GUIDELINES

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Update on diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) — recommendations of Section of Multiple Sclerosis and Neuroimmunology of Polish Neurological Society

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Abstract

Introduction. An expert panel of the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society has developed principles for the management of neuromyelitis optica spectrum disorders (NMOSD). These principles are based on expert opinion and data from the literature published up to May 2023. Recommendations were developed based on the results of the most recent clinical trials, guidelines of foreign and international scientific societies, and the authors' clinical experience.

Clinical implications. The principles for diagnosing NMOSD are discussed, with particular emphasis on serological and neuroimaging diagnosis. Recommendations for the treatment of relapses and chronic immunosuppressive treatment, including the most recent methods of immunotherapy, are also presented. Additionally, the principles of monitoring treatment efficacy and safety are included. Therapy regimens are completed with recommendations for symptomatic treatment. The paper also includes an algorithm for vaccination in patients with NMOSD. Therapeutic management in pregnant women with NMOSD is discussed.

Keywords: recommendations, diagnosis and treatment, neuromyelitis optica spectrum disorders, NMOSD

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are rare autoimmune conditions of the central nervous system (CNS) characterised by inflammatory demyelination, axonal loss and astrocytopathy that lead to the occurrence of pathological lesions within the optic nerves, brain and spinal cord. This condition was first described in the late 19th century.

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However, the relationship between neuromyelitis optica (NMO) and multiple sclerosis (MS) was debated for many decades [1–8]. Researchers and clinicians long considered NMO to be a subvariant of MS. It was not until the discovery of anti-aquaporin-4 antibody (AQP4-IgG) specific to this nosological entity that this syndrome was considered a separate disease. Serum AQP4-IgG is recognised as a diagnostic biomarker and is found in most patients (≥ 80%) with the NMO phenotype [9].

The diagnostic criteria for NMOSD were devised in 2015 (Tab. 1) [10]. Despite the defined diagnostic criteria, early and adequate diagnosis of NMOSD remains challenging in clinical practice. Particular diagnostic problems are related to seronegative cases that require detailed differential diagnosis, which is also sometimes difficult due to the lack of diagnostic biomarkers to differentiate heterogeneous conditions with the same NMOSD phenotype. Serum antibodies against myelin oligodendrocyte glycoprotein (MOG-Ab) are found in some NMOSD patients seronegative for AQP4-IgG [9–19]. Notwithstanding this, anti-MOG antibodies may be associated with a clinical presentation different from that typical of NMOSD.

The development of diagnostic and therapeutic principles is an urgent necessity, as new molecules with the potential to alter the prognosis of NMOSD have emerged in recent years [20–27].

To date, expert recommendations have been developed on a national (e.g. in Germany, USA, and Canada) and international scale (e.g. in Central and South America) [8, 28–35]. Our recommendations summarise the experience of the team specialising in MS and NMOSD and working within the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society.

Diagnosis of NMOSD

NMOSD should be suspected in patients who have experienced clinical involvement of at least one of the following structures: optic nerve, spinal cord, area postrema, brainstem, or diencephalon [9]:

1) diagnosis is based on fulfilling the diagnostic criteria proposed by the international panel of experts chaired by Wingerchuk in 2015 (Tab. 1) [10]
2) management varies according to the serostatus of AQP4-IgG. In the population of patients with negative or unknown AQP4-IgG serostatus, both clinical and radiological criteria must be fulfilled (via a typical image of the spinal cord and/or brain on magnetic resonance imaging, MRI) [8, 28, 31–34]
3) differential diagnosis should primarily exclude MS and diseases with a similar clinical picture (Tab. 2–3) [8, 11, 16–18, 30, 32, 36–38]
4) patients with suspected NMOSD should be diagnosed in a centre with experience in diagnosing and treating demyelinating inflammatory diseases of the central nervous system.

Serological diagnosis of NMOSD

Serum AQP4-IgG titres should be determined in patients with symptoms suggestive of NMOSD. Negative results may be related to the NMOSD phenotype with a different pathomechanism (other unidentified antibodies) or to the low sensitivity of the diagnostic methods. Cell-based assays (CBAs) are the recommended diagnostic methods. Enzyme-linked immunosorbent assays (ELISA) are less sensitive — a positive ELISA result does not need to be confirmed, while a negative ELISA result should be confirmed by CBAs [40–44].

Serological testing should be performed in patients before steroid treatment and plasma exchange. However, this should not delay treatment. Note that false negative results can occur. The samples should be secured for testing before treatment. In the case of negative serological test results for AQP4-IgG in a patient with typical NMOSD symptoms, the test should be repeated 3–6 months after the first determination.

Serum AQP4-IgG testing should be performed in the case of symptoms suggestive of NMOSD, such as optic neuritis, myelitis, or area postrema syndrome, in patients diagnosed with a systemic disease (e.g. systemic lupus erythematosus, Sjögren's syndrome) [8, 36–41].

A comprehensive differential diagnosis should be performed in patients with symptomatology typical of NMOSD with imaging findings (MRI) suggestive of MS (Tables 2 and 3). Serum MOG-Ab titres should be determined using CBAs in patients with symptomatology suggestive of NMOSD in whom anti-AQP4 antibodies are not detected using CBAs.

