The Malaysian Consensus Statements for the Diagnosis and Management of Neuromyelitis Optica Spectrum Disorder (NMOSD)

Malaysian Society of Neurosciences
Persatuan Neurosains Malaysia

MYIMIG
MSIDC-Immunology Interest Group

The Neuroscience Foundation of Malaysia

Malaysian Rare Disorders Society

STATEMENT OF INTENT

These consensus statements are meant for the clinical diagnosis and management of neuromyelitis optica spectrum disorder (NMOSD), based on the best available evidence at the time of their development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the individual management of their patient, based on the patient's presentation and management options available locally.

DISCLAIMER

NMOSD is a heterogeneous immune-mediated condition, and evidence guiding its diagnosis and management continues to evolve. Recommendations described in this e-booklet reflect current knowledge and expert consensus at the time of publication and should be applied with appropriate clinical judgement.

The authors, editors, contributors, publishers, and organisations involved in the development of this e-booklet do not accept responsibility or liability for any injury, loss, or damage arising from the use, misuse, misinterpretation, or application of the information contained herein.

Descriptions of both approved and off-label therapies are included based on available evidence, expert opinion, and real-world clinical practice. Clinicians should consult local and national prescribing guidelines, seek pharmaceutical advice where appropriate, and adhere to ethical and safe prescribing practices when making treatment decisions.

FUNDING STATEMENT

The development of the *Malaysian Consensus Statements for the Diagnosis and Management of Neuromyelitis Optica Spectrum Disorder (NMOSD)* was supported by an unrestricted educational grant from AstraZeneca Rare Disease (Malaysia), which provided funding for editorial support.

The funding body had no role in the development of the recommendations, including the identification of topics, interpretation of evidence, drafting of statements, voting process, or final approval of content. All recommendations and guidance were developed independently by the consensus development committee based on the latest available scientific evidence, expert consensus, and best clinical practice.

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AVAILABILITY

The Malaysian Consensus Statements for the Diagnosis and Management of Neuromyelitis Optica Spectrum Disorder (NMOSD) is available at the following websites:
xxx-xxxx

ISBN

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Foreword by the Director - General of Health, Malaysia

It is a significant milestone for the Malaysian healthcare community as we officially launch the *first Malaysian Consensus Statements on the Management of Neuromyelitis Optica Spectrum Disorder (NMOSD)*. This document serves as a vital blueprint for the standardisation of care for a condition that, while rare, carries a high burden of morbidity if not managed with precision and urgency.

In line with the Ministry of Health's ongoing reform agenda, we are committed to delivering healthcare services that are professional, efficient, and anchored in the latest scientific evidence. NMOSD is a challenging neuroimmunological condition that requires a multidisciplinary approach, spanning from early, accurate biomarker driven diagnosis in our laboratories to high-efficacy therapeutic interventions in our clinical wards.

These consensus statements are particularly important for the Malaysian context. We know that NMOSD affects Asian populations differently and often more frequently than in the West. By establishing local guidelines, we empower our healthcare providers across the country, from primary tertiary centres like Hospital Kuala Lumpur to regional hospitals, to provide equitable, world-class care to all patients.

I would like to congratulate the NMOSD Development Group for their tireless work in adapting global best practices into a framework that is applicable to our local healthcare landscape. Their dedication ensures that our clinical pathways remain at the forefront of medical innovation.

I am confident that the implementation of these consensus recommendations will lead to earlier diagnosis, fewer relapses, and significantly improved quality of life for Malaysians living with NMOSD. Let us continue to work together to strengthen our nation's health security and the well-being of the *rakyat*.

YBhg. Datuk Dr. Mahathar bin Abd Wahab
Director-General of Health, Malaysia
January 2026

Message from the President of the Malaysian Society of Neurosciences (MSN)

It is my distinct honour to present the first *Malaysian Consensus Statements on Neuromyelitis Optica Spectrum Disorder (NMOSD)*. As we move into 2026, the landscape of neuroimmunology is evolving at an unprecedented pace, and with it, our ability to provide more precise, evidence-based care for our patients.

NMOSD was once considered a variant of multiple sclerosis (MS), but we now recognise it as a distinct, often more aggressive, neuroinflammatory condition. In the Asian context, where the prevalence of NMOSD relative to MS is significantly higher than in Western populations, the need for localised clinical guidance has never been more urgent.

These consensus statements represent a milestone for the Malaysian Society of Neurosciences (MSN). They address the critical need for early and accurate diagnosis, utilising the latest biomarker testing and imaging protocols, while providing a framework for the use of emerging high-efficacy therapies. Our goals are to minimise relapses and prevent cumulative disability, which remain the greatest challenges in managing this disorder.

I would like to extend my deepest gratitude to the NMOSD Development Group, Department of Neurology, Hospital Kuala Lumpur, and all expert collaborators from the Institute for Medical Research, Ministry of Health hospitals, and the private healthcare sector who meticulously reviewed the international literature and integrated them into these recommendations by considering local clinical realities. Their commitment ensures that Malaysian neurologists have a robust reference to optimise patient outcomes across the country.

On behalf of the MSN, I hope this document serves as an invaluable resource for healthcare providers, fostering a unified approach to NMOSD management and improving the quality of life for our patients.

Dr. Ahmad Shahir
President, Malaysian Society of Neurosciences (MSN)
January 2026

Message from the Chairman of the Malaysian Neuro-immunology & Neuro-infection Council

I am pleased to see the publication of the *Malaysian Consensus Statements for the Diagnosis and Management of Neuromyelitis Optica Spectrum Disorder (NMOSD)*.

Although the number of NMOSD patients in Malaysia, estimated at around a thousand, is not large, the disease often results in devastating consequences for those affected. I recall several of our former patients, mainly young adult women, who experienced recurrent relapses of paraplegia and loss of vision, and who eventually became permanently wheelchair-bound—or even bedbound—and blind. Some ultimately lost faith in modern medicine.

Fortunately, there has been enormous progress in the understanding of the pathogenesis, diagnosis, investigation, and treatment of NMOSD over the past two decades. Unlike in the past, with modern therapies, most patients are now able to live normal lives.

I am grateful to this dedicated and knowledgeable group of experts, led by Dr Shanthi Viswanathan, for developing these clearly written and practical guidelines that reflect current evidence based on modern scientific medicine.

I am confident that this document will serve as a valuable and authoritative guide for clinicians, healthcare institutions, and treatment funders, including employers, insurance agencies, and charitable trusts.

Emeritus Professor Dato' Tan Chong Tin *MBBS FRCP MD FASc*
Chair
January 2026

Message from the Director of Hospital Kuala Lumpur

It is a privilege to introduce the first *Malaysian Consensus Statements on the Management of Neuromyelitis Optica Spectrum Disorder (NMOSD)*. As the Director of Hospital Kuala Lumpur (HKL), I am immensely proud of the central role our institution has played in the development of these guidelines, which mark a significant leap forward for clinical neuroimmunology in our nation.

In the 2020s, the management of NMOSD had undergone a paradigm shift. We have moved from a generic approach to neuroinflammation toward a highly specialised, biomarker-driven discipline. For a tertiary centre like HKL, which serves as a hub for the most complex neurological cases in the country, the standardisation of these protocols is not merely an academic exercise; it is a clinical necessity.

These consensus statements arrive at a critical juncture in 2026. With the emergence of targeted biologics and advanced diagnostic assays, the gap between clinical research and bedside application must be bridged. These guidelines provide our clinicians with structured, evidence-based pathways to achieve early diagnosis, early treatment of acute relapses and relapse prevention, which are the cornerstones of avoiding long-term disability in our patients.

I wish to commend the expert committee, including our colleagues from the HKL Neurology Department and the Institute of Medical Research, private neurologists, pharmacists and the Malaysian Society of Neurosciences, for their vision and diligence in working toward this consensus. Their collaborative effort ensures that every patient, regardless of where they seek care in Malaysia, can benefit from a standard of excellence that reflects global best practices adapted to our local healthcare landscape.

It is my hope that this document will serve as a definitive guide for healthcare professionals across the Ministry of Health, university hospitals, and the private sector, ultimately leading to better outcomes and a brighter future for those living with NMOSD.

Dato' Dr. Harikrishna Raghavan Nair
Director, Hospital Kuala Lumpur
January 2026

Message from the Chairperson, Technical Committee on Clinical Management and Support Services, National Rare Disease Committee, Ministry of Health

Neuromyelitis Optica Spectrum Disorder (NMOSD) is classified as a rare disease in Malaysia and is included in the National Rare Disease List. Similar to other rare diseases, NMOSD poses significant challenges in terms of diagnosis, management, and access to treatment. Evidence-based guidelines are crucial for standardising care and enhancing patient outcomes. The first Malaysian Consensus Statements on NMOSD will assist healthcare professionals in navigating diagnosis, treatment, and long-term management, particularly in resource-limited environments. Congratulations are extended to the NMOSD Development Group for their contributions to improving clinical resources for rare diseases and aligning with the Malaysian National Policy for Rare Diseases.

Dr Ngu Lock Hock
Consultant Clinical Geneticist & Head, Genetics Department, Hospital Kuala Lumpur
Chairman, Technical Committee on Clinical Management and Support Services
National Rare Disease Committee, Ministry of Health
January 2026

Message from the Chairpersons of the Malaysian Consensus Statements on the Management of Neuromyelitis Optica Spectrum Disorder (NMOSD) Development Committee

Shanthi Viswanathan

Masita Binti Arip

It is with great pride and a profound sense of responsibility that we introduce the first *Malaysian Consensus Statements on the Management of Neuromyelitis Optica Spectrum Disorder (NMOSD)*. This document is the culmination of a dedicated collaborative effort between clinical neurologists, immunologists, pharmacists and patients, designed to provide a unified voice for the management of this complex condition in Malaysia.

For many years, the diagnosis and treatment of NMOSD in our region faced significant hurdles, often due to its clinical overlap with multiple sclerosis and the limited availability of specialised diagnostic assays. However, our understanding has shifted dramatically. We now recognise NMOSD as a distinct, primary astrocytopathy, where early intervention is not just an option but a necessity to prevent devastating and irreversible neurological disability.

As chairs of the development committee, our goal was to bridge the gap between global evidence-based standards and the specific needs of the Malaysian healthcare landscape. These consensus statements address several critical pillars:

1. **The diagnostic journey**: Emphasising the importance of early aquaporin-4 immunoglobulin-G (AQP4-IgG) and myelin oligodendrocyte glycoprotein-immunoglobulin G (MOG-IgG) antibodies testing as the gold standard, alongside high-quality neuroimaging.
2. **Precision treatment**: Providing clear pathways for the use of acute therapies, such as high-dose corticosteroids and plasma exchange, as well as the strategic initiation of maintenance immunosuppression and emerging high-efficacy biologics.
3. **Local nuance**: Accounting for the unique epidemiological profile of NMOSD in Malaysia, where prevalence is notably higher than in Western populations, particularly among certain ethnic groups.

This work would not have been possible without the tireless contributions of our fellow panellists, who represent the breadth of neurology and laboratory medicine in Malaysia. We also wish to acknowledge the Malaysian Society of Neurosciences (MSN) for their unwavering support in facilitating this landmark initiative. In addition to that we would like to acknowledge the secretarial support provided by AstraZeneca Rare Disease (Malaysia) and the medical writer in bringing this consensus to fruition.

Shanthi Viswanathan
Neurologist,
Hospital Kuala Lumpur
January 2026

Masita Binti Arip
Pathologist,
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TERMS OF REFERENCE

This document provides the first consensus-based recommendations developed to guide the diagnosis and management of NMOSD in Malaysia.

Methodology

The Malaysian Consensus Statements for the Diagnosis and Management of NMOSD were developed using a modified Delphi approach to ensure a structured expert input (Figure 1).

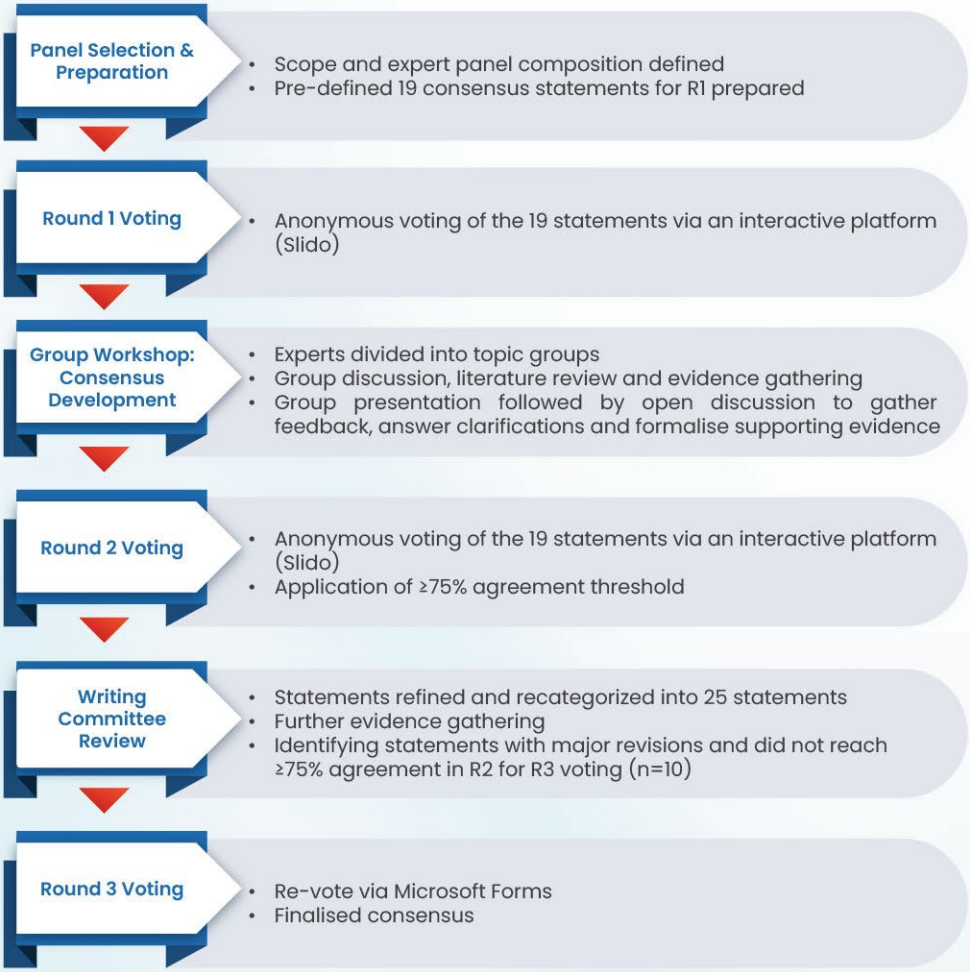


Figure 1. Development of the Malaysian Consensus Statements on NMOSD using the modified Delphi method.

A multidisciplinary panel of experts with expertise in NMOSD was convened from public and private healthcare sectors in Malaysia for an intensive, five-hour in-person workshop held in February 2025.

13	Neurologists
6	Pharmacists
4	Medical microbiologists & immunologists
1	Immunologist & allergist
1	Internal medicine specialist

Before the workshop, a set of predefined consensus statements covering epidemiology, diagnosis, treatment selection, acute management, monitoring, vaccination, and special populations was circulated for review. During the workshop, panel members were divided into topic-specific working groups. Each group reviewed the relevant statements, evaluated supporting evidence through targeted literature review, and presented recommendations to the full panel.

Topic 1	Laboratory testing
Topic 2	Unmet needs & epidemiology
Topic 3	Clinical diagnosis, monitoring & outcome measures
Topic 4a	Acute treatment
Topic 4b	Preventative treatment

Following group presentations, open discussions were conducted to clarify evidence, address differing viewpoints, and refine wording. Statements were then subjected to anonymous voting (Round 1), with a predefined consensus threshold of ≥75% agreement.

Statements that did not reach consensus or required substantial modification were revised and re-circulated for additional rounds of anonymous voting conducted electronically (Rounds 2 and 3). The final consensus comprised 25 statements across eight domains.

Domain 1	**Epidemiology**
Domain 2	**Diagnosis**
Domain 3	**Treatment selection**
Domain 4	**Switching treatments**
Domain 5	**Acute treatments for relapses**
Domain 6	**Monitoring adverse events**
Domain 7	**Use of biologics in pregnancy and breastfeeding**
Domain 8	**Vaccination**

All recommendations were informed by international guidelines and available evidence, and were contextualised to reflect Malaysian clinical practice, resource availability, and healthcare system considerations.

Objectives

- To contextualise international evidence and recommendations for the diagnosis and management of NMOSD for application within the Malaysian healthcare setting.
- To promote awareness of NMOSD among Malaysian healthcare professionals and support earlier recognition and accurate diagnosis.
- To provide practical, consensus-based guidance to inform clinical decision-making across public and private care settings.
- To stimulate policy-level discussions aimed at improving the availability, accessibility, and equitable use of effective, evidence-based therapies with favourable safety profiles in Malaysia.

The scope of this consensus does not address symptomatic management, neuropsychiatric care, or broader aspects of patient health and wellbeing; these areas remain important and should be considered in future initiatives.

Target population

These consensus statements are applicable to adolescents and adults with suspected or confirmed NMOSD, including individuals at risk of NMOSD or presenting with clinical features suggestive of the disease.

Target audience

These consensus statements are intended for healthcare professionals involved in the diagnosis, treatment, and long-term management of patients with NMOSD. These include neurologists, general physicians, family medicine specialists, primary care physicians, medical officers, immunologists, medical microbiologists, pharmacists, nurses, allied health professionals, and other healthcare personnel involved in multidisciplinary NMOSD care across public and private healthcare settings.

