Provincial Clinical Knowledge Topic
Suspected Neuromyelitis Optica Spectrum Disorder, Adult – Inpatient
V 1.0

Revision History

Version	Date of Revision	Description of Revision	Revised By

Important Information Before You Begin

The recommendations contained in this knowledge topic have been provincially adjudicated and are based on best practice and available evidence. Clinicians applying these recommendations should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care. This knowledge topic will be reviewed periodically and updated as best practice evidence and practice change.

The information in this topic strives to adhere to Institute for Safe Medication Practices (ISMP) safety standards and align with Quality and Safety initiatives and accreditation requirements such as the Required Organizational Practices. Some examples of these initiatives or groups are: Health Quality Council Alberta (HQCA), Choosing Wisely campaign, Safer Healthcare Now campaign etc.

Rationale

Neuromyelitis Optica Spectrum Disorder (NMOSD) is relatively rare but devastating neurological disorder characterized by severe episodes of vision loss, spinal cord dysfunction, brainstem and hypothalamic dysfunction.[1-3] Once thought to be a variant of Multiple Sclerosis (MS), it is now clear this is a distinct pathological entity with its own course, prognosis, and treatment plan. NMOSD-related attacks are variable and unpredictable within and between patients; often resulting in permanent disability.[1] Treatment has led to improved morbidity and mortality, although both remain much higher as compared to what is typically observed in MS.[1,4]

NMOSD is most commonly seen in individuals of Asian and Afro-Caribbean descent. In North America, there is one NMOSD case for every 200 MS cases (this number is likely to be higher with newer, more inclusive diagnostic criteria for NMOSD) and prevalence has been estimated to be between 0.52 and 4.4 per 100,000.[5,6] NMOSD patients tend to be older than their typical MS counterparts (mean age is 39 vs 32 years), with a higher preponderance amongst females (female to male ratio is 9:1 in NMOSD as compared to 3:1 in MS).[6,7] In recent years, an NMOSD-like presentation has been linked to another CNS immune disease, known as MOG-associated demyelinating disease. While the exact epidemiology and prevalence of this disease remains under study, this guide will also assist in detecting and caring for such patients in the acute setting as well.[8]

Clinical "red flags" or features that should prompt investigations for NMOSD include: longitudinally extensive transverse myelitis (lesions extending three or more spinal segments), atypical optic neuritis (i.e. bilateral simultaneous optic neuritis or optic neuritis found on MRI to be longitudinally extensive, involving multiple segments of the optic nerve, and/or involving the optic chiasm, optic tracts), and area postrema syndrome (characterized by nausea, vomiting, hiccups and/or abdominal pain with no identifiable gastrointestinal cause).[7] Additionally, autonomic/hypothalamic dysfunction is becoming a more recognized part of NMOSD.[7] While certain centres have a great number of such patients and hence a great wealth of experience with the disease (centres with large Asian populations, the most commonly affected ethnic group), Alberta has a relatively low incidence and prevalence of the disease. For this reason, we believe guidelines to recognition, diagnosis and treatment of both acute and chronic NMOSD will aide both patients and their care providers.

The following guidelines are based on best available evidence and experience in caring for such patients. They are targeted primarily towards neurology and ophthalmology-trained care providers, and the three main presentations of NMOSD*:

1. Longitudinally extensive transverse myelitis (LETM):

   Clinical myelopathy or complete (more often than incomplete) transverse myelitis associated with magnetic resonance imaging (MRI) lesions in the spinal cord extending greater than or equal to 3 vertebral body segments; often lesions extending down from the cervicomedually junction

2. Atypical optic neuritis:

(a) Simultaneous bilateral optic neuritis, and/or optic neuritis found on MRI to be longitudinally extensive, involving multiple segments of the optic nerve, and/or involving the optic chiasm, optic tracts
(b) unilateral optic neuritis with maximal recovery of 20/50 vision (Snellen equivalent) at 1 month, NOT IN THE CONTEXT OF MULTIPLE SCLEROSIS OR OTHER KNOWN CAUSAL ENTITY OUTSIDE OF NMOSD (see Section “Clinical Recommendations, Clinical Question #3” for truncated diagnostic plan for this presentation)

3. Area postrema syndrome (APS):

   A syndrome characterized by prolonged or intractable hiccups, vomiting, severe nausea without an identified gastrointestinal (or abdominal) cause, and associated with MRI lesion in the region of the area postrema.

*Please note that this is not an exhaustive list of possible NMOSD presentations, but other manifestations are less common and less specific (e.g. hypothalamic dysfunction, other brainstem/osmotic demyelination syndromes), and should be evaluated on a case by case basis.

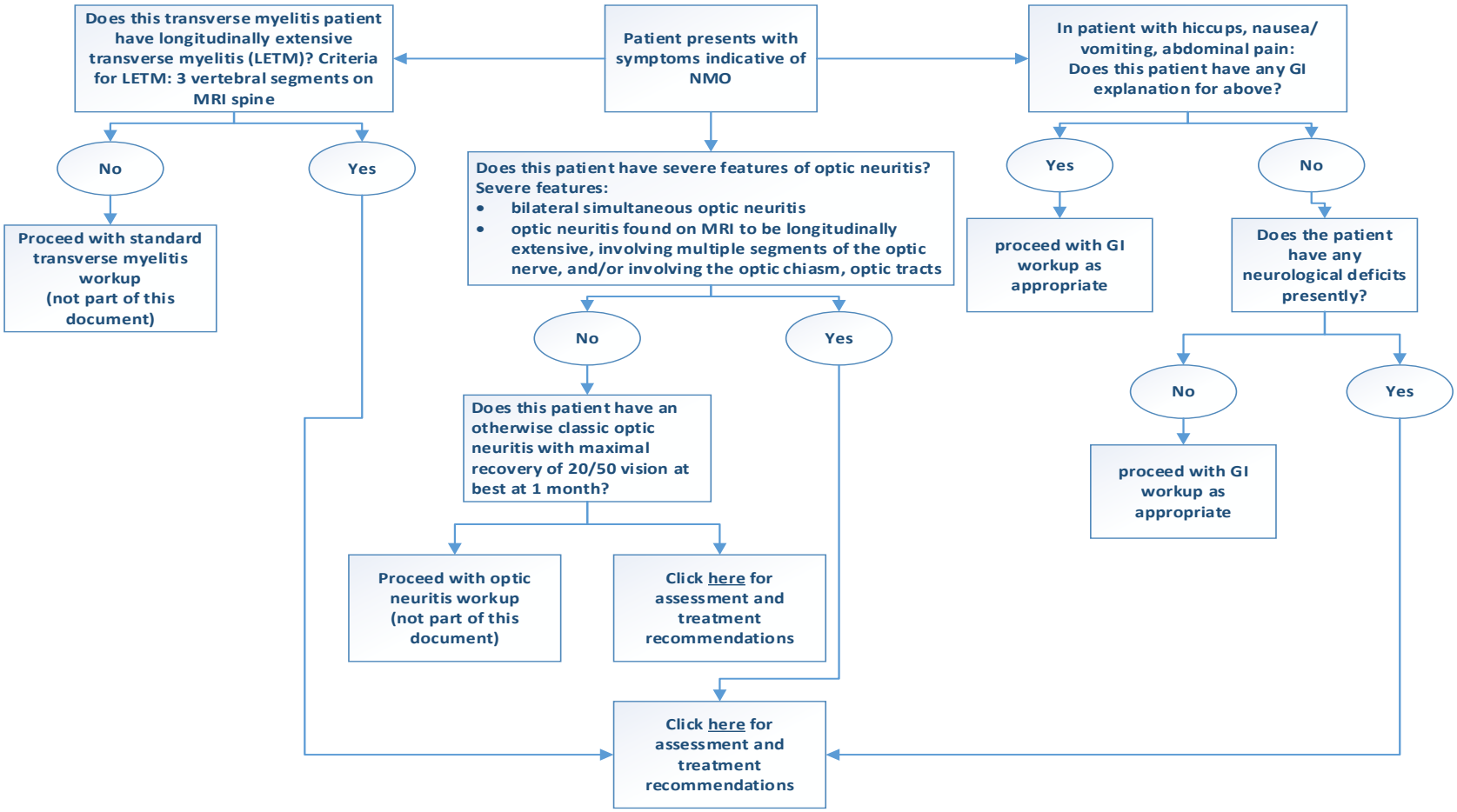
Goals of Management

- Diagnostic approach to suspected NMOSD and mimics
- Acute management algorithm for NMOSD based on best available evidence
- Maintenance therapy and care algorithm for NMOSD based on best available evidence

Clinical Decision Support

- CDS Requirements:
    - References:
        - Please place a link to the Suspected Neuromyelitis Optica Spectrum Disorder, Adult – Inpatient Clinical Knowledge Topic within the Suspected Neuromyelitis Optica Spectrum Disorder, Adult Inpatient Order Set order set in Connect Care
    - Assists: Scoring Tools used to quantify the severity of neurological disability in demyelinating disease:
        - Please see Appendix B

Figure 1: Could This Patient Have NMOSD?



Decision Making

In patient with Transverse Myelitis:

1. Does this transverse myelitis patient have longitudinally extensive transverse myelitis (LETM)?
    - Criteria for LETM: 3 vertebral segments on MRI spine
        a. If yes, follow the guidelines provided in this document.
        b. If no, follow local standard practice for standard transverse myelitis workup

In patient with Optic Neuritis:

1. Does this patient have features of optic neuritis?
    - Severe features:
        - bilateral simultaneous optic neuritis
        - optic neuritis found on MRI to be longitudinally extensive, involving multiple segments of the optic nerve, and/or involving the optic chiasm, optic tracts

    a. If yes, follow the guidelines provided in this document

2. If not "atypical", follow local standard practice for standard optic neuritis workup. Does this patient have an otherwise classic optic neuritis with maximal recovery of 20/50 (Snellen equivalent) vision at best at 1 month?
    a. If yes, follow the starred* guidelines in this document
    b. Otherwise perform a standard optic neuritis workup

In patient with hiccups, nausea/vomiting, abdominal pain:

1. Does this patient have any GI explanation for above?
    a. If no, proceed with guidelines provided in this document
    b. If yes, pursue GI investigations as appropriate
2. Does the patient have any neurological deficits presently?
    a. If yes, proceed with guidelines provided in this document
    b. If no, pursue GI investigations as appropriate

Investigations:

(Antibody testing through Mitogen Advanced Diagnostic Laboratory by default):**

**If Mitogen Advanced Diagnostic Laboratory results are negative or inconclusive for one or more antibodies required for diagnosis, and the index of suspicion remains high for that diagnosis, consider sending sample to Mayo Clinic Laboratories.

