Livestream: NMOSD Unveiled: Optimizing Long-Term Outcomes in Neuromyelitis Optica Spectrum Disorder with Innovative Therapies

SYLLABUS & COURSE GUIDE

A Free, 90-Minute Live Activity
Premiere Date: Wednesday, May 29, 2024
5:00 PM - 6:30 PM ET

Login:
www.cmeoutfitters.com/NMOSDstream

Faculty:
Rosemarie Walch, DO (Moderator)
Marijean Buhse PhD, NP-BC, MSCN, FAAN
Flavia Nelson, MD
Chelsey Tucker (Patient)

Take advantage of our LIVE Q&A segment during this webcast!

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Information for Participants

Statement of Need

Neuromyelitis optica spectrum disorder (NMOSD) is a relatively new term for a group of rare, demyelinating autoimmune diseases affecting the central nervous system (CNS), particularly the optic nerves and spinal cord. In the past, NMOSD was conflated with multiple sclerosis (MS) due to significant similarities in early-stage presentation. However, recent evidence has shown NMOSD to be a unique disorder with an antibody-mediated etiology distinct from MS. Without proper diagnosis and treatment, patients with NMOSD are likely to develop significant and progressive disability with each recurrent attack.

Due to the relatively recent recognition of NMOSD as a distinct diagnostic entity, health care practitioners (HCPs) may lack knowledge and familiarity in its optimal diagnosis and management. It is essential that HCPs understand the etiology and pathophysiology of NMOSD, how novel therapies work to prevent NMOSD attacks, and long-term management strategies that can be utilized in clinical practice.

In this CME Outfitters livestream symposium, expert faculty will discuss strategies to better identify the pathological hallmarks of NMOSD, evaluate diagnostic criteria, utilize established and emerging therapeutics, and implement ongoing care of patients with NMOSD.

Learning Objectives

At the conclusion of this activity, learners will be able to better:

- Identify the pathophysiology of NMOSD including the role of the complement mechanism in the disease state
- Evaluate diagnostic criteria including clinical presentation, AQP4-IgG status, and magnetic resonance imaging (MRI) findings to accurately diagnose NMOSD
- Utilize recently approved and emerging NMOSD therapeutic antibodies in preventing acute episodes, associated damage, and long-term disability
- Implement ongoing care and monitoring of patients with NMOSD to optimize long-term outcomes

Financial Support

Supported by an educational grant from Alexion Pharmaceuticals.

Target Audience

Adult neuroimmunologists, neuroradiologists, neurologists, internists, and ancillary HCPs – physician associates (PAs), nurse practitioners (NPs), nurses, and pharmacists

Credit Information

Jointly Accredited Provider:
In support of improving patient care, CME Outfitters, LLC, is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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This activity was planned by and for the healthcare team, and learners will receive 1.5 Interprofessional Continuing Education Credits for learning and change.

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Nurses (ANCC):
This activity is designated for 1.5 contact hours.

California Residents: This continuing nursing education activity was approved by the California Board of Registered Nursing. CME Outfitters LLC's provider number is CEP15510.

Note to Nurse Practitioners: The content of this CNE activity pertains to Pharmacology.

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ABIM MOC
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.50 medical knowledge MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

MIPS Improvement Activity
Completion of this accredited CME activity meets the expectations of an Accredited Safety or Quality Improvement Program (IA_PSPA_28) for the Merit-based Incentive Payment Program (MIPS). Clinicians should submit their improvement activities by attestation via the CMS Quality Payment Program website.

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Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

Faculty

ROSEMARIE WALCH, DO - MODERATOR
Neuroimmunologist
Memorial Healthcare
Owosso, MI

Rosemarie Walch, DO, earned her Doctor of Osteopathic Medicine degree from Michigan State University College of Osteopathic Medicine. She completed a neurology residency at Ascension Macomb-Oakland Hospital and a multiple sclerosis/neuroimmunology fellowship at the University of Cincinnati/UC Health Waddell Center for Multiple Sclerosis. She is currently a neuroimmunologist at Memorial Healthcare in Owosso, Michigan. Dr. Walch has published in peer-reviewed journals and has had numerous abstracts accepted for oral and poster presentations at many congresses.

Dr. Walch reports the following financial relationships:

Advisory Board: Alexion Pharmaceuticals, Inc.; Bristol Myers Squibb Company; Genentech, Inc./Roche; Genzyme Corporation; and Sanofi

Consultant: Alexion Pharmaceuticals, Inc.; Amgen Inc./Horizon Therapeutics; and TG Therapeutics, Inc.

Grants: CMSC Foundation

Research Support: Alexion Pharmaceuticals, Inc.; Amgen Inc.; Biogen; EMD Serono; Genentech, Inc./Roche; Novartis. Pharmaceuticals Corporation; Roche; Sanofi; and TG Therapeutics, Inc.

Speakers Bureau: Alexion Pharmaceuticals, Inc.; Amgen Inc./Horizon Therapeutics, Inc.; and Biogen

MARIJEAN BUHSE PHD, NP-BC, MSCN, FAAN
Nurse Practitioner at
NYU South Shore Neurologic Associates
Islip, NY

Dr. Marijean Buhse, PhD, ANP, RN, MSCN, FAAN, is a Clinical Professor and Director of the Doctoral Program in Nursing at Stony Brook University School of Nursing, Stony Brook, NY. She is also a Nurse Practitioner at NYU South Shore Neurologic working with persons with Multiple Sclerosis for over 25 years.

Dr. Buhse is the past president of the Multiple Sclerosis Nurses International Certification Board and the treasurer for the International Organization of MS Nurses. Her research has focused on closing existing gaps in knowledge related to care of older adults with multiple sclerosis.

Dr. Buhse reports no financial relationships to disclose.

FLAVIA NELSON, MD
Thomas F. Whigham-Joseph Berger Chair in Neuroimmunology
Professor of Neurology
Chief, CNS Autoimmune Disorders Division
Director, Multiple Sclerosis Center of Excellence
University of Miami Leonard M. Miller School of Medicine
Miami, FL

Flavia Nelson, MD, is a board-certified neurologist specializing in multiple sclerosis (MS) and other neuro-immunologic disorders. After receiving her medical degree from the University of Chihuahua (UACH) in Mexico, she completed a residency in Internal Medicine at Texas Tech University Health Sciences Center, and a neurology residency and a clinical/research fellowship in MS with Jerry Wolinsky

at The Texas Medical Center, UT Houston. 12 years later she became the Interim Director of the Multiple Sclerosis Research Group this same institution, where she also co-directed the MRI-Analysis Center.

