REVIEW OPEN ACCESS

Review of the Longitudinal Management of Autoimmune Encephalitis, Potential Biomarkers, and Novel Therapeutics

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Abstract

Purpose of Review

Increasing awareness and earlier diagnosis of autoimmune encephalitis (AE) have led to a greater number of patients being cared for longitudinally by neurologists. Although many neurologists are now familiar with the general approach to diagnosis and acute immunosuppression, this review aims to provide neurologists with guidance related to management beyond the acute phase of disease, including long-term immunosuppression, monitoring, potential biomarkers of disease activity, outcome measures, and symptom management.

Recent Findings

Observational studies in AE have demonstrated that early diagnosis and treatment is associated with improved neurologic outcomes, particularly in AE with antibodies targeting neuronal cell surface/synaptic proteins. The literature regarding long-term management is evolving. In addition to traditional immunosuppressive approaches, there is emerging use of novel immunosuppressive therapies (ISTs) in case series, and several randomized controlled trials are planned. Novel biomarkers of disease activity and methods to measure outcomes and response to treatment are being explored. Furthermore, it is increasingly recognized that many individuals have chronic symptoms affecting quality of life including seizures, cognitive impairment, fatigue, sleep disorders, and mood disorders, and there are emerging data supporting the use of patient centered outcome measures and multidisciplinary symptom-based care.

Summary

This review aims to summarize recent literature and offer a practical approach to long-term management of adult patients with AE through a multidisciplinary approach. We summarize current knowledge on ISTs, potential biomarkers of disease activity, outcome measures, and long-term sequelae. Further research is needed to answer questions regarding optimal IST, biomarker validity, and sequelae of disease.

Introduction

There have been significant advances in the recognition and diagnosis of autoimmune encephalitis (AE), aided by the discovery of diagnostic autoantibody biomarkers. Observational studies have demonstrated that patients benefit from early administration of immunosuppressive therapy (IST), which improves acute symptoms and limits disability accrual.[1] Increased recognition of AE has contributed to the development of a standardized approach to diagnosis and acute treatment.[2] However, although neurologists are encountering and

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managing acute AE more frequently, many remain less familiar with longitudinal management.

Many patients with AE receive IST and therapeutic monitoring beyond the acute setting, although few studies have examined the efficacy of this practice.[3] Although there are no evidence-based biomarkers available to date, emerging research is encouraging, and there are several clinical tools available to measure outcomes. Most patients experience chronic symptoms that affect quality of life (including seizures, cognitive impairment, fatigue, sleep disorders, and mood disorders), which require multidisciplinary symptom-based care.[4] In this article, we aim to present a practical stepwise approach to longitudinal management of adult patients with AE.

Diagnosis of AE

A diagnosis of AE should be considered in patients presenting with subacute neurocognitive symptoms (developing over weeks to months). Typical features include encephalopathy/cognitive dysfunction and seizures (which are often refractory).[5,6]

Additional features may include dysautonomia, movement disorders, sleep disorders, and neuropsychiatric symptoms.[7-10] Diagnostic criteria for AE require the presence of key clinical manifestations in addition to supportive paraclinical testing, including the presence of diagnostic neural antibodies in the CSF or serum, inflammatory CSF (pleocytosis, elevated protein, and/or intrathecal antibody production), and MRI features (most commonly temporal lobe FLAIR/T2 hyperintensity).[5] It is important to exclude alternative etiologies of encephalopathy including metabolic, infectious, and nutritional causes. The CSF should be evaluated for infectious etiologies including herpes simplex virus, varicella zoster virus, and enteroviruses. For patients in whom the MRI demonstrates unilateral temporal lobe abnormalities, it is also important to consider malignancy (e.g., gliomas or lymphoma) or sequelae of recent seizure activity. It may also be appropriate to evaluate for genetic conditions in the pediatric/adolescent population or neurodegenerative disorders when cognitive decline is more gradual.[11,12]

In cases where an identified neural autoantibody (NAA) has a strong paraneoplastic association, or where the patient has risk factors (increased age, smoking history, or personal/family history of cancer), additional malignancy screening should be undertaken. Testing considerations include CT of the chest/abdomen/pelvis, PET-body, mammogram, and testicular/pelvic ultrasound (where appropriate). At a minimum, age-appropriate cancer screening is advised. If a patient is diagnosed with a high-risk paraneoplastic syndrome and a malignancy is not identified during initial evaluation, cancer surveillance should be repeated every 6–12 months for at least 3–5 years (though data supporting frequency/duration of screening are lacking).[13,14]

Acute IST

IST is the mainstay of acute AE management. First-line IST typically includes IV corticosteroids, IV immunoglobulin (IVIg), and plasma exchange (PLEX). These treatments can be used sequentially or in combination. Some studies suggest that treatment with PLEX and corticosteroids yields better outcomes than corticosteroids alone.[15.] There is limited data comparing first-line agents.[16,17] Regardless of IST choice, prompt initiation of treatment is an important factor in obtaining favorable outcomes.[1,18]

Preimmunosuppression Evaluation

Before initiation of IST, it is essential to screen for latent infections (particularly hepatitis B/C and tuberculosis), varicella zoster (to ensure immunity), and HIV.[19] It is also necessary to obtain a complete blood count (CBC), liver function tests (LFTs), and renal function testing to screen for the presence of baseline cytopenias, liver, and/or renal dysfunction, respectively. In women of childbearing age, pregnancy screening should be performed. It is important to evaluate any medical comorbidities before treatment, including hemodynamic instability, heart failure, thrombotic conditions, active malignancy, and diabetes, which allow for risk stratification/mitigation in certain scenarios (e.g., thrombosis with IVIg or hyperglycemia with corticosteroids).[16,20] Pretreatment laboratory studies and long-term monitoring recommendations for commonly used IST are outlined in Table 1.

Corticosteroids

Corticosteroids exert therapeutic effects through multiple mechanisms: inhibiting lymphocyte and monocyte function, decreasing complement levels, and inhibiting histamine-mediated reactions.[21] In acute AE, corticosteroids are typically administered as 1,000 mg of IV methylprednisolone (or an equivalent dosage of other formulations) for 5 days, followed by oral prednisone (typically starting at 60 mg daily) tapering over several weeks to several months. Prophylaxis against *Pneumocystis jirovecii* with trimethoprim-sulfamethoxazole should be commenced after 1 month of corticosteroid use at doses exceeding 20 mg/d.[21] Proton pump inhibitors are commonly prescribed with corticosteroids, although the evidence supporting this is limited.[22] Cost, availability, and rapid onset of action make corticosteroids an appealing initial choice. Potential side effects include increased susceptibility to infection, worsening glycemic control, blood pressure elevation, and psychological symptoms (anxiety, mania, and low mood). Close monitoring of blood glucose levels and blood pressure in individuals with preexisting diabetes or hypertension is recommended.[21,23]