ABBREVIATIONS

AE	Adverse events
aHUS	Atypical haemolytic uraemic syndrome
ALT	Alanine transminase
AQP4	Aquaporin-4
AQP4-IgG	Aquaporin-4 immunoglobulin
ARR	Annualised relapse rates
ASFA	American Society for Apheresis
AST	Aspartate aminotransferase
AZA	Azathioprine
C5	Complement component 5
C5IT	Complement-5 inhibition therapy
CANOMAD	Chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins, and disialosyl antibodies
CBA	Cell-based assay
CD19	Cluster of differentiation 19
CD20	Cluster of differentiation 20
CI	Contraindications
CNS	Central nervous system
CSF	Cerebrospinal fluid
CYC	Cyclophosphamide
DMT	Disease modifying therapies
ECU	Eculizumab
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-linked Immunosorbent assay
EM	Encephalomyelitis
FFP	Fresh frozen plasma
GC	Glucocorticoid
GFAP	Glial fibrillary acidic protein
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
anti-HBc	Hepatitis B core antibody
anti-HBs	Hepatitis B surface antibody
HGG	Hypogammaglobulinemia

HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
Ig	Immunoglobulin
IL-6	Interleukin-6
IMPDH	Inosin monophosphate dehydrogenase
IMR	Institute for Medical Research
INEB	Inebilizumab
IPND	International Panel for NMO Diagnosis
IRR	Infusion-related reaction
IST	Immunosuppressive therapy
IV	Intravenous
IVIG	Intravenous immunoglobulin
LETM	Longitudinally extensive transverse myelitis
MenACWY	Meningococcal conjugate vaccine (serogroups A, C, W, Y)
MenB	Meningococcal B vaccine
MMF	Mycophenolate mofetil
MOA	Mechanism of action
MOG	Myelin oligodendrocyte glycoprotein
MOGAD	Myelin oligodendrocyte glycoprotein antibody-associated disease
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTX	Methotraxate
N-Momentum study	Inebilizumab for treatment of neuromyelitis optica spectrum disorder (N-Momentum) phase 3 study
NA	Not available
NE	Not evaluable
NEMOS	Neuromyelitis Optica Study Group
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorder
OCB	Oligoclonal bands
OGC	Oral glucocorticosteroid
OLE	Open label extension
ON	Optic neuritis
PLEX	Plasma exchange
PML	Progressive multifocal leukoencephalopathy
PREVENT study	Efficacy of eculizumab in the Prevention of Relapses in Neuromyelitis Optica (PREVENT) phase 3 study

RA	Rheumatoid arthritis
RAV	Ravalizumab
RIN1 study	Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial
RTX	Rituximab
SAkuraSky study	Satralizumab in combination with baseline immunosuppressive therapy international, multicentre, randomised, placebo-controlled, phase 3 study consisting of a double-blind period followed by an open-label extension
SAkuraStar study	Satralizumab monotherapy international, multicentre, randomised, placebo-controlled, phase 3 study consisting of a double-blind period followed by an open-label extension
SAT	Satralizumab
SC	Subcutaneous injection
TB	Tuberculosis
TCZ	Tocilizumab
URTI	Upper respiratory tract injection
US FDA	United States of America Food and Drug Administration
UTI	Urinary tract infection
WBCC	White blood cell count

CONSENSUS STATEMENTS (RESULTS)

Post-round 3 (final) voting, all but one statement (24 out of 25) reached the predefined ≥75% consensus threshold. **Statement 4.2c**, which relates to **switching biologic therapy** based on patient preference, received **61% agreement**. While most neurologists agreed that patient preference is important, several noted that it must be balanced with practical considerations such as medication availability and accessibility. Further details on this discussion are provided under Statement 4.2.

The complete list of consensus statements and final (R3) voting outcomes is presented in Table 1.

Table 1. Consensus statements for the diagnosis and management of NMOSD

Consensus statements	R3 Agreement
Section 1: Epidemiology	
Statement 1.1 High-quality data on NMOSD, including its prevalence and incidence in Malaysia, are essential to guide treatment priorities and address patient-reported needs.	100%
Statement 1.2a NMOSD significantly affects patients' quality of life, including psychosocial, economic, and employment aspects.	100%
Statement 1.2b While important to assess, health-related quality-of-life outcomes in AQP4-IgG–seropositive NMOSD currently lack sufficient evidence to guide treatment decisions.	100%
Section 2: Diagnosis	

Statement 2.1 100%

Accurate diagnosis of NMOSD to differentiate its mimickers are essential.

Statement 2.2 100%

The IPND diagnostic criteria for NMOSD, including biomarker and neuroimaging-based stratification, are applicable in Malaysia and should continue to be used in clinical practice.

** Note: These diagnostic criteria are based on the 2015 IPND recommendations. An updated version is anticipated from the IPND in 2025, which may lead to changes in clinical diagnostic criteria.*

Statement 2.3 95.7%

Accurate, high-quality biomarkers are essential to diagnose seropositive NMOSD and exclude seronegative NMOSD syndromes such as MOGAD, as this influences disease course, treatment decisions, and management costs.

Section 3: Treatment selection

Statement 3.1a 100%

The primary factors to inform selection of biologic therapies in NMOSD are efficacy and safety.

Statement 3.1b 100%

Additional considerations for biologic therapy selection in NMOSD are current disease activity, relapse severity, route of administration acceptability, and potential benefit for comorbidities.

Statement 3.1c 96%

Monitoring and treatment decision-making in AQP4-IgG–seropositive NMOSD patients should be guided by clinical outcomes, MRI findings, and, where available, biomarkers such as serum GFAP and neurofilament light chain.

Statement 3.2 100%

In newly diagnosed AQP4-IgG–seropositive NMOSD, the choice of ECU, RAV, INEB, SAT, RTX, or TCZ should consider patient preferences regarding dosing frequency, route of administration, availability, accessibility and adherence. In addition, the drug's safety profile, the patient's comorbidities and concomitant autoimmune diseases should be considered.

Statement 3.3 100%

In AQP4-IgG–seropositive NMOSD, choice of biologic therapy (RTX, TCZ, RAV, ECU, INEB and SAT) should consider prior maintenance treatment response, with preference for agents with a different mechanism of action following therapy failure.

Statement 3.4 100%

Patients with NMOSD who have disease activity despite treatment with ISTs and/or OGCS may benefit from the addition of on-label biologic therapies.

Statement 3.5 91%

In resource-limited settings where access to biologics is restricted, ISTs with or without steroids may be beneficial, provided there is careful monitoring for long-term AEs and gradual down-titration to the minimal effective dose.

Statement 3.6 95.7%

ECU, RAV, INEB, SAT or RTX should be used as monotherapy in AQP4-IgG–seropositive NMOSD to minimise the risk of AEs associated with concurrent ISTs and steroids.

Statement 3.7 100%

While monotherapy is preferred, ECU, RAV, RTX or SAT may be combined with existing ISTs, with consideration of the short- and long-term safety and tolerability of the ISTs.

Statement 3.8 100%

If ECU, INEB or SAT are started with an IST, patients should be closely monitored for AEs, and ISTs and steroids tapered gradually based on the biologic's onset of action.

Statement 3.9 100%

Adolescents (≥12 years) with AQP4-IgG–seropositive NMOSD should be treated with SAT. ECU, RAV, RTX or INEB may be considered for severe, SAT-refractory cases, though further evidence is needed for broader use.

Section 4: Switching treatments

Statement 4.1 100%

For AQP4-IgG–seropositive NMOSD patients who are stable and relapse-free on off-label ISTs (AZA, MMF, OGCS) or biologics (RTX, TCZ), switching to on-label biologics is not necessary.

Statement 4.2a 94%

If relapses persist after allowing for the onset of action of RAV, ECU, INEB or SAT, patients should be switched to an alternative biologic.

Statement 4.2b 100%

If serious treatment-related AEs occur after initiating RAV, ECU, INEB or SAT and allowing for their onset of action, patients should be switched to an alternative biologic.

Statement 4.2c 61%

After initiating RAV, ECU, INEB or SAT and allowing adequate time for their onset of action, a switch may be considered based on patient preference.

Statement 4.3 100%

When switching between RAV, ECU, INEB and SAT, no washout is needed.

Section 5: Acute treatment for NMOSD relapses

Statement 5.1 100%

Acute NMOSD relapses should be treated with first-line steroids; early PLEX is recommended for severe or steroid-refractory cases, with IVIg as a last resort if PLEX is unavailable.

Statement 5.2 88%

On a case-by-case basis, IV RTX, CYC and ECU may be used for treatment refractory relapses.

Statement 5.3a 100%

In AQP4-IgG–seropositive adults with NMOSD, ECU, RAV, SAT, INEB, RTX or TCZ may be initiated in severe or aggressive fulminant NMOSD after the first attack in treatment naïve patients.

Statement 5.3b 100%

In AQP4-IgG–seropositive adults with NMOSD, ECU, RAV, SAT, INEB, RTX or TCZ may be initiated following relapse despite prior treatment.

Section 6: Monitoring AEs

Statement 6.1 100%

Patients with AQP4-IgG–seropositive NMOSD receiving ECU, INEB, RAV or SAT should be monitored for infections in the short and long term.

Section 7: Use of biologics in pregnancy and in patients who are breastfeeding

Statement 7.1 100%

Data on the use of ECU, RAV, INEB, TCZ or SAT in pregnancy and breastfeeding are limited; further research is needed to guide risk of teratogenicity, severe AEs during pregnancy, and family planning treatment decisions in NMOSD patients.

Statement 7.2

89%

Available data suggest RTX may be used safely on a case-by-case basis before conception, during pregnancy, and while breastfeeding. However, contraception advice is important in all NMOSD patients in the reproductive age.

Note: In post delivery mothers exposed to RTC during pregnancy, monitoring of B-cells in the newborn is needed due to transient neutropenia, and if low, deferring live attenuated vaccines till B-cell levels recover may be needed.

Section 8: Vaccination

Statement 8.1

100%

AQP4-IgG–seropositive NMOSD patients should be up to date with all vaccinations before starting biologic therapies (ECU, RAV, INEB, SAT, RTX or TCZ) unless clinically contraindicated.

Statement 8.2

100%

Meningococcal vaccination guidance for AQP4-IgG–seropositive NMOSD patients receiving RAV or ECU should be clarified to help clinicians ensure coverage of all serogroups, appropriate booster scheduling, and timely reassessment of vaccination status.

AEs, adverse events; AQP4-IgG, aquaporin-4 immunoglobulin G; AZA, azathioprine; CYC, cyclophosphamide; ECU, eculizumab; GFAP, glial fibrillary acidic protein; INEB, inebilizumab; IPND, International Panel for NMO Diagnosis; ISTs, immunosuppressive therapies; IV, intravenous; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; OGCS, oral glucocorticosteroids; PLEX, plasma exchange; RAV, ravulizumab; RTX, rituximab; SAT, satralizumab; TCZ, tocilizumab.

INTRODUCTION TO NMOSD

Neuromyelitis optica spectrum disorder (NMOSD), previously referred to as Devic's disease, is a rare autoimmune condition characterised by **recurrent inflammation and demyelination of the central nervous system (CNS),** predominantly affecting the **optic nerves and spinal cord.**[1]

AQP4 antibody

The understanding of NMOSD has advanced with the discovery of a disease-specific biomarker, the anti-aquaporin-4 (AQP4) antibody, which has significantly refined diagnostic accuracy.[2-7]

AQP4 is a water channel protein expressed in astrocytic foot processes at the blood–brain barrier, spinal cord grey matter, periventricular and periaqueductal regions, and Müller cells of the retina.[3] The distribution of AQP4 accounts for the characteristic clinical manifestations observed in NMOSD.[7]

Epidemiology

Global epidemiological data (Appendix 1) indicate a higher prevalence of NMOSD among Black populations (~10 per 100,000), followed by Asian populations (~3.5 per 100,000), with the lowest prevalence observed in White/Caucasian populations (~1 per 100,000).[8]

Epidemiology in Malaysia

- In Malaysia, NMOSD affects approximately 2 per 100,000 individuals, classifying it as a rare disease.[9]
- Consistent with global observations, a nationwide study reported marked inter-ethnic variation in NMOSD prevalence.
- Ethnic Malays and Chinese comprised the majority of NMOSD cases (47.3% and 46.9%, respectively), while Indians and other indigenous groups formed a small proportion (3.5% and 2.3%, respectively).[9]

Clinical phenotypes

The clinical phenotype of NMOSD is largely shaped by the presence of AQP4 receptors in various CNS regions, contributing to characteristic presentations involving the optic nerves, spinal cord and brain. Moreover, inflammatory mediators such as interleukin-6 (IL-6) and components of the complement cascade have emerged as therapeutic targets, paving the way for newer treatments including IL-6 inhibitors and complement-5 inhibition therapies (C5IT).

CNS inflammatory demyelinating diseases of non-MS type encompasses several antibody-defined and seronegative subtypes. These include AQP4-antibody-seropostive autoimmune astrocytopathy, myelin oligodendrocyte glycoprotein (MOG)-antibody-seropositive inflammatory demyelinating disease, which is now considered a separate entity, and double seronegative disease, some of which may still be NMOSD.[2,10]

- AQP4-positive disease typically presents around age 40 and predominantly affects women (female-to-male ratio up to 9:1).[2,7,9]
- Pathologically, AQP4-antibody-positive NMOSD is defined as an autoimmune astrocytopathic condition, whereas MOG-antibody-positive disease represents a distinct inflammatory demyelinating process.[2]

In recognition of the broader clinical spectrum of the disease, including the involvement of brain syndromes, the term NMOSD was formally introduced in the 2015 International Consensus Diagnostic Criteria.[1]

- These criteria, developed by the International Panel for NMO Diagnosis (IPND), remain the current international standard for NMOSD diagnosis and classification (Appendix 2), pending the release of updated recommendations that may refine distinctions between seropositive NMOSD and seronegative syndromes (Appendix 3).[10]

CONSENSUS STATEMENTS

Section 1: Epidemiology of NMOSD

Statement 1.1

- *High-quality data on NMOSD, including its prevalence and incidence in Malaysia, are essential to guide treatment priorities and address patient-reported needs.*

Statement 1.2a

- *NMOSD significantly affects patients' quality of life, including psychosocial, economic, and employment aspects.*

Statement 1.2b

- *While important to assess, health-related quality-of-life outcomes in AQP4-IgG–seropositive NMOSD currently lack sufficient evidence to guide treatment decisions.*

NMOSD is a rare disease worldwide, with substantial variation in incidence and prevalence across populations and ethnic groups. Interpretation of NMOSD epidemiological data is challenged by heterogeneity in diagnostic criteria, case identification methods, and study design.[8]

- Available epidemiological data are derived predominantly from hospital-based datasets, and interpretation is further complicated by heterogeneity in diagnostic criteria, case ascertainment, and study methodologies, particularly in studies conducted prior to the identification of aquaporin-4 immunoglobulin G (AQP4-IgG)[8]
- The highest NMOSD prevalence and incidence have been reported in the Afro-Caribbean region (10 per 100,000 persons and 0.73 per 100,000 person-years, respectively) and the lowest in Australia and New Zealand.[8]

NMOSD disproportionately affects women and middle-aged adults, with AQP4-IgG–seropositive disease showing particularly strong female predominance.

Within Southeast Asia, data on NMOSD incidence remain scarce.

- A nationwide study from Malaysia reported an incidence rate of 0.39 per 100,000 persons per year.[9]
- A population-based study from a single province in Thailand estimated the incidence at 1.65 per 100,000 persons per year.[11]
- In Singapore, the estimated crude prevalence of AQP4 NMOSD was 3.8 per 10,000 population.[12]

Despite the availability of prevalence estimates, Malaysia continues to lack high-quality, standardised epidemiological studies on NMOSD. Such data are essential not only for improving disease awareness and reducing misdiagnosis, but also for informing healthcare planning, resource allocation, and early intervention strategies.

Misdiagnosis remains common, particularly the misclassification of NMOSD as multiple sclerosis (MS), even in the presence of disease-specific biomarkers, with rates of up to 35% reported.[13] This **frequently leads to inappropriate immunotherapy, increased patient morbidity, and delays in access to targeted treatments.**

From the **patient's perspective**, substantial unmet needs persist.

- **Delayed diagnosis** is common due to the heterogeneous presentation of NMOSD and limited awareness among non-neurologist specialists.
- Patients often **consult multiple healthcare providers before a definitive diagnosis is established**, leading to unnecessary hospital visits and fragmented care.
- In Malaysia, these **challenges are further compounded by** limited access to key diagnostic tools such as magnetic resonance imaging (MRI) and antibody testing, the absence of national guidelines, restricted availability of United States Food and Drug Administration (US FDA)-approved disease-modifying therapies (DMTs), and uneven access to rehabilitation and support services.[14,15]

The **burden of NMOSD** is substantial.

- A large international study involving 502 patients from 15 countries, including Malaysia, reported that 44% experienced job loss, 91% reduced working hours prior to diagnosis, and 39% reported a reduction in income.[16]
- More than half of patients experienced moderate to severe fatigue, while pain and disability significantly affected daily functioning and employment opportunities.
- A national survey in Argentina highlighted disparities in healthcare access based on insurance status, with patients dependent on public services experiencing longer diagnostic delays, reduced access to MRI and biologic therapies, and greater financial burden.[17]

These highlight the **need for robust, locally relevant epidemiological data** to improve early diagnosis, inform equitable treatment access, support health policy development, and enable Malaysian participation in clinical trials for emerging therapies.

SECTION 2: DIAGNOSIS

Statement 2.1

- *Accurate diagnosis of NMOSD to differentiate its mimickers is essential.*

Statement 2.2

- *The IPND diagnostic criteria for NMOSD, including biomarker and neuroimaging-based stratification, are applicable in Malaysia and should continue to be used in clinical practice.*

Statement 2.3

- *Accurate, high-quality biomarkers are essential to diagnose seropositive NMOSD and exclude seronegative NMOSD syndromes such as myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), as this influences disease course, treatment decisions, and management costs.*

Clinical diagnosis

Accurate diagnosis of NMOSD is essential to guide appropriate management and avoid misdiagnosis, particularly with disorders that may present with overlapping features.

The panel recommends the continued use of the 2015 diagnostic criteria proposed by the IPND (Appendix 2),[1] which are applicable without modification in the Malaysian setting.

