EULAR recommendations are to reduce the daily dose by 25% for patients >60 years of age and by 50% for those >75 years of age.
    - Adjustments of the cyclophosphamide dose should also be made according to renal function.
    - The RAVE trial used the following adjustment table for the daily cyclophosphamide dose, which ultimately takes into account both the age and renal function:

Creatinine clearance (ml/min)	Dose (mg/kg/d)
25-49	1.2
15-24	1.0
≤24 or dialysis	0.8
If adjusting the dose requires dividing a 25-mg CYC/CYC placebo capsule (e.g., 50% of a 175-mg pretoxicity dose is 87.5 mg), a participant's dose will be rounded down to the next closest multiple of 25	

Table S5. Dose reductions of oral daily cyclophosphamide as used in the RAVE trial.[16]

Intravenous cyclophosphamide preparation

- ***Dose***: 15 mg/kg administered intravenously over 1-2 hours (same dosage in children). Maximum dose 1200 mg/pulse.
- ***Frequency***: Every 2 weeks for 3 pulses followed by every 3 weeks.
- ***Additional guidance:***
    - Induce a forced diuresis with adequate (approximately 2l) oral or intravenous pre-hydration.
    - Maintain daily oral fluid intake of 2-3l for 3 days post-infusion.
    - Empirical antiemetic therapy, oral or intravenous, pre- and post-infusion should be considered.
    - Mesna administration may be considered (possible regimen) – *evidence for mesna effectiveness in preventing cystitis remains limited and there is no direct evidence for its effectiveness in preventing bladder cancer in humans*:
        - Most often recommended dosing of IV mesna in UK and USA is a total dose equal to 20% (weight/weight) of the total cyclophosphamide dose, in the form of 3 equal doses of

mesna, with the first dose administered 15–30 minutes prior to cyclophosphamide and the others administered 4 hours and 8 hours following cyclophosphamide

- When mesna is given orally, the dose should be equal to 40% of the cyclophosphamide dose (oral or IV). For convenience, a combination of IV and oral doses can be given: an initial IV dose (equal to 6.8% of the cyclophosphamide dose) followed by 2 oral doses (each equal to 13.3% of the cyclophosphamide dose). If the first dose of mesna is administered orally, it should be given 2 hours before cyclophosphamide (oral or IV).
- Other regimens have been proposed by different societies, including the French Vasculitis Study Group (1/3rd of the total IV CYC dose given IV at the time of the infusion, then 1/3rd given again IV or orally 4 hours later and, again, 8 hours later – 1/3rd the dose at H0, H4 and H8).
- Allergy to mesna is rare, but greater than to cyclophosphamide, and most of time benign.

- For patients receiving plasma exchange or dialysis, the CYC dose should be given after the plasma exchange or dialysis session (at least, not immediately prior to the session).

- ***Recommended monitoring:***
  - Check CBC on the day of or day prior to each pulse, withhold the pulse if the WBC < 4 or neutrophils <2, restart at a reduced dose when WBC has recovered.

- ***IV cyclophosphamide dose adjustments for age and renal impairment:***

Age (years)	Creatinine 150-300 µmol/l	Creatinine 300-500µmol/l
< 60	15 mg/kg	12.5 mg/kg
60- 70	12.5 mg/kg	10 mg/kg
> 70	10 mg/kg	7.5 mg/kg

Table S6. Dose reductions of pulsed intravenous cyclophosphamide according to age and renal function.[14]

In patients with AAV aged 65 years and over, a fixed dose of 500 mg per IV cyclophosphamide pulse can be considered (CORTAGE)[22].

Cyclophosphamide and *Pneumocystis jiroveci* Prophylaxis

- *Trimethoprim/sulfamethoxazole*
    - Trimethoprim/sulfamethoxazole preparations; 800/160mg 3 times weekly (Mondays, Wednesdays, and Fridays) should be administered for the duration of cyclophosphamide therapy and for 3 months after switching to maintenance therapy.
    - Contraindicated in patients with sulfa-allergy.
    - Safe in conjunction with azathioprine and leflunomide and at this prophylactic dose in conjunction with methotrexate.
    - Not recommended at 'curative full-dose' i.e. 800/160mg twice daily, in conjunction with methotrexate.
- *Dapsone*
    - Alternative to trimethoprim/sulfamethoxazole in patients with sulfa-allergy.
    - Dapsone (100 mg/d orally) should be administered for the duration of cyclophosphamide therapy and for 3 months after switching to maintenance therapy.
    - Risk of hemolytic anemia even in the absence of G6PD deficiency.
    - Check G6PD status pre-treatment.
    - Suggest regular CBC monitoring in all patients.