Table 1 Pretreatment Testing, Long-Term Safety Monitoring Recommendations, and Potential Long-Term Complications for Common Immunosuppressive Therapies

Drug name	Pretreatment testing[a,b]	Safety monitoring and prophylaxis	Black box warnings and precautions		
Corticosteroid agents (>20 mg/d for >1 mo)	CBC with differential CMP	Laboratory monitoring: CBC with differential (Q6 months) LFTs (Q6 months) Serum creatinine (Q6 months) Screen for osteoporosis (annually) Prophylaxis: PJP prophylaxis Osteoporosis treatment or prophylaxis for at-risk individuals	Black Box Warnings: NONE	Warnings/precautions (cont): Infections Bone density loss Avascular necrosis Hypertension Water retention Hypokalemia Hypocalcemia Peptic ulcers Myopathy Psychiatric derangements Increased intraocular pressure	Warnings/precautions (cont): Left ventricular free-wall rupture following myocardial infarction Hypothalamic-pituitary adrenal axis suppression Congestive heart failure Tendon rupture Pancreatitis Impaired wound healing Glaucoma Cushingoid changes Insulin resistance Corticosteroid insufficiency
Intravenous immunoglobulin (IVIg)	Baseline immunoglobulin levels (IgG, IgM, and IgA) IgA necessary to rule out selective IgA deficiency	Laboratory monitoring: In patients at risk of renal failure, monitoring renal function (including blood urea nitrogen and serum creatinine) Inquire about: Infusion reactions (headache, hypertension, fatigue, nausea, chills, diaphoresis, dizziness, and rash)	Black Box Warnings: NONE	Warnings/precautions: Thrombosis Renal dysfunction Acute renal failure Hyperproteinemia Hyponatremia Aseptic meningitis Hemolysis	
B-cell–depleting therapies	CBC with differential CMP Hepatitis serology Tuberculosis screen HIV screen Baseline serum immunoglobulin levels (IgG and IgM)	Laboratory monitoring: CBC with differential (Q6 months) CD19 count (Q6 months) Immunoglobulin levels (Q6 months) Inquire about: Recurrent infections New diagnosis of malignancy *Consider referral of patients with persistent hypogammaglobulinemia and recurrent infections to Immunology	Black Box Warnings: Life-threatening infusion reactions Mucocutaneous reactions Hepatitis B virus reactivation PML	Warnings/precautions: Infections Reduction in immunoglobulins Infusion reactions PML Malignancies Immune-mediated colitis	Warnings/precautions (cont): Tumor lysis syndrome Cardiac adverse reactions Renal toxicity Bowel obstruction/ perforation Fetal risk
Cyclophosphamide	CBC with differential CMP Hepatitis serology Tuberculosis screen HIV serology Urinalysis Age-appropriate cancer screening	Laboratory monitoring: CBC with differential (Q6 months) LFTs (Q6 months) Serum creatinine (Q6 months) Prophylaxis: PJP prophylaxis	Black box warnings: Severe bone marrow suppression	Warnings/precautions: Hemorrhagic cystitis Secondary malignancies (urinary bladder, myeloproliferative, lymphoproliferative) Acute cardiac toxicity	Warnings/precautions (cont): Infections Anaphylaxis Cytopenias Impaired wound healing Impaired fertility Fetal harm
Mycophenolate mofetil	CBC with differential Hepatitis serology HIV serology Tuberculosis screen	Laboratory monitoring: CBC with differential (Q6 months) LFTs (Q6 months) Serum creatinine (Q6 months)	Black box warnings: Embryofetal toxicity Malignancies (lymphoma, skin) Serious infections	Warnings/precautions Blood dyscrasias Hypogammaglobulinemia Gastric ulceration (with/ without perforation) Colitis Pancreatitis	Warnings/precautions (cont): Infections Acute inflammatory syndrome Depression Insomnia Metabolic derangements Venous thrombosis
Azathioprine	CBC with differential CMP Hepatitis serology HIV serology	Laboratory monitoring: CBC with differential (Q6 months) LFTs (Q6 months)	Black box warnings: Malignancies (T-cell lymphoma in patients	Warnings/precautions: Cytopenias Gastrointestinal hypersensitivity	

Continued

Table 1 Pretreatment Testing, Long-Term Safety Monitoring Recommendations, and Potential Long-Term Complications for Common Immunosuppressive Therapies *(continued)*

Drug name	Pretreatment testing[a,b]	Safety monitoring and prophylaxis	Black box warnings and precautions	
	Tuberculosis screen TMPT genotyping or phenotyping	Serum creatinine (Q6 months)	with inflammatory bowel disease)	Serious infections Fetal harm

Abbreviations: CBC = complete blood count; CD = cluster of differentiation; CMP = comprehensive metabolic panel; Ig = immunoglobulin; LFTs = liver function tests; PJP = *Pneumocystis jirovecii* pneumonia; TMPT = thiopurine methyltransferase.
[a] Age-appropriate vaccinations in addition to pneumococcal, influenza, SARS-COV-2, and varicella zoster should be administered at least 4 weeks before treatment initiation for all long-term immunosuppressive therapies, when possible.
[b] All women of childbearing age should be tested for pregnancy before initiation of long-term immunosuppressive therapies and counseled on the need for contraception to prevent pregnancy while being treated.

Plasma Exchange

PLEX is considered to exert beneficial effect through removal of large molecular weight particles including circulating antibodies, cytokines, and inflammatory mediators from plasma.[16] A total of 5–7 treatment cycles administered every other day (or as hemodynamic status allows) is the standard practice.[16] Although PLEX has a rapid effect, use is limited by restricted availability and the need for central venous access. Side effects can include symptomatic hypotension in patients with underlying dysautonomia or comorbid heart failure. Central venous catheters may increase the risk of sepsis and/or line-associated thromboses. Rarely, dilutional hypofibrinogenemia can occur, for which supplementation with fresh frozen plasma may be needed.[16,17]

Intravenous Immunoglobulin

IVIg contains pooled antibodies from donor blood products extracted from the plasma. IVIg functions through antibody neutralization, alteration of fragment crystallizable region expression, and inhibition/abrogation of activated complement.[24] An initial dose of 2 g/kg is typically administered over 2–5 days.[25] There is a small risk of anaphylaxis in patients with selective IgA deficiency, for which screening should be performed. IVIg does not increase the risk of infection, making it useful in patients with active or high risk of infection. Potential side effects include acute kidney injury, thromboembolic events, headache, aseptic meningitis, and fluid overload (particularly with depressed cardiac function or preexisting renal impairment). Slower infusion rates may ameliorate some risk.[20] IVIg may be also used for maintenance therapy in patients with AE (0.4–1 g/kg monthly). Because IVIg administration can result in false-positive antibody results, care should be taken when interpreting NAA obtained after treatment.