- These criteria clearly define the clinical and biomarker-based features required for diagnosis and are consistent with international standards of care.
- However, the proposed updated criteria (2025) may alter the diagnostic criteria (Appendix 3).

The IPND 2015 criteria define two diagnostic pathways based on AQP4-IgG serostatus.[1] Readers are encouraged to refer to the full IPND 2015 recommendations for detailed criteria.

Seropositive NMOSD diagnosis:

- At least one core clinical characteristic.
- A positive AQPA-Ig results using cell-based assay (CBA).
- Exclusion of alternative diagnoses.

Seronegative NMOSD or unknown aquaporin-4 immunoglobulin (AQP4-Ig) status diagnosis:

- At least two core clinical characteristics with dissemination in space.
- Fulfilment of MRI requirements.*
- Exclusion of alternative diagnoses.

Core clinical characteristics include:

- Optic neuritis (ON)
- Acute myelitis
- Area postrema syndrome
- Acute brainstem syndrome
- Symptomatic narcolepsy or diencephalic syndromes
- Cerebral syndromes with NMOSD-typical brain lesions.

**Note: Please refer to Appendix 2. The full descriptions of the individual MRI orbit, brain and spine changes are beyond the scope of this consensus.*

Differentiating NMOSD from its mimickers remains clinically challenging due to overlapping phenotypes and variability in clinical presentation.[18]

Differential diagnoses for NMOSD encompasses a wide range of conditions including:

- Relapsing–remitting MS
- MOGAD
- Neurosarcoidosis
- Connective tissue diseases (such as systemic lupus erythematosus and Sjögren's syndrome)
- Paraneoplastic syndromes
- Anti-glial fibrillary acidic protein (GFAP)-associated encephalomyelitis
- Infectious and vascular myelopathies
- CNS neoplasms
- Metabolic or hereditary disorders

The consensus group emphasised that while the IPND criteria sufficiently guide the diagnosis of seropositive NMOSD, there remains **a need for improved definitions in cases of recurrent ON, relapsing transverse myelitis and seronegative NMOSD.** The panel acknowledged that certain presentations, such as relapsing ON, with or without a single episode or recurrent episodes of transverse myelitis remain diagnostically challenging, as they may overlap with MS and other CNS inflammatory diseases. In such cases, the panel suggests:

- Close clinical monitoring with serial MRI brain/spine, applying the new McDonald revised 2024 criteria[19,20] using central vein signs and paramagnetic rim lesion, **and**
- Repeated cerebrospinal fluid (CSF) analysis for oligoclonal bands (OCB) to rule out MS, **and**
- Retesting of AQP4-IgG and MOG antibodies to account for possible false-negative results.

Furthermore, the panel noted that the new diagnostic criteria for NMOSD are currently under development; however, the **existing 2015 criteria remain the standard at present.**

Laboratory diagnosis

Disease-specific antibody detection

Reliable laboratory testing is central to confirming NMOSD and distinguishing it from other inflammatory diseases of the CNS. The IPND recommends the use of **highly specific CBAs, either live or fixed, for the detection of AQP4-IgG and MOG-IgG**.[1,18,21]

- In Malaysia, **fixed CBAs, which are commercially available and easier to standardise, are preferred** and can be accessed through the Institute for Medical Research (IMR) and private laboratories.*
- Where enzyme-linked immunosorbent assay (ELISA) is used as an initial screening test, positive results should be confirmed using a CBA to minimise the risk of false-positive findings.[1,18]

**Of the live CBAs, the fluorescence-activated cell sorting, a flow cytometry-based method, is currently the most sensitive. However, it presently unavailable in Malaysia.*[99]

Serum is the preferred sample type due to its higher sensitivity compared to CSF, particularly for AQP4-IgG detection.

- **Routine CSF testing is not recommended**, although it may be considered in selected cases, especially where serum tests are inconclusive or treatment has potentially suppressed antibody levels.
- The presence of AQP4-IgG in CSF correlates with the concentration of AQP4-IgG in serum. Patients with a high AQP4-IgG titre in serum have a higher likelihood of a positive CSF AQP4-IgG result.[22]
- Evidence suggests that AQP4-IgG detected in CSF is almost exclusively derived from peripheral sources.[23]

CSF testing for anti-AQP4-IgG should be reserved for patients with a high clinical suspicion of NMOSD and negative serum testing, recognising that isolated CSF AQP4-IgG positivity is rare.[22]

Antibody testing should ideally be performed before initiation of treatment, as therapies such as corticosteroids, intravenous immunoglobulin (IVIg), and plasma exchange (PLEX) may reduce antibody detectability.

Antibody retesting	• In suspected NMOSD with initial negative results, repeat testing during relapse or an acute attack is recommended. • May also be performed during remission, before starting maintenance therapy or even after initiation of maintenance therapy.
Antibody negative	• Patients testing negative for AQP4-IgG should undergo myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) testing to assess for MOGAD. • The interpretation of test results should include antibody titre, test method, manufacturer, and timing of disease activity and treatment.[1,18]
Borderline results	• Should prompt a careful review of the clinical phenotype and correlation with repeat testing. • If the repeat test is also negative, NMOSD is unlikely unless the presenting phenotype fulfils the criteria for seronegative NMOSD.
Red flags in testing	• Positivity for AQP4-IgG only in CSF. • Positivity for AQP4-IgM or IgA without AQP4-IgG. • Simultaneous positivity for AQP4-IgG and MOG-IgG (extremely rare). • Presence of CSF-restricted OCB, which is rare in NMOSD but common in MS.[18]

When **AQP4-IgG results are borderline, a systematic approach is recommended**.

- **Repeat testing** using a serum CBA may improve diagnostic sensitivity.
- **MS and MOGAD should be excluded** through assessment for OCB, evaluation of characteristic MS lesions on MRI, and MOG-IgG testing if AQP4-IgG remains negative or borderline.
- **Clinical correlation is essential**, particularly with NMOSD-compatible features and MRI findings such as longitudinal spinal cord lesions extending three or more segments.
- Clinicians should also **be aware of sero-reversion**, as AQP4-IgG titres may decline following treatment, potentially resulting in false-negative results.

The proposed algorithm for disease-specific antibody detection in the diagnosis of NMOSD is illustrated in Figure 2. Although we propose sequential testing starting from anti-AQP4-IgG detection, the available commercial kit does offer simultaneous detection of anti-AQP4-IgG and anti-MOG-IgG. This can be done in situations where the clinical presentation is indistinguishable from that of other conditions. The simultaneous testing of both antibodies can be both time and cost-saving.

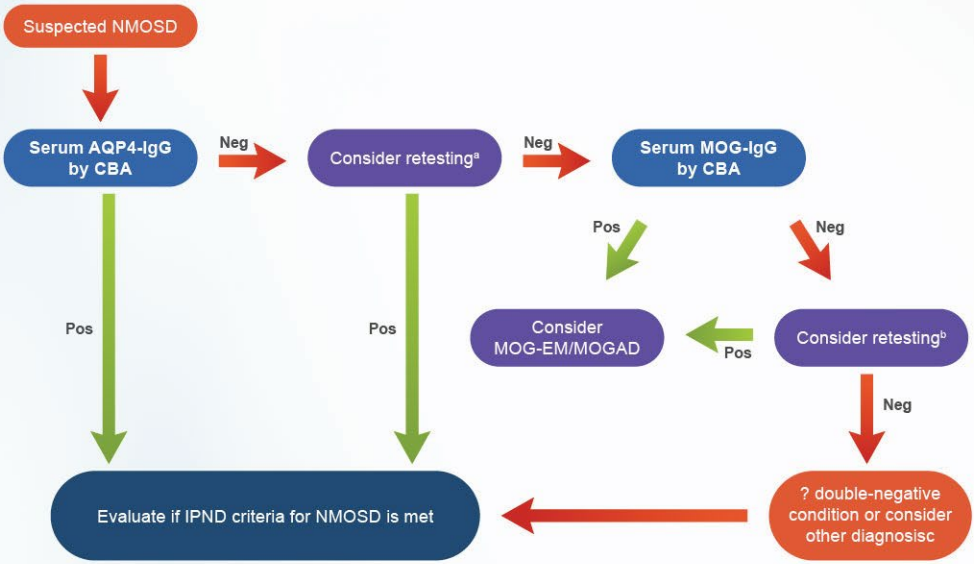


Figure 2. Proposed algorithm for NMOSD laboratory diagnosis. *The current algorithm aligns with the 2015 IPND diagnostic criteria. However, updated recommendations are expected from the IPND in 2025. These may further refine laboratory diagnostic pathways for NMOSD, including potential adjustments to antibody testing and diagnostic thresholds (see Appendix 4).*

[a] Retesting for the anti-AQP4-IgG is recommended during an acute attack or a treatment-free interval. The initial negative result could be influenced by the treatment, such as corticosteroid or PLEX, that the patient received. Serum is the recommended sample for retesting. However, if a CSF sample needs to be sent, we recommend sending a paired serum and CSF sample, as isolated positive anti-AQP4-IgG in CSF is extremely rare. [b] Similar to anti-AQP4-IgG testing, we recommend retesting of the anti-MOG-IgG during another acute attack suggestive of MOGAD and the submission of paired serum and CSF. Isolated CSF positivity for anti-MOG-IgG occurs more frequently than anti-AQP4-IgG, which is between 3 to 29% of the cases. [c] Always evaluate for alternative diagnosis, as many conditions can mimic NMOSD and MOGAD, and vice versa. For the double negative condition, it is also essential to confirm the double negative parameters using a slightly more sensitive assay, such as live CBA; however, this assay is not currently available in Malaysia. AQP4, aquaporin-4; CBA, cell-based assay; CSF, cerebrospinal fluid; EM, encephalomyelitis; IgG, immunoglobulin G; IPND, International Panel for NMO Diagnosis; MOG, myelin oligodendrocyte glycoprotein; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; Neg, negative; NMOSD, neuromyelitis optica spectrum disorder; PLEX, plasma exchange; Pos, Positive. Adapted from Jarius et al 2023.[18]

CSF analysis

CSF testing is not formally required for the diagnosis of NMOSD.

- However, it is **highly recommended for determining differential diagnoses**.[18]
- Pleocytosis is more frequently observed in AQP4-IgG positive NMOSD and MOGAD than in MS. The cells include lymphocytes, neutrophils, and eosinophils.[22]
- OCB are primarily seen in MS but may also be observed in small percentages of patients with NMOSD and MOGAD (10%-15%), albeit transiently.[18,22]

Other laboratory tests

Many conditions can mimic NMOSD or vice versa. Therefore, it is essential to perform additional laboratory tests to rule out alternative diagnoses. The differential diagnoses for NMOSD encompass a range of conditions, including MS, neurosarcoidosis, rheumatic diseases, infectious diseases, vascular diseases, neoplastic and paraneoplastic conditions, genetic, and metabolic disorders.[18] Hence, **further laboratory testing should be based on the careful evaluation** of the potential alternative diagnoses. It is also essential to consider that NMOSD can coexist with other autoimmune conditions in 25-40% of patients with AQP4-IgG-positive NMOSD.[18] Table 2 summarises the different laboratory tests.

Table 2. Summary of laboratory investigations for the diagnosis of NMOSD in a patient with suspected NMOSD

Disease-specific antibody test	**Antibodies:** Anti-AQP4-IgG for NMOSD and anti-MOG-IgG for MOGAD. **Method:** CBA (fixed or live) is recommended as it is sensitive and highly specific. **Sample:** Serum is strongly recommended. CSF is reserved for certain situations. **Clinical correlation:** High titration of the antibodies is generally detected during an acute attack. The antibodies remain detectable during remission and can revert to negative in some patients. Negative results at presentation should be interpretated with caution especially in those already started on IST.

CSF analysis	Important for differential diagnosis purposes. The CSF analysis finding may help to differentiate between NMOSD, MOGAD and MS. **In NMOSD**: CSF pleocytosis with >50 leukocytes/mL is seen in ~35% of patients. The presence of >5/µL of neutrophils (~44%) or eosinophils (~10%) in attack-associated samples may help differentiate NMOSD from MS. Additionally, ~50% show raised WBC counts during acute attacks, and 10–15% have transient OCBs.[1]
Laboratory tests other than disease-specific antibody assay	TRO differential diagnoses like: 1. MOGAD, MS, AIE such as GFAP disease 2. Other connective tissue diseases 3. Infectious diseases such as viral myelitis (HIV, HSV, varicella zoster, enterovirus), neurosyphilis and tuberculosis 4. Genetic diseases such as hereditary ataxias, Wilson's disease, CANOMAD 5. Metabolic diseases like vitamin B12 deficiency, and thyroid disorders 6. CNS vasculitis 7. Neoplastic and paraneoplastic conditions 8. Coeliac disease 9. Sarcoidosis

AIE, autoimmune encephalitis; AQP4, aquaporin-4; CANOMAD, chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins, and disialosyl antibodies; CBA, cell-based assay; CNS, central nervous system; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; GFAP, glial fibrillary acidic protein; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IgG, immunoglobulin G; IST, immunosuppressive therapy; MOG, myelin oligodendrocyte glycoprotein; MOGAD, MOG antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; OCB, oligoclonal bands; TRO, to rule out; WBC, white blood cells. Adapted from Borisow, et. al. 2018.24

SECTION 3: TREATMENT SELECTION

- Recommendations for the treatment selection of NMOSD in this consensus focus on the use of **immunosuppressive therapies (ISTs), biologics, and other pharmacological agents**.
- Patients **may also require symptomatic treatment for a wide range of NMOSD-related issues** such as neuropathic pain, tonic spasms, abnormal muscle tone, sphincter dysfunction, fatigue, sleep disturbances, and neuropsychological symptoms.[25] While research on symptomatic therapies in NMOSD remains limited, clinical approaches can be informed by evidence drawn from MS literature. These strategies are summarised in Appendix 5.

Statement 3.1a

- *The primary factors to inform selection of biologic therapies in NMOSD are efficacy and safety.*

Statement 3.1b

- *Additional considerations for biologic therapy selection in NMOSD are current disease activity, relapse severity, route of administration acceptability, and potential benefit for comorbidities.*

Statement 3.1c

- *Monitoring and treatment decision-making in AQP4-IgG–seropositive NMOSD patients should be guided by clinical outcomes, drug safety profiles, MRI findings, and, when available, biomarkers such as serum GFAP and neurofilament light chain.*

Considerations to inform biological therapy selection and monitoring

1. The panel agreed that efficacy and safety should be the primary considerations when selecting biologic therapies for NMOSD, as outlined in Statement 3.1a.
2. Statement 3.1b was also supported without modification (Figure 3).
   a. Factors such as current disease activity, relapse severity, preferred route of administration, and relevant comorbidities are important in guiding individualised treatment decisions.

b. Reproductive health considerations, including preconception counselling and treatment planning during pregnancy and breastfeeding, were also emphasised.
c. Practical aspects such as treatment accessibility, financial constraints, patient expectations, the need for ongoing monitoring, and adherence to vaccination protocols were identified as key considerations in the selection of DMTs.

The panel agreed that the **IPND criteria for NMOSD monitoring are applicable in the local setting**. Although biomarkers such as IL-6 and GFAP are of interest with evolving evidence for their value in predicting disease severity or treatment response, these tests are not readily available in routine clinical practice.

GFAP/IL-6

GFAP concentrations in both CSF and blood are elevated during NMOSD attacks and correlate with disease-related disability.[26]

- Elevated blood GFAP levels have been observed during remission when compared to healthy individuals and patients with MS or MOGAD, although there is substantial overlap between groups.
- The **hypothesis** that elevated GFAP during remission may reflect astrocyte injury due to increased blood–brain barrier permeability has been suggested, and its role in predicting future attacks is still being studied.

IL-6 is useful in NMOSD diagnosis and has therapeutic implications.

- It is significantly elevated in NMOSD compared to other neuroinflammatory diseases and correlates with relapse severity.
- It has also been proposed as a possible marker to stratify treatment during attacks.
- It is important to consider that NMOSD patients may have elevated IL-6 levels during remission, with levels rising even further during relapse.
- The clinical utility of IL-6 monitoring is still under investigation.[27] Despite evolving and mounting evidence, there is **no current recommendation for the use of IL-6 and GFAP in predicting disease severity or monitoring treatment response**.

MRI

In the context of monitoring, MRI's utility lies in confirming changes associated with new symptoms, prognostication (spinal cord atrophy) and in cases where relapse is suspected.

- It should be performed at the appropriate time according to clinical indication and **not as a serial monitoring tool**.
- While MRI can help differentiate true relapses from pseudo-relapses,[28] it may also detect asymptomatic new brain lesions during follow-up.
- **Pairing MRI with fluid biomarkers** is considered reasonable in symptomatic patients. The predictive value of subclinical disease activity detected on MRI for future relapses and treatment decisions requires further study.

The above monitoring considerations inform treatment selection and decision-making (please refer to Chapter 6: Monitoring for adverse events [AEs] for recommendations on monitoring during treatment); the following section outlines the available therapeutic options for NMOSD.

Statement 3.2

- *In newly diagnosed AQP4-IgG–seropositive NMOSD, the choice of eculizumab (ECU), ravulizumab (RAV), inebilizumab (INEB), satralizumab (SAT), rituximab (RTX), or tocilizumab (TCZ) should consider patient preferences regarding dosing frequency, route of administration, availability, accessibility and adherence. In addition, the drug's safety profile, the patient's comorbidities and concomitant autoimmune diseases should be considered.*

Four monoclonal antibodies, ECU, INEB, SAT and RAV have received the US FDA approval for treating AQP4-IgG–seropositive NMOSD representing a significant advancement in reducing attack frequency in these patients.[29] However, there is a lack of data supporting personalised treatment selection based on mechanism of action (MOA).

- Indirect evidence from clinical trials suggests a **possible benefit of newer monoclonal therapies** over existing off-label treatments, although more head-to-head studies are needed.