MOG antibody-associated disease (MOGAD) is diagnosed based on the criteria developed by Jarius et al. [21]. New diagnostic criteria have recently been proposed [22]. The diagnosis of MOGAD should be considered in patients with symptomatology similar to that of the NMO spectrum (optic neuritis, myelitis, brainstem encephalitis, or encephalitis) in whom AQP4-IgG is not detected (Fig. 1) [18, 21].

Neuroimaging diagnosis of NMOSD

In NMOSD, MRI should be performed according to a standard and reproducible protocol applied in the diagnostic process and follow-up of the disease course and activity. Neuroimaging studies should be performed in reference centres, using at least 1.5 T MRI according to the protocol for MS patients with extended imaging. The 2015 diagnostic criteria are still valid (Tab. 1) [8, 10, 45]. A brain MRI should

Table 1. NMOSD diagnostic criteria for adult patients (from Wingerchuk et al. 2015 [10]; with the authors' permission)

Diagnostic criteria for NMOSD with AQP4-IgG
1. At least one core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
a. At least one core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
b. Dissemination in space (two or more different core clinical characteristics)
c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method
3. Exclusion of alternative diagnoses
Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise 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 and NMOSD with unknown AQP4-IgG status
1. Acute optic neuritis: requires brain MRI showing
a. normal findings or only nonspecific white matter lesions, OR
b. optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over > 1/2 optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥ 3 contiguous segments (LETM) OR ≥ 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

AQP4 — aquaporin-4; IgG — immunoglobulin G; AQP4-IgG — anti-aquaporin-4 antibody; LETM — longitudinally extensive transverse myelitis lesions; NMOSD — neuromyelitis optica spectrum disorders

Table 2. Comparison between AQP4-IgG-positive NMOSD, MOGAD and MS (modified from Jarius et al., 2023; Carnero Contentti et al., 2023; Kim et al., 2017 [8, 23, 38])

	NMOSD	MOGAD	MS
Prevalence/mln	12	20	1,342
Incidence/mln	2	3.4	68
Age at onset	mostly adults, mean age at onset – 40	often children, young adults	adults, mean age at onset – 30
Sex (F:M)	9:1	1:1	3:1
Other antibodies or autoimmune disorders	30–50%	not so often, anti-NMDAR encephalitis	not so often
Optic neuritis	bilateral or unilateral severely impaired visual acuity at onset posterior part, longitudinally extensive lesions, often optic chiasm involvement	bilateral or unilateral severely impaired visual acuity at onset anterior part, longitudinally extensive lesions, often oedema of optic disc	typically unilateral mild to moderately impaired visual acuity at onset, short optic nerve lesions
Myelitis	severe deficit 85% LETM (cervical and thoracic spinal cord); involvement of central part	severe deficit at onset usually LETM (cervical and thoracic spinal cord), conus; 40% STM; grey matter involvement forming an H-sign	mild or moderate deficit at onset usually STM, typically affects periphery of spinal cord along dorsal or lateral columns
Area postrema	20%	rare	never
Recovery after a relapse	risk for poor recovery	usually good recovery	usually good recovery
Course	relapsing	monophasic or relapsing	relapsing, secondary progressive, or primary progressive
Oligoclonal bands	10–20%	10–20%	> 90%

LETM — longitudinally extensive transverse myelitis; STM — short transverse myelitis; NMOSD — neuromyelitis optica spectrum disorders; MOGAD — MOG antibody-associated disease; MS — multiple sclerosis; NMDAR — anti-N-methyl-D-aspartate receptor

Table 3. Diseases mimicking NMOSD (based on [8, 38])

Diagnosis	Symptoms suggestive of diagnosis	Diagnostic examinations
Autoimmune inflammatory		
Acute disseminated encephalomyelitis (ADEM)	**clinical:** • fever, meningeal syndrome, convulsions, alteration in consciousness • age < 18 years • history of infection preceding disease **radiological:** • simultaneous enhancement of many lesions on MRI after contrast administration • lesions within basal ganglia	no specific differential tests • note abnormalities on MRI (see opposite column) • follow-up of clinical and radiological evolution over time
Systemic lupus erythematosus (SLE)	**clinical:** • nephropathy • arthritis • facial erythema • haematological disorders (anaemia)	• serum antinuclear antibodies (ANA) • serum anti-ds-DNA-antibodies
Sjögren's syndrome	**clinical:** • keratoconjunctivitis sicca and xerostomia, especially in presence of another autoimmune connective tissue disease (mostly rheumatoid arthritis) • polyneuropathy or myopathy	anti-Ro (SS-A) and/or anti-La (SS-B)
Behçet's disease	**clinical:** • oral and genital ulcers • uveitis **radiological:** • lesions within basal ganglia	
Neurosarcoidosis	**clinical:** • uveitis • optic and facial nerve involvement • polyneuropathy or multiple mononeuropathy **radiological:** • focal changes in lungs (X-ray, CT) • meningeal enhancement on MRI after contrast administration • simultaneous enhancement of many lesions on MRI after contrast administration	chest X-ray or CT • assessment of serum angiotensin-converting enzyme (ACE) and cerebrospinal fluid (CSF) • gallium scintigraphy of whole body • FDG-PET • ENG • biopsy
Autoimmune GFAP astrocytopathy	fever, myelitis, meningitis, encephalitis, involuntary movements, psychosis, seizures, sphincter disorders, hyponatremia	• GFAP-IgG in CSF • in CSF, pleocytosis and elevated protein concentration • on MRI, linear radial perivascular enhancement after contrast administration; periventricular • paraneoplastic syndrome (ovarian tumour — teratoma) in 20–25%
Neoplasms		
Meningeal carcinomatosis	symptoms of meningeal irritation, headache, nausea, vomiting, impaired consciousness, behavioural changes, balance disorders, speech disorders, radicular pain	• linear meningeal enhancement on MRI • immunophenotyping of cerebrospinal fluid cells
Lymphomas	headache, impaired consciousness, behavioural changes, focal symptoms	• significant radiological variability (MRI) • immunophenotyping of cerebrospinal fluid cells
Paraneoplastic		
Encephalitis associated with collapsin response mediator protein 5 (CRMP5)	psychotic disorders, polyneuropathy, dysautonomia	• anti-CRMP5 antibodies (anti-CV2 antibodies) • small cell lung cancer
Metabolic		
Vitamin B12 deficiency	**clinical:** • concomitant polyneuropathy • gastrointestinal symptoms • megaloblastic anaemia **radiological:** • in cases of myelopathy, typical thoracic spinal cord involvement (posterior funiculi) with hyperintense lesions on T2 and FLAIR sequences, often with atrophy on MRI	• determination of serum B12 vitamin • in borderline levels of serum B12 concentrations, levels of methylmalonic acid (MMA) and homocysteine should be determined • intrinsic factor antibodies • Schilling test