In 2022 Dr. Nelson moved to Minnesota and served as a member of the Center for MRI Research where she worked with UHF 7 and 10.5 magnets. She is a Professor of Neurology and Director of CNS Autoimmune Disorders and the MS Center of Excellence at the University of Miami.

Dr. Nelson serves as both a member and leader in several organizations related to multiple sclerosis and neurology. She is a trailblazer in the imaging of cortical gray matter lesions and their role on cognitive impairment. Her interests also include stem cell transplant in MS.

Dr. Nelson reports the following financial relationships:

Advisory Board: Genentech, Inc. and Horizon Therapeutics

CHELSEY TUCKER
Artist, author, and patient advocate

Diagnosed with a rare autoimmune disease, Neuromyelitis Optica Spectrum Disorder or NMOSD, which leaves her color blind and visually impaired, Chelsey Tucker uses emotion to feel the painting while creating. She paints as an expression of how she sees the world.

NMOSD doesn't just affect Chelsey's vision. During periods of relapse, those with NMOSD often lose feeling in their hands. While this may seem like a deterrent and a provocation to stop painting all together, this is not an option for Chelsey. She needs to create. Her subjects and methods may change depending on her symptoms, but this certainly does not prevent her from maintaining the same level of creativity and professionalism for which she is known. When holding a brush is no longer an option, she will use a technique involving her fingers directly on the canvas.

Residing just outside of Nashville, TN with her husband and their 5 children, Chelsey prioritizes family above all things. She derives a great deal of inspiration from her children, and they support her every step of the way. Chelsey is also a believer in giving back to her beloved NMOSD community as she serves as a patient influencer and rare disease advocate. In addition to advocating for the rare disease community, Chelsey is also an enthusiastic lover of horticulture- particularly flowers. She has provided plants and seeds for countless gardens within her community and enjoys creating hundreds of fresh floral arrangements throughout the growing season.

Most recently, her story and art have been featured in publications like *Vice* and *Women's Health Magazine.*

Ms. Tucker reports no financial relationships to disclose.

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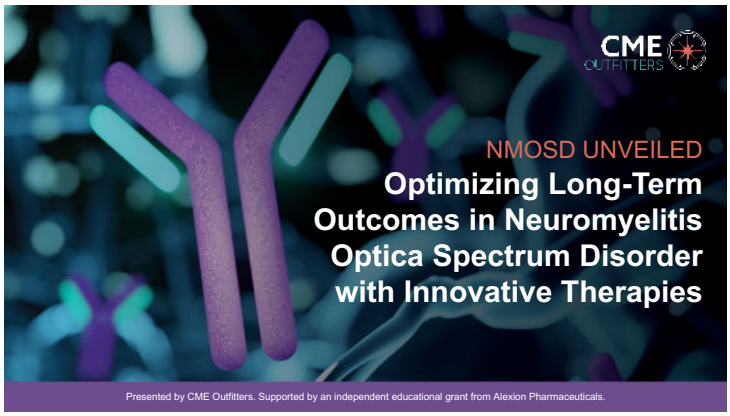

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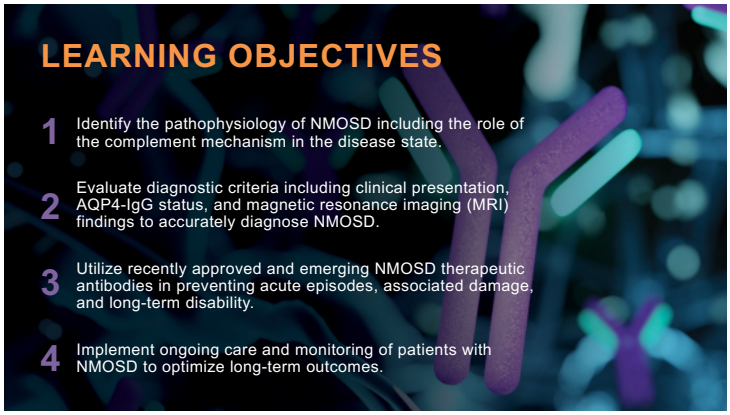
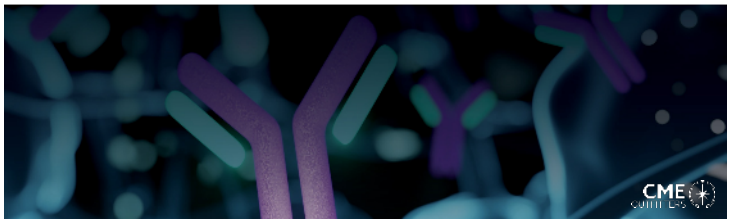
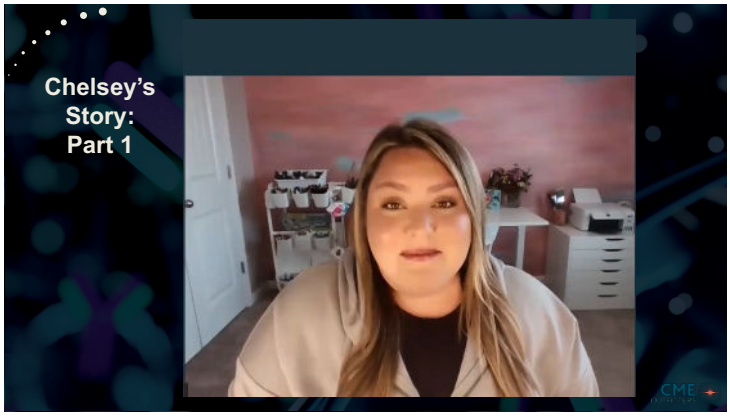


The NMOSD Patient Experience

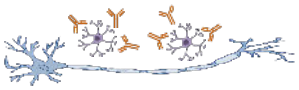
Clinical Course and Unmet Needs



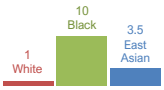


NMOSD Background

Autoimmune, relapsing, demyelinating, CNS astrocytopathy



Global prevalence
per 100,000



Typical age of onset

35 to 40 years

Can present in all ages, rarely in children and older adults

Female-to-male ratio

♀ : ♂

High female predilection, up to 9:1 in seropositive

CNS = central nervous system
Kim S, et al. *Neurology.* 2018;91(22):e2089-e2099. Hor JY, et al. *Front Neurol.* 2020;11:501. Briggs FB, Shaia J. *Multiple Sclerosis Journal.* 2024;30(3):316-324.