- There is evolving evidence on whether **monoclonal antibodies monotherapy** is sufficient for **maintenance therapy** without concurrent steroid use. Some studies support using monoclonals as monotherapy.[30-34] However, real-world data.[35] suggest that certain patient cohorts may still require low-dose corticosteroids (5–10 mg) in combination with monoclonal therapies.
- These treatments may be broadly classified as high-efficacy or low-to-modest efficacy based on published frameworks involving patients with seropositive AQP4 NMOSD (Appendix 6).[36]
- Further research is required to clarify these treatment strategies.

Treatment choice often depends on various factors from the clinician's perspective, including differences in:

- Clinical trial data.
- Perceived efficacy.
- Impact of safety profiles to the specific patient.
- Administration preferences.
- Long-term cost and accessibility[29].
- Safety considerations are essential when selecting therapies, taking into account any comorbid conditions that may increase susceptibility.

The **convenience of treatment** also plays an important role in patient-centred decision-making.

- ECU requires biweekly intravenous (IV) infusions, often needing infusion centre access.
- RAV offers greater convenience with an 8-week interval.
- INEB is infused every six months following induction.
- SAT is a monthly subcutaneous injection (SC) that can be self-administered at home.[29]

Patients and clinicians should **jointly select the most appropriate treatment** based on efficacy, safety, convenience, cost, and accessibility. Additional considerations such as infusion access, self-administration capability, family planning, financial access, and quality-of-life priorities are all part of this personalised treatment strategy.[29]

It was agreed that a broad range of factors should be considered when selecting biologic therapies for newly diagnosed AQP4-IgG-seropositive NMOSD patients.

- The **availability of the therapy** was acknowledged as a key consideration that can influence treatment decisions.
- Other considerations are listed in Figure 3.
- The treatment algorithm for AQP4-IgG-seropositive NMOSD has been adapted from the Neuromyelitis Optica Study Group (NEMOS) guidelines and is illustrated in Figure 4.
- Figure 5 illustrates the treatment for AQP4-IgG-seronegative NMOSD and has similarly been adapted from the NEMOS guidelines.[37]
- The committee acknowledged that though ECU, SAT, RAV and INEB have not been approved for the treatment of seronegative NMOSD, case reports/series have suggested some benefit.[38,39]

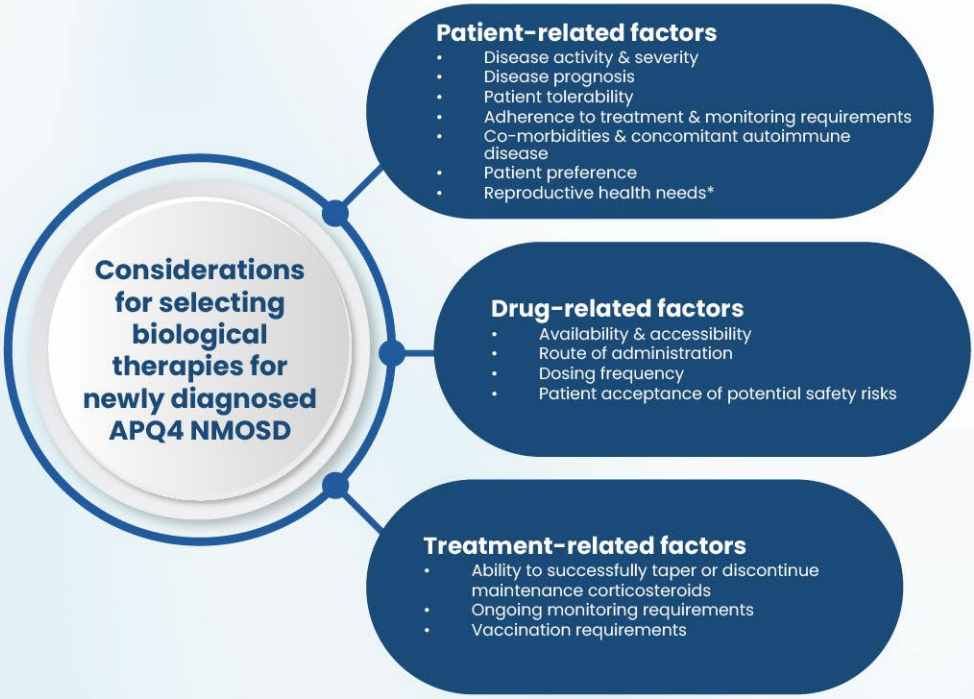


Figure 3. Factors to consider when selecting biological therapies for newly diagnosed APQ4 NMOSD[40,41]

**Reproductive health considerations, include preconception counselling and treatment planning during pregnancy and breastfeeding.*

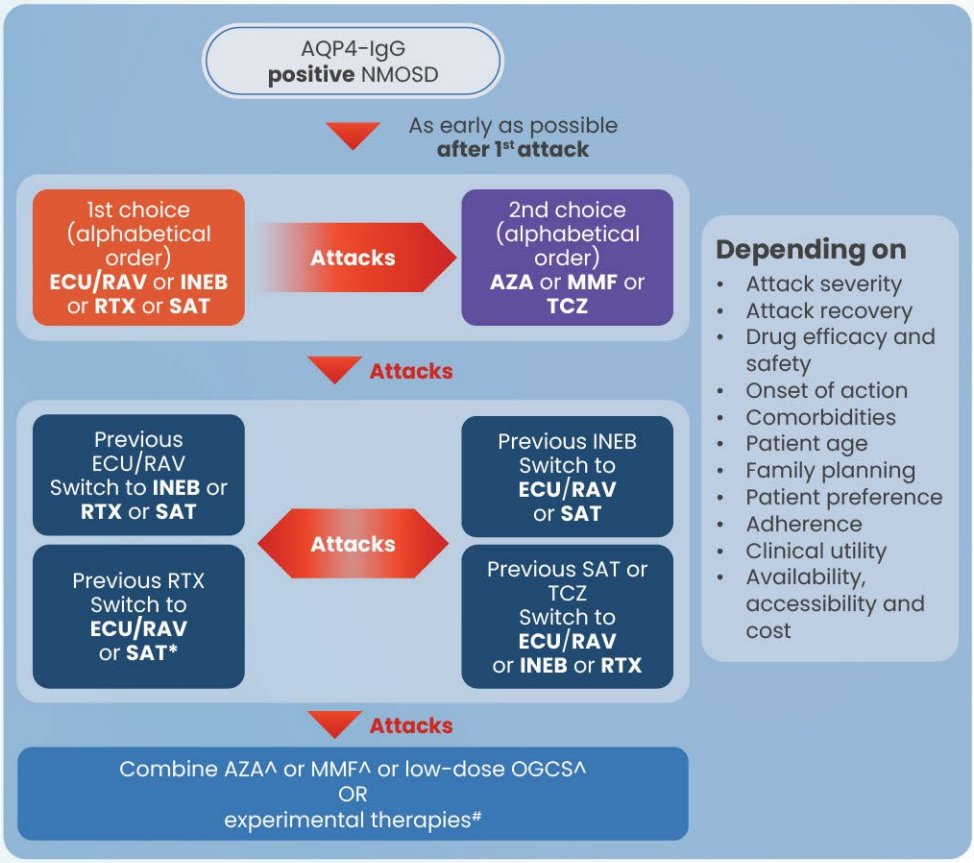


Figure 4. Treatment algorithm for newly diagnosed patients with AQP4-IgG positive NMOSD and switching therapies in case of treatment failure.

*Treatment of patients with APQ4-IgG negative NMOSD is illustrated in Figure 5 *Can switch to INEB, however, it is a hypothetical option with no clinical data; ^if monoclonal antibodies are not accessible or available, a combination of AZA/MMF and OGCS may be used; #experimental therapies examples include intermittent PLEX/immunoadsorption or haematopoietic stem cell transplantation. AQP4-IgG, aquaporin-4 immunoglobulin G; AZA, azathioprine; ECU, eculizumab; INEB, inebilizumab; MMF, mycophenolate mofetil; NMOSD, neuromyelitis optica spectrum disorder; OGCS, oral glucocorticosteroid; PLEX, plasma exchange; RAV, ravalizumab; RTX, rituximab; SAT, satralizumab; TCZ, tocilizumab. Adapted from Kümpfel T, et al. J Neurol. 2024.37*

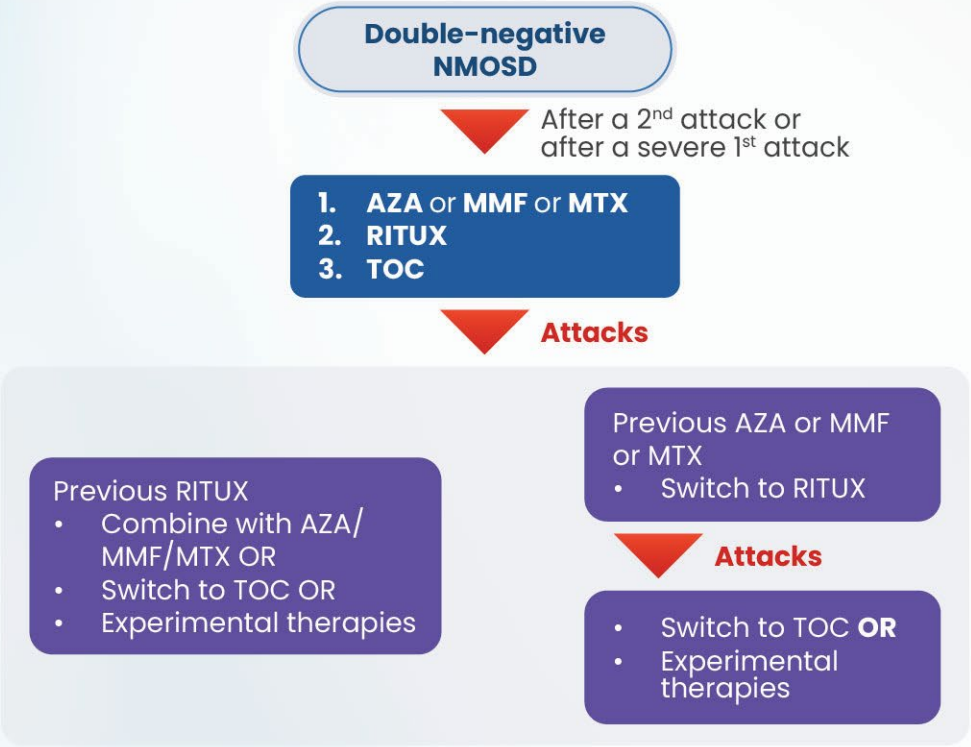


Figure 5. Long-term therapy for double-negative NMOSD.

Experimental therapies include intermittent PLEX/immunoadsoprtion or haematopoietic stem cell transplantation. AZA, azathioprine; MMF, mycophenolate mofetil; MTX, methotraxate; NMOSD, neuromyelitis optica spectrum disorder; PLEX, plasma exchange; RITUX, rituximab; TOC, tocilizumab. Adapted from Kümfel T, et al. J Neurol. 2024; Apóstolos-Pereira SLD, et al. Arq Neuropsiquiatr. 2025.[37,42]

Statement 3.3

- *In AQP4-IgG–seropositive NMOSD, choice of biologic therapy (RTX, TCZ, RAV, ECU, INEB and SAT) should consider prior maintenance treatment response, with preference for agents with a different MOA following therapy failure.*

The panel agreed with this statement and supported the recommendation that, in cases of treatment failure to prior maintenance therapy with biologics, clinicians should consider switching to a biologic therapy with a different MOA from the one previously used.[41,43,44]

There is currently **no universally accepted definition of treatment failure in NMOSD**.

- In clinical practice, treatment failure is **generally determined by expert judgement** and is **characterised by the occurrence of new or recurrent relapses** despite **adequate dose and duration** of IST, provided the **patient has been adherent**.
- Some definitions also incorporate the **development of new MRI lesions as part of treatment failure**.
- A change in therapy may be considered not only when disease activity persists despite appropriate treatment, but also when patients experience intolerable AEs or develop comorbidities that render the current therapy unsuitable.[37]

The panel recognised that NMOSD presents with variable disease severity at onset, ranging from less aggressive attacks to fulminant, rapidly progressive disease.

Patients with severe, aggressive presentations:

- Early initiation of high-efficacy treatments (Appendix 6) that act quickly is recommended to induce remission and speed recovery (such as monoclonal antibodies like RTX).
- These may be administered together with corticosteroids and/or ISTs.

Patients with less aggressive disease where recovery is more favourable:

- Treatment options may include high-dose corticosteroids combined with ISTs or monoclonal antibodies, with the understanding that some of these agents may take longer to achieve therapeutic effect.

Switching therapies may not solely be driven by efficacy or MOA, and should be individualised to the patient's disease activity, tolerability and clinical response, and how fast the response is needed. Patient-related factors such as intolerance to injections or IV administration, logistical challenges, side effect profiles, and comorbidities may also influence treatment selection and the decision to switch biologic therapies. Figure 3 illustrates the treatment algorithm for switching therapies.

Statement 3.4

- *Patients with NMOSD who have disease activity despite treatment with ISTs and/or oral steroids (OGCs) may benefit from the addition of on-label biologic therapies.*

Statement 3.5

- *In resource-limited settings where access to biologics is restricted, OGCs with or without ISTs may be beneficial, provided there is careful monitoring for long-term AEs and gradual down-titration to the minimal effective dose.*

Statement 3.6

- *ECU, RAV, INEB, SAT or RTX may be used as monotherapy in AQP4-IgG–seropositive NMOSD to minimise the risk of AEs associated with concurrent ISTs and steroids.*

Statement 3.7

- *While monotherapy is preferred, ECU, RAV, RTX or SAT may be combined with existing ISTs, with consideration of the short- and long-term safety and tolerability of the ISTs.*

Consistent with the International Delphi Consensus on the Management of AQP4-IgG–seropositive NMOSD,[45] **biologic therapies are recommended as monotherapy where possible**, given the increased risk of infection and higher incidence of AEs associated with combination therapy.[37,45]

- According to the NEMOS guidelines, long-term treatment with ECU, RAV, INEB, RTX or SAT is considered highly effective.[37,46,47]
- Selection of therapy should be individualised based on factors such as cost, attack severity, comorbidities, patient preference, adherence, and safety.
- Switching to monoclonal antibody therapy should be considered when conventional IST fails, and in cases of biologic failure, a switch to an agent with a different MOA is recommended (see Section 4 and Figure 3).
- Bridging therapy with low-dose OGCs for up to 3–6 months may be considered to reduce the risk of early relapse.

Pivotal clinical trials have demonstrated the benefit of biologic therapies in reducing relapse risk in patients with AQP4-IgG–seropositive NMOSD, including those on concurrent ISTs or OGCs.

- In the PREVENT trial, ECU led to an approximately 94% reduction in relapse risk compared to placebo, with patients allowed concurrent IST use.[32]
    - Additionally, ECU is generally well tolerated in patients on IST, and its concurrent use may help reduce the risk of AEs, and serious infections, in those with aggressive disease or when a rapid therapeutic response from a DMT is required.[48]
- In the CHAMPION trial with RAV, which used the placebo arm of PREVENT as comparator, reported a 98.6% reduction in relapse risk.[31]
- The SAKURA trials of SAT also permitted concurrent IST use and demonstrated a 55–62% reduction in relapse risk compared to placebo.[33,34]
- In contrast, the N-MOmentum trial for INEB, which did not include patients on ISTs but allowed OGCs use during initiation, showed a 73% reduction in relapse risk.[30]
- These findings **support the potential benefit of adding biologic therapy to existing IST or steroid regimens** in patients with ongoing disease activity, offering enhanced relapse prevention.[49,50]

While **RTX monotherapy** is considered highly effective in NMOSD, combining it with IST may require careful monitoring, as it may increase the risk of infections (e.g., Pneumocystis jirovecii pneumonia, viral reactivation) and hypogammaglobulinemia (HGG).[51,52] Although evidence supports combined therapy, **the panel expressed a preference for monotherapy** when using RTX.

While biologics are preferred for relapse prevention in AQP4-IgG–seropositive NMOSD, conventional ISTs such as azathioprine (AZA), mycophenolate mofetil (MMF), and OGCs remain viable alternatives, particularly in **resource-constrained environments** such as public healthcare settings.[37]

- Patients who are stable on off-label therapies may continue their current regimen without the need for switching.[46,53]

- However, the panel advised that low-dose OGC monotherapy should only be considered when no other treatment options are available,[54] or in steroid-sensitive patients who experience relapses upon discontinuation. In such cases, steroids should be tapered gradually to the lowest effective dose to minimise long-term AEs.

Statement 3.8

- *If ECU, INEB or SAT are started with an IST, patients should be closely monitored for AEs, and ISTs and steroids tapered gradually based on the biologic's onset of action.*

The panel supported this recommendation and adopted Statement 12 from the International Delphi Consensus on the Management of AQP4-IgG–seropositive NMOSD,[45] which is aligned with evidence from the PREVENT and SakuraSky trials.[32,34]

- These studies demonstrated no significant safety concerns when ECU and SAT were used in combination with background IST.

For INEB, data on combination therapy with IST other than OGCs is currently lacking.[30] In the N-MOmentum trial, patients were allowed to use OGCs during the initiation period, with tapering recommended over a 21-day period.

The following considerations when initiating biologic therapies alongside IST can be considered:[55]

- **Close monitoring for AEs** is essential during the transition to biologics.
  - ECU is associated with an increased risk of meningococcal infections,[56] requiring vaccination before initiation.
  - INEB can increase the risk of respiratory and urinary tract infections (UTIs) due to its action on CD19+ B cells.
  - Although SAT is generally well tolerated, it too carries potential immune-related adverse effects.

- **Slow tapering of ISTs** is recommended to allow biologics sufficient time to exert their therapeutic effect.
    - This approach helps prevent relapses and reduces the risk of over-immunosuppression, which could lead to infections or other complications.
    - Agents commonly requiring tapering include AZA, MMF and OGCs.
- **Understanding the expected onset of action of biologics** is important when planning the taper.
    - As biologics may not provide immediate disease control, bridging therapy with ISTs is often necessary to prevent early disease flares.