- *Atovaquone*
    - Alternative to trimethoprim/sulfamethoxazole in patients with sulfa-allergy.
    - Atovaquone (1500 mg/d orally, at once or in two divided doses of 750 mg) should be administered for the duration of cyclophosphamide therapy and for 3 months after switching to maintenance therapy.

- *Pentamidine aerosolization*
    - Non-preferred alternative to trimethoprim/sulfamethoxazole in patients with sulfa-allergy, because it may be less effective according to the result of a small randomized study in immunocompromised patients with connective tissue diseases[23].
    - Pentamidine isethionate aerosolization (300mg dissolved in 3 mL of sterile water and aerosolized until the nebulizer runs dry; 20-45 minutes) every 4 weeks, should be administered for the duration of cyclophosphamide therapy and for 3 months after switching to maintenance therapy.
    - Can cause bronchospasms.
    - Should be performed in a negative flow or private room to minimize the risk of exposure for others. Pregnant health care workers must not be permitted to administer aerosolized pentamidine and health care workers attempting to conceive should avoid exposure.

Cyclophosphamide and Fertility

- Male and female infertility are potential complications of cyclophosphamide therapy.
- Risk increases with age of patient at time of treatment, duration of therapy and total cumulative cyclophosphamide dose.
- Cyclophosphamide does NOT invariably cause infertility and owing to its significant teratogenicity, appropriate contraceptive measures MUST be taken by male and female patients.
- Referral to, collaboration and/or consultation with a specialist in Reproductive and Fertility Medicine should be considered for patients of child-bearing age.
- Options for fertility preservation include:
    - Gonadal and oocyte cryopreservation (not funded in Canada).
    - Sperm cryobanking for male patients (not systematically funded in Canada).
    - Gonadotrophin releasing hormone (GnRH) agonists, for example *leuprolide* (administered by intramuscular depot injection), administered prior to each cyclophosphamide pulse or for the duration of oral cyclophosphamide therapy. GnRH agonists induce reversible gonadal quiescence and may minimize the risk of premature ovarian/testicular failure (not systematically funded in Canada).
    - In males, testosterone 100 mg IM every 2 weeks for the duration of treatment by either oral or intravenous route[24].
- The severity and acuteness of AAV often prevents the completion of these preservation options before the treatment of AAV must be initiated. In such cases, alternatives to cyclophosphamide should be considered in patients of child-bearing age, when possible.

RITUXIMAB

- **Dose**: Rituximab regime currently approved for the induction of remission of AAV in Canada is 375mg/m^2 x 4 infusions at weekly intervals. Two infusions of 1000mg administered at day 0 and repeated at day 15 is an alternate regime, likely to have comparable efficacy but is not currently mentioned as an approved alternative regimen in Canada.
- At present, the doses of rituximab used in children are the same as those proposed for adults. However, the use of a 2 dose regimen of rituximab 500 mg/m^2 twice 14 days apart is being used relatively frequently in children, being seen as more convenient, less intrusive for the child and the family, and there is no evidence in children on the efficacy of either a 2 dose versus a 4 dose regimen.

- **Administration of rituximab**:
    - May be infused through a peripheral line.
    - Dilute rituximab in 250ml of 0.9% saline (normal saline) or Dextrose-Water 5%.
    - Initial infusion should be given at a rate of 50 mg/hr for the first 30 minutes, increasing 50 mg/hr every 30 minutes as tolerated, for a maximum rate of 400 mg/hr.
    - Subsequent infusions can be started at 100 mg/hr for the first 30 minutes, increasing 100 mg/hr every 30 minutes as tolerated, for a maximum rate of 400 mg/hr.
    - Patients should be observed during infusion and for 30 minutes after infusion for signs of infusion reactions.