NMOSD Clinical Course

90%

Acute relapses

90% of patients experience relapses
70% relapse within 2 years
50% relapse within 1 year

75%

Incomplete recovery

75% of attacks leave patients with residual deficits
5% have no recovery at all

60%

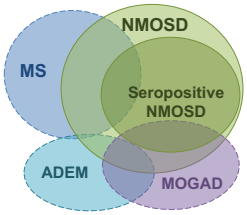
Cumulative disability

60% of patients go blind in at least one eye within 5 years
30% become severely disabled

Jiao Y, et al. *Neurology.* 2013;81(14):1197-1204. Duchow A, et al. *Ann Neurol.* 2024;95(4):720-732. Kleiter I, et al. *Ann Neurol.* 2016;79(2):206-216.
Ghezzi A, et al. *J Neurol.* 2004;251(1):47-52.

NMOSD Misdiagnosis

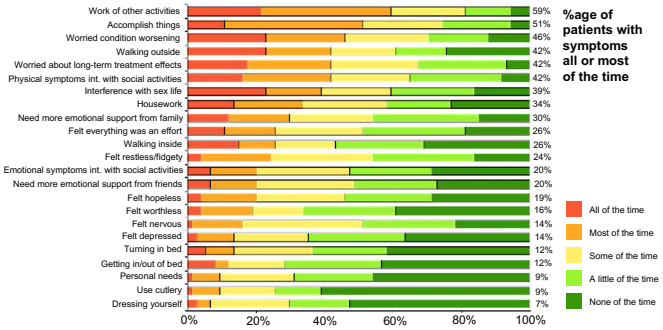
25% to 40% of people currently living with NMOSD were initially misdiagnosed, most often with multiple sclerosis (MS).



- Factors associated with misdiagnosis
  - Area postrema syndrome (APS) without neurological symptoms
  - Longer time to see neuroimmunology specialist and/or undergo MRI
  - Negative serostatus
- Consequences of misdiagnosis
  - Delay in initiating maintenance therapy
  - Inappropriate or harmful treatment
  - Greater frequency and severity of relapses
  - Increased risk of permanent disability

ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin-4 immunoglobulin; MOGAD = myelin oligodendrocyte glycoprotein antibody disease.
Min JK, et al. *Neurol Ther.* 2023;12(2):619-633. Smith AD, et al. *Mult Scler Relat Disord.* 2023;70:104498. Rotstein DL, et al. *Mult Scler Relat Disord.* 2024;83:105434.

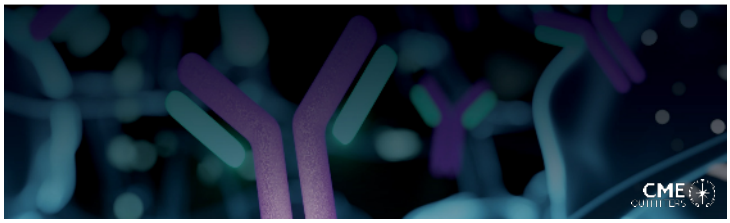
NMOSD Impacts on Quality of Life (QoL)



Eaneff S, et al. *Mult Scler Relat Disord.* 2017;17:116-122.

Inside NMOSD Pathophysiology

Autoantibodies and the Complement Cascade



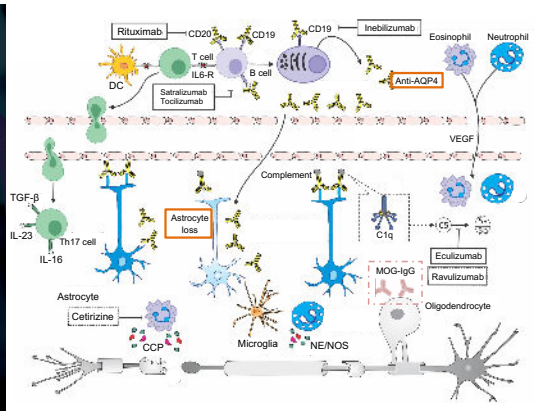
Proposed NMOSD Pathogenesis

- **Aquaporin 4 (AQP4)**
  - Water channel expressed on astrocyte end-feet
  - Regulates bidirectional flow of aqueous material across blood-brain/CSF barrier (BBB)
  - Most prevalent in optic nerve, spinal cord, and brainstem (areas of NMOSD insult)
- **AQP4-IgG autoantibody production**
  - Reactive T cells (Th17) prompt production of autoantibodies (B cells, plasmablasts, IL-6) targeting AQP4
  - AQP4-IgG near 100% specificity for NMOSD
- **Complement activation**
  - AQP4-IgG (or otherwise undiscovered NMO-antibody) binds AQP4 and activates complement
  - Complement cascade promotes neutrophil chemotaxis and MAC deposition (C5)
- **Astrocytopathy**
  - Complement-driven inflammation causes severe astrocyte necrosis (elevated GFAP)
  - Astrocyte loss compromises BBB and promotes further CNS inflammation (NMOSD attacks)
  - Secondary oligodendrogliopathy drives demyelination and axonal degeneration (lesions)

IgG = immunoglobulin G; CSF = cerebrospinal fluid: MAC = membrane attack complex: GFAP = glial fibrillary acidic protein; CNS = central nervous system

Huang TL, et al. *Int J Mol Sci.* 2022;23(14):7908. Wu Y, et al. *Mult Scler Relat Disord.* 2019;27:412-418.
Papadopoulos MC, Verkman AS. *Lancet Neurol.* 2012;11(6):535-544.