Serum:

1. **Routine:** Complete Blood Count (CBC) with differential, Electrolytes (Na, K, Cl, CO2), Creatinine, Urea, ALT, AST, Bilirubin Total, GGT
2. **Additional metabolic:** Vitamin B12, Methylmalonic Acid, Thyroid Stimulating Hormone (TSH), Copper
3. **Immune screen:** ANA Screen [if ANA positive send Systemic Lupus Profile (AI SLP on Mitogen lab requisition)], ANCA/PR3,MPO (AI ANCA on Mitogen lab requisition), C3, C4, Rheumatoid Factor Qualitative, Extractable Nuclear Antigen (AI SCLERO, AI SJS on Mitogen lab requisition), Serum Protein Electrophoresis, Angiotensin Converting Enzyme, Sedimentation Rate, C-Reactive Protein
4. **Specialized antibody testing:** (Mitogen Advanced Laboratory Diagnostics assay first – paper requisition required, can be downloaded at www.mitogen.ca): Aquaporin-4 (AQP-4) antibodies and MOG antibodies (Mitogen lab requisition Neuromyelitis Spectrum Profile AI NMO/AI MOG)**,** Paraneoplastic panel (AI PARA on Mitogen lab requisition)
5. **Infection screen:** Convalescent and active serology for EBV, mycoplasma, herpes family, HIV, VDRL, HTLV if geographically appropriate, Lyme/Rickettsia if appropriate geographic exposure and prodrome/clinical features
6. **Genetic Testing:** Molecular Genetics - Leber Hereditary Optic Atrophy if appropriate (*order MITOS screen on AHS Genetic requisition*), Adrenoleukomyeloneuropathy if appropriate, Biochemical Genetics - Very Long Chain Fatty Acids

CSF:

1. **Routine:** CSF Cell Count, CSF Protein, CSF Glucose, gram stain, CSF Protein Electrophoresis, cytology and flow cytometry
2. **Infection screen:** Cerebrospinal Fluid Culture and Gram Stain, VZV/HSV1&2/CMV/EBV/enterovirus PCR, EBV IgM, mycoplasma, cryptococcus fungal stain, TB, VDRL, HIV (if serum testing positive)
3. **Immune screen:** Paraneoplastic screen (AI PARA on Mitogen lab requisition) if appropriate, we do not suggest routine AQP-4 antibody testing in CSF as it is a less sensitive test than in serum (but may consider later with reserved tube of CSF indicated in #4 below).
4. **Other testing:** Consider reserving tube of CSF for testing at a later time if diagnosis complicated/challenging

Urine/Stool:

1. Urine - Trace Screen 24 hour
2. Ova and Parasite Examination (Schistosomiasis testing of urine/stool if appropriate history/exposure)

Skin:

1. Tuberculin skin test if appropriate
2. Pathergy testing if Bechet's suspected

Diagnostic Imaging:

1. Magnetic Resonance Imaging (MRI)
    a. If LETM presentation:
        - MR Brain Enhanced (MS protocol)
        - MRI C Spine Enhanced and MRI T Spine Enhanced (both MS protocol)
        - May consider adding MR L Spine Enhanced to rule out mimics as appropriate

    b. If atypical optic neuritis presentation
        - MR Orbits & Brain Non-enhanced & Enhanced (MS protocol)
        - MRI C Spine Enhanced and MRI T Spine Enhanced (both MS protocol)
        - May consider adding MR L Spine Enhanced to rule out mimics as appropriate

    c. If APS presentation without GI cause
        - MR Brain Enhanced (MS protocol)
        - MRI C Spine Enhanced and MRI T Spine Enhanced (both MS protocol)
        - May consider adding MR L Spine Enhanced to rule out mimics as appropriate

2. CT Imaging
    a. CT chest (to rule out sarcoidosis) * or preferred chest imaging study at your institution
    b. CT Chest, Abd & Pelvis, Enhanced (if neoplastic screening required)
    c. CT Angio Head Enh (if vasculitis suspected)

3. Nuclear Imaging
    a. NM PET CT Whole Body ((if CT imaging negative/inconclusive and required to rule out sarcoidosis, lymphoma, malignancy)
    b. NM PET Brain (if indicated)

4. Other
    a. Ultrasound Abdomen & Pelvis: US Abdomen, Complete and US Pelvis, Female, Transvesical or US Pelvis, Male (if required to rule out local malignancy &ovarian masses in women)
    b. US Scrotal Study With Doppler if required to rule out testicular cancer in men
    c. Mammography, Bilateral if required to rule out breast cancer

Ophthalmic Testing:

In all presentations, to be done acutely in optic neuritis presentation:

1. Best corrected high-contrast letter visual acuity testing
2. Colour acuity testing
3. Pupillary assessment for relative afferent papillary defect detection
4. Direct or indirect ophthalmoscopy
5. Slit lamp examination
6. Intraocular pressure testing
7. Visual Field Testing
8. If possible, optical coherence tomography (including peripapillary retinal nerve fiber layer, ganglion cell layer thickness, and macular volume)
9. If indicated, visual evoked potentials
10. If indicated, retinal photographs
11. If indicated, fluorescein angiography

Pathology/Tissue Testing

1. If indicated and accessible, lymph node biopsy by appropriate consulting service
2. If indicated and accessible, leptomeningeal enhancing tissue biopsy by appropriate consulting service (likely Neurosurgery)

Acute Therapy for Admission Event

1. Once certain tests are completed (MRI, possibly waiting for CSF if indicated), first-line treatment is IV methylPREDNIsolone sodium succinate 1g once daily for 5 days. In tandem with this, a sleeping aide (LORazepam, zopiclone) may be required. (Grade 1 Recommendation)

2. If disability is severe and/or not responding to steroid therapy in the first few days, consider initiating plasma exchange therapy (may have to transfer patient to a facility that provides this service if not performed locally). The minimum number of exchanges is 5 to 7. If no response to these, it is unlikely more will help, but if some response, may elect to continue. This is based on the fact that 5 exchanges removes > 80% of circulating molecules. If waiting to move patient to a facility for this therapy, can add another 5-day course of IV methylPREDNIsolone sodium succinate. (Grade 1 Recommendation)

3. Do not recommend IV GAMMA GLOBULIN (2g/kg IV in divided doses over either 2 or 5 days), limited evidence of efficacy, but if nothing else available and no response to steroids, can try (Insufficient evidence, may be Grade 2 in special circumstances)

4. Most patients are steroid-dependent, so after course of IV methylPREDNIsolone sodium succinate, continue oral predniSONE at dose 1mg/kg ideal body weight until consultation with an NMO/neuroimmunologist specialist who will determine if and when taper is appropriate. (Grade 1 Recommendation)

5. If no response to plasma exchange and marked disability or ongoing worsening, contact NMO/neuroimmunology specialist for consideration of advanced escalation therapy, typically rituximab, cyclophosphamide, or alternate agent.

Maintenance Therapy

Maintenance therapy would typically be initiated by the demyelinating specialist, possibly in hospital or in outpatient follow-up, and depending on the final diagnosis and test results.

In those patients who meet criteria for NMOSD (Neurology 2015[9]), several options are possible*:

Conventional "Immunosuppressant":

- all of these agents have class IV evidence to support their use
- all agents require the ongoing use of predniSONE 1mg/kg/day for the specific times specified below (Grade 1 recommendation)
- one of many predniSONE tapering schedules is provided see Appendix A
- if no grade is provided, it reflects the fact that no grade could not be assigned based on available literature
- Prolonged corticosteroid use requires the addition of medication for gastroesophageal reflux such as a proton pump inhibitor; a sleep-aide; bone protective agents such as a bisphosphonate; and possible antibiotic prophylaxis such as Trimethoprim/sulfamethoxazole for Pneumocystis pneumonia depending on the duration and other factors, at the discretion of the attending physician

Grade B Evidence (Grade 1 Recommendation):

a. AzaTHIOprine: 2 to 3 mg/kg/day PO (typically 150 mg divided BID or TID) titrated up over 4 to 6 weeks (e.g. 50 mg/day x 1 to 2 weeks, then 100 mg/day x 1 to 2 weeks then 150 mg/day).
    - PredniSONE cannot be tapered for a minimum of 6 months (best evidence is for AZaTHIOprine and predniSONE together)

b. Alternative Therapies:
    - Mycophenolate mofetil: given as total of 1000 to 1500mg PO BID titrated up over 4 weeks in combination with predniSONE 1 mg/kg/day (with no tapering of predniSONE dosing for a minimum of 3 months) can be used in the outpatient setting.
    - Rituximab: which is not available in Canada as a first-line agent for NMOSD can also be used in the outpatient setting in the event of treatment failure. Rituximab induction 1000 mg IV at baseline and again at week 2 OR 375mg/m^2 IV every week for 4 weeks (full order set including pre-medication and PRN medication can be made available by pharmacy, Day Medicine or on Sunrise Clinical Manager order set). This is followed by 1000 mg IV twice (separated by 2 weeks) every 6 months for maintenance.
        - As this will not be used as first-line maintenance therapy, it is unlikely the patient will be on predniSONE. In the event this agent is first-line, unfortunately there are no published studies or guidelines regarding the pace such a taper would take. In discussion with an opinion leader in NMOSD who uses rituximab first line frequently (in the US where it is routinely used as a first-line agent), the predniSONE regimen they use is 20 to 30 mg/day of predniSONE which can then be tapered four weeks after the second of the two 1000 mg induction doses. In first-line rituximab use in another, albeit quite different immune disorder, ANCA positive renal vasculitis, predniSONE is started at 1mg/kg with a taper

only starting after 6 months. Although we cannot formally recommend a specific regimen given the lack of evidence, we suggest discussing this concern with a colleague with experience treating NMOSD if one is unsure.

- Please note that private insurance coverage, or if not available, STEDT (Short Term Exceptional Drug Therapy) approval would be required in advance of ordering these agents (Mycophenolate mofetil and Rituximab) to provide coverage for the cost of these medications in the community.
- To access the STEDT application please access via an AHS Insite link only: http://insite.albertahealthservices.ca/5828.asp

Grade C Evidence

c. Methotrexate – start 10 to 12.5 mg PO every week, can increase up to 25 to 50 mg every week. PredniSONE cannot be tapered for a minimum of 6 months. Requires folic acid supplementation daily (e.g. 1mg/day) except day of methotrexate dose (Grade 2 recommendation)
d. IV GAMMA GLOBULIN – no recommended regimen in literature, very limited number of cases (not recommended)
e. mitoXANTRONE – no one recommended regimen in literature, highly toxic with known long term issues of cardiac and bone marrow toxicity leading to reduced EF and leukemia (not recommended)
f. cyclophosphamide – no one recommended regimen, data too limited (not recommended)

**These above maintenance strategies may or may not apply to those patients who are found to have MOG-associated NMOSD. Maintenance therapy for these patients should be overseen by a demyelinating specialist.*

Suspected Neuromyelitis Optica Spectrum Disorder, Adult Inpatient Order Set

Order Set Keywords: NMO, neuromyelitis optica spectrum disorder, longitudinally extensive transverse myelitis, area postrema syndrome, atypical optic neuritis

General

Admit

☐ Admit to: _____

Goals of Care Designation

"Conversations leading to the ordering of a Goals of Care Designation (GCD), should take place as early as possible in a patient's course of care. The Goals of Care Designation is created, or the previous GCD is affirmed or changed resulting from this conversation with the patient or, where appropriate, the Alternate Decision-Maker.
Complete the Goals of Care Designation (GCD) Order Set within your electronic system, or if using paper process, complete the Provincial Goals of Care Designation (GCD) paper form (http://www.albertahealthservices.ca/frm-103547.pdf)".

