Critical Care Management of Anti-N-Methyl-D-Aspartate Receptor Encephalitis

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Objectives: Anti-N-methyl-D-aspartate receptor encephalitis is considered an immune-mediated form of encephalitis with paraneoplastic and nonparaneoplastic forms. Delay in recognition is common and patients typically present to the ICU without a diagnosis or with complications following a delayed diagnosis. The aim of this review is to provide a focused overview for the ICU clinician regarding presentation, diagnosis, and critical care management.

Data Sources, Study Selection, and Data Extraction: PubMed database search with manual review of articles involving anti-N-methyl-D-aspartate receptor encephalitis.

Data Synthesis: Anti-N-methyl-D-aspartate receptor encephalitis is increasingly encountered in the ICU. The cascade of events initiating anti-N-methyl-D-aspartate receptor antibody formation may involve an infectious trigger particularly in the setting of teratoma. Following a prodrome, most patients develop psychiatric symptoms followed by movement disorder. Classical, psychiatric, and catatonic phenotypes may be distinguished based on the presence and severity of symptoms. Early immunotherapy and low initial cerebrospinal fluid inflammation are independent predictors of positive outcomes in ICU patients. Concomitant organ failure, status epilepticus, and the identification of a tumor did not influence outcome in critically ill patients. Supportive care in the ICU includes management of various manifestations of dyskinesia, status epilepticus, autonomic disorders, and the need for general sedation. Common treatment strategies and limitations are discussed including the emerging role of bortezomib.

Conclusions: Intensivists should be familiar with the presentation and management of anti-N-methyl-D-aspartate receptor encephalitis. Early diagnosis and immediate implementation of steroids, immunoglobulins, and/or plasmapheresis and immune therapy are associated with a good neurologic outcome although response may be delayed. The selection and timing of second-line immune therapy requires further study. (*Crit Care Med* 2018; 46:1514–1521)

Key Words: antibody; anti-N-methyl-D-aspartate receptor encephalitis; encephalitis; intensive care; N-methyl-D-aspartate

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis (ANRE) is an easily misdiagnosed syndrome with a myriad of psychiatric, neurologic, and systemic symptoms. ANRE is a classic example of autoimmune encephalitis occurring both as a paraneoplastic and as a nonparaneoplastic entity. Many disorders previously considered idiopathic such as catatonia, psychosis, or noninfectious encephalitis are now recognized to be mediated by anti-NMDA antibodies (1, 2).

Recognition of the neurologic syndrome that progresses from psychosis, memory deficits, seizures, and language disintegration into a state of unresponsiveness with catatonic features supported by the presence of MRI abnormalities, electroencephalography abnormalities, lymphocytic pleocytosis, and anti-NMDA antibodies is crucial because delayed diagnosis impacts outcome (2, 3). Patients may present to the ICU with incorrect diagnoses such as neuroleptic malignant syndrome (NMS) or acute infectious encephalitis, or without a unifying diagnosis for the management of severe symptoms or complications of ANRE. **Table 1** lists conditions that can mimic ANRE. The limited evidence available suggests that failure to diagnose the condition may occur even in the ICU (3). The aim of this review is to enhance awareness and understanding of ANRE by providing a focused overview for the intensivist regarding presentation, diagnosis, and ICU management.

EPIDEMIOLOGY

The frequency of ANRE remains uncertain. A single ICU analyzed paired serum and cerebrospinal fluid (CSF) samples in 505 patients and identified anti-NMDA antibodies in 1% (1). The cohort comprised of patients 18–35 years old with encephalitis signs/symptoms, seizures, and inflammatory CSF in whom bacterial and viral etiologies were excluded. Another study that recruited 203 patients with encephalitis revealed an anti-NMDA antibody positivity rate of 4% (4). The California

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TABLE 1. Differential Diagnosis of Anti-N-Methyl-D-Aspartate Encephalitis