The transition from conventional IST to biologics such as ECU, INEB or SAT should be done gradually and under close clinical supervision, with the tapering schedule tailored to the individual patient's response and clinical risk.

Statement 3.9

- *Adolescents (≥12 years) with AQP4-IgG–seropositive NMOSD may be treated with SAT. ECU, RAV, RTX or INEB may be considered for severe, SAT-refractory cases, though further evidence is needed for broader use.*

SAT is currently the recommended biologic for use in adolescents aged 12 years and above with AQP4-IgG–seropositive NMOSD. The panel acknowledged that, while other biologics, such as ECU, RAV, RTX, TCZ or INEB, may be considered in severe or refractory cases, additional clinical trials are required to validate their safety and efficacy in this younger population.[37,57]

Utilising off-labelled therapies

Despite the growing body of evidence and regulatory approval supporting the use of biologics such as ECU, RAV, INEB and SAT for NMOSD, off-labelled therapies like RTX, AZA, and MMF continue to play a critical role in real-world clinical practice, especially in resource-limited settings such as Malaysia and other Southeast Asian countries. These agents, although not formally approved for NMOSD, are widely accessible, more affordable, and often used as first-line options due to longstanding clinician experience and favourable outcomes.[50,58-61]

RTX: Shown to be effective in reducing relapse rates and improving disability outcomes.

- A randomised controlled trial in Japan: RTX completely prevented relapses over 72 weeks in AQP4-seropositive patients when compared to placebo.[50]
- Real-world evidence from Thailand: over 79% of NMOSD patients remained relapse-free with RTX, accompanied by significant reductions in annualised relapse rates (ARR) and improvements in disability scores. These benefits were observed even when using lower or CD19-guided dosing regimens, with AEs being mostly mild or manageable.[60]

MMF: In a meta-analysis of over 1000 patients to significantly reduce ARR and improve Expanded Disability Status Scale (EDSS) scores, with a tolerable safety profile.[61]

Long-term data on **AZA**: Consistent use from disease onset was associated with reduced disability accumulation over time, with an estimated 80% reduction in EDSS progression over five years.[58]

TCZ: Demonstrated promising efficacy as an off-labelled treatment for NMOSD, particularly in patients unresponsive to other ISTs.

- A small retrospective study (N=5) with previously failed therapies such as RTX, cyclophosphamide (CYC) or AZA: Treatment with TCZ led to an 88.9% reduction in ARR over one year, with no major safety concerns reported.[62]
- A meta-analysis (nine studies and 153 patients): Showed significant improvements in ARR and EDSS scores, especially among AQP4-IgG positive patients. TCZ's efficacy appeared to be influenced by gender, race, and dosage, while the reduction in disability scores was consistent across subgroups. Most AEs were mild, with only one case of severe infection reported.[63]
- A phase 2 head-to-head trial vs. AZA: TCZ significantly prolonged the time to first relapse and resulted in fewer relapses, including among patients with concomitant autoimmune disease. AEs were comparable between both groups, and the safety profile of TCZ was deemed acceptable.[64]

SECTION 4: SWITCHING TREATMENTS

Statement 4.1

- *For AQP4-IgG–seropositive NMOSD patients who are stable and relapse-free on off-label ISTs (AZA, MMF, OGCs) or biologics (RTX, TCZ), switching to on-label biologics is not necessary.*

The panel supported this statement based on Statement 8 of the International Delphi Consensus on the Management of AQP4-IgG–positive NMOSD.[45]

- Patients who are clinically stable and relapse-free on off-label therapies, such as AZA, MMF, OGCS, RTX or TCZ, do not need to transition to approved biologic treatments.

This recommendation assumes that patients continue to tolerate their current off-label treatment.

- Presently, there is no evidence to suggest that switching to ECU, INEB or SAT offers additional benefit in relapse-free patients.
- The pivotal trials for these agents **excluded participants who were clinically stable and not relapsing**. Further studies comparing the long-term safety profiles of on-label and off-label maintenance therapies are required.

Statement 4.2a

- *If relapses persist after allowing for the onset of action of RAV, ECU, INEB or SAT, patients should be switched to an alternative biologic.*

Statement 4.2b

- *If serious treatment-related AEs occur after initiating RAV, ECU, INEB or SAT and allowing for their onset of action, patients should be switched to an alternative biologic.*

Statement 4.2c

- *After initiating RAV, ECU, INEB or SAT and allowing adequate time for their onset of action, a switch may be considered based on patient preference.*

The panel agreed with these statements, consistent with international recommendations.[37,45]

- Patients should be considered for a switch to an alternative biologic if relapses continue, if serious treatment-related AEs occur, or based on patient preference provided sufficient time has been given for the onset of action of the initial biologic.

The agreement for Statement 4.2c did not reach the ≥75% consensus threshold. This outcome was expected, as most panel members felt that factors such as the individual patient's safety profile, concurrent comorbidities, financial access, and drug availability would take precedence over patient preference. The voting results reflect this perspective.

Statement 4.3

- *When switching between RAV, ECU, INEB and SAT, no washout is needed.*

The panel endorsed this statement in alignment with international guidance.[37,45]

- Switching between RAV, ECU, INEB and SAT does not require a washout period, as immediate initiation of the next biologic is preferred **to reduce the risk of relapse**.
- Although clinical trial protocols typically included a 3–6 month washout phase, this is not reflective of real-world practice.
- When transitioning from RTX to any of these three agents, the switch may be made as soon as B-cell repopulation is confirmed, and lymphocyte counts exceed 800 cells/μL, with minimal washout as long as patient is free from infection.

SECTION 5: ACUTE TREATMENT FOR NMOSD RELAPSE

Statement 5.1

- *Acute NMOSD relapses should be treated with first-line steroids; early PLEX is recommended for severe or steroid-refractory cases, with IVIg as an alternative if PLEX is unavailable or patients refuse it.*

Steroids are recommended as first-line therapy for acute NMOSD relapses in most clinical guidelines, including NEMOS 2023.[37] The commonly used regimen is IV methylprednisolone at a dose of 1 g daily for 3 to 5 days, followed by a tapering course of OGCs over 3 to 6 months.

PLEX or therapeutic plasma exchange (TPE) is also endorsed by guidelines such as NEMOS 2023 and the American Society for Apheresis (ASFA) 2023.[65] as a **second-line option in cases with insufficient response to steroids**, a practice also followed in Malaysia.

- Evidence supports the use of **early PLEX in severe transverse myelitis**. In such cases, early intervention was associated with improved outcomes compared to high-dose steroids alone.[66]
- **Apheresis** (including PLEX/TPE) may also be considered as first-line therapy in patients with a history of poor steroid response, previous requirement for apheresis during relapse, or in those presenting with severe myelitis.
- The **timing of intervention is crucial** as early use of apheresis, particularly as first-line therapy, along with shorter time from symptom onset to initiation and presence of AQP4-IgG, were strong predictors of complete remission.[67]

IVIg is not recommended as a standard treatment for acute relapses but may be considered when both steroids and PLEX are not feasible.[58,68]

Statement 5.2

- *On a case-by-case basis, IV RTX, CYC and ECU, may be used for treating refractory relapses.*

The panel agreed with the use of IV RTX and ECU for **treatment-refractory NMOSD relapses**, based on supporting evidence from clinical trials such as the RIN1 study[50] and the PREVENT trial.[32]

The panel did not support the use of CYC due to concerns about conflicting data, limited dosing flexibility, and its association with severe AE,[37] a minority of experts continued to endorse its use in refractory cases and NMOSD-associated with concomitant connective tissue disease.

- This was primarily because CYC, like RTX, remains more accessible and affordable across both the public and private healthcare sectors in Malaysia, and there is some existing evidence supporting its efficacy in NMOSD.[69-71] As a result, although the statement met the consensus threshold (≥75%), overall agreement was 88%.

Statement 5.3a

- *In AQP4-IgG–seropositive adults with NMOSD, ECU, RAV, SAT, INEB, RTX or RTX may be initiated in severe or aggressive fulminant NMOSD after the first attack in treatment-naïve patients.*

Statement 5.3b

- *In AQP4-IgG–seropositive adults with NMOSD, ECU, RAV, SAT, INEB, RTX or TCZ may be initiated following relapse despite prior treatment.*

It was agreed that **biologic therapies should be considered after the first attack in treatment-naïve patients with severe or fulminant NMOSD, or following relapse in those who have failed prior treatments**.

- These recommendations are supported by evidence from pivotal randomised, double-blind, placebo-controlled time-to-event trials evaluating all five biologic agents (Table 3).
- Although these studies were primarily conducted in AQP4-IgG–seropositive populations, subgroup analyses suggest some potential benefit of SAT and INEB in AQP4-IgG–seronegative patients.[34,72,73] Based on this limited evidence, treatment with FDA-approved biologics may be considered in selected patients with **true seronegative NMOSD**.

Table 3. Summary of pivotal trials

Agent	AQP4-IgG status at enrolment	Previous IST	Concomitant IST in active arm	Attacks (p-value)	Duration of treatment /OLE
RTX[50]	Pos: 38 (100%)	None on RTX	No, OGC tapered during initiation period	0% v 37%, (Difference 36.8%, 95% CI 12.3, 65.5; p=0.0058)	Median 72.1 weeks/ Mean 20.5 months
	Neg: 0			NE	
INEB[30]	Pos: 213 (92.6%)	66% primarily AZA and GC, including 7% on RTX	No, OGC during initiation period only	12% v 39% (HR 0.272, 95% CI 0.150, 0.496; p<0.001)	Up to 28 weeks/ Mean 3.2 years up to 4.5 years (median)
	Neg: 17 (7.4%)			NA^	
ECU*[32]	Pos: 143 (100%)	78% on IST at baseline, including 27% with previous RTX	Yes	3% v 43% (HR 0.06, 95% CI 0.02, 0.20; p<0.001)	Median 89.4 weeks/ Median 132 weeks, up to 277 weeks
	Neg: 0			NE	
RAV[31]	Pos: 58 (100%)	48% on IST at baseline; 86% previous IST, including 36% with previous RTX	Yes	0% vs 43% (HR 0.014, 95% CI 0.000, 0.103; p<0.0001)	Median 73.5 weeks/ ongoing during publication
	Neg: 0			NE	
SAT[34] (SAkuraSky)	Pos: 55 (66.3%)	78% with previous IST before IST add-on at baseline, including 4.9% with RTX	Yes	11% vs 43% (HR 0.21, 95% CI 0.06,0.75)	Median 107.4 weeks/ Median 4.4 years
	Neg: 28 (33.7%)			36% vs 43% (HR 0.66, 95% CI 0.20-2.24)	

SAT[33] (SAkuraStar)	Pos: 63 (66.3%)	87% with previous IST or other and 13% with previous B-cell depleting therapies	No	22% vs 56.5% (HR 0.26, 95% CI 0.11,0.63)	Median 92.3 weeks/ Median 4 years
	Neg: 31 (32.6%)			45.5% vs 33.3% (HR 1.19, 95% CI 0.30, 4.78)	

*^Of the 17 patients with AQP4-IgG seronegativity, randomisation resulted in 13 patients treated with INEB and only four with placebo. There were three attacks in the INEB arm and none in the placebo arm owing to the small seronegative sample.[30] *Eculizumab was not evaluated in AQP4-IgG–seronegative NMOSD in pivotal trials, but case reports show potential benefit in this population.[39,74] These reports suggest relapse-free periods and improved function after treatment, although further studies are needed to confirm efficacy and safety.*

AQP4-IgG, aquaporin-4 immunoglobulin G; AZA, azathioprine; ECU, eculizumab; GC, glucocorticoid; HR, hazard ratio; INEB, inebilizumab; IST, immunosuppressive therapy; NA, not available; NE, not evaluated; OGC, oral glucocorticoid; OLE, open-label extension; RAV, ravulizumab; RTX, rituximab; SAT, satralizumab.

SECTION 6: MONITORING FOR ADVERSE EVENTS

Statement 6.1

- *Patients with AQP4-IgG–seropositive NMOSD receiving ECU, INEB, RAV, RTX or SAT should be monitored for infections in the short and long term.*

This recommendation aligns with the NEMOS guidelines. These monoclonal antibodies, which disrupt immune pathways to control disease activity, may increase susceptibility to bacterial infections of the upper respiratory tract and urinary tract, as well as meningococcal infections and infections caused by encapsulated bacteria.

Monitoring should include complete blood cell counts, differential white blood cell counts, and clinical surveillance for infections to ensure patient safety during both the short- and long-term course of treatment.[37]

- Frequency of blood and clinical monitoring should be conducted every 4-weekly for the first three months and subsequently every 3-6 months.
- Specifically for patients receiving RTX, additional monitoring of serum Ig levels and CD19/CD20 cell counts is recommended.
    - Monitoring of CD19/CD20 cell counts may be used to guide retreatment, with re-dosing considered once levels exceed 1% of peripheral blood lymphocytes.
    - While standard protocols used fixed 6-month dosing, CD19/CD20 monitoring allows an individualised approach, enabling delayed retreatment in slow repopulators (beyond 6-12 months) and earlier retreatment in fast repopulators.
- Tables 4 and 5 list a summary of approved and off-label NMOSD therapies including their mechanisms, dosing, monitoring and safety considerations.

Table 4. Approved NMOSD therapies – mechanism of action, dosing and safety considerations:

Drug name	MOA	Dose	CI	Risk/ Precautions	Pre-screening / suggested monitoring	AEs	Vaccination
INEB[75]	CD19-directed cytolytic antibody, causing B-cell depletion within 2 weeks and full effects seen after 6-8 weeks.	Initial dose: 300 mg IV infusion day 1 and 14 followed by subsequent doses 300 mg IV infusion every 6-monthly. Premedication to be administered 30-60 minutes before each infusion with intravenous corticosteroids, oral antihistamine and oral antipyretics.	Prior life-threatening infusion reaction, active HBV infection and active or untreated latent TB.	IRR including anaphylaxis, risk of infections (HBV reactivation, PML, TB), HGG.	HBV and TB screening, and serum Ig testing. Before every dose determine if there is an active infection.	Infections (opportunistic infection, URTI and UTI), arthralgia, headache, IRR, back pain, reduced immunoglobulins, lymphopenia, neutropenia.	Vaccination with live or live-attenuated vaccines is not recommended during treatment. Administer all immunisations according to immunisation guidelines, and at least 4 weeks before initiation for live or live-attenuated vaccines.
ECU[76]	Recombinant humanised monoclonal antibody that acts on the terminal complement protein C5. Effect is immediate: 1-2 weeks	Initial dose: 900 mg IV infusion weekly for the first 4 weeks followed by 1200 mg IV infusion on the 5th week and 1200 mg IV infusion 2 weekly thereafter. Administer at recommended dosage time points, or within 2 days of these time points. Supplemental dosing is required in the setting of concomitant plasmapheresis or PLX, or FFP infusion	Unresolved serious *Neisseria meningitidis* infection.	Serious meningococcal infections, serious infections with *Neisseria* species.	Blood cell count and differential WBCC.	Infection (*Neisseria* species, URTI, nasopharyngitis, influenza), diarrhoea, arthralgia and back pain, dizziness, contusion.	Meningococcal vaccination at least 2 weeks before initiation.

RAV[77]	Humanised monoclonal antibody that acts on the terminal complement protein C5. Effects seen in 1-2 weeks	IV weight-based, loading dose of 2400–3000 mg on day 1 followed by 3000–3600 mg maintenance dose after 2 weeks and then once every 8 weeks. Weight **40kg to <60kg:** Loading dose: IV 2400 mg as a single dose. Maintenance dose: IV 3000 mg once every 8 weeks starting 2 weeks after the loading dose. Weight **60kg to <100kg:** Loading dose: IV 2700 mg as a single dose. Maintenance dose: IV 3300 mg once every 8 weeks starting 2 weeks after the loading dose. Weight **≥ 100kg:** Loading dose: IV 3000 mg as a single dose. Maintenance dose: IV 3600 mg once every 8 weeks starting two weeks after the loading dose. **Note:** Indicated in AQP4-IgG positive NMOSD and each dose is based on the weight at the time of treatment.	Unresolved serious *Neisseria meningitidis* infection	Patients with any other systemic infection such as serious meningococcal and Neisseria species other than *Neisseria meningitidis* infections. IRR monitoring during infusion, interrupt for reactions, and institute appropriate supportive measures.	Blood cell count and differential WBCC.	Serious meningococcal infection and infections with other encapsulated bacteria, headache, IRR, back pain, pyrexia	Meningococcal vaccination at least 2 weeks before initiation.

SAT[78]	IL-6 receptor antagonist, effects seen after 12 to 24 weeks.	Loading dose: For the first 3 administrations is SC 120 mg at weeks 0, 2, and 4. Maintenance dose: SC 120 mg every 4 weeks. Missed/delayed dose management: **< 8 weeks during maintenance period** Administer SC 120mg as soon as possible and reset dosing schedule to every 4 weeks. **Loading period:** *Second loading dose is delayed or missed* Administer as soon as possible then 3rd and final loading 2 weeks later. *Third loading dose is delayed or missed* Administer as soon as possible and administer 1st maintenance dose 4 weeks later **8 weeks to < 12 weeks** 120 mg SC at 0 and 2 weeks followed by 120 mg every 4 weeks. **≥ 12 weeks** 120 mg SC at weeks 0, 2, and followed by 120 mg every 4 weeks	Known hypersensitivity to SAT or any of the inactive ingredients, active HBV infection, active or untreated latent TB.	Delay treatment in active infection until the infection is resolved, elevated liver enzymes, neutropenia.	HBV, TB and liver transaminase screening are required **before the first dose**. Before every dose determine if there is an active infection. Monitor ALT and AST levels during treatment; treatment interruption may be required. Monitor neutrophils counts during treatment.	Nasopharyngitis, headache, URTI, gastritis, rash, arthralgia, pain in the extremities, fatigue, nausea, injection-related reactions. Neutropenia, thrombocytopenia, liver enzymes elevation, hypertriglyceridemia, hypercholesterolemia, decrease in C3, C4 and fibrinogen. Immunogenicity may be present.	Vaccination with live or live-attenuated vaccines is not recommended during treatment. Administer all immunisations according to immunisation guidelines, and at least 4 weeks before initiation for live or live-attenuated vaccines and at least 2 weeks before initiation for non-live vaccines.