NMOSD Immuno-pathology and Therapeutic Targets



DC = dendritic cells, IL = interleukin, TGF = tumor growth factor, C = complement, CCP = cytotoxic cation proteins, NE = neutrophil elastase, NOS = nitric oxide species, VEGF = vascular endothelial growth factor

Carnero Contentti E, Correale J. *J Neuroinflammation.* 2021;18(1):208

AQP4-IgG Antibody Testing

Frequency and distribution of positive results yielded by different AQP4-IgG assays in patients with clinical NMOSD diagnosis

	Assay type	Results					
	M1-ELISA	–	–	–	+	+	–
	M1 CBA			+	+		
	M1 FACS			+	+		
	M23-FACS	–	–	+	+	+	–
Group 1	Patients	1	0	3	10	0	2
N tested	380						
Positive	16 (4%)						
Group 2	Patients	0	3	3	17	1	0
N tested	813						
Positive	24 (4%)						
Group 3	Patients	2	1	2	0	0	0
N tested	31						
Positive	5 (14%)						

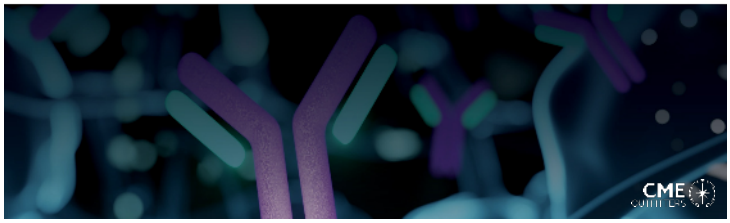
- **Cell-based assays (CBA) preferred**
  - Fluorescence-activated cell sorting (FACS) nearly 100% specific for AQP4-IgG
  - Other CBAs > 90% specific
  - 70-90% sensitivity overall
- **ELISA and immunohistochemistry assays**
  - Commercially available, but not preferred
  - Sensitivity affected by fluctuating antibody titers
  - Concern for false positives
  - Re-testing recommended if uncertain
- **Serum preferred over CSF**
  - Serum testing is more sensitive and less invasive
  - Consider CSF only if serum is inconclusive

ELISA = enzyme-linked immunosorbent assay

Fryer JP, et al. *Neurol Neuroimmunol Neuroinflamm.* 2014;1(1):e11. Alkabie S, Budhram A. *Front Neurol.* 2022;13:912050.

NMOSD Diagnosis

Clinical, Serological, and Radiological Criteria



Patient case: Angela

Angela, a 32-year-old African American female, presents to the ED with an acute onset of neurological symptoms. She reports malaise and fatigue followed by persistent nausea and vomiting for the past 2 days. Today she woke up with severe weakness and numbness in her lower extremities, leading to difficulty with walking and standing. She also reports a band-like sensation around her abdomen and urinary retention.

Assessment:

Upon examination, Angela has decreased strength in her legs (2/5 MRC), hyperreflexia, and a sensory level at T6. Cranial nerve exam reveals mild facial asymmetry and difficulty with gag reflex.

Past medical history:

Migraines (dx age 30): Accompanied by visual disturbances, nausea, and vomiting; managed with prophylactic propranolol 20 mg PO twice daily

Hypothyroidism (dx age 26): Managed with levothyroxine 175 mcg PO daily

Family history: Mother has Sjögren's Syndrome. No other significant family medical history.

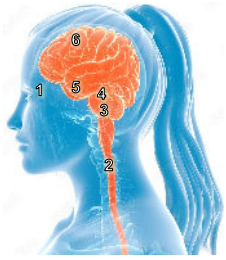
MRC = Medical Research Council scale for muscle strength; PO = by mouth/oral

? Which of Angela's presenting symptoms most strongly suggests brainstem involvement?

A. Malaise and fatigue
B. Persistent nausea and vomiting
C. Severe weakness and numbness in lower extremities
D. Band-like sensation around her abdomen
E. I don't know

NMOSD Core Clinical Characteristics

1. **Optic neuritis**
2. **Acute myelitis**
3. **Area postrema syndrome (APS)**
4. Acute brainstem syndrome (ABS)
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions



Wingerchuk DM, et al. *Neurology.* 2015;85(2):177-189. Jarius S, et al. *J Neurol.* 2023;270(7):3341-3368.

NMOSD Clinical Presentation

Transverse myelitis
- Weakness/paralysis of limb, torso, +/or respiratory muscles
- Painful tonic spasms
- Sharp, shooting, radicular pain
- Pruritis, numbness, tingling, or burning sensations
- Bladder, bowel +/or sexual dysfunction

Optic neuritis
- Unilateral > bilateral partial or complete blindness
- Loss of visual acuity or color saturation
- Retrobulbar pain that worsens with eye movement
- Abnormal/asymmetrical pupillary response to light

Area postrema syndrome (APS)
- Intractable nausea, vomiting, +/- hiccups

+/-

Brainstem, diencephalic, +/or cerebral syndromes
- Symptomatic narcolepsy +/- autonomic dysfunction
- Difficulty speaking, swallowing, +/or breathing
- Facial paralysis
- Severe headache, visual disturbances, altered mental status
- Vertigo, hearing loss, tinnitus
- Encephalopathy, hydrocephaly, seizures
- Fulminant neurogenic respiratory failure

Wingerchuk DM, et al. *Neurology*. 2015;85(2):177-189. Jarius S, et al. *J Neurol*. 2023;270(7):3341-3368. Jarius S, et al. *Clin Exp Immunol*. 2014;176(2):149-164

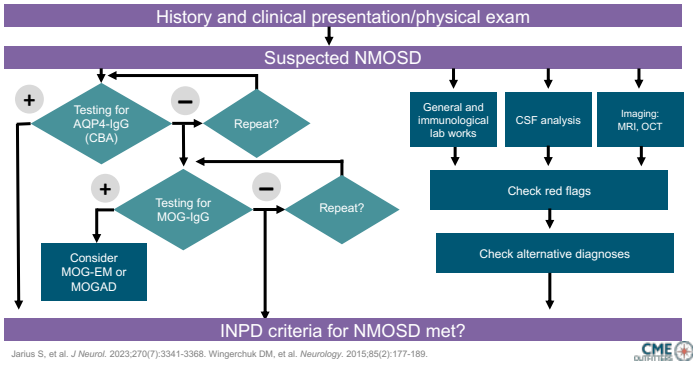
NMOSD Diagnostic Criteria

2015 International Panel for NMOSD Diagnosis (IPND)

NMOSD with AQP4-IgG	NMOSD without AQP4-IgG (or unknown)
• ≥ 1 core clinical characteristic • Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) • Exclusion of alternative diagnoses (i.e., sarcoidosis, neoplastic/paraneoplastic, vascular, chronic infection, etc.)	≥ 2 core clinical characteristic occurring as a result of one or more clinical attacks and meeting all of the following requirements: • ≥ 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or APS • Dissemination in space (≥ 2 core clinical characteristics) • Fulfillment of additional MRI requirements, as applicable • Negative test for AQP4-IgG using best available detection method, or testing unavailable • Exclusion of alternative diagnoses

Wingerchuk DM, et al. *Neurology*. 2015;85(2):177-189.