Long-Term IST

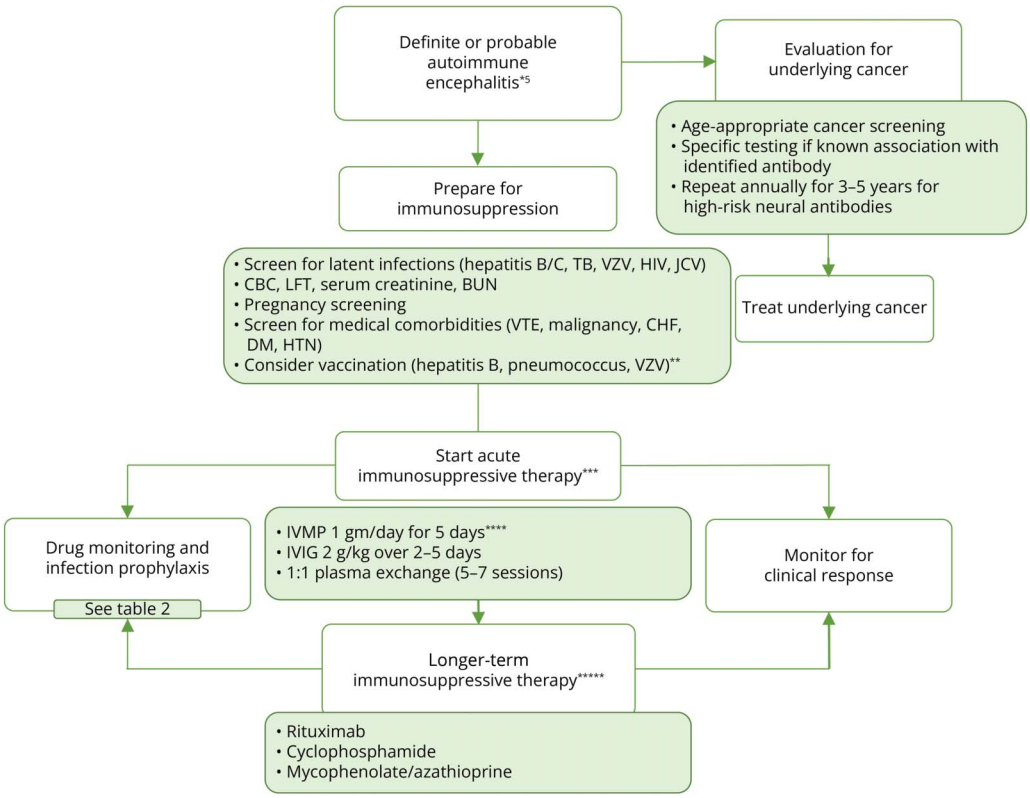
Long-term ISTs are often initiated early when there is no response to first-line treatment or severe disease. However, there may be circumstances where patients are adequately managed with acute therapies only.[1,25,26] There is limited data available regarding the efficacy of and clinical indications for long-term ISTs, though this is often done with the goal of improving disease severity, reducing chronic corticosteroid exposure, providing extended disease control, and reducing risk of relapse.[3,27,28]

Commonly used long-term ISTs include rituximab, cyclophosphamide, and less frequently, mycophenolate mofetil (MMF) or azathioprine (AZA).[1,26,29,30] The decision to initiate long-term ISTs should consider individual patient characteristics including response to acute IST, severity of disease, and disease course (relapsing). Other pertinent factors include age, medical comorbidities, concurrent (or future) cancer treatment, potential side effects, and patient preference. The NAA cellular target (extracellular/synaptic or intracellular) may suggest potential pathophysiology of disease and thus therapeutic response. Intracellular targets may be less responsive to antibody removal/blocking therapies.[31] Patients with AE with extracellular/synaptic proteins may respond well to multimodal ISTs including B-cell–depleting therapies, such as rituximab.[31] By contrast, patients with paraneoplastic autoimmune encephalitis (often with intracellular NAAs) may be less responsive to antibody removal/blocking therapies and may respond to T-cell direct therapies, such as cyclophosphamide.[31] However, further research is needed to better determine predictive factors for therapeutic response and optimal duration of immunosuppression. Figure 1 depicts a proposed approach to treatment, emphasizing key aspects of acute and long-term management.

Rituximab

Rituximab is a partially humanized monoclonal antibody (mAb) targeting the cluster of differentiation (CD)–20 surface antigen on lymphocytes, which results in depletion of naïve and memory B cells. Long-lived plasmablasts are preserved.[32] Initial treatment typically follows 1 of 2 protocols: IV infusion in two 1,000 mg doses 2 weeks apart or 375 mg/kg/m^2 administered weekly over 4 weeks. Infusion reactions are common but can be mitigated by pretreatment with low-dose corticosteroids, antipyretics, and antihistamines. Rarely, anaphylactic reactions may occur.[1,26] Its efficacy and favorable side-effect profile make rituximab a common choice for long-term management.[26]

Figure 1 Approach to Treatment of Autoimmune Encephalitis



* Infectious etiologies, and other alternative pathologies have been reasonably excluded. ** Vaccination should ideally be completed 2-4 weeks prior to starting rituximab, cyclophosphamide, mycophenolate/azathioprine. *** If incomplete or poor response to first-line immunotherapies after 2-4 weeks, consider second-line agents (rituximab or cyclophosphamide) without further delay. **** Or equivalent dose of alternative corticosteroid. This can be followed with a prolonged course of oral steroids or weekly pulse-dose steroids for 4-12 weeks. ***** Refer to text for dosing recommendations. TB = tuberculosis; VZV = varicella zoster virus; CBC = complete blood count; LFT = liver function test; BUN = blood urea nitrogen; VTE = venous thromboembolic disease; CHF = congestive heart failure; DM = diabetes mellitus; HTN = hypertension; IVMP = intravenous methylprednisolone; IVIG = intravenous immunoglobulin.

Notably, rituximab and other B-cell–depleting therapies are associated with reduced humoral response to vaccines and development of hypogammaglobulinemia with prolonged use. An increased risk of infection (typically upper respiratory and urinary tract infections) has been reported.[33] Patients treated with B-cell–depleting therapies have reduced response to vaccination against severe acute respiratory syndrome coronavirus subtype 2 and were more likely to develop severe disease compared with those receiving other IST.[34] Routine monitoring of immunoglobulin levels (every 6 months) to screen for secondary hypogammaglobulinemia is recommended. If immunoglobulin G (IgG) levels are persistently below 700 mg/dL and/or immunoglobulin M (IgM) levels are persistently below 20 mg/dL in patients experiencing recurrent infections, referral to an immunologist for consideration of adjuvant IVIg may help reduce infection risk.[33] Progressive multifocal leukoencephalopathy has been reported with rituximab use in other patient populations.[35]