Paraneoplastic encephalitis
Infectious encephalitis
Other immune-mediated encephalitis
Neuroleptic malignant syndrome
Schizophrenia or other psychosis
Catatonia
Serotonin syndrome
Toxic encephalopathy
Bipolar disorder
Stiff person syndrome
Sepsis
Meningitis
Mitochondrial encephalopathy
Primary dysautonomia
Acute disseminated encephalomyelitis
Cerebral metastasis
Porphyria

TABLE 2. Diagnostic Criteria for Autoimmune Encephalitis (11)

All Three Criteria Must Be Met
1. Subacute onset of short-term memory loss, altered mental status, or psychiatric symptoms
2. At least one of the following:
New focal CNS finding
Unexplained seizures
Cerebrospinal fluid pleocytosis with > 5 WBCs/mm^3
Suggestive MRI features (see text)
3. Alternative etiologies excluded

Encephalitis Project, a registry of encephalitis cases, evaluated 47 cases over a 3½-year period in which young patients had a sign or symptom suggestive of possible ANRE; of those, 32 were confirmed (5). The Hospital of the University of Pennsylvania (HUP) identified 400 cases, many on a referral basis, over the course of 3 years, suggesting that the prevalence may be higher than initially believed (although the definition of encephalitis was not specified) (6).

Paraneoplastic forms of ANRE primarily affect females, and the mean age is 19 years old. Up to 59% of cases occur in the presence of an underlying tumor, typically an ovarian teratoma, whereas only 5% of cases in males are associated with a tumor (2, 7). The presence of an ovarian teratoma is more common among females of childbearing age (50%) compared with those younger than 14 years old (9%) (2, 8). ANRE has occurred in patients with other tumors, including mediastinal teratomas, testicular tumor, Hodgkin lymphoma, small-cell lung carcinoma, and neuroblastoma, but the association is less certain given the relative rarity—1.7% of patients in the HUP series (2, 6, 9). Among older patients, carcinoma is the more common tumor identified. ANRE has been increasingly reported in infants and young children, but with a more equal gender distribution and lower incidence of tumors (8, 9).

PATHOPHYSIOLOGY

ANRE is a subclass of autoimmune encephalitis with a complex immunobiology that is not completely elucidated. It meets criteria required to classify a disorder as autoimmune: it has a disease-specific autoantibody that alters the function of its target, and antibody elimination leads to improvement or reversal of the disease (8, 10). **Table 2** summarizes the diagnostic criteria for autoimmune encephalitis.

The priming event can vary, but it is thought that an infection initiates a costimulatory signal required for T- and B-cell cross-talk with resultant formation of autoantibody secreting plasma cells. The list of potential-inducing pathogens includes *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis*, influenza A and B, herpes simplex virus (HSV), Epstein Barr virus, and retroviruses (2, 7). Tumor cells may serve as the antigenic presenter to the dendritic cell or macrophage. Tumor presence is not universal, so an isolated adjunctive pathogen may elicit autoantibody production via molecular mimicry. Extra-CNS NMDA receptors are present in neurons as well as kidney, parathyroid, bone, pancreas, myocardium, and lung tissue. Infection in any of these tissues can trigger autoimmunity (10). These hypothesized triggers all converge at the point of malfunctioning T- and B-cell tolerance. B-cell activation, clonal expansion, and plasma cell differentiation result in anti-NMDA receptor antibody secretion with subsequent class switch to immunoglobin (Ig) G1 and IgG3 autoantibodies that may enter the CNS in areas of blood-brain barrier (BBB) disruption. Alternatively, activated B cells may cross the BBB, allowing for differentiation and intrathecal autoantibody formation.