AE, adverse events; ALT, alanine transaminase; AST, aspartate aminotransferase; AQP4-IgG, aquaporin 4 immunoglobulin G positive; C3, complement component 3; C4, complement component 4; C5, complement component 5; CI, contraindications; ECU, eculizumab; FFP, fresh frozen plasma; HBV, hepatitis B virus; HGG, hypogammaglobulinemia; Ig, immunoglobulin; IL-6, interleukin 6; IMPDH, inosin monophosphate dehydrogenase; INEB, inebilizumab; IRR, infusion-related reaction; IV, intravenous; MOA, mechanism of action; NMOD, neuromyelitis optica disease syndrome; PLX, plasma exchange; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; RAV, ravalizumab; RTX, rituximab; SAT, satralizumab; SC, subcutaneous injection; TB, tuberculosis; URTI, upper respiratory tract infection; UTI, urinary tract infection; WBCC, white blood cell count.

Table 5. Off-label NMOSD therapies – mechanisms, dosing and safety considerations.

Drug name	MOA	Dose	CI	Precautions	Suggested monitoring	AEs	Vaccination
GC[37,79]	Suppression of inflammatory cytokines	For attacks/acute episodes: IV daily, 1000–2000 mg over 3–5 days. To taper: oral daily dose starting with 1 mg/kg/day or 20–30 mg/day, reduce to 10–15 mg in 2–3 weeks depending on the prescribed regimen. For long-term use: oral, 1x/day, individualised dose (ideally ≤7.5 mg/day).	Hypersensitivity to steroids or any component of the formulation.	Alternation of endocrine functions, infections, decrease bone density, cataracts, behavioural and mood disturbances. Calcium and vitamin D prophylaxis for GC doses ≥2.5 mg/day for >3 months.[80]	BP monitoring. With long-term use: fracture risk assessment, bone densitometry, eye examination, blood glucose, and CV monitoring Blood cell count and WBCC, liver enzymes, electrolytes, blood glucose. Use of GC in combination with PPIs and thrombosis prophylaxis.	Fluid retention, alteration in glucose tolerance, BP elevation, behavioural and mood changes, increased appetite, weight gain, lymphopenia, liver enzymes elevation.	Administration of live or live attenuated virus vaccines (with IS doses of corticosteroids) is contraindicated. Smallpox vaccines should not be given. May administer killed or inactivated vaccines.

AZA[37,79]	Purine analogue that inhibits the activation and differentiation of lymphocytes.	Initiation: 50mg daily, titrate upward 50 mg every 2–4 weeks to achieve peak dose of 2–3 mg/kg/day.	Hypersensitivity to AZA or any component of the formulation.	URTI, UTI and opportunistic infections. Drug-induced fever. Drug interactions including with allopurinol, anti-viral and anticoagulants. Photosensitisation (skin). Increased cancer risk with prolonged treatment (>10 years).	Blood cell count and differential WBCC, liver enzymes	Lymphocytopenia, pancytopenia, elevation of liver enzymes and GI side effects Myelosuppression (neutropenia, thrombocytopenia, and anaemia) in individuals with low or intermediate TPMT (thiopurine S-methyltransferase) activity or NUDT15 gene mutations.	Administration of live vaccines is not recommended during treatment.
MMF[37,79]	Inhibits the enzyme IMPDH.	Oral, 1000–2000 mg/day in 2 divided doses. May be up titrated to a maximum dose of 3000 mg/day in 2 divided doses.	Hypersensitivity to MMF, mycophenolic acid, mycophenolate sodium, or any component of the formulation. MMF should not be used in patients allergic to polysorbate 80. Pregnancy.	URTI, UTI and opportunistic infections. Increased cancer risk, teratogenic and embryotoxic effects.	Blood cell count and differential WBCC, liver enzymes. Regular screening for cancer (by dermatologist and gynaecologist).	Anaemia, elevation in liver enzymes, GI side effects, diarrhoea, leukopenia, sepsis, vomiting, opportunistic infection.	Live attenuated vaccines should be avoided.

RTX[37,79]	B-cell depletion within 4 weeks, full onset of action after 8–12 weeks.	IV with premedication (IV steroids, antipyretics, and antihistamines). Usual initial dose: 1000 mg at day 1 and day 15, followed by 500–1000 mg every 6 months.	Known type 1 hypersensitivity to murine proteins or any component of the formulation. Patients who have or have had PML or with severe active infections.	URTI, UTI and opportunistic infections (including PML), HBV reactivation, infusion-related pseudo-allergic reactions due to cell lysis, severe mucocutaneous reactions, leukopenia, neutropenia, late-onset neutropenia, and HGG.	During therapy: Differential WBCC. Serum Ig. CD19/20-positive B-cell counts:[81] • Baseline measurement: Before initiating therapy. • 1st follow-up: 1-3 months after administration to confirm adequate depletion. • Subsequently: Every 3-6 months to track B-cell recovery. IRRs (allergic). HBV test.	Nausea, exanthema, headache	Live virus vaccines is not recommended before or during treatment. Administer all immunisations according to immunisation guidelines, and at least 4 weeks before initiation for non-live vaccines.
TCZ [37,82,83]	IL-6 receptor antagonist	IV or SC 6-8mg/kg every 4-6 weeks.	Known hypersensitivity to TCZ or any component of the formulation.	Serious Infections – do not administer TCZ during an active infection, including localised infections. If a serious infection develops, interrupt TCZ until the infection is controlled. GI perforation—use with caution in patients who may be at increased risk. Neutropenia, thrombocytopenia, elevated liver enzymes, lipid abnormalities.	Laboratory monitoring is recommended due to potential consequence of treatment-related changes in neutrophils, platelets, lipids, and liver function tests.	Injection-related reactions, headache, serious infections, neutropenia, thrombocytopenia, elevated liver enzymes.	Avoid live vaccines during TCZ treatment. Administer all immunisations according to immunisation guidelines.

MTX[84,85]	Dihydrofolic acid reductase antagonist.	7.5–25 mg once weekly Folic acid/folinic acid should be given on non-MTX days to reduce its AEs.	Pregnancy, known hypersensitivity to MTX or any component of the formulation.	Serious infection, neurotoxicity, secondary malignancies, tumour lysis syndrome.	Blood cell counts, GI reactions, liver enzymes, renal profile.	Ulcerative stomatitis, leukopenia, nausea, abdominal distress, infection, malaise, fatigue, chills, fever, dizziness.	Administering live vaccines is not recommended. Administer all immunisations according to immunisation guidelines.

AE, adverse events; AZA, azathioprine; BP, blood pressure; CI, contraindications; CV, cardiovascular; GC, glucocorticoid; GI, gastrointestinal; HBV, hepatitis B virus; Ig, immunoglobulins; IL-6, interleukin 6; IMPDH, inosin monophosphate dehydrogenase; IRR, infusion-related reaction; IST, immunosuppression; IV, intravenous; MMF, mycophenolate mofetil; MOA, mechanism of action; MTX, methotrexate; PML, progressive multifocal leukoencephalopathy; RTX, rituximab; TCZ, tocilizumab; SC, subcutaneous injection; TB, tuberculosis; TLS, tumour lysis syndrome; URTI, upper respiratory tract infection; UTI, urinary tract infection; WBCC, white blood cell count.

Section 7: Use of biologics in pregnancy and during breastfeeding

Statement 7.1

- *Data on the use of ECU, RAV, INEB, TCZ or SAT in pregnancy and breastfeeding are limited; further research is needed to guide risk of teratogenicity, severe adverse events during pregnancy, and family planning treatment decisions in NMOSD patients.*

Statement 7.2

- *Available data suggest RTX may be used safely on a case-by-case basis before conception, during pregnancy, and while breastfeeding. However, contraception advice is important in all NMOSD patients in the reproductive age.*

These statements are in line with the NEMOS 2023 recommendations.[37] Women of reproductive age with AQP4-IgG–positive NMOSD should receive early pre-pregnancy counselling, including discussions on family planning and immunotherapy use during pregnancy.

- Treatment **should not be discontinued solely due to the intention to conceive.**
- The decision to continue therapy should be individualised, considering disease stability, the safety profile of each drug, and patient preference. Among the available options, RTX is generally preferred due to relatively greater safety data in pregnancy.[37]

Continuation of biologics such as ECU, RAV and TCZ **may be considered.**[86,87]

- If biologics are maintained during pregnancy, **close maternal and fetal monitoring for infections is essential.**
- In cases of anti–B-cell therapy exposure, umbilical cord blood B-cell levels should be measured, and timing of infant live vaccinations planned accordingly[37] due to risk of foetal B-cell depletion.

- Emerging case reports suggest that ECU and RAV may be viable options during pregnancy, with no adverse outcomes observed in the infants (Table 6).[86,88]

- These early findings are encouraging, though further studies and long-term safety data are needed.[86,87]

Table 6. Considerations when using ECU and RAV during pregnancy

Parameter	ECU	RAV
MOA	Inhibit terminal complement by binding to C5	
Infection risk	Higher risk of maternal infections with potential foetal impact	
Placental transfer	Cross placenta via Fc receptors especially in the 2nd and 3rd trimesters	
Potential foetal effects	• Preterm birth • Low birth weight • Foetal/neonatal death • Growth restriction	
Infusion frequency	Up to 20 infusions in pregnancy (biweekly dose)	Up to 5 infusions in pregnancy (8 weekly dose)
Infusion volume	Lower per dose	~3x higher per infusion
Cumulative volume	25% higher over pregnancy	Lower overall exposure
FDA adverse event reports in aHUS	4,919 total AEs; 93 pregnancy-related; 33 foetal effects	722 total AEs; 9 pregnancy-related; 1 foetal effect
Pregnancy data	>300 cases reported (manufacturer); no controlled trials; case-based outcomes generally favourable	Fewer cases, but similar maternal outcomes; no published collective report

AE, adverse event; aHUS, atypical haemolytic uraemic syndrome; C5, complement component 5; ECU, eculizumab; FDA, (United States) Food & Drug Administration; MOA, mechanism of action; RAV, ravalizumab. Adapted from the aHUS Alliance website.[89]

During lactation, monoclonal antibodies are considered viable as minimal amounts are transferred into breastmilk and further reduced by oral digestion. Though data remain limited, available reports suggest RTX and ECU may be safely used during breastfeeding.[90-93]

Section 8: Vaccination

Statement 8.1

- *AQP4-IgG–seropositive NMOSD patients should be up to date with all vaccinations before starting biologic therapies (ECU, RAV, INEB, SAT, RTX or TCZ) unless clinically contraindicated.*

Statement 8.2

- *Meningococcal vaccination guidance for AQP4-IgG–seropositive NMOSD patients receiving RAV or ECU should be clarified to help clinicians ensure coverage of all serogroups, appropriate booster scheduling, and timely reassessment of vaccination status.*

These statements are based on the NEMOS guidelines. Vaccinations should be updated according to national guidelines **prior to initiating biologic therapies, unless clinically contraindicated.**

- **Therapy should not be delayed** in patients with active disease due to incomplete vaccination status.
- Guidance on meningococcal vaccination for those receiving ECU or RAV should clarify serogroup coverage, booster schedules, and timing of reassessment. The United States Centers for Disease Control and Prevention recommends meningococcal vaccination against the different serotypes (MenACWY and MenB) for those on complement inhibitors, ideally, **two weeks before starting therapy.**
    - Patients can begin therapy before completing the vaccination, if delaying treatment poses a greater risk than contracting meningococcal disease.[94]
- Further research is needed to understand the impact of vaccinations on disease activity and immunisation response during long-term treatment.[37]

The vaccination schedule for AQP4-IgG–seropositive NMOSD patients should follow the Malaysian Guidelines for Adult Immunisation.[95]

Additional references also highlight the importance of updating vaccinations before starting biologic therapies such as ECU, RAV, INEB, SAT, RTX and TCZ (Table 7).[94,96-98]

Table 7. Pre-screens and vaccination for AQP4-seropositive NMOSD receiving biologic therapies

Vaccine/ screening	Biologic class (examples)	Required action	Minimum pre-treatment timing
Meningococcal (MenACWY & MenB)	Complement inhibitors (Eculizumab, Ravulizumab)	Mandatory vaccination against all serogroups (A, C, W, Y, B). Required lifelong boosters.	≥2 weeks prior to first dose.
Meningococcal (MenACWY & MenB)	B-Cell depleters, IL-6 Inhibitors (Rituximab, Inebilizumab, Satralizumab, Tocilizumab)	Recommended (Standard inactivated ACIP guidelines).	≥2 weeks prior to first dose.
Chickenpox (Varicella Zoster Virus)	All biologics (Live Vaccine)	Mandatory serology check. If seronegative, administer live-attenuated vaccine.	≥4 weeks prior to first dose.
Hepatitis B (Screening)	All biologics	Mandatory screening for HBsAg, anti-HBc, and anti-HBs.	Prior to initiation.
Hepatitis B (Vaccine for susceptible patients)	All biologics	If susceptible (all serology negative), administer inactivated Hepatitis B vaccine series.	≥2 weeks prior to first dose.

Influenza (Inactivated)	All biologics	Recommended annually (inactivated only; live nasal spray is contraindicated during treatment).	≥2 weeks prior to first dose (to optimize response).
Pneumocystis or Toxoplasma (Prophylaxis)	All biologics (Risk-Adapted)	Prophylaxis (typically Trimethoprim/sulfamethoxazole) is strongly recommended if using B-cell depleters and/or concomitant high-dose corticosteroids (≥20 mg/day for ≥4 weeks).	Initiated concurrently with or before high-risk treatment.

Minimum pre-treatment timing refers to the recommended interval between vaccine administration or screening and the initiation of biologic therapy to ensure optimal immunogenicity and safety. ACIP, Advisory Committee on Immunisation Practices; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; MenACWY, meningococcal conjugate vaccine (serogroups A, C, W, Y); MenB, meningococcal B vaccine.

Conclusion

The recommendations in this Malaysian consensus statement provides a comprehensive framework for the diagnosis and management of NMOSD, adapted to the local healthcare landscape. While grounded in international evidence and guidelines, the recommendations have been tailored to reflect the real-world clinical practice in Malaysia, including diagnostic access, and treatment availability. The consensus addresses critical aspects of NMOSD care ranging from clinical suspicion and differential diagnosis, through appropriate testing strategies for AQP4-IgG, to acute and long-term treatment, switching approaches, and patient monitoring.

Central to this statement is the recognition that AQP4-IgG serostatus is key in guiding diagnostic certainty and treatment strategies. Early diagnosis and timely treatment initiation are crucial to ensure good patient outcomes. The panel supports the use of approved biologics for AQP4-IgG–seropositive NMOSD and outlines recommendations for their initiation, switching, and potential combination with conventional ISTs. For resource-limited settings, guidance is also provided for the use of oral corticosteroids and conventional ISTs, with emphasis on gradual tapering and safety monitoring.

As new data emerge and local treatment options evolve, this consensus aims to serve as a practical reference for Malaysian clinicians managing NMOSD. Regular updates to integrate future advances and ensure alignment with both international best practices and the needs of local patients will be necessary. Its ultimate goal is to improve the quality and consistency of NMOSD care across Malaysia and to support equitable access to timely, accurate diagnosis and effective therapy.

Appendices

Appendix 1: Global Epidemiological Approximation of NMOSD

Prevalence	Ethnic Predisposition	Highest Recorded Prevalence
Varies wortdwide, ranging from <1 to >5 per 100,000 individuals depending on the population studied.	More common in populations of Asian and African descent compared with Caucasians.	The highest prevalence reported globally is in Martinique.