Cyclophosphamide

Cyclophosphamide is an alkylating agent metabolized in the liver to active metabolites that are taken up by actively dividing cells, which interfere with DNA cross-linking and inhibit cell proliferation (including B and T cells).[30] For AE, weight-based dosing between 600 and 1,000 mg/m^2 IV or 1–2 mg/kg/d orally may be used both in the acute setting and for maintenance therapy (up to 3–6 months). Cyclophosphamide should be administered with both predose and postdose hydration to reduce the risk of renal toxicity when administered IV. Use of 2-mercaptoethane sulfonate sodium (MESNA), which is added to predose and postdose hydration, can decrease the risk of hemorrhagic cystitis related to the metabolite acrolein.[1,30] Cyclophosphamide also results in myelosuppression and therefore is not typically given with other chemotherapeutic agents (a consideration for paraneoplastic AE).[30]

Long-term use of cyclophosphamide is associated with increased risk of malignancy and gonadal/cardiac toxicity, related to total cumulative dosage; however, risk with short-term use is probably low. Fertility counseling/referral to a fertility clinic for preservation of sperm/ova may be considered for reproductive age patients for long-term administration. Baseline CBC with differential, LFTs, and urinalysis (UA) should be completed before treatment. The nadir of

resultant leukopenia typically occurs between days 10 and 14 after administration. Monitoring of CBC, LFTs, and UA should be performed once every 1–2 weeks for the first 3 months and monthly thereafter.[30] Prophylaxis against *Pneumocystis jirovecii* with trimethoprim-sulfamethoxazole should be given to all patients.

Mycophenolate Mofetil

MMF is a prodrug of mycophenolic acid, which inhibits inosine monophosphate dehydrogenase, decreasing the formation of guanine nucleotides, resulting in decreased cell division in bone marrow (including leukocyte precursors). MMF is administered orally as a 500 mg tablet twice daily and titrated to 1,000 mg twice daily after 2 weeks.[36] CBC and LFTs should be checked before treatment. Potential side effects include myelosuppression, hypersensitivity reactions, gastrointestinal upset, liver injury (transaminitis and hepatitis), and an increased risk of skin cancer. Monitoring of CBC and LFTs should be performed weekly for the first month, biweekly during months 2 and 3, and then monthly thereafter.[36] MMF is not often used for acute treatment of AE given lag in therapeutic effect.[27,28] A recent systematic review of MMF confirmed its teratogenicity and found an association with first trimester pregnancy loss.[37] Therefore, in women of childbearing age, pretreatment counseling should be completed.

Azathioprine

AZA is a prodrug of 6-mercaptopurine that inhibits amidotransferase enzymes, resulting in decreased cell division in bone marrow. AZA is initiated at a dose of 1.5 mg/kg/d and gradually up-titrated to 2–3 mg/kg/d based on tolerability and CBC parameters (either decline in leukocyte count and/or increase in red blood cell mean corpuscular volume).[36] In addition to baseline CBC and LFTs, measurement of thiopurine methyltransferase (TMPT) levels before treatment with AZA is required. Patients with low TMPT levels require dose reduction because deficiency results in accumulation of AZA and subsequent toxicity.

Similar to MMF, AZA is not typically used for acute treatment, given the lag in therapeutic effect and slow titration schedule. The monitoring schedule and side-effect profile of AZA is comparable with that of MMF. Third trimester exposure may result in immunosuppression and bone marrow suppression of the newborn. However, this risk may be mitigated with dose adjustment.[37] If used in women of childbearing age, pretreatment counseling should be completed.

Experimental Therapies

Several therapies are currently under investigation as potential treatment options for AE (Table 2). Proteosome inhibition (bortezomib[38]), interleukin-6 receptor antagonism (tocilizumab,[39-41] satralizumab[42,43]), and mAbs targeting CD19 (inebilizumab),[44] CD38 (daratumumab[45-47]), and the neonatal Fc receptor (rozanolixizumab[48]) have been reported, but it is important to emphasize that the evidence for efficacy has not yet been proven in larger samples. Furthermore, several of these therapies have been administered after conventional ISTs, and therefore, it is not known whether clinical improvement was attributable to therapeutic lag. Clinical trials investigating some of these therapies (inebilizumab, rozanolixuzumab, satralizumab, and bortezomib) are currently underway.[49-55]

Satralizumab and Tocilizumab

Tocilizumab and satralizumab both block IL-6 receptors.[41] IL-6 plays a critical role in B-cell differentiation, cytotoxic T-cell differentiation, Th17 cell proliferation, and plasma cell survival. Targeting IL-6 has effects beyond those seen with traditional B-cell blockade. Tocilizumab has established efficacy in a variety of rheumatologic conditions and NMOSD with a tolerable side-effect profile.[42,43,56] In one cohort of undifferentiated AE refractory to rituximab therapy at 1 month, patients treated with tocilizumab had earlier and more sustained improvement in modified Rankin scale (mRS) compared with additional rituximab or no additional therapy.[39] A prospective study of anti-NMDARe patients also found that early addition of tocilizumab to conventional regimens resulted in larger improvements in mRS and Clinical Assessment Scale in Autoimmune Encephalitis (CASE) scores.[41] Both studies and smaller case series found tocilizumab to be well tolerated, with infection and neutropenia being the most common drug-related adverse events.[39-41] Satralizumab is currently being studied in MOGAD, anti-NMDARe, and anti–leucine-rich glioma-inactivated 1 protein (LGI1) encephalitis.[53,54]

Daratumumab

Daratumumab is a human mAb targeting CD-38 present on long-lived plasma cells and other lymphoid and myeloid cell populations. It is approved for the treatment of refractory multiple myeloma. Case reports/series in refractory AE have shown reduction in serum and CSF antibody titers and shift in peripheral immune profile.[47] CASE scores improved in most, but overall mRS remained poor in the majority. Infections were frequent, and 2 patients died (sepsis, cardiac arrest). Notably, treatments were used in rapid succession with other ISTs making it difficult to determine the impact of this therapy alone.[45-47,57]

Bortezomib

Bortezomib is a proteasome inhibitor that leads to sequestration of abnormal proteins in cells by preventing degradation through ubiquitin-proteasome pathways, resulting in apoptosis. It is particularly effective in clearing plasma cells hypothesized to be pathogenic in rituximab-refractory AE. Case series/reports and 1 prospective study reported improvement in mRS scores and reduction in serum/CSF NMDA-R IgG titers.[38] Commonly reported side effects include peripheral neuritis, cytopenias, and infection. A clinical trial is ongoing in patients with severe AE.[49,55]

Table 2 Experimental Therapies Reported or Under Investigation for Autoimmune Encephalitis