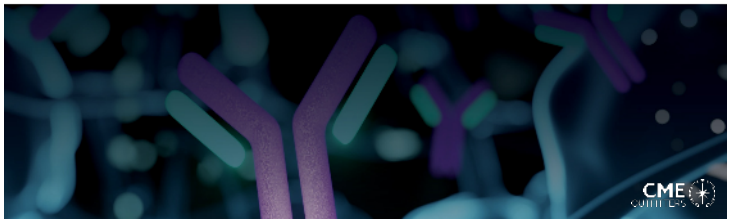
Proposed NMOSD Diagnostic Algorithm



Jarius S, et al. *J Neurol*. 2023;270(7):3341-3368. Wingerchuk DM, et al. *Neurology*. 2015;85(2):177-189.

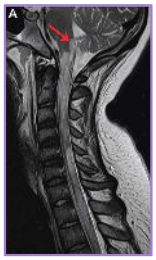
It's Demyelinating, It's Relapsing, but It's Not MS

Red Flags and Clinical Pearls



Patient Case: Angela

Angela is started on high-dose corticosteroids and sent for lab work and imaging.



Laboratory analysis:

Serum
- Anti-AQP4-IgG: Positive
- Anti-MOG-IgG: Negative

CSF
- Oligoclonal bands: Absent
- Protein level: Elevated (100 mg/dL)
- WBC count: Elevated (20 cells/μL)

Additional findings:

MRI: Sagittal T2-weighted brain/spine MRI shows poorly delineated hyperintense signal changes within an enlarged spinal cord extending over 8-9 spinal segments (LETM). A hyperintense dorsal medulla/area postrema lesion is also seen.

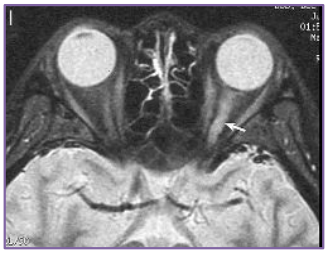
WBC = white blood cell. Costello F. *Continuum (Minneap Minn).* 2022;28(4):1131-1170.

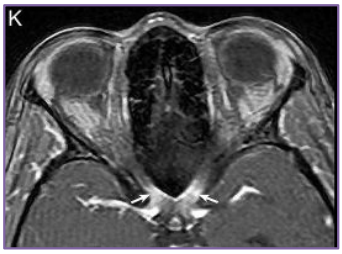
? Which combination of findings in Angela's workup is *most* specific for NMOSD?

A. Anti-AQP4-IgG positive + LETM
B. Anti-AQP4-IgG positive + absent CSF oligoclonal bands
C. LETM + absent CSF oligoclonal bands
D. Anti-AQP4-IgG positive + Anti-MOG-IgG negative
E. I don't know

MRI: Acute Optic Neuritis

NMOSD requires normal findings or only nonspecific white matter lesions, *OR* optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesions ≥ half the length of the optic nerve or involving optic chiasm.

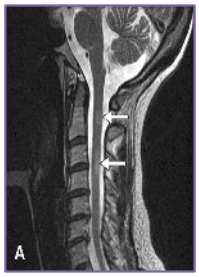




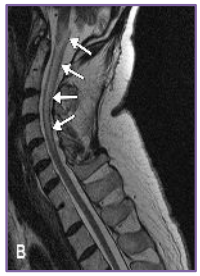
Wingerchuk DM, et al. *Lancet Neurol.* 2007;6(9):805-815.

MRI: Spinal Cord Lesion Phenotype

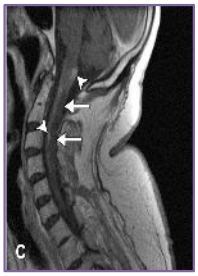
NMOSD myelitis requires LETM ≥ 3 contiguous segments, *OR* focal atrophy ≥ 3 contiguous segments in patients with history of acute myelitis.



MS



NMOSD

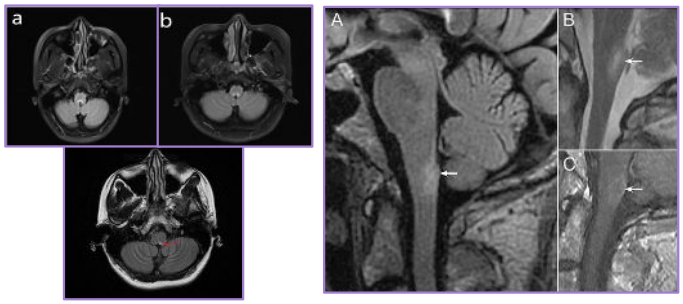


NMOSD

Wingerchuk DM, et al. *Lancet Neurol.* 2007;6(9):805-815.

MRI: Area Postrema Syndrome

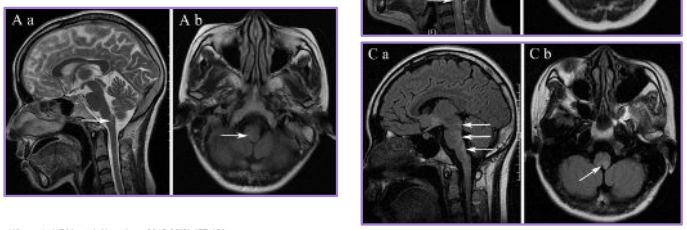
NMOSD requires associated dorsal medulla oblongata/area postrema lesions.



Wingerchuk DM, et al. *Neurology*. 2015;85(2):177-189. Lu Z, et al. *PLoS One*. 2011;6(8):e22766.

MRI: Other Brainstem Syndromes

NMOSD requires associated periependymal brainstem lesions.



Wingerchuk DM, et al. *Neurology*. 2015;85(2):177-189.
Lu Z, et al. *PLoS One*. 2011;6(8):e22766.