→

Table 3 cont. Diseases mimicking NMOSD (based on [8, 38])

Diagnosis	Symptoms suggestive of diagnosis	Diagnostic examinations
Genetic		
Adrenomyeloneuropathy	**clinical:** • concomitant polyneuropathy **radiological:** • symmetrical periventricular lesions	• VLCFA assessment • genetic testing • ENG
Hereditary spastic paraplegia	progressive spastic paraparesis of lower limbs, sphincter disorders	• genetic testing • brain and spinal cord MRI
Hereditary Leber optic neuropathy	slow, painless loss of vision, possibility of abnormal colour discrimination and impaired pupillary response to light	• genetic testing

ADEM — acute disseminated encephalomyelitis; MRI — magnetic resonance imaging; CT — computed tomography; ANA — antinuclear antibodies; SLE — systemic lupus erythematosus; anti-ds-DNA-antibodies — anti-(double stranded)-DNA antibodies; GFAP-IgG — glial fibrillary acidic protein immunoglobulin G; CRMP5 — collapsin response mediator protein 5; FDG-PET — fluorodeoxyglucose-positron emission tomography; MMA — methylmalonic acid; VLCFA — very long chain fatty acids; ENG — electroneurography

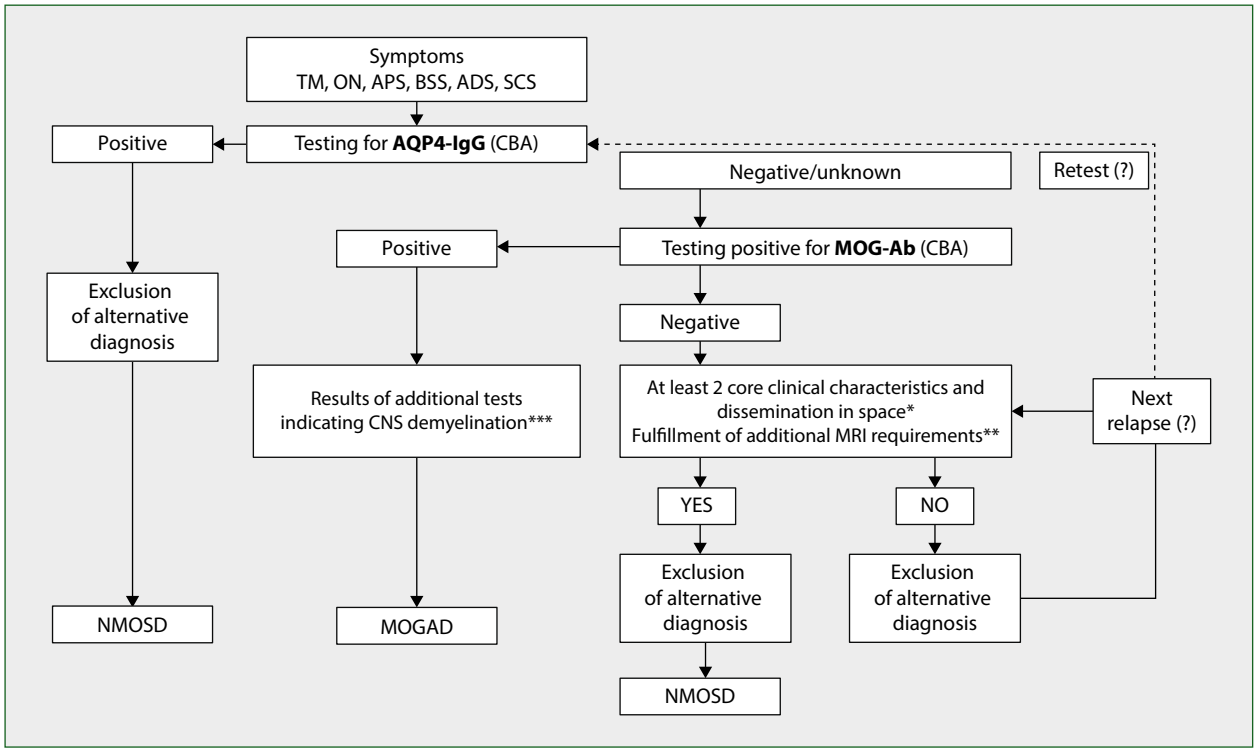

Figure 1. Diagnostic algorithm for neuromyelitis optica spectrum diseases (NMOSD). ON — optic neuritis; TM — transverse myelitis; LETM — longitudinally extensive transverse myelitis; APS — area postrema syndrome; BSS — brainstem syndrome; ADS — acute diencephalic syndrome; SCS — symptomatic cerebral syndrome; AQP4-IgG — anti-aquaporin-4 antibody; MOG-Ab — antibodies against myelin oligodendrocyte glycoprotein; MOGAD — MOG antibody associated disease; *at least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of following requirements: ON, TM with LETM or APS; dissemination in space (two or more different core clinical characteristics); **according to Table 1; ***MRI or electrophysiological test results (VEP in patients with isolated ON)

be performed before and after contrast administration to differentiate between NMOSD and MS. Although most lesions are not typical of MS, some 10-20% of patients fulfill the radiological Barkhof criteria.

An MRI scan of the spinal cord should be performed in patients with suspected NMOSD before and after contrast administration. This should include at least two segments of the spinal cord (i.e. cervical and thoracic). In the acute phase of the disease, the presence of longitudinally extensive transverse myelitis (LETM) typical of NMOSD is often reported. LETM includes lesions extending the length of three or more vertebral segments. In short-segment myelitis (STM), defined as spinal cord lesions extending fewer than three vertebral segments and a normal brain MRI or MRI not meeting the MS criteria, AQP4-IgG should be tested and a follow-up spinal MRI should be considered [23, 46–50].