The NMDA receptor target of the autoantibodies is one of three types of inotropic glutamate receptors (NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, and kainate). It is a transmembrane receptor comprised of two glycine-binding (NR1) and two glutamate-binding (NR2) subunits, with eight NR1 isoforms and four NR2 isoforms, each with distinct distributions and phenotypic properties. The autoantibodies are likely directed toward the coregulatory GluN1 (NR1) subunit of both synaptic and extrasynaptic NMDA receptors within the hippocampus, brain stem, and neocortex (8). However, autoantibody binding to the GluN2 (NR2) subunit has not been entirely excluded (12). Brain pathology reveals low T-cell and complement infiltration, supporting a reversible clinical condition predominated by antibody-mediated capping and receptor internalization, rather than an apoptotic process (2, 13). The clinical symptoms depend on the antibody titer and location and correlate to the degree of synaptic dysfunction (2).

TABLE 3. Symptoms of Anti-N-Methyl-D-Aspartate Receptor Encephalitis (2, 8, 9)

Domain	Signs/Symptoms
Cognitive	Disorientation, inattentiveness, memory formation and recall impairment, sleep-wake cycle alterations
Language	Anomic aphasia, dysarthria, echolalia, mutism
Psychiatric	Mood lability, irritability, anxiety, apathy, paranoia, mania, illusions, hallucinations, delusions, catatonia
Seizures	Generalized tonic-clonic (most common), partial complex, nonconvulsive
Movement disorders	Orofacial and lingual dyskinesia (characteristic), echopraxia, opisthotonus, chorea, dystonic limb posturing, rigidity, oculogyric crisis, opsoclonus-myoclonus, catatonic posturing
Dysautonomia	Brady- or tachyarrhythmias, paroxysmal hypo- or hypertension, hypo- or hyperventilation, paroxysmal hypo- or hyperthermia, hypersalivation

CLINICAL PRESENTATION

ANRE typically occurs in phases: prodromal, psychiatric, movement disorder, and disorders of consciousness, but the sequence may vary and symptoms can overlap (2, 14). Initially, patients may receive an erroneous diagnosis such a nonspecific infection, acute psychiatric illness, viral encephalitis, or NMS. As the illness progresses, it often remains undiagnosed, with up to 87% progressing to coma, and 70–80% being admitted to the ICU for the management of associated complications such as central hypoventilation, new-onset seizures/status epilepticus, coma, dysautonomia, or violent dyskinesia (6, 8, 9). **Table 3** summarizes common symptoms associated with ANRE.

A prodrome occurs in most patients with symptoms mimicking a viral infection, for example, fever, headache, respiratory or gastrointestinal symptoms, or nonspecific psychiatric symptoms such as changes in sleep, appetite, and concentration (2, 12, 15). Within weeks, more severe symptoms, usually psychiatric, manifest and prompt medical attention (77% of patients being evaluated by a psychiatrist) (15, 16).

The clinical course varies in sequence and severity, with a progression of overlapping cortical and subcortical neuropathology. The initial symptoms may be subtle, including fluctuating cognitive and language impairment, irritability, anxiety, and mood lability, with worsening psychiatric symptoms over days to weeks. Intensive care admission occurs after the development of more severe symptomatology: neuropsychiatric (catatonia, coma, seizures), movement disorders (hyperkinetic or bradykinetic), dysautonomia, or respiratory failure (2, 6). Decreased consciousness is seen in up to 88% of patients with a dissociative state akin to that elicited by NMDA antagonists (2, 17).

Movement disorders affect up to 86% of patients and are heterogeneous, but orofacial and lingual dyskinesia are fairly typical (2, 12). Seizures occur in up to 76% of patients, with generalized tonic-clonic seizures being most common. Other types including focal motor, convulsive status epilepticus, nonconvulsive status epilepticus, and epilepsia partialis continua (6, 18). Seizures can emerge and recur at any time throughout the course, often arising in the early stages and waning in frequency and intensity with disease progression (19, 20).