		Evidence for use		Outcomes		
Immunosuppressive agent	**Mechanism of action**	**AE**	**Other CNS/PNS immune-mediated disorders**	**AE**	**Other CNS/PNS immune-mediated disorders**	**Planned clinical trials**
Inebilizumab	Anti-CD19 ($CD20^{-}$ plasmablasts and plasma cells) → more extensive and sustained B-cell suppression		NMOSD n = 230: Phase 3; double-blind; RCT[44]		HR 0.272 of attack in patients receiving inebilizumab (21/174 vs 22/56)[44] Equal incidence of AE. 5% serious AE in drug arm vs 9% in placebo arm[44]	ExTINGUISH: Moderate-severe anti-NMDARe (NCT04372615)[50] clinicaltrials.gov/ct2/show/NCT04372615
Tocilizumab	Anti-IL6-R → ↓B-cell proliferation and differentiation	AE n = 91: Retrospective, single-center cohort of patients with AE refractory to first-line therapy and after rituximab[39] Seronegative refractory pediatric AE n = 3: Case series[40] NMDAR IgG n = 78: Retrospective single-center cohort study of anti-NMDARe patients[41]	NMOSD: n = 118 phase 2; open-label; RCT[56]	More favorable mRS in tocilizumab vs additional RTX or observation[39] Rapid improvement following with sustained improvement at 6 mo[40] Early addition of tocilizumab to first-line immunosuppressive therapy and RTX was associated with lower CASE scores[41]	Median time to first relapse longer in tocilizumab vs.AZA; 8/59 vs 28/59 relapsed[56]	
Satralizumab	Anti-IL6-R→ ↓B-cell proliferation and differentiation		NMOSD n = 83: Phase 3, double-blind, placebo-controlled RCT[42] NMOSD n = 95:Phase 3, double-blind, placebo controlled, parallel-group RCT[43]		Relapse occurred in 8/41 (satralizumab) vs 18/42 (placebo)[42] Relapses occurred in 19/63 (satralizumab) vs 16/32 (placebo)[43]	Cielo (NCT05503264)[53]: anti-NMDARe, anti-LGI1e clinicaltrials.gov/ct2/show/NCT05503264 Meteoroid (NCT05271409)[54]: MOGAD clinicaltrials.gov/ct2/show/NCT05271409
Rozanolixizumab	Anti-FcR→ prevents IgG recycling and leads to unbound IgG being eliminated		MG n = 43: Phase 2a, double-blind, placebo-controlled, RCT[48]		Well-tolerated but did not show statistically significant benefit on outcomes[48]	(NCT04875975)[51]: anti-LGI1e (NCT05063162)[52]: MOGAD
Daratumumab	Anti-CD38 → plasma cell depletion	Anti-NMDARe n = 1; case report in NMDA-Re refractory to first-line therapy, RTX and bortezomib[45] CASPR2e IgG n = 1: Case report refractory to first-line therapy, RTX, bortezomib[46] AE+ n = 7; retrospective, single-center case series (5 AE, 2 PNS autoimmune diseases)[47]		Improvement in clinical status after 10 cycles of treatment at follow-up[45] Improvement in clinical status after 13 cycles and reduction of IgG levels including protective vaccine titers. Death due to Gram-negative septicemia[46] Improvement in mRS in 7/7 patients with reduction in disease-specific autoreactive antibodies[47]	Improvement in mRS in 7/7 patients with reduction in disease-specific autoreactive antibodies[47]	(NCT05403138)[e78]: NMOSD clinicaltrials.gov/ct2/show/NCT05403138
Bortezomib	Ubiquitin proteasome inhibitor → plasma cell depletion	Anti-NMDARe n = 29: Systematic review of case reports/series[38]		16/29 patients had a favorable outcome after bortezomib and 11/29 patients developed side effects[38]		NCT03993262[55]: severe AE

Abbreviations: AE = autoimmune encephalitis; AZA = azathioprine; CASE = Clinical Assessment Scale in Autoimmune Encephalitis; CASPR2e = contactin-associated protein-like 2 encephalitis; CD = cluster of differentiation; IgG = immunoglobulin G; IL = interleukin; LGI1e = leucine-rich, glioma-inactivated 1 protein encephalitis; MG = myasthenia gravis; MOGAD = myelin oligodendrocyte glycoprotein antibody disorder; mRS = modified Rankin scale; NMDARe = N-methyl D-aspartate receptor encephalitis; NMOSD = Neuromyelitis Optica Spectrum Disorder; PNS = Peripheral Nervous System; RCT = Randomized Clinical Trial; RTX = Rituximab.

Natalizumab

Natalizumab is a mAb targeting alpha-4-integrin inhibiting the migration of activated T lymphocytes into the CNS. A phase 2 trial of natalizumab in patients with anti-Hu paraneoplastic neurologic syndromes found that only 1 of 4 patients with AE had improvement in mRS.[58] Case reports of its use in checkpoint inhibitor–associated AE refractory to steroids and PLEX reported functional improvement, resolution of MRI abnormalities, and reduction in steroid dose.[59,60]

Other Potential Novel Therapies

Inebilizumab, targeting CD-19 positive cells, is being studied in a clinical trial of anti-NMDARe.[44,50] Rozanolixizumab, targeting neonatal Fc receptor, is being studied in a clinical trial of anti-LGI1 encephalitis and MOGAD.[48,51,52] There are case reports/series describing the use of basiliximab (interleukin-2 receptor blocker), tofacitinib (Janus kinase inhibitor), and intrathecal methotrexate in refractory NMDARe and seronegative AE.[e1–e3] A clinical trial investigating ocrelizumab (CD-20 mAb) in AE failed to meet recruitment goals.[e4]

Potential Longitudinal Biomarkers of Disease Activity and Treatment Response

Blood and CSF Biomarkers

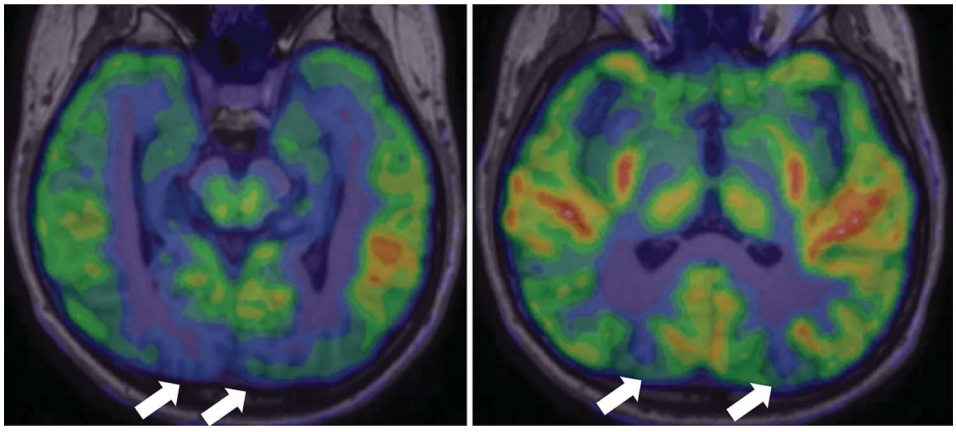
There is ongoing research into serologic biomarkers of disease activity. A study of anti-NMDARe demonstrated that serum NAA titers do not adequately reflect disease activity/relapse or response to treatment.[e5] One study examining serial CSF from a heterogenous sample of patients with AE found no significant change in CSF parameters (except for OCB resolution in patients with anti-NMDARe) that coincided with clinical improvement.[e6] Several studies have investigated serum neurofilament light chain (sNfL) and other markers of neurodegeneration as potential aids to diagnosis and disease activity.[e7–e10] sNfL levels may be useful in ascertaining disease relapse or ongoing disease activity because levels often increase within weeks of symptom onset.[e8] sNfL may also be helpful in differentiating between disease activity, pseudorelapses, and fluctuation of chronic symptoms, although further research is needed to determine this. Other biomarkers that have been shown to be elevated during the acute phase of the disease in AE include CSF levels of IL-10, TNF-alpha, IL-6, and neopterin.[e11-e13]