Attention: If patient already has a diagnosis NMOSD, scroll to go to treatment section at the end of this order set

Diet and Nutrition

☐ Regular Diet
☐ Other: _____

Patient Care

Activity

☐ Activity as Tolerated

Vital Signs

☐ Vital Signs every _____ hour(s)

Consider if cord involvement is affecting intercostal or diaphragm function

☐ Vital Capacity – Forced Vital Capacity

Intake and Output

In LETM, there are typically urinary symptoms, order accordingly

☐ Intake and Output
☐ In and Out Catheter – Post Void Residual, *(if evidence of retention ideally clean intermittent catheterization)* See your institution's Bladder Care Protocol
☐ Foley Catheter PRN, if unable to void

Respiratory Interventions

☐ O2 Therapy - Titrate to Saturation: Maintain SpO2 level greater than or equal to _____ %
Only if respiratory muscles appear affected

Laboratory Investigations Routine

Hematology (includes coagulation):

- ☑ Complete Blood Count (CBC) with differential

Chemistry

- ☑ ALT
- ☑ AST
- ☑ Bilirubin Total
- ☑ Creatinine
- ☑ Electrolytes (Na, K, Cl, CO2)
- ☑ GGT
- ☑ Urea

Metabolic

- ☑ Vitamin B12
- ☑ Methylmalonic Acid
- ☑ Thyroid Stimulating Hormone (TSH)
- ☑ Serum Ceruloplasmin

Immune Screen

- ☑ ANA Screen
  Only if ANA positive:
  - ☐ Systemic Lupus Profile (AI SLP on Mitogen lab requisition)
- ☑ ANCA/PR3,MPO (AI ANCA on Mitogen lab requisition)
- ☑ C3
- ☑ C4
- ☑ Rheumatoid Factor Qualitative
- ☑ Extractable Nuclear Antigen (AI SCLERO, AI SJS on Mitogen lab requisition)
- ☑ Serum Protein Electrophoresis
- ☑ Angiotensin Converting Enzyme
- ☑ Sedimentation Rate
- ☑ C-Reactive Protein

Specialized Antibody Testing: *In special circumstances, the physician may want to send the assay to Mayo Clinic Laboratories, in which event you should contact a demyelinating specialist and/or your zone's laboratory services for further guidance and http://www.mayomedicallaboratories.com/test-catalog/)*

- ☑ AQP-4 antibody and MOG antibody (Mitogen lab requisition Neuromyelitis Spectrum Profile AI NMO/AI MOG) *Mitogen Advanced Laboratory Diagnostics assay first – paper requisition required, can be downloaded at www.mitogen.ca AND attached to provincial laboratory requisition form). In special circumstances, the physician may want to send the assay to Mayo Clinic Laboratories, in which event you should contact a demyelinating specialist and/or your zone's laboratory services for further guidance and http://www.mayomedicallaboratories.com/test-catalog/)*
- ☐ Paraneoplastic screen (AI PARA on Miotogen lab requisition)

Infection screen

- ☑ Epstein-Barr Virus Antibody Panel
  - Convalescent and active serology (lgG and IgM)
- ☑ mycoplasma
- ☑ herpes family

☑ HIV
☑ VDRL
If presentation and geographically appropriate
☐ HTLV
☐ Lyme

Genetic Testing
☐ Molecular Genetics - Leber Hereditary Optic Atrophy if appropriate (*order MITOS screen on AHS Genetic requisition*)
☐ Biochemical Genetics – Adrenoleukomyeloneuropathy - Very Long Chain Fatty Acids

Cerebral Spinal Fluid (CSF)
Consider reserving tube of CSF for testing at a later time if diagnosis complicated/challenging
☑ CSF Cell Count
☑ CSF Protein
☑ CSF Glucose

Please Note: CSF Protein Electrophoresis = CSF Oligoclonal Bands. For assessment of CSF Oligoclonal Bands, Serum Protein Electrophoresis is REQUIRED to determine if the CSF Oligoclonal Bands (if detected) are truly generated by an immune process within the CNS or if they are just a reflection of peripheral immune activation.)
☑ CSF Protein Electrophoresis
☑ Serum Protein Electrophoresis
☑ cytology
☑ flow cytometry

Infection Screen
☑ Cerebrospinal Fluid Culture and Gram Stain
☑ VZV/HSV1&2/CMV/EBV/enterovirus PCR
☑ EBV IgM
☑ Mycoplasma
☑ cryptococcus fungal stain
☑ TB
☑ VDRL (only if serum already sent)
☑ HIV (if serum testing positive)

Immune:
☐ Paraneoplastic screen (AI PARA on Mitogen lab requisition), specimen type: CSF
☐ AQP-4 antibody and MOG antibody (Mitogen lab requisition Neuromyelitis Spectrum Profile AI NMO/AI MOG) *Mitogen Advanced Laboratory Diagnostics assay first – paper requisition required, can be downloaded at www.mitogen.ca AND attached to provincial laboratory requisition form). In special circumstances, the physician may want to send the assay to Mayo Clinic Laboratories, in which event you should contact a demyelinating specialist and/or your zone's laboratory services for further guidance and http://www.mayomedicallaboratories.com/test-catalog/*

Urine/Stool
☐ Ova and Parasite Examination (*Schistosomiasis testing of urine/stool if appropriate history/exposure*)

Skin

☐ Tuberculin skin test if appropriate
☐ Pathergy testing if Bechet's suspected

Pathology/Tissue Testing

☐ If indicated and accessible, lymph node biopsy by appropriate consulting service
☐ If indicated and accessible, leptomeningeal enhancing tissue biopsy by appropriate consulting service (likely Neurosurgery)

Diagnostic Imaging

CT Imaging

Or preferred chest imaging study at your institution

☑ CT chest, to rule out sarcoidosis

If neoplastic screening required

☐ CT Chest, Abdomen & Pelvis, Enhanced

If vasculitis suspected

☐ CT Angiography Head Enhanced

☐ Other: _____

Other Imaging

If required to rule out local malignancy; ovarian masses in women

☐ Ultrasound Abdomen & Pelvis
☐ US Abdomen, Complete
☐ US Pelvis, Female, Transvesical
☐ US Pelvis, Male

If required to rule out testicular cancer in men

☐ US Scrotal Study With Doppler

If required to rule out breast cancer

☐ Mammography, Bilateral

Magnetic Resonance Imaging (MRI)

If LETM presentation or APS presentation

☑ MR Brain Enhanced

OR

☐ MR Orbits & Brain Non-enhanced & Enhanced (*if optic neuritis presentation*)

AND

☑ MR C/T/L (*select all*):

- MR C Spine Enhanced
- MR L Spine Enhanced
- MR T Spine Enhanced

Nuclear Imaging

If required to rule out sarcoidosis, lymphoma, malignancy and CT negative/inconclusive

☐ NM PET CT Whole Body

☐ NM PET Brain

Other Test

Ophthalmic Testing

In all presentations, to be done acutely in optic neuritis presentation:

☑ Best-corrected high contrast letter visual acuity testing
☑ Colour acuity testing
☑ Pupillary assessment for relative afferent papillary defect detection
☑ Ophthalmoscopy, direct or indirect
☑ Slit lamp examination
☑ Intraocular Pressure
☑ Visual Field Testing
☑ If possible, optical coherence tomography (including peripapillary retinal nerve fiber layer, ganglion cell layer thickness, and macular volume
☐ If indicated, visual evoked potentials
☐ If indicated, retinal photos
☐ If indicated, fluorecein angiography

Intravenous Therapy

All patients require at a minimum a NS lock (for gadolinium dye administration for MRI). If plasma exchange is likely to occur, insertion of central venous catheter (jugular) should be performed as early as is reasonable.

☑ Intravenous Cannula – Insert: Initiate IV for MRI
☐ Place IJ Venous Cath Temp (*if plasma exchange is likely to occur*)

DVT Prophylaxis

☐ Sequential Compression Device: Apply continuously

Anticoagulant Medications

☐ enoxaparin 40 mg SUBCUTANEOUSLY every 24 hours
OR
☐ dalteparin 5000 units SUBCUTANEOUSLY every 24 hours

If weight less than 40 kg consider

☐ enoxaparin 30 mg SUBCUTANEOUSLY every 24 hours
OR
☐ dalteparin 2500 units SUBCUTANEOUSLY every 24 hours

Medications

First Line Treatment
☑ methylPREDNISolone sodium succinate 1g IV daily for 5 days
AND THEN
Recommend 1mg/kg ideal body weight
☑ predniSONE _____ mg PO daily (*until consultation with an NMO/neuroimmunologist specialist who will determine if and when taper is appropriate*)

Sleep Aid
☐ LORazepam 0.5 to 1 mg SL every night PRN for 5 days

Choose one
☐ zopiclone 3.75 mg PO every night PRN for 5 days
☐ zopiclone 5 mg PO every night PRN for 5 days
☐ zopiclone 7.5 mg PO every night PRN for 5 days

If disability is severe and/or not responding to steroid therapy in the first few days, initiate Plasma Exchange Therapy. The minimum number of exchanges is 5 to 7. If waiting to move patient to a facility for this therapy, can add another 5 day course of 1g/day IV methylPREDNIsolone sodium succinate.

If no plasma exchange available and no response to steroids:
☐ IV GAMMA GLOBULIN 2 g/kg divided over 2 to 5 days

☐ Contact NMO/neuro-immunology specialist if no response to plasma exchange and marked disability or ongoing worsening; for consideration of advanced escalation therapy (*typically rituximab, cyclophosphamide or other*)

Consults and Referrals

☑ MD Consult – Neurology: If not already under care of Neurology, then a Neurology consult with transfer of care should be undertaken
☑ MD Consult – Neurology: If available, a consult from the demyelinating specialist if needed in addition to Neurologist
☑ Ophthalmology Referral: for consult/assessment (*may not be required as an inpatient*)
☐ MD Consult – Apheresis Service. (*typically special service associated with Nephrology or Hematology*)
☐ MD Consult – Rheumatology Reason for consult:_____
☐ MD Consult - General Surgery: for tissue biopsy
☐ MD Consult - Neurosurgery: for tissue biopsy
☐ Physiotherapy Consult. Reason for consult:_____
☐ Occupational Therapy Consult. Reason for consult: _____
☐ Social Work: Reason for consult:_____
☐ Psychology/spiritual support: Reason for consult: _____
☐ Homecare: Reason for consult: _____
☐ Inpatient neurorehabilitation referral: Reason for consult:_____

In the case of a known NMOSD patient requiring inpatient care for suspected relapse

- ☑ Rule out active infection (urinalysis, urine C&S, CBC, blood cultures and CXR if indicated)
- ☑ Order MRI studies of relevant CNS areas as indicated
- ☑ Contact patient's demyelinating specialist/clinic. If not available contact neurologist or demyelinating specialist on service
- ☑ If infection not an issue, start acute therapy for admission event pathway** or if patient is known to respond best to a particular acute therapy such as Plasmapheresis, start this first.
    - ** See Figure 1 (page 8) of Suspected Neuromyelitis Optica Spectrum Disorder, Adult – Inpatient Clinical Knowledge Topic on the Knowledge Viewer:
        - http://insite.albertahealthservices.ca/klink/ckv.asp
- ☑ Routine and supportive care as above

Relevant Policies, Procedures, Guidelines, Clinical Knowledge and Practice Topics

Additional Guidelines

Revised 2015 NMOSD Criteria can be found at:

https://s3.amazonaws.com/gjcf-wp-uploads/wp-content/uploads/2016/05/16155924/NMOSD_Diag_Crit_2015_IPND1.pdf

Disposition Planning

1. Considerations for admission
    - For diagnosis of patient with complex neurological issue
    - In a known NMOSD patient, the admission should be made if (a) rapid myelopathic symptoms (b) APS/severe pain (c) disabling vision loss that are all escalating quickly as the need for the addition of PLEX and supportive therapy and rehab are likely

2. Considerations for Discharge/Transfer
    - Patients should have required laboratory testing and follow-up reviewed in detail prior to discharge, as well as indications to return to hospital and a contact physician/clinic
    - Patients should have counselling from the inpatient pharmacist about any immunosuppressive agents on which they remain (e.g. prednisone, azathioprine, etc.).