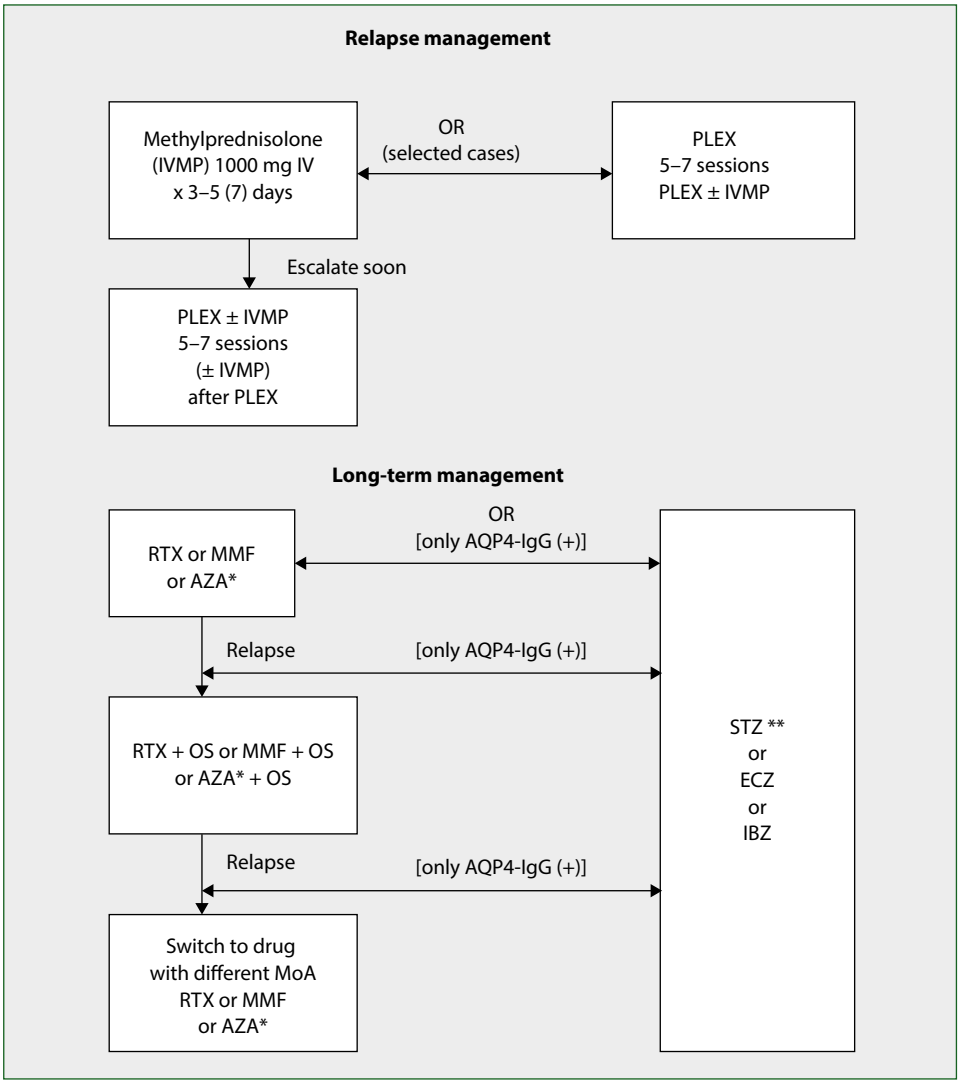

Figure 2. Recommended treatment algorithm for acute and long-term management for patients with NMOSD. IV — intravenous; PLEX — plasma exchange; IVIG — intravenous immunoglobulins; AZA — azathioprine; OS — oral steroids; AQP4-IgG — anti-aquaporin-4 antibody; STZ — satralizumab; ECZ — eculizumab; IBZ — inebilizumab; MoA — mechanism of action; *recommended if rituximab (RTX) or/and mycophenolate mofetil (MMF) is unavailable; **available in Poland in drug programme reimbursed by National Health Fund (NFZ, Narodowy Fundusz Zdrowia) since 2022

In patients with optic neuritis and suspected NMOSD, orbital MRI, including T1-weighted sequences before and after contrast administration, should be taken into consideration. MRI shows extensive (more than half of the nerve) unilateral or bilateral optic nerve involvement and/or involvement of the optic chiasm typical of NMOSD [47–49].

Treatment of NMOSD

Recommendations for relapse management

The mainstay of treatment of NMOSD relapses includes methylprednisolone intravenous — *i.v.* (1g/d for 3–5 days, in some cases up to seven days) and/or plasma exchange (PLEX) (Fig. 2) [31, 32]. Oral steroid therapy should be continued with gradual dose tapering, depending on the severity of the relapse. Severe relapses should be treated with PLEX as the first-line treatment. Plasmapheresis is also used in patients who did not previously respond to methylprednisolone *i.v.* [33, 51–54]. An algorithm for treatment with PLEX is given in Table 6. In addition, administration of polyvalent immunoglobulins *i.v.* should be considered (Fig. 2) [33, 34, 55].

Recommendations for chronic immunosuppressive treatment

Please note that the following recommendations do not apply to MOGAD.

Table 4. Recommended immunosuppressive therapy in long-term management for seronegative and seropositive patients with neuromyelitis optica spectrum disorders (NMOSD) (modified from [29, 33, 57–60])

Medication and dosage	Mechanism of action	Most common and important side effects	Recommendations and comments
Oral steroids (OS) ***methylprednisolone/prednisone*** • **Relapse managemen** • **methylprednisolone** *i.v.* 1,000 mg/d; 3–5 (max 7) days with oral tapering • **Bridging therapy** (start of therapy with AZA/MMF/RTX) **prednisone** or equivalent (OS) 1mg/kg once daily for 3–6 mo. + AZA/MMF or 1–2 mo. + RTX; then slow tapering over 3–6 mo. • **Add-on therapy** (in case of suboptimal response to AZA/MMF) **prednisone** or equivalent (OS) 5–10 mg once daily	binding to intracellular receptors → modulation of gene transcription; anti-inflammatory and immunosuppressive	infections, weight gain, oedema, hyperglycaemia, hypertension, gastric irritation, insomnia, psychosis, rash, avascular necrosis of hip, cushingoid appearance	could be used during pregnancy