Neuroimaging

For patients with abnormalities on imaging, repeat imaging can be used to evaluate for evolution and/or resolution of abnormalities following treatment.[e14] Neuroimaging may also aid in confirming relapses if there are new/worsening abnormalities.[e15] However, conventional brain MRI can be insensitive to disease activity in some encephalidities[e14] and therefore may have a limited role as a measure of disease activity and/or relapse. Longitudinal MR volumetric analyses have been explored in a few studies that have shown hippocampal and mesiotemporal atrophy in different subgroups of AE,[e16,e17] though it is unclear whether volume changes represent ongoing inflammation or degenerative changes related to damage acquired during the acute phase.

The potential role of 18-fluorodeoxyglucose (FDG)–PET in longitudinal management has been reported in case studies demonstrating resolution of mesiotemporal hypermetabolism in patients with anti-LGI1 and anti–α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R) encephalitis.[e18,e19] One series found that putaminal hypermetabolism was distinct to anti-LGI1e with resolution of mesiotemporal and putaminal hypermetabolism after treatment.[e20] Occipital hypometabolism has been observed in anti-NMDARe (See Figure 2).[e21–e25] There can be challenges in the

Figure 2 Occipital Hypometabolism in NMDARe



Flurodeoxyglucose (FDG) PET/CT of the brain showing marked occipital hypometabolism (arrows) in an adolescent male with new onset refractory status epilepticus and anti-N-methyl-D-aspartate receptor (NMDAR) IgG encephalitis. This pattern may help distinguish anti-NMDAR encephalitis from other forms of autoimmune encephalitis and is more common in those with severe disease (modified Rankin scale 4-5).

application of FDG-PET in clinical practice due to variable interpretation and lack of specificity with confounders (including seizure activity and medications), therefore, the role in longitudinal care requires further research.

Seizure Diaries and EEG Monitoring

Seizures can be evaluated through thorough history review and/or a seizure diary (when feasible). EEG abnormalities seen in AE are heterogenous and include focal epileptiform discharges, slowing or seizures over the temporal lobes, extreme delta-brush pattern in anti-NMDARe,[e26] multifocal epileptiform discharges or seizures, subclinical seizures, and/or nonconvulsive status epilepticus.[e26,e27] A caveat is anti-LGI1e in which faciobrachial dystonic seizures may not be evident on EEG.[e28] An EEG may also help to determine (1) epileptic vs nonepileptic events, (2) semiology, (3) frequency, and (4) severity. A prolonged recording may be useful when infrequent seizures are suspected.[e19] Video EEG offers the advantage of correlating signs and symptoms with the EEG recording, aiding in elucidating semiology and localization.

Cognitive Assessments

Cognitive assessments may have a role in assessing treatment response and/or detecting clinical worsening. Cognition can be assessed with a brief bedside cognitive screening instrument such as the Montreal Cognitive Assessment (MOCA), Mini-Mental State Examination (MMSE), or more extended screening such as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[e29-e31] A study in 29 patients with AE showed that improvements in RBANS performance, measured before and 4–5 weeks after treatment, were clinically significant and in agreement with clinical impression of improvement.[e32] Cognitive screening measures are easily applied in the outpatient clinic, allowing a convenient longitudinal measure, which may be repeated over time.

Although cognitive screening tools may be a useful measure of clinical improvement and treatment response, they lack the sensitivity to detect more subtle cognitive impairments, which may be better evaluated with neuropsychological testing.[e30,e31,e33] A broad assessment of cognitive abilities is recommended, assessing, at minimum, measures of episodic learning/memory, basic and sustained attention, processing speed, executive functions, and complex figure copy. Initial neuropsychological assessment is ideally conducted following the acute and initial dynamic recovery phase with follow-up at least annually for the first 1–2 years.[e34]

Neurophysiology Studies

Nerve conduction studies, electromyography, and autonomic testing may be used longitudinally to assess the peripheral nervous system involvement (neuropathy, sensory neuronopathy, radiculopathy, myasthenic syndromes, autonomic neuropathy, and hyperexcitability) for patients with paraneoplastic neurologic disorders (e.g., antineuronal nuclear autoantibody 1[ANNA1]/Hu-IgG, collapsin-response mediator protein 5/CV2-IgG, amphiphysin), and contactin-associated protein-like 2 (CASPR2)-IgG, or stiff person syndrome (glycine-R-IgG and GAD-65-IgG).[e35–e37]

Sleep studies are occasionally used to evaluate patients with AE with sleep manifestations including narcolepsy, insomnia, parasomnias, and sleep disordered breathing (anti-NMDARe, anti–immunoglobulin-like cell adhesion molecule 5 (IgLON5, and anti-Ma-1/2).[7,10,e38] Sleep alterations, especially insomnia, may precede encephalitic symptoms by several weeks.[e39] Beyond the acute encephalitic stage, some patients continue to experience sleep disturbances.[e39,e40] Video polysomnography can provide objective evidence of abnormal sleep and may demonstrate absence or reduction of sleep or identify abnormal sleep patterns such as prolonged sleep latency, fragmented sleep, early awakenings, and apneas.[e41,e42] The absence of normal non-REM sleep on EEG (sleep spindles, K-complexes, and high-amplitude delta slowing) is highly sensitive for sleep disturbances related to AE.[e41,e42] A mean sleep latency test may also be helpful in assessing patients with suspected narcolepsy.[e43]

Movement disorders are frequently observed in patients with anti-NMDARe (orofacial dyskinesias and dystonia), anti-IgLON-5 (parkinsonism), anti-CRMP-5/CV-2 (chorea and ataxia), and anti-GAD65 (stiff person syndrome and ataxia).[9,e44,e45] These abnormalities can be evaluated objectively by using video gait analysis or surface electromyography (EMG).