- **Premedication**:
    - Methylprednisolone 100 mg IV in 50mL 0.9% sodium chloride injection, 15-30 min pre infusion
    - Acetaminophen 650-1000mg PO 15-30 minutes prior to infusion
    - Diphenhydramine 50 mg PO or chlorpheniramine 10mg IV, 15-30 minutes pre-infusion
    - Consider withholding anti-hypertensive medications 12 hrs prior to and throughout infusion due to potential occurrence of hypotension

- **There are no formal recommendations for monitoring patients on rituximab. The following may be considered at baseline and 3-6 monthly intervals**:
    - CD19 B lymphocyte subsets.
    - Immunoglobulin levels (risk of hypogammaglobulinemia post-rituximab).
    - ANCA (if ever positive pre-treatment).
    - CBC (risk of delayed neutropenia in up to 9% of the patients).

- **Rituximab and *Pneumocystis jiroveci* prophylaxis**:
    - We recommend prophylaxis against *P. jiroveci* (with trimethoprim/sulfamethoxazole in patients without known allergy to this antibiotic) in patient treated with rituximab.

- **Rituximab and HBV (hepatitis B)**:
    - Serology against HBV (with HBs Ag and HBc Ab) must be controlled prior to rituximab initiation, as rituximab can reactivate HBV in infected patients.
    - We recommend referral to hepatologists prior to starting rituximab for patients with chronic HBV infection (HBs Ag +). These patients must receive an anti-HBV treatment if rituximab is given. A referral for patients with HBs Ag negative but HBc Ab + is also recommended for consideration of a similar antiviral treatment and/or close biological and virological monitoring.
    - When timely feasible, non-immunized patients should be offered HBV vaccination prior to starting rituximab, ideally at least 4 weeks before. The efficacy of HBV vaccination after having started rituximab is not determined (that of other vaccines such as against influenza or pneumococcal infections is much lower in patients having received rituximab within the year prior to vaccination compared to the general population).

METHOTREXATE (MTX)

- **Target dose**: 20-25mg/week. Can be given orally or subcutaneously/intramuscularly. Methotrexate can be initiated directly at the target dose or started at 15 mg/week and increased incrementally to improve patient tolerance. However, in the NORAM study, time-to-remission was longer with methotrexate compared to cyclophosphamide in patient with limited GPA if started initially at a lower starting dose of 15mg per week.

- **Additional guidance**:
  - Use with caution in mild-moderate renal impairment (dose adjustment may be required), avoid in severe renal impairment.

Table S9. Dose adjustments in patients with renal insufficiency

Creatinine clearance / GFR (mL/min)	% standard dose to administer
>80	Full Dose
80-60	75
<60-50	50–66
<50	Consider alternative therapy Do not give more than 30–50%
<10	Avoid the use

  - Concomitant folic acid, suggest 1–5mg daily except MTX day.
  - In children, the dose is 10–15mg/m2 per week (maximum 25mg per week)
  - Teratogenic: contraceptive advice MUST be given to male and female patients. Drug must be discontinued for a minimum of 3 months prior to conception (applies to male and female patients).

- **Recommended monitoring**: check CBC, LFTs and renal function monthly, or in adherence with local protocols.

AZATHIOPRINE

- **Target dose:** 2mg/kg/day, maximum 200mg/day (can be initiated at target dose or increased incrementally to improve patient tolerance).

- **Additional guidance**:
    - TPMT enzyme levels can be checked prior to initiating therapy according to local policy and availability of TPMT testing.
    - At present, the dose of azathioprine used in children is the same as that used in adults.
    - Safe in pregnancy and at time of conception.

- **Recommended monitoring**: check CBC 2 weeks after starting therapy and every 1-2 months thereafter or according to local protocols.

LEFLUNOMIDE

- **Target dose**: 20mg/day. Range 10-30mg/day.

- **Additional guidance**:
    - Leflunomide safety and efficacy in children<18 years old have not been fully evaluated.
    - Teratogenic: contraceptive advice MUST be given to male and female patients. Drug must be discontinued for a minimum of 6 months prior to conception (male and female patients). If conception is planned (or occurs while taking leflunomide), consider cholestyramine washout after discontinuation of the drug.