3. Home care and rehabilitation services as indicated (PT/OT/neuro-rehab admission)

4. Outpatient follow-up
    - All patients should be seen in follow-up in an MS specialty clinic within 6-8 weeks upon discharge.
    - Refer to Ophthalmologist if not seen as an inpatient.
    - The family practitioner of all patients should receive a detailed discharge summary including medications and adverse events/monitoring at the time of discharge. A reliable contact number of a neurologist who is able to provide advice in urgent situations should also be clearly indicated on this document. In centres with trainees, the staff neurologist should review the document to ensure NMOSD information is accurate and sign off on the document immediately. It should also be faxed to the family practitioner's office upon discharge to ensure its timely and secure arrival. If possible, we suggest contacting the family practitioner at the time of discharge to ensure receipt of this document and to clarify any concerns.

5. Patient and Family education/discharge instructions
    - In centres with Multiple Sclerosis (MS) specialists, suggest an inpatient visit to the MS clinic to become acquainted with the facility.

Rural Considerations

Given limited access to investigations and specialists outside of city centers, we advise rural care providers to contact the closest on-call Neurologist if they suspect a patient may have features of NMOSD. Acutely unwell patients should be transferred to Calgary or Edmonton as these are the only centers in the province with access to plasmapheresis.

Clinical Questions & Recommendations

Population, Patient or Problem: Patients with known NMOSD, suspected NMOSD, and those with LETM, atypical optic neuritis (bilateral simultaneous optic neuritis, optic neuritis found on MRI to be longitudinally extensive, involving multiple segments of the optic nerve, and/or involving the optic chiasm, optic tracts), and/or area postrema syndrome.
Intervention, Prognostic Factor, Exposure: Best evidence for diagnostic investigation algorithms, and acute and maintenance therapy
Comparison: No comparator group
Outcome: Best evidence to assist in diagnosis and management of NMOSD in Alberta.
Design: Systematic review, expert opinion

Search Keywords: Neuromyelitis Optica (MESH), Neuromyelitis Optica Spectrum Disorder (mp), Devic's Disease (mp), Devic's (mp), NMO (mp), NMOSD (mp), Longitudinally extensive transverse myelitis (mp), Aquaporin-4 (mp, may have a MESH heading), Bilateral optic neuritis (mp), Chronic relapsing inflammatory optic neuropathy (mp), CRION (mp), diagnosis AND therapy separately, systematic review separately

Search Results:
1. Diagnosis Search (+systematic review) - 405 (393+12 systematic reviews)→ 233 abstracts/papers reviewed → 123 graded and selected
2. Therapy Search (+systematic review) - 341 (336+5 systematic reviews)→ 98 abstracts/papers reviewed → 78 graded and selected

Quality of Evidence: Listed with each recommendation above

Strength of Recommendation: Listed with each recommendation above Patients with known NMOSD, suspected NMOSD, and those with LETM, atypical optic neuritis (bilateral simultaneous optic neuritis, optic neuritis found on MRI to be longitudinally extensive, involving multiple segments of the optic nerve, and/or involving the optic chiasm, optic tracts), and/or area postrema syndrome.

Clinical Question #1: In Adult patients who meet the criteria for Neuromyelitis Optica Spectrum Disorder, which investigations should be performed for exclusion of differential diagnoses or confirmation of NMOSD?

Clinical Recommendation #1:
We recommend the following investigations:
Serum: CBC with differential, electrolytes, creatinine, urea, ESR, CRP, ALT, AST, bilirubin (total), GGT, vitamin B12, Methylmalonic acid, TSH, serum copper

Immune/Infection screen: ANA (if ANA positive send Systemic Lupus Profile), ANCA/PR3,MPO, C3, C4, Rheumatoid Factor Qualitative, Extractable Nuclear Antigen, Serum Protein Electrophoresis, Angiotensin Converting Enzyme, Sedimentation Rate, C-Reactive Protein, ACE, AQP-4 antibodies, MOG antibodies, convalescent and active serology for EBV, mycoplasma, herpes family, HIV, VDRL

CSF: cell count, protein, glucose, gram stain, oligoclonal banding (requires serum oligoclonal banding to be sent at same time to be performed), cytology and flow cytometry, bacterial C&S, VZV/HSV1&2/CMV/EBV/enterovirus PCR, EBV IgM, mycoplasma, cryptococcus fungal stain, TB, VDRL

Diagnostic Imaging: (1) If LETM presentation - MRI brain + gadolinium (MS protocol), MRI C/T/L spine + gadolinium (MS protocol), (2) If optic neuritis presentation - MRI brain + gadolinium (MS protocol), MRI orbits and optic nerves + gadolinium, MRI C/T/L spine (MS protocol), (3) If APS presentation without GI cause - MRI brain + gadolinium (MS protocol), MRI C/T/L spine (MS protocol), CT chest (to rule out sarcoidosis)

Ophthalmological Testing: Direct fundoscopy, High and low contrast visual acuity testing, Ishihara colour plate testing, Slit lamp examination, Ocular pressure testing, Visual Field Testing (HVF 30/2), Optical Coherence Tomography, Visual Evoked Potentials, If indicated, retinal photographs, If indicated, fluorescein angiography

Additional tests can be added from detailed list above under appropriate circumstances

Quality of Evidence: Grade A,B

Strength of Recommendation: Grade 1

Clinical Question #2: In Adult patients who present with the optic neuritis phenotype of unilateral vision loss = > 20/50 (Snellen equivalent) one month after onset (with or without intervention), which investigations should be performed for exclusion of differential diagnoses or confirmation of NMOSD?

Clinical Recommendation #2:
We recommend the following lab investigations:
Serum: CBC with differential, electrolytes, creatinine, urea, ESR, CRP, ALT, AST, bilirubin (total), GGT, vitamin B12, methylmalonic acid, TSH, serum copper

Immune/Infection screen: ANA (if ANA positive send Systemic Lupus Profile), ANCA/PR3,MPO, C3, C4, Rheumatoid Factor Qualitative, Extractable Nuclear Antigen, Serum Protein Electrophoresis, Angiotensin Converting Enzyme, Sedimentation Rate, C-Reactive Protein, ACE, AQP-4 antibodies, MOG antibodies , convalescent and active serology for EBV, mycoplasma, herpes family, HIV, VDRL

Diagnostic Imaging: MRI brain + gadolinium (MS protocol), MRI orbits and optic nerves + gadolinium, MRI C/T/L spine (MS protocol), CT chest (to rule out sarcoidosis)

Ophthalmic Testing: Direct fundoscopy, High contrast visual acuity testing, Slit lamp examination, Intraocular pressure testing, Visual Field Testing/Perimetry, Optical Coherence Tomography (if possible), Visual Evoked Potentials (if indicated, retinal photographs (if indicated), fluorescein angiography (if indicated)

Additional tests including CSF studies can be added from detailed list above under appropriate circumstances (e.g. to rule out lymphoma or other malignancies, and infections such as CNS syphilis or mycoplasma)

Quality of Evidence: Grade A,B

Strength of Recommendation: Grade 1

Clinical Question #3: In Adult patients currently receiving emergent treatment for presumed NMOSD firstly with a 5-day course of 1g/day of IV methylprednisolone Na succinate, when would one consider escalating emergent therapy, and with what agent(s)?

Clinical Recommendation #3:
We recommend considering escalating beyond the initial course of IV methylPREDNIsolone if:

a) The patient continues to decline even after the initiation of IV methylPREDNIsolone (even prior to the completion of the 5 day course)
b) The patient fails to show signs of improvement on the neurological examination after completing the 5 day course of IV methylPREDNIsolone

Escalation options, in order of strength of recommendation, include:

a) Initiating plasmapharesis for a minimum of 5 to 7 exchanges if available.

b) If (a) not immediately available, then initiating another 5-day course of 1g/day of IV methylPREDNIsolone sodium succinate and consider arranging transfer to a facility where plasmapharesis is available.

c) If still waiting for access to plasmapharesis, could consider a course of IVIg (2g/kg total IV divided over 2 to 5 days, but limited evidence.

d) If failing or unresponsive to plasmapheresis, consider consulting a demyelinating or neuroimmunological specialist to initiate rituximab induction (375mg/m2 IV every week x 4 weeks or 1000mg IV every 2 weeks for two doses). Technically this is not a rapid induction.

e) If deteriorating despite rituximab, consider consulting a demyelinating or neuroimmunological specialist to initiate chemotherapeutic induction (typically cyclophosphamide).

Quality of Evidence: Grade B,C

Strength of Recommendation: Grade 1-2

Clinical Question #4: In Adult patients who meet the criteria for Neuromyelitis Optica Spectrum Disorder, which maintenance medication combination is most beneficial for prevention of future relapse events?

Clinical Recommendation #4:
We recommend azathioprine 2 to 3 mg/kg/day PO (typically 150mg divided BID or TID) titrated up over 3 to 4 weeks in combination with predniSONE 1 mg/kg/day, with no tapering of prednisone dosing for a minimum of 6 to 12 months. Alternatively, mycophenolate mofetil for a total of 1000 to 1500mg PO BID titrated up over 4 weeks in combination with predniSONE 1 mg/kg/day, with no tapering of predniSONE dosing for a minimum of 3 months, can be considered. Rituximab would be a first line recommendation (grade B, grade 1), but is not available as a first-line agent in Alberta for this indication.

Quality of Evidence: Grade B

Strength of Recommendation: Grade 1

Analytics

Analytics – Outcome Measure #1

Name of Measure	The number of days a patient admitted with Suspected Neuromyelitis Optica Suspected Disorder remains in the hospital until discharged home.
Definition	For all patients admitted to the hospital with Suspected Neuromyelitis Optica Suspected Disorder, we will measure the number of consecutive days the patient is in the hospital prior to discharge. This will be for all zones, and sites.
Rationale	Intended to obtain a baseline of what the average LOS for patients admitted with this disorder.
Notes for Interpretation	N/A
Cited References	N/A

Analytics – Outcome Measure #2

Name of Measure	The number of days a patient admitted with Suspected Neuromyelitis Optica Suspected Disorder remains in the hospital until discharged home.
Definition	For all patients admitted to the hospital with Suspected Neuromyelitis Optica Suspected Disorder, we will measure the number of consecutive days the patient is in the hospital prior to discharge. This will be for all zones, and sites.
Rationale	Intended to obtain a baseline of what the average LOS for patients admitted with this disorder.
Notes for Interpretation	N/A
Cited References	N/A

Appendix A: Prednisone Tapering

PredniSONE tapering should be relatively slow, once a steroid-sparing agent has become effective, or it is deemed there is no role for a steroid sparing agent. A sizable proportion of NMOSD patients are steroid sensitive, and this may become evident during the taper. The following is a sample tapering schedule.