Azathioprine (AZA) target dose: 2.5–3 g/kg/daily in divided doses; *p.o.* • **inpatient**: start 25mg daily and then increase by 25 mg daily • **outpatient**: start 25 mg daily and then increase by 50 mg weekly	inhibits purine synthesis resulting in inhibition of DNA, RNA and protein synthesis; T- and B--lymphocyte apoptosis	infections, diarrhoea, vomiting, elevated LEs, rash, hypersensitivity, increased risk of malignancy depending on therapy duration (lymphoma, skin cancers and other cancers), bone marrow suppression	AZA is recommended if MMF or RTX is unavailable AZA should be combined with OS until its full effect (at least 6 months) lymphopenia (< 500–1,000/μL) or an elevated MCV (at least 5 points from baseline) is a useful marker of adequate dose TPMT activity and metabolites could help to monitor use of AZA AZA could be used during pregnancy
Mycofenolate mofetil (MMF) Target dose: 750–1,500 mg twice daily (median dose: 1,000 mg, twice a day), *p.o.* • Start at 500 mg twice a day for 1–2 weeks and then increase to 1,000 mg twice a day	prodrug of mycophenolic acid, an inhibitor of inosine-5′— monophosphate dehydrogenase → interference with proliferation of T- and B- lymphocytes	leukopenia, diarrhoea, vomiting, sepsis, increased risk of malignancy (lymphoma, skin cancers and other cancers), teratogenicity, reports on development of progressive multifocal leukoencephalopathy (PML) (not in NMOSD)	MMF should be combined with OS until its full effect (at least 4–6 months) lymphocyte count should decrease to 1,000–1,500/μL, following a plasma trough level of 1–2 μg/mL is a useful marker of adequate dose
Rituximab (RTX) drug given *i.v.* following premedication: clemastine *i.v.* + paracetamol (acetaminophen) *i.v.* + methylprednisolone *i.v.* • **Induction therapy:** — 1 g with retreatment at 2 weeks — 100 mg with retreatment at 2 weeks — 375 mg/m^2 *i.v.* once weekly for 4 weeks — 100 mg *i.v.* once weekly for 3 weeks • **maintenance therapy with fixed time intervals:** — 1 g *i.v.* every 6 mo. — 375mg/m^2 *i.v.* every 6 mo. • **maintenance therapy based on lymphocyte CD19(+) or CD27(+) count:** 1 g *i.v.* or 100 mg *i.v.* or 375 mg/m^2 *i.v.* when — CD19(+) count: > 0.01% x 10^9/L or > 0.1% of total lymphocytes; > 0.5% PBMC or — CD27(+) count: > 0.05% PBMC in first 2 years and then > 0.1% PBMC	chimeric monoclonal antibody against human CD20	minor infections (urinary and respiratory tract), non-serious infusion-related reactions, HBV and TBC reactivations	RTX + OS until its full effect (at least 1–2 mo) Monitoring B cells [CD19(+)/CD20(+)/CD27(+)] could be useful to plan retreatment RTX could be used during pregnancy or overlapping syndrome (NMOSD and MS) In severe hypogammaglobulinaemia (< 150 μg/dl) and/or frequent or severe infections with IgG levels between 150 and 300 μg/dl supplementation of IVIg 400 mg/kg every 4 weeks targeting a serum level > 800–1,000 μg/dl is recommended