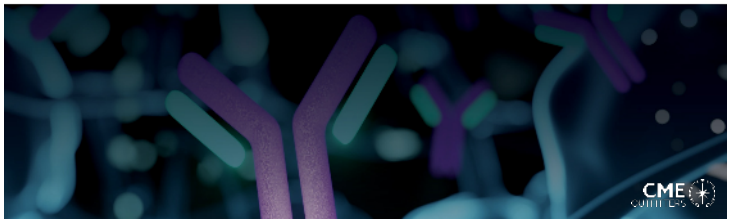
Red Flags: NMOSD vs MS vs MOGAD

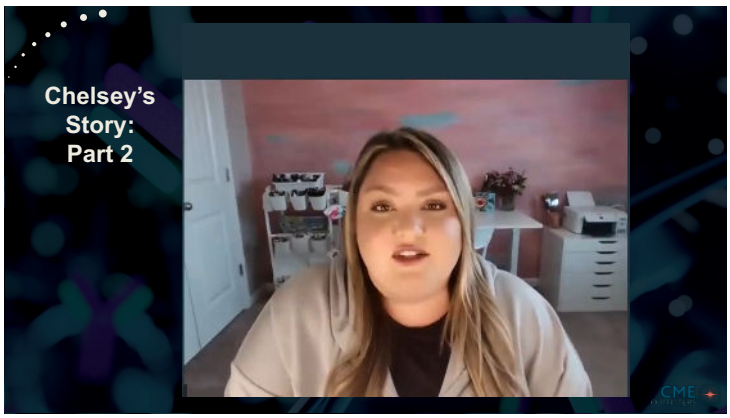
	NMOSD	MS	MOGAD
AQP4-IgG seropositive	Mostly	No	No
Attack recovery	Usually incomplete	Usually complete	Incomplete (first is worst)
Secondary progressive course	Rare	Common	No
Optic neuritis presentation	Unilateral > bilateral	Unilateral	Bilateral > unilateral
ADEM presentation	Rare	Rare	Common
CSF oligoclonal bands	Rare	Common	Rare
Lesion location	Mostly central	Mostly peripheral	Mostly peripheral
Cortical or juxtacortical lesions	Rare	Common	Rare
Spinal cord lesions	Long (≥ 3 segments)	Short	Involves conus medullaris
African or Asian descent	Common	Uncommon	No predilection

Wingerchuk DM, et al. Neurology. 2015;85(2):177-189. Jarius S, et al. *J Neurol*. 2023;270(7):3341-3368. Cortese R, et al. Neurology. 2023;100(3):e308-e323. Wildner P, et al. *Mult Scler Relat Disord*. 2020;37:101452. doi:10.1016/j.msard.2019.101452

NMOSD Treatment

Optimizing Outcomes from Acute to Chronic Management





Importance of NMOSD Treatment

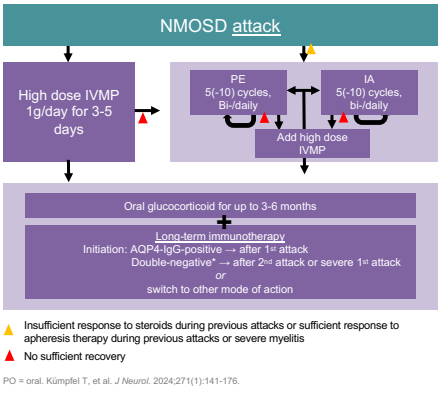
- **Recovery after attack/relapse typically poor and incomplete**
  - Attack: emergence of new NMOSD-related symptoms and/or exacerbation of pre-existing ones for > 24 hours, with or without new/enlarging or enhancing MRI lesions*
  - Pseudo-attack: worsening of pre-existing neurological symptoms attributed to non-NMOSD clinical factors, such as infections, fever, injury, comorbidities, medications, psychiatric disorders
- **Incomplete recovery leads to accumulating disability**
  - Every attack can leave residual disability and worsen quality of life
  - Subsequent attacks tend to increase in severity and duration over time
- **Inappropriate treatment worsens disease**
  - Increase in disease activity, relapse frequency, and/or relapse severity associated with initiation of many MS drugs (interferon-β, glatiramer acetate, natalizumab, alemtuzumab, fingolimod, dimethyl fumarate)
  - Mitoxantrone and cyclophosphamide not recommended due to limited effectiveness and high risk of severe adverse effects

*The necessity of MRI changes to classify NMOSD attacks is widely debated with experts on both sides
Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176. Kessler RA, et al. *Neurol Neuroimmunol Neuroinflamm.* 2016;3(5):e269.

NMOSD Treatment Goals and Options

- **Acute: minimize attack damage through rapid initiation and early escalation of acute therapies**
  - High-dose corticosteroids†: typically, intravenous methylprednisolone (IVMP)
  - Apheresis: therapeutic plasma exchange (PE) or immunoadsorption (IA)
- **Chronic: prevent relapses and therefore worsening disability through early initiation of long-term maintenance therapies**
  - Traditional* immunosuppressive therapy (IST): low-dose corticosteroids, azathioprine†, mycophenolate mofetil†
  - Traditional* monoclonal antibody (mAb): rituximab†
  - Approved mAb: eculizumab, inebilizumab, satralizumab, ravulizumab
- **Symptomatic: maximize quality of life**
  - Patient specific and symptom guided

*Traditional therapies are used off-label, as there were no FDA-approved therapies for NMOSD maintenance prior to 2019.
†not FDA-approved for the treatment of NMOSD
PLEX = therapeutic plasma exchange, IA = immunoadsorption
Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176.



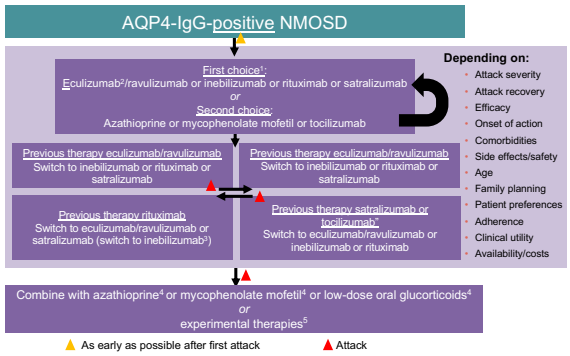
PO = oral. Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176.