- **Recommended monitoring**: check CBC, renal function and LFTs at least monthly initially or according to local protocols.

MYCOPHENOLATE MOFETIL

- **Target dose**: 2-3g/day, incremental escalation of dose advised.

- **Additional guidance:**
  - Not first-line remission maintenance therapy. For use in patients who fail alternate maintenance agents.
  - Similar doses in adults and children.
  - Teratogenic: contraceptive advice MUST be given and the drug discontinued for a minimum of 3 months prior to conception.

- **Recommended monitoring**: CBC, renal function should be monitored at least monthly initially or according to local protocols.

INTRAVENOUS IMMUNOGLOBULINS

- **Dose**: 2 g/kg infused over 2-5 days every month.

- **Additional guidance**:
  - Duration of therapy dependent on response and advice from a referral center for vasculitis.
  - Possible during pregnancy.
  - Does not increase the risk of infection as opposed to all other immunosuppressants.
  - Screen for IgA deficiency, as patients with IgA deficiency are at increased a risk for anaphylaxis if given the most common used IV immunoglobulin preparations (specific IV immunoglobulin preparations depleted in or with lower levels of IgA should be used instead).

Appendix 4. Vaccinations in ANCA-associated vasculitis

The response to vaccination in patients receiving immunosuppressive therapy may be reduced, although to date this is not quantified. Whenever possible, it is advisable that patients requiring vaccination should do this prior to receiving immunosuppressive therapy. In reality this is extremely difficult in patients with AAV and treatment should NOT be delayed to facilitate vaccination. Refer to http://www.phac-aspc.gc.ca for update information on recommended vaccinations and contra-indications to available vaccinations.

Recommended Vaccines

We suggest that all patients with AAV receiving immunosuppressive therapy, including low-dose glucocorticoids, receive:

- Seasonal influenza vaccine every year.
- Pneumococcal vaccine, according to current vaccination guidelines.

Live Vaccines

Most of the live vaccines are contra-indicated in patients with AAV receiving immunosuppressive therapy. These include:

- Yellow fever vaccine
- Live-attenuated Ty21a typhoid vaccine
- Oral live-attenuated polio vaccine (Sabin)
- Live attenuated (intranasal) influenza vaccine

- **Measles, Mumps, Rubella (MMR) live vaccine**: refer to http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-meas-roug-eng.php#immuno for more information:

"If indicated, MMR vaccine should be administered at least 4 weeks before the initiation of immunosuppressive therapy to reduce the risk of disease caused by the vaccine strain. If MMR vaccine cannot be given prior to initiation of immunosuppressive therapy, a period of at least 3 months should elapse after immunosuppressive drugs (except high-dose systemic corticosteroids) have been stopped before administration of live vaccines to reduce the risk of disease caused by the vaccine strain. A period of at least 4 weeks should elapse between discontinuation of high-dose systemic steroids and the administration of MMR vaccine. The interval between discontinuation of immunosuppressive drugs and MMR vaccine administration may vary with the intensity of the immunosuppressive therapy, underlying disease and other factors.

If immunosuppressive therapy cannot be stopped, live vaccines are generally contraindicated, although the risk-to-benefit ratio may favour immunization if only low doses of immunosuppressive drugs are required and there is significant risk of development of disease. The safety and efficacy of live, attenuated vaccines during low dose intermittent or maintenance therapy with immunosuppressive drugs (other than corticosteroids) are unknown.

Immunosuppressive drugs have been reported to cause reactivation of latent tuberculosis infection and predisposition to other opportunistic infections. Therefore, until additional information becomes available, avoidance of MMR vaccines during intermittent or low dose chemotherapy or other immunosuppressive therapy is prudent.

Corticosteroid therapy is not a contraindication to administering live vaccine when steroid therapy is short-term (i.e., less than 14 days); or a low-to-moderate dose (less than 2 mg/kg/day for a child or less than 20 mg/day of prednisone or its equivalent per day for an adult); or long-term, alternate-day treatment with short-acting preparations; or maintenance physiologic replacement therapy; or administered topically, inhaled, or locally injected (e.g., joint injection).