If starting dose of oral predniSONE is 60mg per day:

- Decrease dose by 5mg every 2-3 weeks
- Once at 20mg/day decrease to 20mg alternating with 15mg daily for 2 weeks
- Then 15mg/day for 2 weeks
- Then 15mg alternating with 10mg daily for 2 weeks
- Then 10mg/day for 2 weeks
- Then 10mg alternating with 5mg daily for 2 weeks
- Then 5mg/day for 2 weeks
- Then 5mg every other day for 2 weeks

  Then done

Appendix B: Expanded Disability Status Scale

Table #. Expanded Disability Status Scale

Score	Result
0	Normal Neurological Exam
1.0	No disability, minimal signs in 1 functional status (FS)
1.5	No disability, minimal signs in more than 1 FS
2.0	Minimal disability in 1 FS
2.5	Mild disability in 1 or Minimal disability in 2 FS
3.0	Modrate disability in 1 FS or mild disability in 3 to 4 FS, though fully ambulatory
3.5	Fully ambulatory but with moderate disability in 1 FS and mild disability in 1 or 2 FS; or moderate disability in 2 FS; or mild disability in 5 FS
4.0	Fully ambulatory without aid, up and about 12hrs a day despite relatively severe disability. Able to walk without aid 500 meters
4.5	Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk without aid 300 meters
5.0	Ambulatory without aid for about 200 meters. Disability impairs full daily activities
5.5	Ambulatory for 100 meters, disability precludes full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters with or without resting
6.5	Constant bilateral support (cane, crutch or braces) required to walk 20 meters without resting
7.0	Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 hours a day
7.5	Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but may require motorized chair for full day's activities
8.0	Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self-care functions, generally effective use of arms
8.5	Essentially restricted to bed much of day, some effective use of arms, retains some self-care functions
9.0	Helpless bed patient, can communicate and eat
9.5	Unable to communicate effectively or eat/swallow
10	Death due to MS

Online version [25, 26]

- http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/10-2-3-29-EDSS_Form.pdf

References in Guide

1. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53(5): 1107-1114.

2. Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. Brain 2012;135(pt 6): 1834-1849.

3. Popescu BFG, Lennon VA, Parisi JE, et al. Neuromyelitis optica unique area postrema lesions: nausea, vomiting, and pathogenic implications. Neurology 2011;76(14): 1229-1237.

4. Jarius S, Wildemann B. The history of neuromyelitis optica J Neuroinflamm 2013, 10:8

5. Wingerchuk BG. Neuromyelitis optica in western countries: Establishing diagnostic criteria and characterization of the spectrum. Neurology Asia 2008;13: 161 – 166.

6. Pandit L, Asgari N, Apiwattanakul M, et al. Demographic and clinical features of neuromyelitis optica: A review. Mult Scler 2015;21(7): 845–853.

7. Mealy MA, Wingerchuk DM, Greenberg BM, et al. Epidemiology of neuromyelitis optica in the United States: A multicenter analysis. Arch Neurol 2012;69(9): 1176-1180.

8. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Eidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neurolinflamm 2016;13: 280.

9. Wingerchuk DM, Banwell N, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015; 85(2): 177–189.

References Used to Generate Guidelines

Diagnosis

1. Apiwattanakul M, Asawavichienjinda T, Pulkes T, et al. Diagnostic utility of NMO/AQP4-IgG in evaluating CNS inflammatory disease in Thai patients. Journal of the Neurological Sciences 320;2012: 118–12

2. Manrignier R, de Seze J, Vukusic S, et al. NMO-IgG and Devic's neuromyelitis optica: a French Experience. Mult Scler 2008;14: 440-445.

3. Marignier R, Bernard-Valnet R, Giraudon P, et al. Aquaporin-4 antibody–negative neuromyelitis optica Distinct assay sensitivity–dependent entity. Neurology 2013;80:2194–2200.

4. Marnetto F, Hellias B, Granieri L, et al. Western blot analysis for the detection of serum antibodies recognizing linear Aquaporin-4 epitopes in patients with Neuromyelitis Optica. J Neuroimmunol 2009;217: 74-79.

5. Matiello M, Lennon VA, Jacob A, et al. NMO-IgG predicts the outcome of recurrent optic neuritis. Neurology 2008;70:2197–2220.

6. Matsuoka T, Matsushita T, Kawano Y, et al. Heterogeneity of aquaporin-4 autoimmunity and spinal cord lesions in multiple sclerosis in Japanese. Brain 2007;130: 1206-1223.

7. Chan KH, Kwan JSC, Ho PWL, et al. Aquaporin-4 autoantibodies in neuromyelitis optica spectrum disorders: comparison between tissue-based and cell-based indirect immunofluorescence assays. Journal of Neuroinflammation 2010, 7:50.

8. Chang KH. Lyu RK, Chen CM, et al. Distinct features between longitudinally extensive transverse myelitis presenting with and without anti-Aquaporin 4 antibodies. Mult Scler 2012;19(3): 299-307.

9. Chanson J-B, Alame M, Collongues N, et al. Evaluation of Clinical Interest of Anti-Aquaporin-4 Autoantibody Followup in Neuromyelitis Optica. Clinical and Developmental Immunology 2013;2013: 1-7.

10. Fazio R, Malosio ML, Lampasona V, et al. Antiacquaporin 4 antibodies detection by different techniques in neuromyelitis optica patients. Mult Scler 2009;15(10): 1153-1163.

11. Harirchian MH, Aghamollaii V, Tafakhori A, et al. Seroprevalence of NMO-IgG Antibody in Neuromyelitis optica (NMO) and Its Specificity in Differentiating NMO from Other Demyelinating Diseases with Overlap Symptoms: An Iranian Experience. Iran J Allergy Asthma Immunol 2015;14(1): 98-104.

12. Hoftberger R, Sabater L, Marignier R, et al. An Optimized Immunohistochemistry Technique Improves NMO-IgG Detection: Study Comparison with Cell-Based Assays. PLOS One 2013;8(11): e79083.

13. Isobe N, Yonekawa T, Matshushita T, et al. Clinical Relevance of Serum Aquaporin-4 Antibody Levels in Neuromyelitis Optica. Neurochem Res 2013;38: 991-1001.

14. Jarius S, Aboul-Enein F, Waters P, et al. Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. Brain 2008:1-9. doi:10.1093/brain/awn240

15. Jarius S, Franciotta D, Paul F, et al. Cerebrospinal fluid antibodies to aquaporin-4 in neuromyelitis optica and related disorders: frequency, origin, and diagnostic relevance. J Neuroinflamm 2010;7:52.

16. Jarius S, Probst C, Borowski K, et al. Standardized method for the detection of antibodies to aquaporin-4 based on a highly sensitive immunofluorescence assay employing recombinant target antigen. J Neurol Sci 2010;291: 52-56.

17. Jarius S, Jacboi S, de Seze J, et al. Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders. Mult Scler 2011;17(9): 1067-1073.

18. Jiao Y, Fryer JP, Lennon VA, et al. Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. Neurology 2013;81: 1197-1204.

19. Kang E-S, Min J-H, Lee KH, et al. Clinical Usefulness of Cell-based Indirect Immunofluorescence Assay for the Detection of Aquaporin-4 Antibodies in Neuromyelitis Optica Spectrum Disorder. Ann Lab Med 2012;32: 331-338.

20. Kim Y-S, Jung S-W, Kim Y, et al. Detection of Anti-Aquaporin-4 Antibodies in Neuromyelitis Optica: Comparison of Tissue-Based and Cell-Based Indirect Immunofluorescence Assays and ELISA. J Clin Lab Anal 2012;26: 184-189.

21. Kim W, Li J-E, Li XF, et al. Quantitative measurement of anti-aquaporin-4 antibodies by enzyme-linked immunosorbent assay using purified recombinant human aquaporin-4. Mult Scler 2012;18(5): 578-586.

22. Long Y, Qiu W, Lu Z, et al. Aquaporin 4 Antibodies in the Cerebrospinal Fluid Are Helpful in Diagnosing Chinese Patients with Neuromyelitis Optica. Neuroimmunomodulation 2012;19:96–102.

23. Long Y, Zheng Y, Shan F, et al Development of a cell-based assay for the detection of anti-aquaporin 1 antibodies in neuromyelitis optica spectrum disorders. Journal of Neuroimmunology 2014;273: 103–110.

24. Mader S, Lutterotti A, Di Pauli F, et al. Patterns of Antibody Binding to Aquaporin-4 Isoforms in Neuromyelitis Optica, PloS one 2010;5(5): e10455.

25. Paul F, Jarius S, Atkas O, et al. Antibody to Aquaporin 4 in the Diagnosis of Neuromyelitis Optica. PLoS one 2007;4(4): e133.

26. Pittock S, Lennon VA, Bakshi N, et al. Seroprevalence of Aquaporin-4–IgG in a Northern California Population Representative Cohort of Multiple Sclerosis. JAMA Neurol 2014;71(11): 1433-1436.

27. Ruiz-Gaviria R, Baracaldo I, Castaneda C, et al. Specificity and sensitivity of aquaporin 4 antibodydetection tests in patients with neuromyelitis optica: A meta-analysis. Multiple Sclerosis and Related Disorders 2015;4: 345-349.

28. Siritho S, Apiwattanakul M, Nakashima I, et al. Features of anti-aquaporin 4 antibody-seronegative Thai patients with neuromyelitis optica spectrum disorders: A comparison with seropositive cases. J Neurol Sci 2014; 341: 17-21.

29. Siuko M, Tienari PJ, Saastamoinen K-P, et al. Neuromyelitis optica and aquaporin-4 (AQP4) autoantibodies in consecutive optic neuritis patients in Southern Finland. Acta Ophthalmol 2014;92: 387–391.

30. Smith CH, Waubant E, Langer-Gould A. Absence of Neuromyelitis Optica IgG Antibody in an Active Relapsing-Remitting Multiple Sclerosis Population. J Neuro-Ophthalmol 2009;29: 104–106.

31. Tzartos JS, Stergio C, Kilidireas K, et al. Anti-Aquaporin-1 Autoantibodies in Patients with Neuromyelitis Optica Spectrum Disorders. PLoS one 2013;8(9): e74773.

32. Waters PJ, MckEon A, Leite MI, et al. Serologic diagnosis of NMO: A multicenter comparison of aquaporin-4-IgG assays. Neurology 2012;78: 655-671.

33. Weinshenker NG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis Optica IgG Predicts Relapse after Longitudinally Extensive Transverse Myelitis. Ann Neurol 2006;59: 566–569.

34. Y Yang, Huang D-h, Wu W-p, et al. The role of aquaporin-4 antibodies in Chinese patients with neuromyelitis optica. Journal of Clinical Neuroscience 2013;20: 94–98.

35. Yang C-S, Zhang D-Q, Wang J-H, et al. Clinical Features and Sera Anti-Aquaporin 4 Antibody Positivity in Patients with Demyelinating Disorders of the Central Nervous System from Tianjin, China. CNS Neuroscience & Therapeutics 2014;20: 32–39.

36. Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicenter study of 175 patients. Journal of Neuroinflammation 2012, 9: 14.

37. Jarius S, Wildemann B. Aquaporin-4 Antibodies (NMO-IgG) as a Serological Marker of Neuromyelitis Optica: A Critical Review of the Literature. Brain Pathology 2013;23: 661–683.

38. Kitley J, Leite MI, Kuker W, et al. Longitudinally Extensive Transverse Myelitis With and Without Aquaporin 4 Antibodies. JAMA Neurol. 2013;70(11):1375-1381.

39. Kim SM, Waters P, Vincent A, et al. Sjögren's syndrome myelopathy: spinal cord involvement in Sjögren's syndrome might be a manifestation of neuromyelitis optica. Mult Scler 2009;15: 1062–1068.