OS — oral steroids; *i.v.* — intravenous; mo — month/s; AZA — azathioprine; MMF — mycophenolate mofetil; RTX — rituximab; PBMC — peripheral blood mononuclear cells; MCV — mean corpuscular volume; TPMT — thiopurine methyltransferase; MS — multiple sclerosis; IgG — immunoglobulin G; IVIg — intravenous immunoglobulins; DNA — deoxyribonucleic acid; RNA — ribonucleic acid; LEs — liver enzymes (aspartate aminotransferase and alanine aminotransferase); HIV — human immunodeficiency virus; HBV — hepatitis B virus; VZV — varicella zoster; TBC — tuberculosis; ECG — electrocardiogram; HAHA — Human Anti-human Antibody

Table 5. Recommended registered therapy in long-term management for seropositive patients with neuromyelitis optica spectrum disorders [NMOSD AQP4-IgG (+)] (modified from [8, 26–29])

Medication and dosage	Mechanism of action	Most common and important side effects	Recommendations and comments
Eculizumab (ECZ) **Intravenous *(i.v.)*** 900 mg weekly during the first 4 doses starting on day 1, followed by 1,200 mg every 2 weeks starting at week 4	humanised monoclonal antibody, which inhibits complement protein C5 → inhibition of terminal complement cascade	minor infections (respiratory tract, nasopharyngitis and urinary), non-serious infusion-related reactions, increased risk of meningococcal and encapsulated bacterial infections	efficacy and safety obtained in PREVENT trial (randomised, placebo-controlled time-to-event trial in AQP4-IgG-positive NMOSD patients); All NMOSD patients must receive meningococcal vaccination 14 days prior to first dose of ECZ
Satralizumab (STZ)* **Subcutaneous (SC)** 120 mg at weeks 0, 2 and 4 and then every 4 weeks	humanised anti-interleukin 6 receptor (IL-6R) monoclonal antibody type IgG2	minor infections, non-serious infusion-related reactions	Data from pooled analysis from two phase III, randomised, double-blind, placebo-controlled studies in + and - AQP4-IgG NMOSD patients; Sakura-Sky was an add-on therapy study (STZ with AZA, MMF or OS); Sakura-Start was a monotherapy study
Inebilizumab (IBZ) **Intravenous (*i.v.*)** 300 mg in 2 doses on days 1 and 15 and then 3,000 mg every 6 mo.	humanised monoclonal antibody against CD19	minor infections (urinary and respiratory tract), non-serious infusion-related reactions, arthralgia	efficacy and safety obtained in N-MOmentum study (double blind, randomised placebo-controlled phase II/III trial in (+) and (-) AQP4-IgG NMOSD patients)
Tocilizumab (TCZ) **Intravenous (IV)** 8 mg/kg every 4 weeks	humanised monoclonal antibody against interleukin-6 receptor (IL-6R)	anaemia, non-serious infusion-related reactions, infections (TBC, opportunistic), elevated LEs, hypertension	efficacy and safety obtained in TANGO (randomised, open-label, parallel-group study comparing TCZ vs AZA in (+) and (-)AQP4-IgG NMOSD patients) TCZ could be considered in pregnant women with severe NMOSD

*available in Poland in drug programme reimbursed by National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*) since 2022; SC — subcutaneous; AZA — azathioprine; MMF — mycophenolate mofetil; OS — oral steroids; ECZ — eculizumab; *i.v.* — intravenous; AQP4-IgG — anti-aquaporin-4 antibody; LEs — liver enzymes (aspartate aminotransferase and alanine aminotransferase); TBC — tuberculosis; IL-6R — interleukin-6 receptor

Table 6. Principles of PLEX procedure at Department of Neurology, Medical University of Warsaw

- 5–7 PLEX sessions every other day (it is possible to perform first two sessions day by day)
- during each PLEX session, c.110% of plasma volume should be exchanged (equivalent of 50–55 ml plasma/kg)
- 3.5% solution of human albumin as replacement fluid is recommended. It is also possible to use frozen plasma
- continuous vital signs monitoring, including blood pressure and ECG during PLEX session
- laboratory tests: complete blood count, albumin level, electrolytes determined before and c.4 hours (or next day depending on session schedule) after each PLEX session
- if a coagulation profile is checked, a decreased level of fibrinogen or extended APTT with no clinical signs of haemorrhagic diathesis are not contraindications to PLEX session
- following last PLEX session, removal of central vein catheter and sending it for bacteriological testing is recommended