Dysautonomia occurs in up to 70% of patients and typically peaks during the initial movement disorder phase. The classic presentation is paroxysmal hypertension and sinus tachycardia; however, temperature dysregulation (hypo- or hyperthermia, as high as 43.4°C), bradycardia, hypotension, gastrointestinal dysmotility, and sialorrhea are also common (6, 10, 13, 21). These changes tend to subside over time but may persist throughout the disease course. In one series, 7% of ICU patients experienced dysautonomic cardiac arrest (3). Central hypoventilation occurs in up to 70% of patients and necessitates endotracheal intubation in 20% (2, 13). Ventilatory compromise usually develops as coma ensues during the later stages of the psychiatric phase, but it may occur earlier when consciousness is still preserved. Although less common, patients may present with central neurogenic hyperventilation (22).

The presenting symptoms are notably broad and may manifest slight variations across age spectrums and between genders, reflecting the variability of NMDA (NR1/NR2) receptor expression, maturation, and distribution. **Table 4** summarizes

TABLE 4. Anti-N-Methyl-D-Aspartate Receptor Encephalitis Phenotypes and Duration of Symptoms as Proposed by DeSena et al (14)

Classification	Psychiatric	Seizures	Movement	Catatonia
Type 1: classic	Minimal to ≈50% of the time	≈50% of the time	≈50% of the time	Minimal to ≈50% of the time
Type 2: psychiatric	Most of the time	Minimal	Minimal to ≈50% of the time	Absent or minimal
Type 3: catatonic	Minimal to ≈50% of the time	Minimal to ≈50% of the time	Most of the time	Most of the time

a recent proposal to classify certain ANRE phenotypes, which may be associated with different degrees of clinical response and recovery (14).

DIAGNOSIS

Conditions that mimic ANRE include other immune-mediated encephalitis, serotonin syndrome, toxic ingestions, porphyria, and paraneoplastic syndromes (2, 12). When these diagnoses are being considered, the differential should include ANRE, and the patient's history and physical examination should be considered in this context. Likewise, new-onset seizures (particularly with neurobehavioral symptoms) in a young person raise the possibility of ANRE. The characteristic clinical picture of a prodrome with new-onset psychiatric symptoms should prompt a laboratory and radiologic investigation to confirm or rule out the diagnosis of ANRE.

Spinal fluid abnormalities are detected in up to 90% of patients with ANRE (2). Typical findings include mild-to-moderate lymphocytic pleocytosis (up to 90%, with a median WBC count of 23/mm^3), mildly elevated protein (up to 30%, with a median protein level of 24 mg/dL), CSF-specific oligoclonal bands (in up to 60%, but may not be prominent until later stages), and anti-NMDA receptor antibodies. It is imperative to send paired serum and CSF antibody titers as they may be synthesized intrathecally, with reports of positive CSF and negative serum titers, especially when diagnosis is delayed or after aggressive immunotherapy (2, 10). Almost all patients have positive CSF antibodies, making it a much more sensitive test than serum antibodies. Determination of CSF antibody titers is useful as they correlate with clinical outcome and can be repeated to follow treatment response. In the later phases of recovery, it is possible to observe high serum with low or undetectable CSF titers (12, 23). Spinal fluid analysis may reveal HSV infection, and clinicians may erroneously assume that they are treating HSV although HSV is merely a viral trigger of ANRE (24).

Electroencephalography is typically abnormal, showing nonspecific focal or generalized slowing with predominant rhythmic activity in the δ-θ range, especially in those manifesting catatonia (12, 25). A unique electroencephalography pattern termed "extreme delta brush" is present in up to 30% of patients (26). Extreme delta brush on electroencephalography is associated with a more prolonged illness. Electroencephalography monitoring is also useful to differentiate complex hyperkinetic movement disorders that can mask underlying seizures.