40. Kim SM, Go MJ, Sung J-J, et al. Painful Tonic Spasm in Neuromyelitis Optica: Incidence, Diagnostic Utility, and Clinical Characteristics. Arch Neurol. 2012;69(8): 1026-1031.

41. Usmani N, Bedi G, Lam BLL, et al. Association Between Paroxysmal Tonic Spasms and Neuromyelitis Optica. Arch Neurol. 2012;69(1):121-124.

42. Zavada J, Nytrova P, Wandinger KP, et al. Seroprevalence and specificity of NMO-IgG (anti-aquaporin 4 antibodies) in patients with neuropsychiatric systemic lupus erythematosus. Rheumatol Int 2013; 33:259–263.

43. Kremer L, Mealy M, Jacob A, et al. Brainstem manifestations in neuromyelitis optica: a multicenter study of 258 patients. Mult Scler 2014;20(7): 843-847.

44. Bergamaschi R, Jarius S, Robotti M, et al. Two cases of benign neuromyelitis optica in

patients with celiac disease. J Neurol 2009;256: 2097-2099.

45. Asgari N, Voss A, Streenstrup T, et al. Interferon Alpha Association with Neuromyelitis Optica. Clinical and Developmental Immunology 2013, Article ID 713519,

46. Fuji C, Tokuda T, Ishigami N, et al. Usefulness of serum S100B as a marker for the acute phase of aquaporin-4 autoimmune syndrome. Neuroscience Letters 2011;494: 86–88.

47. Majed M, Fryger JP, Mckeon A, et al. Clinical utility of testing AQP4-IgG in CSF: Guideline for physicians. Neurol Neuroimmunol Neuroinflamm 2016;3:e231; doi: 10.1212/NXI.0000000000000231

48. Uzawa A, Mori M, Ito M, et al. Markedly increased CSF interleukin-6 levels in neuromyelitis optica, but not in multiple sclerosis. J Neurol 2009;256: 2082–2084

49. Uzawa A, Mori M, Sato Y, et al. CSF interleukin-6 level predicts recovery from neuromyelitis optica relapse. J Neurol Neurosurg Psychiatry 2012;83(3): 339-340.

50. Kitley J, Waters P, Woodhall M, et al. Neuromyelitis Optica Spectrum Disorders With Aquaporin-4 and Myelin-Oligodendrocyte Glycoprotein Antibodies A Comparative Study. JAMA Neurol 2014;71(3): 276-283.

51. Sato DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibodypositive and AQP4 antibody-positive NMO spectrum disorders. Neurology 2014;82:474–481.

52. Taso W-C, Lyu R-K, Ro L-S, et al. Clinical Correlations of Motor and Somatosensory Evoked Potentials in Neuromyelitis Optica. PLoS one 2014; 9(11): e113631.

53. Wingerchuk DM, Weinshenker BG. The emerging relationship between neuromyelitis optica and systemic rheumatologic autoimmune disease. Mult Scler 2012:18(1): 5-10.

54. Wu L, Huang D, Yang Y, et al. Combined Screening for Serum Anti-Nuclear and Anti-Aquaporin-4 Antibodies Improves Diagnostic Accuracy for Distinguishing Neuromyelitis Optica from Multiple Sclerosis. Eur Neurol 2014;72:103–108.

55. Cabrera-Gomez J, Quevedo-Stolongo L, Gonzalex-Quevedo A, et al. Brain magnetic resonance imaging findings in relapsing neuromyelitis optica. Mult Scler 2007; 13: 186-192.

56. Downer JJ, Leite MI, Carter R, et al. Diagnosis of neuromyelitis optica (NMO) spectrum disorders: is MRI obsolete? Neuroradiology 2012; 54:279–285

57. Kim W, Park MS, Le SH, et al. Characteristic brain magnetic resonance imaging abnormalities in central nervous system aquaporin-4 autoimmunity. Mult Scler 2010;16(10): 1229–1236.

58. Kim SH, Huh S-Y, Hyun JW, et al. A Longitudinal Brain Magnetic Resonance Imaging Study of Neuromyelitis Optica Spectrum Disorder. PloS one 2014;9(9): e108320.

59. Kim HJ, Paul F, Lana-Peixoto MA, et al. MRI characteristics of neuromyelitis optica

spectrum disorder: An international update. Neurology 2015;84:1165–1173.

60. Nasir S, Kerr DA, Birnbaum J, et al. Nineteen Episodes of Recurrent Myelitis in a Woman With Neuromyelitis Optica and Systemic Lupus Erythematosus. Arch Neurol. 2009;66(9):1160-1163.

61. Liao M-F, Chang K-H, Lyu R-K, et al. Comparison between the cranial magnetic resonance imaging features of neuromyelitis optica spectrum disorder versus multiple sclerosis in Taiwanese patients. BMC Neurology 2014, 14:218.

62. Matsushita T, Isobe N, Matsuoka T, et al. Reappraisal of brain MRI features in patients with multiple sclerosis and neuromyelitis optica according to anti-aquaporin-4 antibody status. Journal of the Neurological Sciences 2010;291: 37–43

63. Matthews L, Marasco R, Jenkinson M, et al. Distinction of seropositive NMO spectrum disorder and MS brain lesion distribution. Neurology 2013;80:1330–1337.

64. Mealy MA, Whetsone A, Orman G, et al. Longitudinally extensive optic neuritis as anMRI biomarker distinguishes neuromyelitis optica from multiple sclerosis. J Neurol Sci 2015;355: 59-63.

65. Nakamura M, Miyazawa I, Fujihara K, et al. Preferential spinal central gray matter involvement in neuromyelitis optica An MRI study. J Neurol 2008;255: 163-170.

66. Wang F, Liu Y, Duan Y, et al. Brain MRI abnormalities in neuromyelitis optica. European Journal of Radiology 2011;80: 445-449.

67. Yonezu T, Ito S, Mori M, et al. “Bright spotty lesions” on spinal magnetic resonance imaging differentiate neuromyelitis optica from multiple sclerosis. Mult Scler 2014;20(3): 331-337.

68. Zhang L, Wu A, Zhang B, et al. Comparison of deep gray matter lesions on magnetic resonance imaging among adults with acute disseminated encephalomyelitis, multiple sclerosis, and neuromyelitis optica. Mult Scler 2014;20(4): 418-423.

69. Kim W, Kim S-H, Huh S-Y, et al. Brain Abnormalities in Neuromyelitis Optica Spectrum Disorder. Multiple Sclerosis International 2012; Article ID 735486: 1-10.

70. Calabrese M, Oh MS, Favaretto A, et al. No MRI evidence of cortical lesions in neuromyelitis optica. Neurology 2012; 79: 1671–1676.

71. Bolat S, Berfing G, Dengler R, et al. Fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in the diagnosis of neurosarcoidosis. J Neurol Sci 2009;287: 257-259.

72. Chen X, Zeng C, Luo T, et al. Iron deposition of the deep grey matter in patients with multiple sclerosis and neuromyelitis optica: A control quantitative study by 3D-enhanced susceptibility-weighted angiography (ESWAN). European Journal of Radiology 2012;81: e633– e639.

73. Duan Y, Liu Y, Liang P, et al. Comparison of grey matter atrophy between patients with

neuromyelitis optica and multiple sclerosis: A voxel-based morphometry study. European Journal of Radiology 2012;81: e110–e114.

74. Jeantroux J, Kremer S, Lin XZ, et al. Diffusion tensor imaging of normal-appearing white matter in neuromyelitis optica. Journal of Neuroradiology 2012;39: 295-300.

75. Klawiter EC, Xu J, Naismith RT, et al. Increased radial diffusivity in spinal cord lesions in neuromyelitis optica compared with multiple sclerosis. Mult Scler 2012; 18(9): 1259–1268.

76. Matthews L, Kolind S, Brazier A, et al. Imaging Surrogates of Disease Activity in Neuromyelitis Optica Allow Distinction from Multiple Sclerosis. PloS one 2015; doi:10.1371/journal.pone.0137715.

77. Bennett JL, de Seze J, Lana-Piexoto ML, et al. Neuromyelitis optica and multiple sclerosis: Seeing differences through optical coherence tomography. Mult Scler 2015;21(6): 678–688.

78. Jindhara P, Hedges TR, Mendoza-Santiesteban CE, et al. Optical coherence tomography of the retina: applications in neurology. Current Opinion in Neurology 2010; 23:16–23.

79. Naismith RT, Tutlam NT, Xu J, et al. Optical coherence tomography differs in neuromyelitis optica compared with multiple sclerosis. Neurology 2009;72: 1077–1082.

80. Park K-A, Kim J, Oh SY. Analysis of spectral domain optical coherence tomography measurements in optic neuritis: differences in neuromyelitis optica, multiple sclerosis, isolated optic neuritis and normal healthy controls. Acta Ophthalmol. 2014: 92: e57–e65.

81. Ratchford JN Quigg ME, Conger A, et al. Optical coherence tomography helps differentiate neuromyelitis optica and MS optic neuropathies. Neurology 2009;73: 302-308.

82. de Seze J, Blanc F, Jeanjean L, et al. Optical Coherence Tomography in Neuromyelitis Optica. Arch Neurol 2008;65(7): 920-923

83. Burman K, Raininko R, Fagius J. Bilateral and recurrent optic neuritis in multiple sclerosis. Acta Neurol Scand 2011: 123: 207–210.
84. Petzgold A, Plant GT. Diagnosis and classification of autoimmune optic neuropathy. Autoimmunity Reviews 2014;13: 539-545.

85. Behbehani R. Expanding the spectrum of neuromyelitis optica: friend or foe? Curr Opin Ophthalmol 2007;18:459–462.

86. Chanson J-B, Zephir H, Collongues N, et al. Evaluation of health-related quality of life, fatigue and depression in neuromyelitis optica. European Journal of Neurology 2011;18: 836–841.

87. Feng Y-q, Guo N, Huang F, et al. Anti-tuberculosis treatment for Devic's neuromyelitis optica. Journal of Clinical Neuroscience 2010;17: 1372–1377.

88. Sato D, Fujihara K. Neuromyelitis optica without typical opticospinal phenotype. Mult Scler 2010;16(10): 1154-1155.

89. Ying L, Guixian Z, Chuanzhen L, et al. Differentiation of neuromyelitis optica from multiple sclerosis in a cohort from the mainland of China. Chinese Medical Journal 2014;127(18):3213-3218.

90. Ringelstein M, Kleiter I, Ayzenberg I, et al. Visual evoked potentials in neuromyelitis optica and its spectrum disorders. Mult Scler 2014;20(5): 617-620.

91. Bourne B, Zephir H, Ongagna J-C, et al. Long-term Follow-up of Acute Partial Transverse Myelitis. Arch Neurol. 2012;69(3):357-362

92. Kitley JL, Leite MI, George JS, et al. The differential diagnosis of longitudinally extensive transverse myelitis. Mult Scler 2012;18(3): 271-285.

93. Scott TF, Forhman EM, de Seze J, et al. Evidence-based guideline: Clinical evaluation and treatment of transverse myelitis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011;77: 2128-2134.

94. Sepulveda M, Blanco Y, Rovira A, et al. Analysis of prognostic factors associated with longitudinally extensive transverse myelitis. Mult Scler 2012;19(6): 742-748.

95. Aboul-Enein F, Seifert-Held T, Mader S, et al. Neuromyelitis Optica in Austria in 2011: To Bridge the Gap between Neuroepidemiological Research and Practice in a Study Population of 8.4 Million People. PLoS one 2013;8(11): e79649.