Global prevalence of NMOSD varies across regions and ethnic populations. Higher prevalence has been reported in Asian and African populations. The highest recorded prevalence worldwide has been reported in Martinique. Data approximated from Papp et al 2021;8 Tian et al. 2020;100 and Musubire et al. 2021.101

Appendix 2: The IPND NMOSD diagnostic criteria for adult patients

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. AQP4-IgG positivity with CBA
3. Exclude differential diagnoses*

Diagnostic criteria for NMOSD without AQP4-IgG or with unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring in a single or separate attacks and meeting ALL the following:
    a. At least 1 core clinical characteristic MUST BE optic neuritis, acute myelitis with LETM, OR area postrema syndrome
    b. Dissemination in space of ≥2 different core clinical characteristics
    c. Other additional MRI requirements where relevant
2. AQP4-IgG negativity with CBA or if testing is unavailable
3. Exclude differential diagnoses*

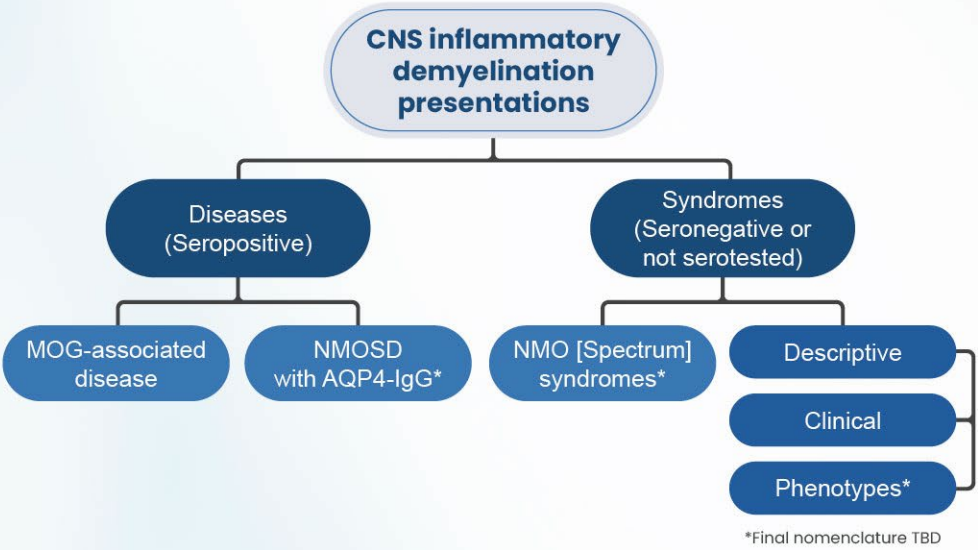
Core clinical characteristics are:

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome, i.e. unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Additional MRI requirements for NMOSD without AQP4-IgG or with unknown AQP4-IgG status	
Acute optic neuritis	Brain MRI with normal findings or only non-specific white matter lesions OR optic nerve MRI with T2-hyperintensive lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 the optic nerve length or optic chiasm involvement
Acute myelitis	An associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute myelitis
Area postrema syndrome	Associated dorsal medulla/area postrema lesions
Acute brainstem syndrome	Associated peripendymal brainstem lesions

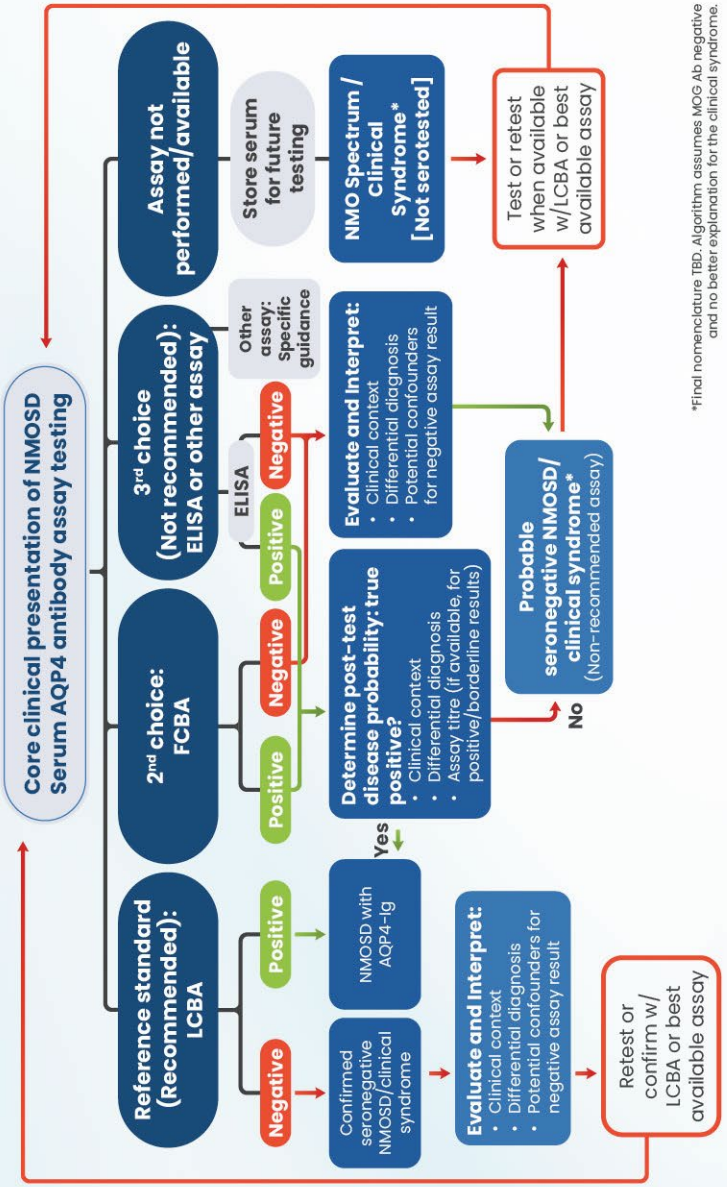
**See Table 2 for NMOSD red flags and section on considerations for AQP4-IgG serologic and other laboratory testing in the referenced article. [Wingerchuk 2015] AQP4, aquaporin-4; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis lesions; NMOSD, neuromyelitis optica spectrum disorders. Adapted from Wingerchuk et al. 2015.*[1]

Appendix 3: Proposed 2025 IPND algorithm for the classification of NMOSD



AQP4-IgG, aquaporin 4 immunoglobin G; CNS, central nervous system, MOG, myelin oligodendrocyte glycoprotein; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; TBD, to be determined.[10]

Appendix 4: Proposed 2025 IPND algorithm for APQ4 testing in diagnosing NMOSD



Ab, antibody; AQP4, aquaporin 4; AQP4-IgG, aquaporin 4 immunoglobin G; ELIZA, enzyme-linked immunosorbent assay; FCBA, fixed cell-based assay; LCBA, live cell-based assay; MOG, myelin oligodendrocyte glycoprotein; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; TBD, to be determined.[10]

Appendix 5: Summary of various symptomatic treatments for NMOSD

Symptoms	Suggested symptomatic treatments
Neuropathic pain and itch	• In early active lesions: Multi-drug anti-neuroinflammatory treatment such as minocycline, peroxisome proliferator-activated receptor agonist, cell cycle inhibitors, statins and progesterone. • Ketamine or memantine for NMDA receptor blockage. • Other neuropathic pain drugs include antiepiletics (gabapentin, pregabalin and levetiracetam), and SNRIs (duloxetine). • Subcutaneous BTXI into selected areas and ITB have been investigated in small populations. • Opioids may help but has conflicting efficacy data. • Non-pharmacological therapy using transcutaneous electrical nerve stimulation (Scrambler ST-5 TENS device).
Tonic spasms and involuntary movements	• Combination of antiepiletics (carbamazepine, oxcarbazepine, gabapentin, and/or pregabalin) with muscle relaxants (baclofen and/or tizanide). • BTXI or ITB. • Specifically for tonic spasms: Phenytoin, carbamazepine or oxcarbazepine appear to be more beneficial than gabapentin and muscle relaxants, though long-term therapy may be required. Additionally, antidepressants (venlafaxine or amitriptyline) has been used as second line therapy. • Carbamazepine resistance or intolerance may benefit from other medications such as topiramate, lacosamide and ITB. However, the evidence is derived from case reports.
Spasticity and muscle tone	• Oral antispasticity agents including baclofen and/or tizanidine. However, they may cause

abnormalities *(Evidence solely based on MS studies and clinical experience)*	sedation and interfere with motor function, or • Local BTXI to the affected areas, or • In patients with diffuse spasticity and intolerant to oral agents or resistant to oral agents at tolerable doses, ITB may be beneficial. • Combination of the above three approaches may be beneficial for some patients with severe spasticity and tonic spasms. • Muscle relaxants may worsen gait in patients with lower limb weakness, and is not recommended. • Non-pharmacological therapies as adjuvant to pharmacological treatment is essential. They include daily stretching, exercise and physical therapy.
Bladder dysfunction	• Non-pharmacological strategies such as bladder retraining, scheduling fluid intake and pelvic floor exercises. • Pharmacological treatment with anti-muscarinic medications or selective beta-3 adregenic receptor agonists is the standard therapy if non-pharmacological management is unsuccessful. These may be combined with desmopressin and clean intermittent self-catheterisation if post-void residual volume is elevated. • Sacral neuromodulation therapies may be beneficial if pharmacological treatment is not successful. • In patients refractory to all forms of treatment, a long-term indwelling catheter (urethral or suprapubic) may be considered. It will require strategies to reduce risk of infection and regular catheter replacement.
Bowel dysfunction	• Commonly, constipation is treated with dietary fibres, laxatives, stimulants and stool softeners. • Severe or complex dysfunction including faecal incontinence might be managed with sacral neuromodulation or posterior tibial nerve stimulation. • Patients with refractory dysfunction may require a colostomy.

Sexual dysfunction	• No specific treatment for sexual dysfunction in NMOSD. However, phosphodiesterase inhibitors may be beneficial for erectile dysfunction in men and sexual arousal disorder in women.
Fatigue	• Non-pharmacological strategies such as a detailed evaluation of modifiable causes of fatigue, adequate treatment of sleep disorders and depression. Additionally, discontinuing sedatives that are not needed or reducing their dose may be helpful. Beyond that light exercise can help alleviate fatigue. • Pharmacological options are amantadine, modafinil and methylphenidate that have shown some positive impact in clinical practice. However, a recent randomised placebo-controlled trial demonstrated that none of these medications influenced fatigue.
Sleep disorders	• Modafinil may be trialled in patients with symptomatic narcolepsy or excessive daytime sleepiness. • Sleep-time continuous positive airway pressure for patients with obstructive sleep apnoea can improve sleep quality and fatigue. • Restless leg syndrome following spinal attacks may be responsive to dopamine agonists or gabapentin.

BTXI, botulinum toxin injections; ITB, intrathecal baclofen; NMDA, N-methyl-D-aspartate; NMOSD, neuromyelitis optica spectrum disorder; SNRI, serotonin-noradrenaline reuptake inhibitor. Source Abboud H, et al. J Neurol. 2022.[25]

Appendix 6: Categorisation of NMOSD maintenance treatments by efficacy

High-efficacy treatments	RAV, ECU, INEB, RTX, SAT, TCZ
Low-to-moderate efficacy treatments	AZA, MMF, CYC, long-term OGCS, long-term intermittent IVIg, MTX

The categorisation of high-efficacy versus low to modest-efficacy treatments is based on the framework and definitions used in Li X, et al. Ann Clin Transl Neurol. 2025[36] that explored the different treatments in patients with seropositive AQP4 antibodies. The inclusion of complement C5 inhibitors (ECU and RAV) as high-efficacy treatments is supported by indirect evidence and class effect considerations.[31,36]

AQP4, aquaporin-4; AZA, azathioprine; C5, complement component 5; CYC, cyclophosphamide; ECU, eculizumab; INEB, inebilizumab; IVIg, intravenous immunoglobulin; OGCS, oral glucocorticosteroids; MMF, mycophenolate mofetil; MTX, methotrexate; RAV, ravulizumab; RTX, rituximab; SAT, satralizumab, TCZ, tocilizumab.

References

1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. Jul 14 2015;85(2):177-89. doi:10.1212/wnl.0000000000001729
2. Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. *Curr Opin Neurol*. Jun 2019;32(3):385-394. doi:10.1097/wco.0000000000000694
3. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med*. Aug 15 2005;202(4):473-7. doi:10.1084/jem.20050304
4. Jarius S, Wildemann B. An early case of neuromyelitis optica: on a forgotten report by Jacob Lockhart Clarke, FRS. *Mult Scler*. Nov 2011;17(11):1384-6. doi:10.1177/1352458511411758
5. Lucchinetti CF, Guo Y, Popescu BF, Fujihara K, Itoyama Y, Misu T. The pathology of an autoimmune astrocytopathy: lessons learned from neuromyelitis optica. *Brain Pathol*. Jan 2014;24(1):83-97. doi:10.1111/bpa.12099
6. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology*. Sep 22 1999;53(5):1107-14. doi:10.1212/wnl.53.5.1107
7. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*. Sep 2007;6(9):805-15. doi:10.1016/s1474-4422(07)70216-8
8. Papp V, Magyari M, Aktas O, et al. Worldwide Incidence and Prevalence of Neuromyelitis Optica: A Systematic Review. *Neurology*. Jan 12 2021;96(2):59-77. doi:10.1212/wnl.0000000000011153
9. Viswanathan S, Wah LM. A nationwide epidemiological study on the prevalence of multiple sclerosis and neuromyelitis optica spectrum disorder with important multi-ethnic differences in Malaysia. *Mult Scler*. Oct 2019;25(11):1452-1461. doi:10.1177/1352458518792430
10. Wingerchuk DM, Marignier R, Palace J, et al. IPND 2025: Revised Consensus Criteria, Classification, and Nomenclature for Neuromyelitis Optica Spectrum Disorders. Presented at ECTRIMS Congress; September 24-26, 2025; Barcelona, Spain. Late-Breaking Abstract P427.
11. Tisavipat N, Jitpratoom P, Siritho S, et al. Epidemiology and Burden of NMOSD, MS, and MOGAD in Thailand: a Population-Based Study. *Neurology*. 2022;99(23_Supplement_2):S34-S34. doi:doi:10.1212/01.wnl.0000903292.80558.d3
12. Tan K, Yeo T, Yong KP, et al. Central nervous system inflammatory demyelinating diseases and neuroimmunology in Singapore—Epidemiology and evolution of an emerging subspecialty. *Neurology and Clinical Neuroscience.* 2021;9(4):259-265. doi:https://doi.org/10.1111/ncn3.12479
13. Carnero Contentti E, Rotstein D, Okuda DT, Paul F. How to avoid missing a diagnosis of neuromyelitis optica spectrum disorder. *Mult Scler*. Jan 2025;31(1):8-22. doi:10.1177/13524585241292797
14. Carroll WM, Grisold W. World Federation of Neurology Needs Registry Survey 2021. *J Neurol Sci*. Oct 15 2024;465:123124. doi:10.1016/j.jns.2024.123124
15. Solomon AJ, Marrie RA, Viswanathan S, et al. Global Barriers to the Diagnosis of Multiple Sclerosis: Data From the Multiple Sclerosis International Federation Atlas of MS, Third Edition. *Neurology*. Aug 8 2023;101(6):e624-e635. doi:10.1212/wnl.0000000000207481
16. Hjerthen IG, Hacker CT, Pandit L, et al. 37. Underemployment, Work Hour Reduction, and Income Loss: A Global, Multi-centered, Cohort Study of Neuromyelitis Optica. *Multiple Sclerosis and Related Disorders*. 2024/12/01/ 2024;92:105998. doi:https://doi.org/10.1016/j.msard.2024.105998

17. Tkachuk V, Balbuena Aguirre ME, Alonso R, et al. Barriers to access and unmet needs to neuromyelitis optica spectrum disorders care in an Argentinean cohort. *Mult Scler Relat Disord*. Feb 2023;70:104485. doi:10.1016/j.msard.2022.104485
18. Jarius S, Aktas O, Ayzenberg I, et al. Update on the diagnosis and treatment of neuromyelits optica spectrum disorders (NMOSD) - revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part I: Diagnosis and differential diagnosis. *J Neurol*. Jul 2023;270(7):3341-3368. doi:10.1007/s00415-023-11634-0
19. Dugue A. The 2024 revised MacDonald Criteria: AAN 2025 highlights. *Neurol AMJ*. 2025;2(1):26-29. doi:10.33590/neurolamj/ZSFM1010
20. Montalban X, Lebrun-Frénay C, Oh J, et al. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. *The Lancet Neurology*. 2025;24(10):850-865. doi:10.1016/S1474-4422(25)00270-4
21. Jeyalatha MV, Therese KL, Anand AR. An Update on the Laboratory Diagnosis of Neuromyelitis Optica Spectrum Disorders. *J Clin Neurol*. Mar 2022;18(2):152-162. doi:10.3988/jcn.2022.18.2.152
22. Cacciaguerra L, Flanagan EP. Updates in NMOSD and MOGAD Diagnosis and Treatment: A Tale of Two Central Nervous System Autoimmune Inflammatory Disorders. *Neurol Clin*. Feb 2024;42(1):77-114. doi:10.1016/j.ncl.2023.06.009
23. Akaishi T, Misu T. Anti-aquaporin-4 antibody (AQP4-IgG) and anti-myelin oligodendrocyte glycoprotein antibody (MOG-IgG) in the cerebrospinal fluid. *Neural Regen Res*. May 2024;19(5):949-950. doi:10.4103/1673-5374.385293
24. Borisow N, Mori M, Kuwabara S, Scheel M, Paul F. Diagnosis and Treatment of NMO Spectrum Disorder and MOG-Encephalomyelitis. *Front Neurol*. 2018;9:888. doi:10.3389/fneur.2018.00888
25. Abboud H, Salazar-Camelo A, George N, et al. Symptomatic and restorative therapies in neuromyelitis optica spectrum disorders. *J Neurol*. Apr 2022;269(4):1786-1801. doi:10.1007/s00415-021-10783-4
26. Schindler P, Aktas O, Ringelstein M, et al. Glial fibrillary acidic protein as a biomarker in neuromyelitis optica spectrum disorder: a current review. *Expert Rev Clin Immunol*. Jan 2023;19(1):71-91. doi:10.1080/1744666x.2023.2148657
27. Haramati A, Rechtman A, Zveik O, Haham N, Brill L, Vaknin-Dembinsky A. IL-6 as a marker for NMOSD disease activity. *J Neuroimmunol*. Sep 15 2022;370:577925. doi:10.1016/j.jneuroim.2022.577925
28. Solomon JM, Paul F, Chien C, Oh J, Rotstein DL. A window into the future? MRI for evaluation of neuromyelitis optica spectrum disorder throughout the disease course. *Ther Adv Neurol Disord*. 2021;14:17562864211014389. doi:10.1177/17562864211014389
29. Holian AH, Weinshenker BG. Emerging Role of Targeted Monoclonal Antibodies in Neuromyelitis Optica Spectrum Disorders. *BioDrugs*. Jul 2025;39(4):573-589. doi:10.1007/s40259-025-00729-x
30. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet*. Oct 12 2019;394(10206):1352-1363. doi:10.1016/s0140-6736(19)31817-3
31. Pittock SJ, Barnett M, Bennett JL, et al. Ravulizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. *Ann Neurol*. Jun 2023;93(6):1053-1068. doi:10.1002/ana.26626
32. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. *New England Journal of Medicine*. 2019;381(7):614-625. doi:doi:10.1056/NEJMoa1900866
33. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol*. May 2020;19(5):402-412. doi:10.1016/s1474-4422(20)30078-8
34. Yamamura T, Kleiter I, Fujihara K, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. *N Engl J Med*. Nov 28 2019;381(22):2114-2124. doi:10.1056/NEJMoa1901747