In general, live attenuated vaccines are contraindicated during monoclonal antibody treatment or in infants exposed to monoclonal antibodies. Monoclonal antibodies taken during pregnancy will be transferred to the fetus and their effects may persist after birth. Infants who have been exposed to monoclonal antibodies, either during pregnancy or from breastfeeding, should have B-cell enumeration. B cell enumeration should be normal before vaccination with live vaccines. Consultation with an immunologist is advised. Vaccination status should be reviewed prior to commencing monoclonal antibodies." (Accessed on October 5, 2014 on http://www.phac-aspc.gc.ca).

- **Varicella-Zoster live vaccine**: since most patients have prior immunity to varicella, the Public Health Agency of Canada http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-herp-zona-eng.php#immther suggests that "it is reasonable to consider the varicella zoster vaccine in patients receiving low dose immunosuppression therapy" defined as:

- Methotrexate ≤ 0.4mg/kg/week
- Azathioprine ≤ 3.0 mg/kg/day
- Prednisone ≤ 20 mg /day

Appendix 5. Canadian prescribing regulations for rituximab

Available from the authors on request.

Appendix 6. Existing provincial criteria for rituximab coverage

Available from authors on request.

Appendix 7. Useful websites and links

Additional information on vasculitis for physicians is available from the following websites:

- CanVasc, Canadian vasculitis research network (with updated list of CanVasc centers, tools including score [BVAS, VDI, FFS etc] and list of studies on vasculitis ongoing in Canada): http://www.canvasc.ca
- Vasculitis Clinical Research Consortium (VCRC): http://rarediseasesnetwork.epi.usf.edu/vcrc/index.htm
- French Vasculitis Study Group (FVSG): http://www.vascularites.org/
- EUVAS European vasculitis study group: http://www.vasculitis.org/
- The Johns Hopkins Vasculitis Center Website: http://www.hopkinsvasculitis.org/
- Cleveland Clinic CME Website – Vasculitis: http://www.clevelandclinicmeded.com/specialties/RheumatologyImmunology.aspx?id=148&name=Rheumatology+%2f+Immunology
- RheumInfo.com: http://rheuminfo.com/
- PEXIVAS trial website: http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/renal/pexivas/index.aspx
- RITAZAREM trial website: http://www.rarediseasesnetwork.org/vcrc/ritazarem/index.htm
- BVAS v3 online calculator: http://www.epsnetwork.co.uk/BVAS/bvas_flow.html
- Osteoporosis Canada (with last updated version of the Canadian clinical practice guidelines for the diagnosis and management of osteoporosis in Canada): http://www.osteoporosis.ca/

Vasculitis patient associations and support groups

- Canadian Vasculitis Foundation: http://www.vasculitis.ca/
- US-based Vasculitis Foundation: http://www.vasculitisfoundation.org/
- Churg–Strauss syndrome Association: http://www.cssassociation.org/
- French Association Wegener Infos et autres Vascularites : http://asso.orpha.net/WIV2/cgi-bin/site/
- Vasculitis Clinical Research Consortium (VCRC) patient contact registry: http://www.rarediseasesnetwork.org/vcrc/registry/index.htm

Appendix 8. CanVasc centers and core members *(a regularly updated list can be downloaded on http://www.canvasc.ca)*

Executive committee 2014-2018
(4 years mandates, renewable once)

President: Dr. Christian Pagnoux
Vice-president: Dr. Nader Khalidi
Secretary-Treasurer: Dr. Lillian Barra

Past president: Simon Carette (2010-2014)