96. Asgari N. Epidemiological, clinical and immunological aspects of neuromyelitis optica (NMO). Dan Med J 2013;60: (10): B4730.

97. Bichuetti DB, Oliveira EML, Souza NA, et al. Neuromyelitis optica in Brazil: a study on clinical and prognostic factors. Mult Scler 2009;15: 613-619.

98. Bouyon M, Collongues N, Zephir H, et al. Longitudinal follow-up of vision in a neuromyelitis optica cohort. Mult Scler 2013;19(10): 1320-1322.

99. Cree BAC, Goodin DS, Hauser SL. Neuromyelitis optica. Seminars in Neurology 2002;22(2): 105-122.

100. Faxio R, Radaelli M, Furlan R. Neuromyelitis optica: Concepts in evolution. J Neuroimnumol 2011;231: 100-104.

101. Adiman E, Ozakbas S. The limited demyelinating diseases: the voyage of optic neuritis and transverse myelitis to multiple sclerosis and neuromyelitis. Expert Review of Neurotherapeutics 2011;451. DOI: http://dx.doi.org.ezproxy.lib.ucalgary.ca/10.1586/ern.11.16

102. Iyer A, Elsone L, Appleton R, et al. A review of the current literature and a guide to the early diagnosis of autoimmune disorders associated with neuromyelitis optica. Autoimmunity 2014; 47(3): 154-161.

103. Jarius S, Wiledmann B. The history of neuromyelitis optica. J Neuroinflammation 2013;10:8.

104. Kim S-H, Kim W, Li X-F, et al. Clinical spectrum of CNS aquaporin-4 autoimmunity. Neurology 2012;78: 1179-1185.

105. Lana-Peixoto MA. Devic's neuromyelitis optica: A critical review. Arq Neuropsiquiatr 2008;66(1): 120-138.

106. Makhani N, Bigi S, Banwell B, et al. Diagnosing neuromyelitis optica. Neuroimag Clin N Am 2013;23 279–291.

107. Matiello M, Jacob A, Wingerchuk DM, et al. Neuromyelitis optica. Curr Opin Neurol 2007;20:255–260.

108. McKeon A, Fryer JP, Apiwattanakul M, et al. Diagnosis of Neuromyelitis Spectrum Disorders: Comparative Sensitivities and Specificities of Immunohistochemical and Immunoprecipitation Assays. Arch Neurol. 2009;66(9):1134-1138.

109. Sato DK, Callegaro D, Lana-Peixoto MA, et al. Seronegative Neuromyelitis Optica Spectrum - The challenges on disease definition and pathogenesis. Arq Neuropsiquiatr 2014;72(6):445-450.

110. Sepulveda M, Armangue T, Sola-Valls N, et al. Neuromyelitis optica spectrum disorders Comparison according to the phenotype and serostatus. Neurol Neuroimmunol Neuroinflamm 2016;3: e225; doi: 10.1212/NXI.0000000000000225.

111. Weinshenker B. Western vs optical-spinal MS: Two diseases, one treatment? Neurology 2005;64: 594-595.

112. Wingerchuk DM, Lennon VA, Pittock SJ, et al. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66: 1485-1489.

113. Wingerchuk DM, Weinshenker BG. Acute Disseminated Encephalomyelitis, Transverse Myelitis, and Neuromyelitis Optica. Continuum (Minneap Minn) 2013;19(4):944–967.

114. Mealy MA, Wingerchuk DM, Greenberg BM, et al. Epidemiology of Neuromyelitis Optica in the United States: A Multicenter Analysis. Arch Neurol. 2012;69(9):1176-1180.

115. Morrow MJ, Wingerchuk DM. Neuromyelitis optica. Journal of Neuro-Ophthalmology 2012;32:154–166.

116. Lana-Peixoto MA, Callegaro D. The expanded spectrum of neuromyelitis optica – evidences for a new definition. Arq Neuropsiquiatr 2012;70(10):807-813.

117. Weinshenker BG. Neuromyelitis optica in western countries: Establishing diagnostic criteria and characterization of the spectrum. Neurology Asia 2008;13: 161-166.

118. Ghezzi A, Bergamaschi R, Martinelli V, et al. Clinical characteristics, course and

prognosis of relapsing Devic's Neuromyelitis Optica. J Neurol 2004;251: 47-52.

119. Bergamaschi R, Ghezzi A. Devic's neuromyelitis optica: clinical features and prognostic factors. Neurol Sci 2004;25: S364-367.

120. Wingerchuk DM, Hogancamp WF, O'Brien PC, et al. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53: 1107.

121. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica: Clinical predictors of a relapsing course and survival. Neurology 2003;60: 848-853.

122. Wingerchuk DM, Lennon VA, Luchinetti CF, et al. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6: 805-814.

123. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Eidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neurolinflamm 2016;13: 280.

Treatment:

1. Constanzi C, Mariello M, Luchinetti CF, et al. Azathioprine: Tolerability, efficacy, and predictors of benefit in neuromyelitis optica. Neurology 2011;77:659–666.

2. Elsone L, Kitley J, Luppe S, et al. Long-term efficacy, tolerability and retention rate of azathioprine in 103 aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder patients: a multicentre retrospective observational study from the UK. Mult Scler 2014;20(11): 1533–1540.

3. Qui W, Kermode AG, Li R, et al. Azathioprine plus corticosteroid treatment in Chinese patients with neuromyelitis optica. Journal of Clinical Neuroscience 2015; 22: 1178–1182.

4. Elsone L, Panicker J, Mutch K, et al. Role of intravenous immunoglobulin in the treatment of acute relapses of neuromyelitis optica: experience in 10 patients. Mult Scler 2014;20(4): 501–504

5. Magraner MJ, Coret F, Casanova B. The effect of intravenous immunoglobulin on neuromyelitis Optica. Neurología 2013;28(2): 65—72

6. Roed HG, Langkilde A, Sellebjerg F, et al. A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. Neurology 2005; 64:804–810.

7. Wingerchuk DM. Neuromyelitis Optica: Potential Roles for Intravenous Immunoglobulin. J Clin Immunol 2013;33 (Suppl 1):S33–S37.

8. Cabre P, Olindo S, Marignier R, et al. Efficacy of mitoxantrone in neuromyelitis optica spectrum: clinical and neuroradiological study. J Neurol Neurosurg Psychiatry 2013;84:511–516.

9. Kim S-H, Kim W, Park MS, et al. Efficacy and Safety of Mitoxantrone in Patients With Highly Relapsing Neuromyelitis Optica. Arch Neurol 2011;68(4):473-479.

10. Kitley JL, Leite MI, Matthews LAE, et al. Use of Mitoxantrone in Neuromyelitis Optica. Arch Neurol 2008;68(8): 1086.

11. Weinstock-Guttman B, Ramanthan M, Lincoff N, et al. Study of Mitoxantrone for the Treatment of Recurrent Neuromyelitis Optica (Devic Disease). Arch Neurol 2006;63:957-963.

12. Huh S-O, Kim S-H, Hyun J-W, et al. Mycophenolate Mofetil in the Treatment of Neuromyelitis Optica Spectrum Disorder. JAMA Neurol 2014;71(11):1372-1378

13. Jacob A, Matiello M, Weinshenker BG, et al. Treatment of Neuromyelitis Optica With Mycophenolate Mofetil: Retrospective Analysis of 24 Patients. Arch Neurol 2009;66(9):1128-1133

14. Kitley J, Elsone I, George J, et al. Methotrexate is an alternative to azathioprine in neuromyelitis optica spectrum disorders with aquaporin-4 antibodies. J Neurol Neurosurg

Psychiatry 2013;84:918–921

15. Ramanthan RS, Malhotra K, Scott T. Treatment of neuromyelitis optica/neuromyelitis optica spectrum disorders with methotrexate. BMC Neurology 2014, 14:51

16. Bonnan M, Valentino R, Olindo S, et al. Plasma exchange in severe spinal attacks associated with neuromyelitis optica spectrum disorder. Mult Scler 2009; 15: 487–492

17. Llufriu S, Castillo J, Blanco Y, et al. Plasma exchange for acute attacks of CNS demyelination Predictors of improvement at 6 months. Neurology 2009; 73:949–953

18. Kim S-H, Kim W, Huh S-O, et al. Clinical Efficacy of Plasmapheresis in Patients with Neuromyelitis Optica Spectrum Disorder and Effects on Circulating Anti-Aquaporin-4 Antibody Levels. J Clin Neurol 2013;9:36-42

19. Lim Y-M, Pyun S-Y, Kang B-H, et al. Factors associated with the effectiveness of plasma exchange for the treatment of NMO-IgG-positive neuromyelitis optica spectrum disorders. Mult Scler 2012; 19(9) 1216–1218

20. Greenberg BM, Graves D, Remington G, et al. Rituximab dosing and monitoring strategies in neuromyelitis optica patients: creating strategies for therapeutic success. Mult Scler 2012;18(7): 1022-1026.

21. Jacob A, Weinshenker BG, Volich I, et al. Treatment of Neuromyelitis Optica With Rituximab Retrospective Analysis of 25 Patients. Arch Neurol 2008;65(11):1443-1448

22. Kim S-H, Heong IH, Hyun J-W, et al. Treatment Outcomes With Rituximab in 100 Patients With Neuromyelitis Optica: Influence of FCGR3A Polymorphisms on the Therapeutic Response to Rituximab. JAMA Neurol 2015;72(9):989-995

23. Kim S-H, Hyun J-W, Jeong IH, et al. Anti-JC virus antibodies in rituximab-treated patients with neuromyelitis optica spectrum disorder. J Neurol 2015;262:696–700

24. Kim S-H, Kim W, Li XF, et al. Repeated Treatment With Rituximab Based on the Assessment of Peripheral Circulating Memory B Cells in Patients With Relapsing Neuromyelitis Optica Over 2 Years. Arch Neurol. 2011;68(11):1412-1420

25. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

26. Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

27. McKeon A, Pittock S. Individualized Rituximab Treatment for Neuromyelitis Optica Spectrum Disorders. JAMA Neurology 2013;70(9):1102-1104

28. Pellkofer HL, Krumbholz M, Berthele A, et al. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. Neurology 2011; 76:1310–1315

29. Kim S-H, Huh S-Y, Lee SJ, et al. A 5-Year Follow-up of Rituximab Treatment in Patients With Neuromyelitis Optica Spectrum Disorder. JAMA Neurol 2013;70(9):1110-1117

30. Cree BAC, Lamb S, Morgan K, et al. An open label study of the effects of rituximab in neuromyelitis optica. Neurology 2005;64:1270-1272.

31. Watanabe S, Misu T, Miyazawa I, et al. Low-dose corticosteroids reduce relapses in neuromyelitis optica: a retrospective analysis. Mult Scler 2007;13:968-974.

32. Bichuetti DB, Lobato de Oliveira EN, Oliveira DM, et al. Neuromyelitis Optica Treatment: Analysis of 36 Patients. Arch Neurol 2010;67(9):1131-1136

33. Bomprezzi R, Postevka E, Campagnolo D, et al. A Review of Cases of Neuromyelitis Optica. The Neurologist 2011;17:98–104

34. Jeong IH, Park B, Kim S-H, et al. Comparative analysis of treatment outcomes in patients with neuromyelitis optica spectrum disorder using multifaceted endpoints. Mult Scler 2016;22(3): 329-339.