35. Sen S, Tuncer A, Terzi M, et al. Severe disease reactivation in seropositive neuromyelitis optica spectrum disorders patients after stopping eculizumab treatment. *Mult Scler Relat Disord*. Nov 2023;79:104949. doi:10.1016/j.msard.2023.104949
36. Li X, Xue B, Li J, et al. High-Efficacy Treatment in Neuromyelitis Optica Specturm Disorder Patients With Seropositive AQP4 Antibodies-A Real-World Study. *Ann Clin Transl Neurol*. Oct 2025;12(10):1983-1991. doi:10.1002/acn3.70128
37. Kümpfel T, Giglhuber K, Aktas O, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) - revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: Attack therapy and long-term management. *J Neurol*. Jan 2024;271(1):141-176. doi:10.1007/s00415-023-11910-z
38. Cobo-Calvo Á. 2025 diagnostic criteria for NMOSD: implications for double seronegative cases. Presented at ECTRIMS Congress; September 24-26, 2025; Barcelona, Spain. Available at: https://www.neurologylive.com/view/evolving-approaches-seronegative-nmosd-new-diagnostic-criteria-lvaro-cobo-calvo. Accessed January 2026.
39. Ramirez AD, Romero R. Eculizumab Therapy in a Seronegative Patient with NMOSD: A Case Report (P10-14.009). *Neurology*. 2024;102(7_supplement_1):3707. doi:doi:10.1212/WNL.0000000000205329
40. Anderson M, Levy M. Advances in the long-term treatment of neuromyelitis optica spectrum disorder. *J Cent Nerv Syst Dis*. 2024;16:11795735241231094. doi:10.1177/11795735241231094
41. Vishnevetsky A, Kaplan TB, Levy M. Transitioning immunotherapy in neuromyelitis optica spectrum disorder – when and how to switch. *Expert Opinion on Biological Therapy*. 2022/11/02 2022;22(11):1393-1404. doi:10.1080/14712598.2022.2145879
42. Apóstolos-Pereira SLD, Damasceno A, Piccolo AC, et al. 2025 Brazilian guidelines for the management of neuromyelitis optica spectrum disorder in adults and children. *Arq Neuropsiquiatr*. Nov 2025;83(11):1-21. doi:10.1055/s-0045-1812471
43. Okuda DT, Moog TM, McCreary M, Cook K, Burgess KW, Smith AD. Treatment transitions in neuromyelitis optica spectrum disorder increase risk for disease advancement. *Mult Scler Relat Disord*. Nov 2023;79:105041. doi:10.1016/j.msard.2023.105041
44. Zhou J, Yang X, Wang X, et al. Immunotherapy for neuromyelitis optica spectrum disorder: a comparative analysis of efficacy and safety of azathioprine, mycophenolate mofetil, tacrolimus, and rituximab. *Front Neurol*. 2025;16:1559118. doi:10.3389/fneur.2025.1559118
45. Paul F, Marignier R, Palace J, et al. International Delphi Consensus on the Management of AQP4-IgG+ NMOSD: Recommendations for Eculizumab, Inebilizumab, and Satralizumab. *Neurol Neuroimmunol Neuroinflamm*. Jul 2023;10(4)doi:10.1212/nxi.0000000000200124
46. Aungsumart S, Youngkong S, Dejthevaporn C, et al. Efficacy and safety of monoclonal antibody therapy in patients with neuromyelitis optica spectrum disorder: A systematic review and network meta-analysis. *Front Neurol.* 2023;14:1166490. doi:10.3389/fneur.2023.1166490
47. Wingerchuk DM, Fujihara K, Palace J, et al. Long-Term Safety and Efficacy of Eculizumab in Aquaporin-4 IgG-Positive NMOSD. *Ann Neurol.* Jun 2021;89(6):1088-1098. doi:10.1002/ana.26049
48. Palace J, Wingerchuk DM, Fujihara K, et al. Benefits of eculizumab in AQP4+ neuromyelitis optica spectrum disorder: Subgroup analyses of the randomized controlled phase 3 PREVENT trial. *Mult Scler Relat Disord.* Jan 2021;47:102641. doi:10.1016/j.msard.2020.102641
49. Novi G, Bovis F, Sciolla C, et al. Long-Term Effectiveness and Safety of Rituximab in Neuromyelitis Optica Spectrum Disorder: A 5-Year Observational Study. *CNS Drugs.* Jul 2025;39(7):693-705. doi:10.1007/s40263-025-01191-7

50. Tahara M, Oeda T, Okada K, et al. Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. Apr 2020;19(4):298-306. doi:10.1016/s1474-4422(20)30066-1
51. Isobe N, Oda T, Yamaguchi T, et al. Incidence and Risk Factors for Serious Infections in Patients with Neuromyelitis Optica Spectrum Disorder: A Claims Database Study in Japan. *Neurology and Therapy.* 2025/07/17 2025;doi:10.1007/s40120-025-00794-y
52. Kim SH, Park NY, Kim KH, Hyun JW, Kim HJ. Rituximab-Induced Hypogammaglobulinemia and Risk of Infection in Neuromyelitis Optica Spectrum Disorders: A 14-Year Real-Life Experience. *Neurol Neuroimmunol Neuroinflamm.* Sep 2022;9(5)doi:10.1212/nxi.0000000000001179
53. Yin Z, Qiu Y, Duan A, et al. Different monoclonal antibodies and immunosuppressants administration in patients with neuromyelitis optica spectrum disorder: a Bayesian network meta-analysis. *J Neurol.* Jun 2023;270(6):2950-2963. doi:10.1007/s00415-023-11641-1
54. Akaishi T, Takahashi T, Fujihara K, et al. Early Treatment Initiation With Oral Prednisolone for Relapse Prevention Alleviates Depression and Fatigue in Aquaporin-4-Positive Neuromyelitis optica Spectrum Disorder. *Front Neurol.* 2021;12:608149. doi:10.3389/fneur.2021.608149
55. Demuth S, Collongues N. Disease-modifying treatments for neuromyelitis optica spectrum disorder in the context of a new generation of biotherapies. *Rev Neurol (Paris).* Jan-Feb 2025;181(1-2):42-51. doi:10.1016/j.neurol.2024.01.008
56. McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. High Risk for Invasive Meningococcal Disease Among Patients Receiving Eculizumab (Soliris) Despite Receipt of Meningococcal Vaccine. *MMWR Morb Mortal Wkly Rep.* Jul 14 2017;66(27):734-737. doi:10.15585/mmwr.mm6627e1
57. Breu M, Glatter S, Höftberger R, et al. Two Cases of Pediatric AQP4-Antibody Positive Neuromyelitis Optica Spectrum Disorder Successfully Treated with Tocilizumab. *Neuropediatrics*. Jun 2019;50(3):193-196. doi:10.1055/s-0039-1684004
58. Bichuetti DB, Perin MMM, Souza NA, Oliveira EML. Treating neuromyelitis optica with azathioprine: 20-year clinical practice. *Mult Scler.* Jul 2019;25(8):1150-1161. doi:10.1177/1352458518776584
59. Hayes MTG, Adam RJ, McCombe PA, Walsh M, Blum S. Long-term efficacy and safety of rituximab in the treatment of neuromyelitis Optica Spectrum disorder. *Mult Scler J Exp Transl Clin.* Apr-Jun 2024;10(2):20552173241257876. doi:10.1177/20552173241257876
60. Ongphichetmetha T, Jitprapaikulsan J, Siritho S, Rattanathamsakul N, Detweeratham T, Prayoonwiwat N. Efficacy and safety of rituximab in multiple sclerosis and neuromyelitis optica spectrum disorder. *Sci Rep.* Feb 12 2024;14(1):3503. doi:10.1038/s41598-024-53838-y
61. Songwisit S, Kosiyakul P, Jitprapaikulsan J, Prayoonwiwat N, Ungprasert P, Siritho S. Efficacy and safety of mycophenolate mofetil therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. *Sci Rep.* Oct 7 2020;10(1):16727. doi:10.1038/s41598-020-73882-8
62. Carreón Guarnizo E, Hernández Clares R, Castillo Triviño T, et al. Experience with tocilizumab in patients with neuromyelitis optica spectrum disorders. *Neurologia (Engl Ed).* Apr 2022;37(3):178-183. Experiencia con tocilizumab en pacientes con espectro de la neuromielitis óptica. doi:10.1016/j.nrl.2018.12.013
63. Wang Y, Zhao M, Yao M, et al. Tocilizumab treatment in neuromyelitis optica spectrum disorders: Updated meta-analysis of efficacy and safety. *Mult Scler Relat Disord.* Dec 2023;80:105062. doi:10.1016/j.msard.2023.105062
64. Zhang C, Zhang M, Qiu W, et al. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. *Lancet Neurol.* May 2020;19(5):391-401. doi:10.1016/s1474-4422(20)30070-3

65. Connelly-Smith L, Alquist CR, Aqui NA, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. *J Clin Apher.* Apr 2023;38(2):77-278. doi:10.1002/jca.22043
66. Abboud H, Petrak A, Mealy M, Sasidharan S, Siddique L, Levy M. Treatment of acute relapses in neuromyelitis optica: Steroids alone versus steroids plus plasma exchange. *Mult Scler.* Feb 2016;22(2):185-92. doi:10.1177/1352458515581438
67. Kleiter I, Gahlen A, Borisow N, et al. Apheresis therapies for NMOSD attacks: A retrospective study of 207 therapeutic interventions. *Neurol Neuroimmunol Neuroinflamm.* Nov 2018;5(6):e504. doi:10.1212/nxi.0000000000000504
68. Viswanathan S, Wong AH, Quek AM, Yuki N. Intravenous immunoglobulin may reduce relapse frequency in neuromyelitis optica. *J Neuroimmunol.* May 15 2015;282:92-6. doi:10.1016/j.jneuroim.2015.03.021
69. Kessler RA, Mealy MA, Levy M. Treatment of Neuromyelitis Optica Spectrum Disorder: Acute, Preventive, and Symptomatic. *Curr Treat Options Neurol.* Jan 2016;18(1):2. doi:10.1007/s11940-015-0387-9
70. Kim W, Kim HJ. An update on biologic treatments for neuromyelitis optica spectrum disorder. *Expert Review of Clinical Immunology.* 2023/01/02 2023;19(1):111-121. doi:10.1080/1744666X.2023.2151441
71. Wang L, Liu K, Tan X, et al. Remedial Effect of Intravenous Cyclophosphamide in Corticosteroid-Refractory Patients in the Acute Phase of Neuromyelitis Optica Spectrum Disorder-Related Optic Neuritis. *Front Neurol.* 2020;11:612097. doi:10.3389/fneur.2020.612097
72. Bennett JL, Fujihara K, Saiz A, et al. Long-Term Efficacy and Safety of Satralizumab in Patients With Neuromyelitis Optica Spectrum Disorder From the SAkuraMoon Open-Label Extension Study. *Neurol Neuroimmunol Neuroinflamm.* Sep 2025;12(5):e200450. doi:10.1212/nxi.0000000000200450
73. Marignier R, Pittock SJ, Paul F, et al. AQP4-IgG-seronegative patient outcomes in the N-MOmentum trial of inebilizumab in neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord.* Jan 2022;57:103356. doi:10.1016/j.msard.2021.103356
74. Digala L, Katyal N, Narula N, Govindarajan R. Eculizumab in the Treatment of Aquaporin-4 Seronegative Neuromyelitis Optica Spectrum Disorder: A Case Report. *Front Neurol.* 2021;12:660741. doi:10.3389/fneur.2021.660741
75. Inebilizumab. Prescribing information. Available at: https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/uplizna/uplizna_fpi_english.pdf.
76. Alexion Pharmaceuticals Inc. SOLIRIS® (Eculizumab) prescribing information. 2019.
77. Ravulizumab-CWVZ. Prescribing information. Available at: https://alexion.us/-/media/alexion_global/documents/regulatory/north-america/usa/2024/english/ultomiris_uspi.pdf.
78. Satralizumab-MWGE. Prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761149s000lbl.pdf.
79. Clinical Neurophysiology Neuromuscular Section. Myasthenia gravis (MG): Malaysian consensus statement (1st edition). 2025. Available at: https://www.neuro.org.my/assets/guideline/Myasthenia%20Gravis%20(MG).pdf.
80. Malaysian Osteoporosis Society; Ministry of Health Malaysia; Academy of Medicine Malaysia. Clinical Practice Guidelines: Management of Osteoprosis. 3rd edition. 2022.
81. Praxis Medical Insights. Management of patients taking rituximab. Available at: https://praxismed.org/article/8567fe17-76ab-4ee0-b7fb-ac7db025cc57?z=358283. Accessed January 2026.
82. Hao Q, Grobelna A. Tocilizumab for Neuromyelitis Optica Spectrum Disorder: CADTH Health Technology Review [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2023 Mar. Available from: https://www.ncbi.nlm.nih.gov/books/NBK596339/.

83. Actemra (Tocilizumab). Highlights of Perscribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf. Accessed November 2025.
84. Methotrexate. Highlights of Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/040054s015,s016,s017.pdf. Accessed November 2025.
85. Papadopoulos MC, Bennett JL, Verkman AS. Treatment of neuromyelitis optica: state-of-the-art and emerging therapies. *Nat Rev Neurol.* Sep 2014;10(9):493-506. doi:10.1038/nrneurol.2014.141
86. Jacob A, Mahmoud A, Eldweik L, Mubashir A. Transplacental transfer of ravulizumab in a pregnant woman with neuromyelitis optica: a case report. *BMJ Neurol Open.* 2025;7(2):e001286. doi:10.1136/bmjno-2025-001286
87. Ladha P, Amatya S, Kagzi Y, et al. Pregnancy Outcomes in Neuromyelitis Optica Spectrum Disorder: A Meta-Analysis of Pharmacotherapeutic Agents (P11-8.020). *Neurology.* 2025;104(7_Supplement_1):2004.
88. Tommaso G, Damiano P, Pietro I. Eculizumab treatment during pregnancy in a patient with AQP4-IgG-seropositive NMOSD: A case report. *Mult Scler.* Apr 2025;31(5):615-617. doi:10.1177/13524585241283648
89. aHUS Alliance. Pregnancy exposure impact: eculizumab and ravulizumab. Available at: https://www.ahusallianceaction.org/pregnancy-exposure-impact-eculizumab-and-ravulizumab/?utm_source=chatgpt.com. Accessed October 2025.
90. Ciplea AI, Langer-Gould A, de Vries A, et al. Monoclonal antibody treatment during pregnancy and/or lactation in women with MS or neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm.* Jul 2 2020;7(4)doi:10.1212/nxi.0000000000000723
91. Krysko KM, LaHue SC, Anderson A, et al. Minimal breast milk transfer of rituximab, a monoclonal antibody used in neurological conditions. *Neurol Neuroimmunol Neuroinflamm.* Jan 2020;7(1)doi:10.1212/nxi.0000000000000637
92. LaHue SC, Anderson A, Krysko KM, et al. Transfer of monoclonal antibodies into breastmilk in neurologic and non-neurologic diseases. *Neurol Neuroimmunol Neuroinflamm.* Jul 2020;7(4)doi:10.1212/nxi.0000000000000769
93. Kelly RJ, Höchsmann B, Szer J, et al. Eculizumab in Pregnant Patients with Paroxysmal Nocturnal Hemoglobinuria. *New England Journal of Medicine.* 2015;373(11):1032-1039. doi:doi:10.1056/NEJMoa1502950
94. Center for Disease Control and Prevention (US). Vaccines & Immunizations: Altered immunocompetence. Available at: https://www.cdc.gov/vaccines/hcp/imz-best-practices/altered-immunocompetence.html. Accessed October 2025.
95. Malaysian Society of Infectious Diseases and Chemotherapy. Guidelines for Adults Immunisation. Available at: https://adultimmunisation.msidc.my/wp-content/uploads/2023/11/AIG-3rd-edition-2023.pdf. Accessed October 2025.
96. Centers for Disease Control and Prevention (US). Clinical guidance for managing meningococcal disease risk in patients receiving complement inhibitor therapy. Available at: https://www.cdc.gov/meningococcal/hcp/clinical-guidance/complement-inhibitor.html. Accessed October 2025.
97. Araujo-Neto JM, Guimarães GS, Fernandes FF, Soares MA. Hepatitis B Surface Antibody (Anti-HBs) Kinetics during Rituximab Chemotherapy and Performance of Hepatitis B Vaccine before Immunosuppression: Two Prospective Studies. *Viruses.* Aug 15 2022;14(8)doi:10.3390/v14081780
98. Gomes A, Feo LB, Silva GD, et al. Reducing infection risk in multiple sclerosis and neuromyelitis optica spectrum disorders: a Brazilian reference center's approach. *Arq Neuropsiquiatr.* Oct 2022;80(10):1057-1066. Redução do risco de infeção em esclerose múltipla e doença do espectro neuromielite óptica: abordagem de um centro de referência brasileiro. doi:10.1055/s-0042-1754348

Note: References 99-101 were added at a later stage during the development of this document and therefore do not reflect the original sequential order of the reference list.

99. Mayo Clinic Laboratories. CNS demyelinating disease. Available at: https://news.mayocliniclabs.com/neurology/demyelinating-disease/cns-demyelinating-disease/. Accessed March 2026.

100. Tian DC, Li Z, Yuan M, et al. Incidence of neuromyelitis optica spectrum disorder (NMOSD) in China: a national population-based study. *Lancet Regional Health - Western Pacific*. 2020;2:100021.

101. Musubire AK, Derdelinckx J, Reynders T, et al. Neuromyelitis optica spectrum disorders in Africa: a systematic review. *Neurol Neuroimmunol Neuroinflamm*. 2021;8:e1089.

"Sustained, integrated informed action, not just awareness, changes lives. Together for NMOSD, we turn uncertainty into clarity, isolation into community, and knowledge into actionable hope and impact., so that no Malaysian patient has to face this journey alone."

Puan Nadirah, President, Malaysian Rare Disease Society.

The Malaysian Consensus Statements for the Diagnosis and Management of NMOSD Development Committee would like extend their gratitude to Dr Lim Su Yin, Consultant Neurologist and Senior Lecturer, School of Medicine, Faculty of Health and Medical Sciences, Taylors Univeristy, Malaysia, for reviewing this document.