Province	City	Principal core member (level 1)	Associated core members (level 2)	Affiliated core members /colleagues (level 3)	Contact
Ontario	Toronto	Dr. Simon Carette; Dr. Rae Yeung (Ped.)	Dr. Christian Pagnoux; Dr. Heather Reich (Nephr.)	Dr. Laurence Rubin; Dr. Joanne Bargman (Nephr.); Dr. Ian Witterick (ENT); Dr. Joanne Bargman (Nephr.); Dr. Mary Bell	Division of Rheumatology, Mount Sinai Hospital and University Health Network, 60 Murray Street, Ste 2-220 Toronto, Ontario M5T 3L9 Tel. 416-586-4800 Ext. 8549 or 5519 E-mail: VasculitisClinic@mtsinai.on.ca
	Hamilton	Dr. Nader Khalidi	Dr. Michael Walsh (Nephr.); Dr. Gerard P. Cox (Respi.); Dr. Parameswaran Nair (Respi.)		Division of Rheumatology St. Joseph's Healthcare Hamilton 25 Charlton Suite 708, Hamilton, Ontario, L8N 4A6 Phone: 905-521-9034 Fax: 905-521-8099
	Ottawa	Dr. Nataliya Milman	Dr. Douglas C. Smith	Dr. Shaun Kilty (ENT); Dr. Brendon McCormick (Nephr.); Dr. Peter Magner (Nephr.); Dr. Nav Voduc (Respi.); Dr. Shawn Aaron (Respi.); Dr. Kanigsberg (Derm.); Dr. Marco Gomez (Lung Pathol.)	Arthritis Centre at the Ottawa Hospital, Riverside Campus 1967 Riverside Drive, box 37, K1H 7W9, Tel: 613-738-8400, ext. 81871 Fax: 613-738-8228
	Kingston	Dr. Tanveer Towheed	Dr. Marie Clements-Baker; Dr. Michel Melanson (Neurol.)	Dr. Andre Tan (ENT); Dr. David Holland (Nephr.); Dr. Christine D'Arsigny (Respi.)	Department of Medicine Queen's University Room 2066, Etherington Hall, Kingston, Ontario, K7L 3N6 Phone: 613-533-6896 Fax: 613-533-2189
	London	Dr. Lillian Barra	Dr. Shih Han Susan Huang (Nephr.)	Dr. William Clark (Nephr.); Dr. Robert McFadden (Respi.)	Monsignor Roney Building, level D2 268 Grosvenor St. London, Ontario N6A 4V2

					Phone: 519-646-5986 Fax: 519-646-6072
	Newmarket	Dr. Carter Thorne	Dr. Nooshin Samadi		43 Lundys Lane Newmarket Ontario L3Y 3R7 Phone: (905) 895-1666 Fax: (905) 895-2413

	Cambridge	Dr. Leilani Famorca	Dr. Brian Hanna		Langs Community Centre 1145 Concession Road Cambridge, Ontario, N3H 4L5 Phone: 519-743-4351 Fax: 519-653-8279
Québec	Sherbrooke	Dr. Patrick Liang	Dr. Ariel Masetto; Dr. Guylaine Arsenault	Dr. Dominique Dorion (ENT); Dr. Martin Plaisance (Nephr.); Dr. Pierre Larrivée (Respi.); Dr. François Lamontagne (ICU)	Division of Rheumatology Centre Hospitalier Universitaire de Sherbrooke 580 Bowen Sud, Sherbrooke, Québec, J1G 2E8 Phone: 819-346-1110 x13549 Fax: 819-564-5265
	Montréal	Dr. Michelle Goulet ; Dr. Christian Pineau	Dr. Yves Troyanov; Dr. Eric Rich; Dr. Soumeya Brachemi; Dr. Mona Ben Mrad	Dr. Evelyne Vinet; Dr. Emil Nashi; Dr. Ann E. Clarke	McGill University MUHC Lupus and Vasculitis clinic 1650 Cedar Avenue AG 163 Montréal, Québec, H3G 1A4 Phone: 514 934 8037
	Québec	Dr. Judith Trudeau	Dr. David Philibert (Nephr.); Dr. Paul Fortin	Dr. Renée Leclerc (GIntern.); Dr. Nathalie Roy (Rheum. - Levis); Dr. Claude Blier (Rheum. - Levis)	Division of Rheumatology CHAU de Lévis Lévis, QC, G7A 2R9
Nova Scotia	Halifax	Dr. Christine Dipchand; Dr. Volodko Bakowsky	Dr Colm McParland (Respi.)	Dr. John Hanly	Nova Scotia Rehabilitation Center QEII HSC 1341 Summer Street, Halifax, Nova Scotia, B3H 4K4 Phone: 902-473-3818 Fax: 902-473-7019
British Columbia	Vancouver	Dr. Kam Shojania; Dr. David Cabral (Peds)	Dr. John Esdaile; Dr. Kim Morishita (Peds); Dr. Barry Kassen; Dr. Pearce Wilcox (Respi.); Dr. Natasha Dehgahn; Dr. Corisande Baldwin	Dr. Phil Teal (Neuro.); Dr. Adeera Levin (Nephr.); Dr. Amin Javek (ENT); Dr. Jan Dutz (Derm-rheum.); Dr. Avina-Zubieta	Vancouver General Hospital and St. Paul's Hospital Vancouver, British Columbia, V6Z 2C7 Phone: 604-806-9400 Fax: 604-269-3736
Alberta	Edmonton	Dr. Elaine Yacyshyn	Dr. Joanne Homik; Dr. Allan Murray (Nephr.)	Dr. Neesh Pannu (Nephr.); Dr. M Allegretto (ENT); Dr. M. Bibeau (Respi.);	Division of Rheumatology University of Alberta 562 Heritage Medical research center, Edmonton, Alberta, T6G 2S2 Phone: 780-407-2121