35. Likar N, Mothe RK, Esam H, et al. Epidemiology and Current Treatment of Neuromyelitis Optica: A Systematic Review. Value in Health 2015;18: A750-751.

36. Mealy MA, Wingerchuk DM, Palace J, et al. Comparison of Relapse and Treatment Failure Rates Among Patients With Neuromyelitis Optica: Multicenter Study of Treatment Efficacy. JAMA Neurol 2014;71(3):324-330.

37. Torres J, Pruitt A, Balcer L, et al. Analysis of the treatment of neuromyelitis optica. Journal of the Neurological Sciences 2015;351: 31–35

38. Biswas A, Mukjerjee A. Therapy of NMO spectrum disorders. Ann Indian Acad Neurol 2015 Sep; 18(Suppl 1): S16–S23.

39. Carroll WM, Saida T, Kim HJ, et al. A guide to facilitate the early treatment of patients with idiopathic demyelinating disease (multiple sclerosis and neuromyelitis optica). Mult Scler 2012;19(10): 1371-1380.

40. Cree B. Neuromyelitis Optica: Diagnosis, Pathogenesis, and Treatment. Current Neurology and Neuroscience Reports 2008, 8: 427 – 433

41. Kessler RA, Mealy MA, Levy M. Treatment of Neuromyelitis Optica Spectrum Disorder: Acute, Preventive, and Symptomatic. Curr Treat Options Neurol 2016;18: 2

42. Kleiter I, Gahlen A, Borisow N, et al. Neuromyelitis Optica: Evaluation of 871 Attacks and 1,153 Treatment Courses. Ann Neurol 2016;79:206–216

43. Kleiter I, Gold R. Present and Future Therapies in Neuromyelitis Optica Spectrum Disorders. Neurotherapeutics 2016;13:70–83

44. Khoshnam M, Freedman MS. Disease-specific therapy of idiopathic inflammatory

demyelinating disorders. Expert Review of Neurotherapeutics 2012:12(9): p1113-1124.

45. Papadopoulos MC, Bennett JL, Verkman AS. Treatment of neuromyelitis optica: state-of-the-art and emerging therapies. Nat Rev Neurol 2014;10:493–506.

46. Sherman E, Han MH. Acute and Chronic Management of Neuromyelitis Optica Spectrum Disorder. Curr Treat Options Neurol 2015;17: 48

47. Vodopivec I, Matiello M, Prasad S. Treatment of neuromyelitis optica. Curr Opin Ophthalmol 2015, 26:476–483

48. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: Recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol 2013; DOI 10.1007/s00415-013-7169-7

49. Sato S, Callegaro D, Lana-Peixoto MA, et al. Treatment of neuromyelitis optica: an evidence based review. Arq Neuropsiquiatr 2012;70(1):59-66

50. Arkai M, Matsuoka T, Miyamoto K, et al. Efficacy of the anti–IL-6 receptor antibody tocilizumab in neuromyelitis optica: A pilot study. Neurology 2014;82: 1302-1306.

51. Bichuetti DB, Lobato Oliveira EM, de Castro Boulos F, et al. Lack of Response to Pulse Cyclophosphamide in Neuromyelitis Optica: Evaluation of 7 Patients. Arch Neurol 2012;69(7): 938-939.

52. Gartzen K, Limmroth V, Putzki N. Relapsing neuromyelitis optica responsive to glatiramer acetate treatment. European Journal of Neurology 2007;14: e12–e13.

53. Kageyama T, Komori M, Miyamoto K, et al. Combination of cyclosporine A with corticosteroids is effective for the treatment of neuromyelitis optica. J Neurol 2013;260:627–634

54. Kieseier BC, Stuve O, Dehmel T, et al. Disease Amelioration With Tocilizumab in a Treatment-Resistant Patient With Neuromyelitis Optica: Implication for Cellular Immune Responses. JAMA Neurol 2013;70(3):390-393.

55. Ringelstein M, Ayzenberg I, Harmel J, et al. Long-term Therapy With Interleukin 6 Receptor Blockade in Highly Active Neuromyelitis Optica Spectrum Disorder. JAMA Neurol 2015;72(7):756-763

56. Tanaka M, Kinoshita M, Tanaka K. Corticosteroid and tacrolimus treatment in neuromyelitis optica related disorders. Mult Scler 2015;21(5):669.

57. Tsakiri A, Kallenbach K, Fuglo D, et al. Simvastatin improves final visual outcome in acute optic neuritis: a randomized study. Mult Scler 2012;18(1): 72-81.

58. Matiello M, Pittock SJ, Porrata L, et al. Failure of Autologous Hematopoietic Stem Cell Transplantation to Prevent Relapse of Neuromyelitis Optica. Arch Neurol 2011;68(7): 953-954.

59. Burton JM, Storek P, Duggan P, et al. Autologous Hematopoietic Stem Cell Transplantation in Neuromyelitis Optica – An Update. Annual Meeting of the American Academy of Neurology. Neurology 2015;84 (Meeting Abstracts): P5.259.

60. Araki M, Aranmai T, Matsuoka T, et al. Clinical improvement in a patient with neuromyelitis optica following therapy with the anti-IL-6 receptor monoclonal antibody Tocilizumab. Mod Rheumatol 2013;23:827–831

61. Ayzenberg I, Kleiter I, Schroder A, et al. Interleukin 6 Receptor Blockade in Patients With Neuromyelitis Optica Nonresponsive to Anti-CD20 Therapy. JAMA Neurol 2013;70(3):394-397

62. Greco R, Bondnaza A, Vago L, et al. Allogeneic hematopoietic stem cell transplantation for neuromyelitis optica. Ann Neurol 2014;75(3): 447-453.

63. Asgari N, Kyvik KO, Steenstrup T, et al. Antibodies against interferon-beta in neuromyelitis optica patients. Journal of the Neurological Sciences 2014;339: 52–56

64. Azzopardi L, Cox AL, McCarthy CL, et al. Alemtuzumab use in neuromyelitis optica spectrum disorders: a brief case series. J Neurol 2016;263: 25-29.

65. Barnett MH, Prineas JW, Buckland ME, et al. Massive astrocyte destruction in neuromyelitis optica despite natalizumab therapy. Mult Scler 2012;18(1): 108-112.

66. Gelfand JM, Cotter J, Klingman J, et al. Massive CNS monocytic infiltration at autopsy in an alemtuzumab-treated patient with NMO. Neurol Neuroimmunol Neuroinflammation 2014;1: e34; doi: 10.1212/NXI.0000000000000034

67. Harmel J, Ringelstein M, Ingwersen J, et al. Interferon-β-related tumefactive brain lesion in a Caucasian patient with neuromyelitis optica and clinical stabilization with Tocilizumab. BMC Neurology 2014;14:247

68. Jacobs A, Hutchinson M, Elsone L, et al. Does natalizumab therapy worsen Neuromyelitis optica? Neurology 2012;79:1065-1066.

69. Jurynczyk M, Zaleski K, Selmai K. Natalizumab and the development of extensive brain lesions in neuromyelitis optica. J Neurol 2013;260:1919-1921.

70. Kim S-H, Kim W, Li XF, et al. Does interferon beta treatment exacerbate neuromyelitis optica spectrum disorder? Mult Scler 2012;18(10): 1480-1483.

71. Kitley J, Evangelou N, Kuker W, et al. Catastrophic brain relapse in seronegative NMO after a single dose of Natalizumab. J Neurol Sci 2014;339: 223-225.

72. Kleiter I, Hellwig K, Berthele A, et al. Failure of Natalizumab to Prevent Relapses in Neuromyelitis Optica. Arch Neurol 2012;69(2):239-245

73. Min J-H, Kim BJ, Lee KH. Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. Mult Scler 2012;18(1): 113-115.

74. Palace J, Leite MI, Nairne A, et al. Interferon Beta Treatment in Neuromyelitis Optica: Increase in Relapses and Aquaporin 4 Antibody Titers. Arch Neurol 2010;67(8):1016-1017

75. Shimizu Y, Yokoyama K, Misu T, et al. Development of extensive brain lesions following interferon beta therapy in relapsing neuromyelitis optica and longitudinally extensive myelitis. J Neurol 2008;255: 305-307

76. Shimizu J, Hatanaka Y, Hasegawa M, et al. IFN beta-1b may severely exacerbate Japanese optic-spinal MS in neuromyelitis optica spectrum. Neurology 2010;75: 1423-1427.

77. Uzawa A, Mori M, Hayakawa S, et al. Different responses to interferon beta-1b treatment in patients with neuromyelitis optica and multiple sclerosis. European Journal of Neurology 2010;17: 672–676

78. Wang K-C, Lin K-H, Lee T-C, et al. Poor Responses to Interferon-Beta Treatment in Patients with Neuromyelitis Optica and Multiple Sclerosis with Long Spinal Cord Lesions. PLoS one 2014;9)6): e98192

79. Yoshii F, Moriya Y, Ohnuki T, et al. Fingolimod-induced leukoencephalopathy in a patient with Neuromyelitis optica spectrum disorder. Multiple Sclerosis and Related Disorders 2016;7: 53–57

Additional Readings and General References

1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015;85(2): 177–189.

2. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: Recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol* 2013; DOI 10.1007/s00415-013-7169-7.

3. https://guthyjacksonfoundation.org

4. Kupersmith MJ, Gal RL, Beck RW, et al. Visual function at baseline and 1 month in acute optic neuritis. *Neurology* 2007;69: 508–514.

5. Bennett JL, J de Seze J, Lana-Peixoto M, et al. Neuromyelitis optica and multiple sclerosis: Seeing differences through optical coherence tomography. *Mult Scler* 2015;21(6): 678–688.

Acknowledgements

We would like to acknowledge the contributions of the clinicians who participated in the development of this topic. Your expertise and time spent are appreciated.

Name	Title	Zone
Knowledge Lead		
Ronak Kapadia	Physician, Neurology	Provincial
Ted Roberts	Physician, Neurology	
Topic Lead		
Jodie Burton	Physician, Neurology	
Fiona Costello	Physician, Neurology	
Working Group Members		
Penny Smith	Neurologist	Edmonton Zone
Jacqueline Baker	Neurologist	Central Zone
John Klassen	Nephrologist / apheresis expert	Calgary Zone
James Scott	Neuro Radiologist	Calgary Zone
Jim Lewis	Neuro Ophthalmologist	Edmonton Zone
Sharon Peters	Registered Nurse	Calgary Zone
Margaret Prociuk	Registered Nurse	Edmonton Zone
Siobhan Bast	Registered Nurse	Calgary Zone
Clinical Support Services		
Kirsten George-Phillips	Pharmacy Information Management Governance Committee (PIM-GC) *on behalf of* Pharmacy Services	Provincial
James Wesenberg	*on behalf of* Laboratory Services - Provincial Networks	Provincial
Bernice Lau	*on behalf of* Diagnostic Imaging Services	Provincial
Carlota Basualdo-Hammond & Marlis Atkins	*on behalf of* Nutrition & Food Services	Provincial
Clinical Informatics Lead		
Ja-Neen Simmie	*RN, BScN*	Provincial

Additional Contributors

Thank you to all provincial stakeholders who participated in the review process for this topic. Your time spent reviewing the knowledge topics and providing valuable feedback is appreciated.

For questions or feedback related to this knowledge topic please contact Clinical Knowledge Topics by emailing ClinicalKnowledgeTopics@albertahealthservices.ca