Patient-Reported Outcome Measures: Mood and Quality-of-Life Assessments

Standardized assessments of mood such as the Patient Health Questionnaire–9 and Generalized Anxiety Disorder–7 may be used to screen for depression and anxiety and monitor changes over time.[e46,e47] Patient-Reported Outcomes Measurement Information System (PROMIS) and Quality of Life in Neurologic Disorders (NEURO-QoL) may be useful in assessing the overall quality of life and functional status and can be monitored longitudinally.[e48,e49]

Aggregate Clinical Scales

Objective clinical scales may be used to measure physical disability. The mRS (initially developed for patients with stroke) has been used to grade functional outcomes but has limited applicability to AE due to its focus on motor outcomes (and lack of sensitivity for neurocognitive/behavioral symptoms).[e50] A more recently described disease severity score, the CASE score, consists of 9 AE symptom subscores (presence/history of seizure, memory dysfunction, psychiatric symptoms, alteration of consciousness, language problems, dyskinesia/dystonia, gait instability and ataxia, brainstem dysfunction, and weakness) and has been found to have high and intraobserver and interobserver reliability and correlates well with mRS.[e51-e53] The Scale for the Assessment and Rating of Ataxia [SARA] may be helpful for patients in which ataxia is a prominent feature.[e54] This tool has previously been evaluated in other hereditary and idiopathic conditions.[e55,e56]

Potential Prognostic Biomarkers and Scoring Tools

Blood and CSF

There are mixed results on the use of sNfL as a prognostic biomarker.[e57] Some studies have shown an association between higher levels of sNfL with higher mRS scores at admission and 1-year follow-up, while others did not replicate this.[e8,e10,e58] Although elevated in patients with anti-NMDARe, levels of sNfL do not seem to correlate with short or long-term outcomes when adjusted for age.[e8] More recently, additional biomarker candidates including osteopontin, interleukin (IL)–6, IL-17A, chitinase-3-like 1 (CHI3L1), chemokine CXC ligand 13 (CXCL-13), CXC ligand 10 (CXCL-10), and S100 proteins have been explored for use in neurologic disease (including AE), with CHI3L1 and osteopontin having been explored specifically for use in anti-NMDARe.[e11-e13,e59] Studies to further explore and validate the use of these potential biomarkers are needed.

EEG

Early EEG abnormalities during the acute encephalitic phase of anti-NMDARe have been associated with poorer outcomes.[e60] The presence of an extreme delta brush pattern (Figure 3) and higher percentage of delta waves may also serve as predictors of a poorer prognosis.[e26,e61] A small pediatric study also showed an association between loss of sleep architecture and worse outcome at 1 year.[e62] There is limited data on the use of EEG in long-term monitoring of patients with AE, an area that requires further research.

Neuroimaging

The presence of MRI lesions (particularly hippocampal lesions) early in the disease course may be associated with worse outcomes.[e14,e63] A pediatric study found that the presence of T2 hyperintense lesions in the frontal and occipital lobes were associated with worse mRS scores in patients with anti-NMDARe.[e64] Further studies using standardized MRI and validation cohorts are needed.

Prognostic Scores

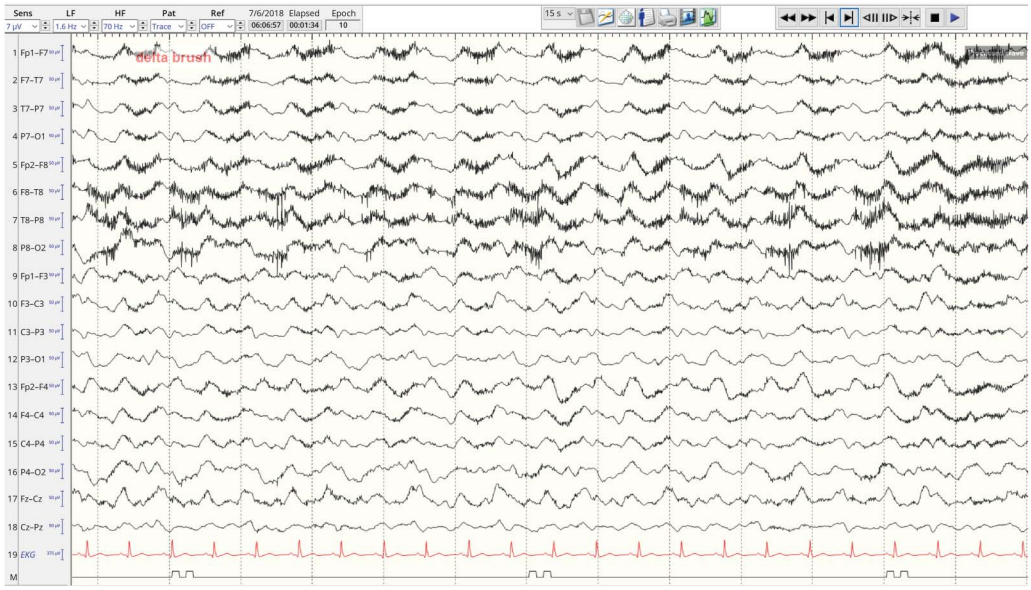
Prognostic scoring systems, such as the NMDA-Re One-Year Functional Status (NEOS) score, may be useful but are limited to 1-year outcomes and are condition specific, restraining applicability.[e63] Although initially used to predict seizure outcomes in response to IST, the Response to Immunotherapy score may be used to predict favorable outcomes to immunosuppression in patients with AE.[e65] Table 3 summarizes monitoring tools, markers of disease activity, prognostic scores, and outcome measures.

Acute Symptom Management

Behavioral/Psychiatric Symptoms

Approximately half of patients with anti-NMDARe are misdiagnosed initially with schizophrenia, depression, or anxiety.[e66] Manic symptoms, psychosis, and suicidal behaviors can occur during the acute phase of anti-NMDARe or signal relapse.[e67] Psychosis, agitation, and mania often require a comprehensive approach in collaboration with an experienced psychiatrist, including use of 1 or a combination of medications including benzodiazepines, antipsychotics, and/

Figure 3 Extreme Delta Brush in NMDARe



Extreme delta brush EEG pattern seen in young African woman with anti-NMDAR encephalitis. High amplitude delta waves are seen with overriding faster frequencies.

Table 3 Monitoring Tools, Markers of Disease Activity, Severity Rating Scale, Prognostic Scores, and Outcome Measures