				Dr. R. Damant (Respi.)	Fax: 780-407-6055
	Calgary	Dr. Aurore Fifi-Mah Dr. Susan Benseler (Peds)	Dr. Diane Mosher; Dr. Charlene Fell (Respi.); Dr. Marinka Twilt (Peds)	Dr. Marvin Fritzler	South Health Campus 4448 Front St SE Calgary, Alberta, T3M 1M4 Tel: 403 956 2493 Fax: 403 956 3835
Manitoba	Winnipeg	Dr. Navjot Dhindsa	Dr. David Robinson		Section of Rheumatology University of Manitoba Arthritis Centre RR149-800 Sherbrook Street Winnipeg Manitoba Canada R3A 1M4
Saskatchewan	Saskatoon	Dr. Regina Taylor-Gjevre	Dr. Bindu Nair; Dr. Jim Barton (Nephr.); Dr. Julian Midgley (Nephr. Peds)	Dr. Peter D Spafford (ENT); Dr. Judith Klassen (Nephr.); Dr. Mark E Fenton (Respi.); Dr. Peter Hull (Derm.)	Department of Medicine Royal University Hospital University of Saskatchewan 103 Hospital Drive Saskatoon, Saskatchewan, S7N 0W8 tele: 306 966 8271 fax: 306 966 8381
Newfoundland	Saint Johns	Dr. Majed Khraishi			

Appendix 9. Disclosure and conflicts of interest of the working group core members

- Lucy McGeoch: None to declare.
- Marinka Twilt: None to declare.
- Leilani Famorca: None to declare.
- Volodko Bakowsky: fees for serving on advisory boards from Hoffman-LaRoche.
- Lillian Barra: honoraria from Hoffman-LaRoche, Abbvie, Amgen and UCB (<$5,000).
- Susan Benseler: None to declare.
- David Cabral: None to declare.
- Simon Carette: None to declare.
- Gerard P. Cox: fees for serving on advisory board from Hoffman-LaRoche (2013)
- Christine Dipchand: None to declare.
- Navjot Dhindsa: honoraria from Hoffman-LaRoche and Abbvie.
- Aurore Fifi-Mah: fees for serving on advisory boards from Hoffman-LaRoche.
- Michelle Goulet: None to declare.
- Nader Khalidi: fees for serving on advisory Boards from Hoffman-LaRoche, Bristol-Myers Squibb, UCB; lecture fees from Hoffman-LaRoche.
- Majed Khraishi: None to declare.
- Patrick Liang: honorarium for lectures from Hoffman-LaRoche, Abbvie, Bristol-Myers Squibb, Janssen, Pfizer; financial support for clinical project from Hoffman-LaRoche.
- Nataliya Milman: None to declare.
- Christian A. Pineau: fees for serving on advisory boards from Hoffman-LaRoche.
- Heather Reich: fees for providing advisory services to Hoffman-LaRoche, AMGEN and Alexion.
- Nooshin Samadi: None to declare.
- Kam Shojania: lecture and consultation fees from Hoffman-LaRoche (< $5,000).
- Regina Taylor-Gjevre: None to declare.
- Tanveer A. Towheed: None to declare.
- Judith Trudeau: fees for serving on advisory boards for Hoffman-LaRoche and Bristol-Myers Squibb; grant for attending scientific meetings on vasculitis by Hoffman-LaRoche.
- Michael Walsh: None to declare.
- Elaine Yacyshyn: None to declare.
- Christian Pagnoux: fees for serving on advisory boards from Hoffman-La Roche, Genzyme, and GlaxoSmithKline; lecture fees from Roche, Bristol-Myers Squibb, and EuroImmune; grant support from Hoffman-La Roche Roche; coordinator of the 2007 French Vasculitis Study Group recommendations (Protocole national de diagnostic et de soins – vascularites nécrosantes systémiques; under the aegis of the Haute Autorité de Santé).