Once NMOSD is diagnosed, chronic treatment should be started as early as possible to reduce the risk of relapse because in NMOSD each relapse is associated with a high risk of irreversible neurological deficits [31, 32]. The recommended types of immunotherapy in NMOSD (Tab. 4–5) [24, 29, 36, 56–60] are as follows:

I. drugs used in seropositive and seronegative NMOSD:
— non-selective immunosuppressants, such as:
  - azathioprine (AZA)
  - mycophenolate mofetil (MMF)
  - long-term oral corticosteroids or combination therapy (immunosuppressants + corticosteroids)
— monoclonal antibody: *i.v.* cycles of rituximab (RTX) also in combination therapy [29–33, 58]

II. drugs used in seropositive NMOSD in which the following antibodies show high efficacy (they can be used as the first-line treatment):
— eculizumab (ECZ) *i.v.* as monotherapy
— inebilizumab (IBZ) *i.v.* as monotherapy
— satralizumab (STZ) *s.c.* as monotherapy or combination therapy with other immunosuppressive drugs (e.g. corticosteroids, AZA, or MMF) [27–34].

Monitoring treatment of NMOSD

In chronically treated patients, the effectiveness of therapy should be monitored by clinical evaluation (assessment

Table 7. Pharmacological options for symptomatic therapy in NMOSD (modified from [30, 61])

Symptomatic therapy	Indications	Common daily dosage	Side effects
Anticonvulsants			
Gabapentin	neuropathic pain	300–3,600 mg	dizziness, drowsiness, fatigue, falls
Pregabalin	tonic spasms	50–300 mg	dizziness, drowsiness, fatigue, falls
Carbamazepine	neuropathic pain	100–1,200 mg	dizziness, drowsiness, nausea, vomiting, ataxia, hyponatremia, agranulocytosis, skin rash
Oxcarbazepine	tonic spasms	150–1,200 mg	
Levetiracetam	neuropathic pain	250–1,000 mg	irritability, agitation, drowsiness
	tonic spasms		
	neuropathic pain		
	tonic spasms		
	neuropathic pain		
Muscle relaxants			
Oral baclofen	spasticity	50–80 mg	sedation, dizziness, drowsiness, nausea, vomiting, urinary retention
Tizanidine	tonic spasms	2–36 mg	sedation, dizziness, drowsiness, nausea, liver injury
Botulinum toxin injections	spasticity,	50–300 units	focal weakness, dysphagia, dry mouth, urinary retention (depending on site of injection)
	tonic spasms		
	focal spasticity or dystonia		
	overactive bladder		
	tonic spasms		
	neuropathic pain		
Antidepressants			nausea, somnolence, hypertension, liver injury, serotonin syndrome
Duloxetine	neuropathic pain	30–120 mg	
Venlafaxine	depression and anxiety	37.5–225 mg	nausea, somnolence, hypertension, liver injury, serotonin syndrome
Amitriptyline	neuropathic pain	12.5–150 mg	sedation, dry mouth, constipation
	depression and anxiety		
	neuropathic pain		
	depression and anxiety		
Medications for bladder dysfunction	overactive bladder	5–30 mg	dry mouth, constipation, urinary retention, cognitive decline
Oxybutynin		7.5–15 mg	
Darifenacin		5–10 mg	
Solifenacin			
Mirabegron	overactive bladder	25–50 mg	hypertension, constipation, urinary retention

of relapse rates, progression of disability) and periodic MRI of the brain and/or spinal cord with the frequency depending on clinical condition [31–33].

Symptomatic treatment

Immune-modulating therapies for relapse prevention of NMOSD have evolved rapidly over the past few years. However, a significant unmet need is the determination of best practice related to chronic symptomatic management [30, 61]. Chronic symptoms have a profound effect on a patient's quality of life. Pharmacological options for symptomatic therapy in NMOSD are set out in Table 7.

Specific situations of patients with NMOSD

Disease activity in NMOSD can be increased in the postpartum period, but, unlike in MS, also appears to be increased during pregnancy. Furthermore, obstetric complications, including miscarriage and preeclampsia, may also commonly occur in patients with NMOSD. Therefore, stabilisation of the disease before conception is recommended [61, 62]. Several case series have reported an elevated relapse risk during pregnancy compared to the prepartum period, which can result in an accumulation of disability [63, 64]. Moreover, pregnancy-related hyperemesis gravidarum, severe nausea, or vomiting may be confused with area postrema syndrome (NMOSD-associated

Table 8. Therapies for patients with NMOSD and pregnancy[a, b] (modified from [62])