NMOSD Acute Attack Therapy

- Initiate immediately upon attack confirmation
- Begin apheresis early if IVMP elicits inadequate response
- Apheresis alone or adjunct with IVMP may be first-line for patients with supporting history of response or severe myelitis
- Intravenous immunoglobulins (IVIg) occasionally considered in patients with contraindications to IVMP and apheresis
- Acute therapy must be followed by PO corticosteroid taper to prevent subsequent attacks

NMOSD Maintenance Therapy

- Start immediately after first clinical attack or upon confirmed diagnosis
- Treatment choice is highly variable and patient specific, but approved mAb preferred over traditional IST whenever possible
- As no therapy is approved for seronegative NMOSD, treatment recommendations are driven by expert opinion



[1]in alphabetical order; [2]use approved only after the 2nd attack in some countries; [3]hypothetical option, no clinical data; [4]in countries where mAb are not available, a combination of azathioprine/mycophenolate mofetil and glucocorticoids may be used; [5]e.g., intermittent plasma exchange/immunoadsorption or hematopoietic stem cell transplantation. In children or in case of contraindications to other therapies intravenous immunoglobulins may be used; methotrexate and tacrolimus may be used if other therapies are not available. Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176.

Traditional Immunosuppressants

All off-label therapies with modest empirical efficacy

- **Mycophenolate mofetil (CellCept®): 1000-2000 mg PO daily**
  - Takes 4-6 months for full effect; corticosteroid coverage needed in interim
  - Major safety concerns: teratogenicity, pancytopenia, hypertension, ulcers, hepatotoxicity, pulmonary toxicity, nephrotoxicity, increased risk of serious infection and malignancy
- **Azathioprine (Imuran®): 2-3 mg/kg PO daily**
  - Takes 2-6 months for full effects; corticosteroid coverage needed in interim
  - Major safety concerns: teratogenicity, hypofertility, pancytopenia, pancreatitis, hepatotoxicity, pulmonary toxicity, increased risk of serious infection and malignancy
- **Corticosteroids: low-dose (ideally ≤ 7.5 mg/day PO prednisone equivalent)**
  - Immediate effects; often used as add-on therapy
  - No controlled data on optimal dosing or tapering; low-dose desired to limit adverse effects
  - Major safety concerns: bone fractures, diabetes, dyslipidemia, cardiovascular disease, myopathy, cataracts, ulcers, skin thinning, impaired wound healing, adrenal suppression, Cushing's syndrome, psychiatric effects, increased risk of infection

PO = per os (orally, by mouth)
Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176. Chan K-H, Lee C-Y. *International Journal of Molecular Sciences.* 2021; 22(16):8638.

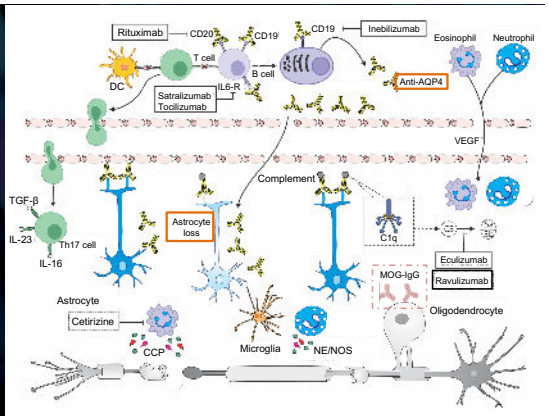
Traditional mAb: Rituximab (RITUXAN®)

Most robust activity amongst off-label therapies

- Anti-CD20+ mAb; B-cell depletion within 4 weeks, full onset in 8-12 weeks
- Dosing: typically, 1000 mg IV on days 1 and 14, then 500-1000 mg every 6 months thereafter
- Efficacy: no adequately powered RCTs; retrospective reviews demonstrate 70-96% reduction in relapse rate
- AEs: infusion reactions, URTI, late-onset neutropenia, hypogammaglobulinemia, reactivation of viral illness
- Caution: ongoing concerns about FCGR3A-V158F polymorphism impacting efficacy and ultimately memory B-cell depletion

MOA = mechanism of action, AE = adverse effects, URTI = upper respiratory tract infection
Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176. Wang Y, et al. *Mult Scler Relat Disord.* 2021;50:102843. Kim SH, et al. *JAMA Neurol.* 2015;72(9):989-995.

NMOSD Immuno-pathology and Therapeutic Targets



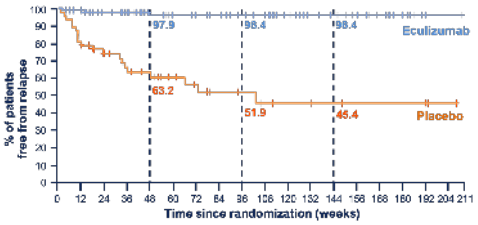
Carnero Contentti E, Corraele J. *J Neuroinflammation.* 2021;18(1):208

Eculizumab (SOLIRIS®): Anti-C5 mAb

90-minute IV: 900 mg/week x 4, 1200 mg/week x 1, then 1200mg every 2 weeks
Immediate onset within 1-2 weeks

PREVENT: Time-to-event double-blind RCT

- AQP4-IgG**(+)** NMOSD with 2 relapses in last year or 3 relapses in last 2 years, including ≥ 1 in last 12 months + EDSS ≤ 7 (N = 143)
- Randomized 2:1 to eculizumab or placebo (**+/- continued traditional IST**)



94% relative reduction in risk of relapse with eculizumab vs placebo (0.06 HR, p < 0.0001)

AEs: headache, URTI, arthralgias/myalgias, GI upset

Caution: anemia, leukopenia, fungal infections, allergic infusion reactions

REMS: meningococcal vaccination due to risk of encapsulated bacteria infection

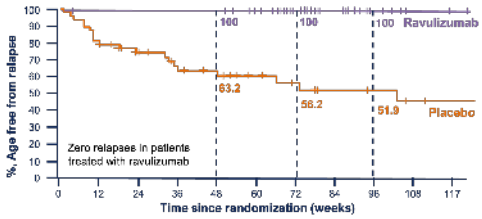
EDSS = expanded disability status scale, GI = gastrointestinal
Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176. Pittock SJ, et al. *N Engl J Med.* 2019;381(7):614-625.