REFERENCES

1. Aasarod K, Bostad L, Hammerstrom J, Jorstad S, Iversen BM. Renal histopathology and clinical course in 94 patients with Wegener's granulomatosis. Nephrol Dial Transplant 2001;16:953-60.
2. Maguchi S, Fukuda S, Takizawa M. Histological findings in biopsies from patients with cytoplasmic-antineutrophil cytoplasmic antibody (cANCA)-positive Wegener's granulomatosis. Auris Nasus Larynx 2001;28 Suppl:S53-8.
3. Schnabel A, Holl-Ulrich K, Dalhoff K, Reuter M, Gross WL. Efficacy of transbronchial biopsy in pulmonary vaculitides. Eur Respir J 1997;10:2738-43.
4. Duna GF, Calabrese LH. Limitations of invasive modalities in the diagnosis of primary angiitis of the central nervous system. J Rheumatol 1995;22:662-7.
5. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488-98.
6. Gluth MB, Shinners PA, Kasperbauer JL. Subglottic stenosis associated with Wegener's granulomatosis. Laryngoscope 2003;113:1304-7.
7. Langford CA, Sneller MC, Hallahan CW, Hoffman GS, Kammerer WA, Talar-Williams C, et al. Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. Arthritis Rheum 1996;39:1754-60.
8. Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2007;66:605-17.
9. Stone JH. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum 2003;48:2299-309.
10. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 1996;75:17-28.
11. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore) 2011;90:19-27.
12. 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.
13. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36-44.
14. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670-80.
15. Lapraik C, Watts R, Bacon P, Carruthers D, Chakravarty K, D'Cruz D, et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology (Oxford) 2007;46:1615-6.
16. 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.
17. WGET. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352:351-61.
18. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. Cmaj 2010;182:1864-73.
19. Leib ES, Saag KG, Adachi JD, Geusens PP, Binkley N, McCloskey EV, et al. Official Positions for FRAX((R)) clinical regarding glucocorticoids: the impact of the use of glucocorticoids on the estimate by FRAX((R)) of the 10 year risk of fracture from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX((R)). J Clin Densitom 2011;14:212-9.
20. McCloskey EV, Binkley N. FRAX((R)) Clinical Task Force of the 2010 Joint International Society for Clinical Densitometry & International Osteoporosis Foundation Position Development Conference. J Clin Densitom 2011;14:181-3.

21. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford) 2014;53:2306-9.
22. Pagnoux C, Quemeneur T, Ninet J, Diot E, Kyndt X, de Wazieres B, et al. Treatment of Systemic Necrotizing Vasculitides in Patients over 65 Years. Arthritis Rheumatol 2015.
23. Kimura M, Tanaka S, Ishikawa A, Endo H, Hirohata S, Kondo H. Comparison of trimethoprim-sulfamethoxazole and aerosolized pentamidine for primary prophylaxis of Pneumocystis jiroveci pneumonia in immunocompromised patients with connective tissue disease. Rheumatol Int 2008;28:673-6.
24. Masala A, Faedda R, Alagna S, Satta A, Chiarelli G, Rovasio PP, et al. Use of testosterone to prevent cyclophosphamide-induced azoospermia. Ann Intern Med 1997;126:292-5.