Therapy	Length of washout period per label	Length of washout period per pharmacokinetic/ /pharmacodynamic placental transfer and potential risksc	Characteristics
Azathioprine (AZA)	no recommendations	continuation during pregnancy could be considered	reassuring safety data across case series for various indications
Mycophenolate mofetil (MMF)	6 weeks	6 weeks	embryotoxicity, pregnancy loss
Rituximab (RTX) anti-CD20 (IgG1)	6 months (FDA) 12 months (EMA)	2 months; could be continued if maternal benefits outweigh potential foetal risks	intermediate half-life but prolonged biological activity after administration; reassuring emerging safety data with pregnancy exposures; consider checking newborn B cells and lymphocytes
Satralizumab (STZ) anti-IL6R (IgG2)	no recommendations	2 months	in monkeys treated during pregnancy, no adverse effects on maternal animals or foetal development, however, some neonatal immune concerns
Inebilizumab (IBZ) anti-CD19 (IgG1)	6 months (FDA) 12 months (EMA)	2 months; could be continued if maternal benefits outweigh potential foetal risks	intermediate half-life but prolonged biological activity after administration; consider checking newborn B cells and lymphocytes
Eculizumab (ECZ) IgG2/4 kappa anti-C5 antibody	no recommendations	2 months; could continue if maternal benefits outweigh potential foetal risks	reassuring safety data for infants of women with paroxysmal nocturnal haemoglobinuria treated during pregnancy
Tocilizumab (TCZ) anti-IL6R (IgG1)	no recommendations	3 months	abortifacient and embryotoxic, possible delayed delivery in monkeys treated during pregnancy; in humans, possible increased risk of miscarriage, preterm birth, and lower birth weight in women with rheumatoid arthritis but potentially confounded by methotrexate comedication

IgG — immunoglobulin G; a — treatments reviewed in Wallach et al. [70]; b — pregnancy data reviewed in Mao-Draayer et al. [71]; c — washout refers to period during which drug has to be stopped before conception attempts can begin

symptoms of intractable nausea, vomiting, or hiccups) [61]. If new neurological symptoms arise and doubt exists about their nature, an MRI without gadolinium should be obtained [65]. During pregnancy, short courses of glucocorticoids are generally considered safe. Methylprednisolone, prednisone, and prednisolone are preferred in pregnancy, as they do not enter the foetal circulation. In contrast,c.80% of a maternal dose of dexamethasone can cross the placenta into the foetal circulation unmetabolised [56, 66]. Either PLEX or intravenous immunoglobulins (IVIG) can be used in NMOSD for steroid-resistant relapses. IVIG (0.4 g/kg/d) is preferred in pregnancy because of lower risks of circulatory instability (such as maternal hypotension, which potentially can result in decreased placental perfusion and foetal oxygenation) [67, 68]. Therefore, when PLEX is chosen, maintaining an adequate maternal intravascular volume by saline infusions during the procedure is essential. In the second or third trimester, the patient should lay on her left side to avoid compression of the inferior vena cava by the gravid uterus [67, 68]. Recommendations for immunosuppressive therapies in relation to pregnancy are set out in Table 8 [70, 71].

In NMOSD, infection, vaccination and therapies interact with each other, and these interactions need to be managed to minimise the risk of infection and maximise the benefits of vaccination. Vaccinations that reduce the risk of infection have been shown to stabilise the course of the disease. Some therapies alter the course, increase the risk of specific infections, and affect the efficacy of vaccinations. The effects of vaccination depend on various factors, including the vaccination type (live attenuated or inactivated) or the patient's vaccination history (primary vaccination, revaccination, or booster vaccination). The effects of these factors can also be influenced by a variety of patient-specific characteristics, including age, sex, comorbidities, immune status, or co-medication and drug interactions (Tab. 9) [72–76].

Table 9. Suggested intervals between immunotherapies and vaccinations (modified from [72–76])

Main mechanism of action	Drug	Interval from vaccine to treatment (weeks)		Live vaccine during therapy permitted	Interval from treatment to live vaccine
		Inactivated vaccine	Live vaccine		
Direct depletion or cytolysis	Rituximab (RTX)	> 4	> 4	No	12 months + normal B cell count
	Inebilizumab (IBZ)	> 4	> 4	No	After B cell repletion
Impairment of cell proliferation	Azathioprine (AZA)	2–4	4	No	> 3 months
	Mycophenolate mofetil (MFM)	2–4	> 4–6	No	> 2 months
Pleiotropic effects	Tocilizumab (TCZ)	4[a]	4	No	Not studied
	Satralizumab (STZ)	2–4	4	No	Not studied
	Eculizumab (ECZ)	2–4	4	Not advised	Not studied
	Glucocorticosteroids[b]	0	0	Yes	None
	Glucocorticosteroids[b] for > 2 weeks	2–4	4	No	> 2 months
	IVIg	2–4	2–4	Yes	> 3 months (diminished response to measles vaccine up to one year)
	PLEX	2–4	2–4	Not advised	None

Information based on prescribing information and [1–4]. IVIg — intravenous immunoglobulin; [a] — where possible, shorter intervals can lead to reduced immune response. If shorter intervals are unavoidable, testing for antibody responses to vaccination and/or additional vaccination might be necessary; [b] — equivalent to < 20 mg prednisolone daily

Conclusions

The diagnosis and treatment of NMOSD continue to be challenges that require specific clinical experience. The diagnosis should be made according to the 2015 criteria. Immune therapy of NMOSD is undergoing dynamic changes related to the registration of new generation drugs, i.e. monoclonal antibodies with different mechanisms of action and high efficacy in inhibiting disease progression, mainly in patients with anti-AQP4 antibodies [24–27, 30–33].

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