Ravulizumab (ULTOMIRIS®): Anti-C5 mAb

Weight-based IV infusion: day 1 loading dose, day 15 maintenance dose every 8 weeks
Immediate onset within 1-2 weeks

CHAMPION-NMOSD: Time-to-event external comparator RCT

- AQP4-IgG**(+)** NMOSD with ≥ 1 relapse in last 12 months + EDSS ≤ 7 (n = 58 ravulizumab, n = 47 external placebo arm from PREVENT)
- Continued IST allowed



98.6% relative reduction in risk of relapse with ravulizumab vs placebo (0.014 HR, p < 0.0001)

AEs: headache, UTI, arthralgia, myalgia, URTI

Caution: anemia, leukopenia, fungal infections, allergic infusion reactions

REMS: meningococcal vaccination due to risk of encapsulated bacteria infection

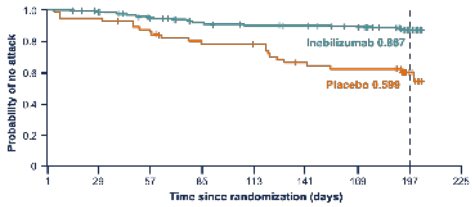
Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176. Pittock SJ, et al. *Ann Neurol.* 2023;93(6):1053-1068.

Inebilizumab (UPLIZNA®): Anti-CD19 mAb

90-minute IV with triple pre-medication: 300 mg on day 1 and 15, then every 6 months
B-cell depletion within 2 weeks, full onset in 6-8 weeks

N-MOmentum: Time-to-event double-blind RCT

- AQP4-IgG**(+/-)** with 1 relapse in last 1 year or 2 relapses in last 2 years + EDSS ≤ 8 (N = 230)
- Randomized 3:1 to inebilizumab or placebo (+ corticosteroid days 1-21 **only**)



In AQP4(+) only: 77% relative reduction in risk of relapse with inebilizumab vs placebo (0.27 HR, p < 0.0001)

AEs: UTI, URTI, arthralgias

Caution: life-threatening infusion reactions, opportunistic infection, viral reactivation, hypogammaglobulinemia, teratogenic

Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176. Cree BAC, et al. *Lancet.* 2019;94:1352–63.

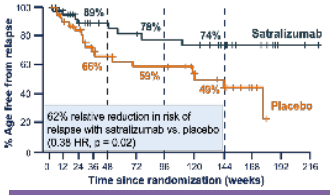
Satralizumab (ENSPRYNG®): Anti-IL-6 mAb

Ages 12+ approved

Self-administered SC: 120mg every 2 weeks x 3, then every 4 weeks; full onset in 12-24 weeks

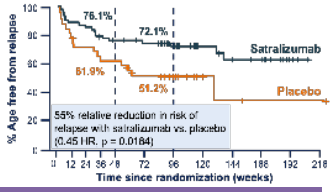
SAkuraSky: Time-to-event double-blind RCT

- AQP4-IgG**(+/-)** with ≥ 2 relapses in last 2 years including ≥ 1 in last 1 year + EDSS ≤ 6.5 (N = 83; **n = 8 aged 12-17 years**)
- Randomized 1:1 satralizumab or placebo (**+ continued IST**)



SAkuraStar: Time-to-event double-blind RCT

- AQP4-IgG**(+/-)** with ≥ 1 relapse in last year + EDSS ≤ 6.5 (N = 95)
- Randomized 2:1 satralizumab or placebo (**no IST allowed**)

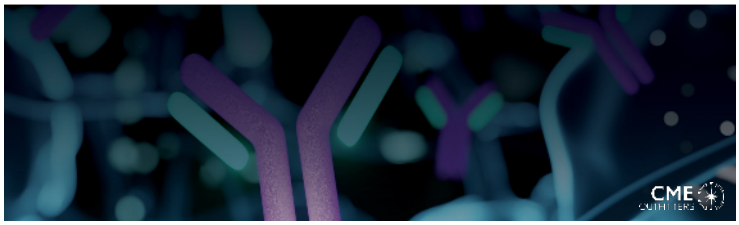


Pooled analysis: 75% risk reduction in AQP4-IgG(+), no significant difference in AQP4-IgG(-)
AEs: injection reactions, headache, arthralgia, URTI, neutropenia, thrombocytopenia, elevation in LFTs/cholesterol/triglycerides

LFTs = liver function tests. Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176. Yamamura T, et al. *N Engl J Med.* 2019;381(22):2114-2124. Traboulsee A, et al. *Lancet Neurol.* 2020;19(5):402-412. Yamamura T, et al. Mult Scler Relat Disord. 2022;66:104025.

Long-Term Follow-up

Ongoing Monitoring and Supportive Patient Care



Ongoing Monitoring Needs

- **Neurological assessments**
  - Routinely or as clinically indicated
  - Purpose: monitor disease activity, residual symptoms, response to treatment
- **Brain and spinal cord imaging**
  - Routinely or if new symptoms occur
  - Purpose: detect new lesions, assess disease burden, guide treatment adjustments
- **Laboratory tests**
  - Antibody titers: AQP4-IgG and/or MOG-IgG periodically or as indicated
  - Labs: CBC, BMP, GFAP, others as indicated by treatment protocol
  - Purpose: monitor treatment effects, potential seroconversion, comorbidities
- **Treatment monitoring**
  - IST and mAb: regular assessment of efficacy, side effects, opportunistic infections, long-term safety concerns, QoL

Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176. Abboud H, et al. *J Neurol.* 2022;269(4):1786-1801.

Symptomatic and Supportive Care

Motor dysfunction	Vision impairment	Neuropathic pain and paresthesias	Spasticity and tonic spasms
Bladder, bowel, and sexual dysfunction	Fatigue and disordered sleep	Pregnancy	Psychiatric/ cognitive impairments
Infection and vaccines	Autoimmune comorbidities	Psychosocial support	Patient/care partner education

Kümpfel T, et al. *J Neurol.* 2024;271(1):141-176. Abboud H, et al. *J Neurol.* 2022;269(4):1786-1801.

SMART Goals

- Recognize the patient experience and impacts of living with NMOSD.
- Increase the rate of accurate NMOSD diagnoses by implementing the latest diagnostic criteria and cell-based antibody testing.
- Distinguish NMOSD from MS lesions (or lack thereof) on brain and spinal cord imaging.
- Reduce time to initiation of NMOSD maintenance therapy in newly diagnosed patients.
- Implement appropriate monitoring and supportive care measures to optimize patient quality of life.

QUESTIONS & ANSWERS

Thank you for joining us.
Don't forget to collect your credit.

Additional Resources

To learn more, scan the QR code and click on the "Materials" tab to access additional educational resources

To Request and Collect Credit

To receive CME/CE credit for this activity, scan the appropriate QR code to log into or create an account.

In Person

Virtual

Livestream: NMOSD Unveiled: Optimizing Long-Term Outcomes in Neuromyelitis Optica Spectrum Disorder with Innovative Therapies