Potential longitudinal measures of disease activity and treatment response		
Blood and CSF[a]	Serum neurofilament light chain (sNfLNfL)	Change in levels (increase) may reflect disease activity
Neuroimaging	MRI	Evolution/resolution of lesions and/or contrast enhancement
	18-FDG positron emission tomography (PET)	Evolution/resolution of regional hypometabolism/hypermetabolism Caution interpreting nonspecific findings
Seizure evaluations	Electroencephalography or seizure diary	Expert interpretation required
Cognitive evaluations	Montreal Cognitive Assessment (MOCA)[e30]	Range 0–26 (no cognitive impairment—severe cognitive impairment)
	Mini-Mental State Examination (MMSE)[e31]	Range 0–30 (no cognitive impairment—severe cognitive impairment)
	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[e29]	Range 40–160 (extremely low cognitive function—very superior cognitive function)
	Neuropsychological testing	Expert interpretation required
Neurophysiology[b]	Nerve conduction studies (NCS), electromyography (EMG), somatosensory evoked potentials (SSEP), surface electromyography (EMG)	Expert interpretation required
	Video polysomnography (PSG)	Expert interpretation required
	Mean sleep latency test (MSLT)	Expert interpretation required
Patient-reported outcome measures	Patient Health Questionnaire (PHQ)–9[e46]	Range 0–27 (no depression—severe depression)
	Generalized Anxiety Disorder–7 (GAD-7)[e47]	Range 0–21 (no anxiety—severe anxiety)
	Patient-Reported Outcomes Measurement Information System (PROMIS) score[e48]	Components rated on a scale of 1–5 (higher scores equals more of the concept being measured); composite scores based on T-score metric for each domain
	Neurologic Quality of Life (NeuroQOL) score[e49]	Components rated on a scale of 1–5 (higher scores equals more of the concept being measured); composite score based on *T* score metric for each domain
Aggregate clinical scales	Scale for the assessment and rating of ataxia (SARA)[e54]	Range 0–40 (no ataxia—severe ataxia)
	Modified Rankin scale (mRS)[e50]	Range 0–6 (no disability—death)
	Clinical Assessment Scale in Autoimmune Encephalitis (CASE)[e51]	Range 0–27 (mild encephalitis—severe encephalitis)
Potential prognostic biomarkers and scores		
Blood and CSF[a,e11-13,e59]	sNfL, osteopontin, interleukin (IL)– 6, IL-17A, chitinase-3–like 1 (CHI3L1), chemokine CXC ligand 13 (CXCL-13), CXC ligand 10 (CXCL-10)	
EEG[e26,e61]	Extreme delta brush, delta wave ratio	Presence of either of these during the acute phase is associated with worse prognosis
Neuroimaging[e14,e63]	Early hippocampal lesions (anti-NMDARe)	Presence of this finding is associated with poor prognosis
Prognostic scores	Response to immunotherapy (RITE) score[e65]	Range 0–19 (good response to therapy—poor response to therapy)
	anti-NMDA-R Encephalitis One-Year Functional Status (NEOS) score[e63]	Range 0–5 (good functional prognosis—poor functional prognosis)

See eTable 1 for expanded Table 3.
[a] Not yet validated for clinical use.
[b] Only recommended for patients with additional peripheral nervous system manifestations, stiff person syndrome, or sleep abnormalities.

or mood stabilizers along with nonpharmacologic measures.[e66,e68] Corticosteroids used in the treatment of AE may result in exacerbation of psychiatric symptoms.

Seizures

Acute symptomatic seizures in AE are often refractory to antiseizure medications (ASMs) and should be used in conjunction with IST when appropriate.[18,e69] There is little evidence to suggest that 1 ASM is favorable to another, though one study reported better response rates with sodium channel blockers compared with levetiracetam.[e70] Occasionally, a medically induced coma achieved with anesthetic medications (e.g., midazolam, propofol, and/or pentobarbital) is needed to effectively manage status epilepticus until IST takes effect.[e71]

Movement Disorders

Benzodiazepines may be useful in the treatment of myoclonus, catatonia, dystonia, and spasticity. For spasticity, muscle relaxants such as baclofen or tizanidine may be used when symptoms are multifocal, whereas targeted therapy (such as botulinum toxin injections) may be more useful for focal symptoms.

Dysautonomia

During the acute stage, dysautonomia is a frequent cause for intensive care unit admission in patients with anti-NMDARe. Wide fluctuations in blood pressure, heart rate, and body temperature often require continuous monitoring and vasopressor support.

Chronic Symptom Management

Despite *good* mRS score outcomes reported across multiple studies, there are several important long-term clinical sequelae arising from AE, which affect quality of life beyond the acute phase of the disease.[e72] Neurocognitive symptoms (including impaired concentration, memory problems, and processing speed), mood disorders, sleeping difficulties, seizures, and fatigue are commonly seen and may be underrecognized.[4,e73-e75] A multidisciplinary approach (with utilization of occupational therapy, speech therapy, neuropsychology, social work, and health psychology) is recommended in successfully managing patients with AE longitudinally. Given the significant impact sequelae of AE have on patients and their caregivers, patient organizations and peer-support groups can be highly valuable for patients.

Cognition

Cognitive impairment is seen in 50%–100% of patients with AE at long-term follow-up. Almost all domains can be affected, most commonly attention, memory, fluency, and visuospatial domains.[e72,e73,e75-e77] Long-term deficits may be more common in older patients, when treatment was delayed, or in patients who experienced status epilepticus at initial presentation or required a higher burden of ASMs.[4,e72]

Mood

Mood symptoms are commonly reported residual symptoms of AE, particularly anxiety and depression.[e53] Most recover from acute psychotic symptoms following treatment (when present), though nearly half may require 1 or more psychiatric medications to manage residual symptoms.[4]

Seizures

Most patients with AE experience seizure reduction and even seizure freedom with IST.[e69,e77] Factors increasing the likelihood of developing chronic epilepsy may include treatment delay and antibody subtype. Seizures may be underrecognized and underreported in patients with anti-LGI1 and anti-CASPR2 AE. Prolonged video-EEG may aid in determination of seizures. For many patients, it may be possible to wean ASMs after the acute encephalitis phase.[4,e72]

Future Directions

Although significant progress has been made in increasing awareness of AE leading to more efficient diagnosis and treatment, patients continue to suffer from unmet needs regarding optimal longitudinal care. One recognized barrier to research in AE is its rarity, limiting well-powered studies. Larger collaborative observational studies with greater power to evaluate safety and efficacy of treatments, to identify and validate disease biomarkers (for disease activity, treatment response, and prognosis), and to develop reliable measures of clinical outcomes are needed.

Several randomized control trials are planned for the evaluation of novel therapies, which may provide greater evidence for use and insight into disease pathophysiology. Further evidence is needed to guide selection of acute and long-term ISTs, patient selection, and duration of therapy.

Development and validation of AE-specific clinical outcome measures that incorporate symptoms relevant to this population are important. These must assess chronic symptoms beyond what is measured with current scales and include measures of cognitive function, mood, fatigue, and other PROs.

Ideally, research needs to focus on the evaluation of biomarker-defined cohorts that have similar pathophysiology (as opposed to examining pooled cohorts with various antibody biomarkers) to reduce heterogeneity in studies and to provide more precise disease-specific recommendations.

Importantly, more research is needed in AE management in limited resource settings, where cost and availability of NAA testing is a barrier to timely diagnosis. Many of the ISTs used for both acute and long-term management and the monitoring tools and resources discussed earlier are not available in low- and middle-income countries. Future research should include data from these populations and take these limitations into consideration.

Increased awareness has led to a growing demand for better longitudinal care of patients with AE. Novel therapeutics with the intent to target disease-specific processes are emerging, and research to identify biomarkers of disease activity and treatment response is underway. In this study, we have summarized a pragmatic approach for comprehensive longitudinal and multidisciplinary management of this unique patient population.

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