Contrast-enhanced MRI is abnormal in 30–50% of patients, with mild and nonspecific T2 or fluid attenuation inversion recovery signal hyperintensity in cortical/subcortical areas of the hemispheres, cerebellum, brain stem, or spinal cord (2, 27, 28). Demyelination on MRI should trigger diagnostic exploration for overlapping diseases as they can occur in up to 4% of patients with ANRE (10). Depending on the course and severity of the disease, repeat imaging may remain normal, display minimal change from baseline, or reveal a degree of brain atrophy. All patients, particularly females given the association with ovarian teratomas, should undergo screening with MRI, CT, or pelvic and transvaginal ultrasound because surgical resection of an associated tumor may improve time to treatment response and overall outcome (2, 6). In the critically ill patient, ultrasound is more practical because it can be performed at the bedside and should be used as an initial screening tool. Traditional serum tumor markers associated with pelvic malignancies are often negative and do not have a defined value in the diagnosis of ANRE (2).

INTENSIVE CARE MANAGEMENT

The ICU management of patients with ANRE comprised of supportive care, symptom management, immune modulation, and tumor resection. Mechanical ventilation may be compelled by central hypoventilation or sedatives/anesthetics required to manage hyperkinetic movements, status epilepticus, chest wall rigidity, autonomic instability, or profound catatonia (2, 21). Aspiration pneumonia, atelectasis, or pulmonary embolism may also contribute to respiratory failure (6, 21). Psychosis-driven agitation, violent hyperkinetic movements, spastic rigidity, and hypersalivation can complicate ventilatory management (2, 12, 13). The median duration of mechanical ventilation is 38 days (range, 2–82 d); thus, tracheostomy is common and may facilitate patient comfort (21).

The best approach to improve ventilator synchrony is a multimodal strategy targeting specific symptoms. Antipsychotics will not resolve agitation secondary to acute psychosis but may lessen the burden enabling other necessary treatments. Second generation antipsychotics (SGA) are recommended over first generation antipsychotics (FGA), especially attempting to avoid high-potency dopamine 2 (D_2) antagonists (fluphenazine, trifluoperazine, perphenazine, haloperidol, and pimozide) which are more likely to cause dyskinesia. Dyskinesia, extrapyramidal symptoms, and NMS symptoms overlap those of ANRE, creating potential for misdiagnosis and adverse clinical consequences if inadvertently attributed to ANRE (29). Olanzapine, clozapine, and loxapine offer theoretically attractive choices because they may prevent NMDA receptor antagonist toxicity. Chlorpromazine, aripiprazole, quetiapine, risperidone, and ziprasidone have also been used (29). Sedation with propofol, dexmedetomidine, midazolam, or fentanyl infusions may be needed to facilitate mechanical ventilation.

Anti-NMDA antibodies can affect several different basal ganglia areas, resulting in complex movement disorders. Treatment should target the observed movement disorder. Choreoathetosis and ballismus are generally best treated with D_2 antagonists, traditionally typical FGA; however, atypical SGA may alleviate symptoms in some patients. If dyskinesia develops or worsens while the patient is receiving a D_2 antagonist for either movement disorders or agitation, the possibility of drug-induced dyskinesia should be considered. Risk increases with escalating doses and time of exposure. For refractory cases, consideration should be given to vesicular monoamine transporter type 2 (VMAT2) inhibitors

(tetrabenazine, deutetrabenazine, and valbenazine) or sedation with benzodiazepines, barbiturates, or propofol (30). Oral-facial dyskinesia should be treated similarly, but adding a bite block and considering early tracheostomy are crucial to minimize mouth and tongue trauma. In cases of isolated dystonia, a trial of minimizing D_2 antagonists and initiating carbidopa/levodopa may be reasonable. If deemed to be a dopamine nonresponder, trihexyphenidyl, gabapentin, or baclofen can be considered, again conserving VMAT2 inhibitors or general sedation for refractory cases (30).

Dysautonomia treatment is symptom driven; however, aggressive treatment should be minimized to limit toxicity. Most patients are young and healthy before presentation, so they are able to tolerate some degree of dysautonomia without adverse consequences. If persistent and severe, hyperthermia can be treated with antipyretics and cooling devices, hypothermia with rewarming devices, tachycardia with rate control agents, bradycardia with chronotropic agents or pacing, hemodynamic instability with vasoactive agents, and hypersalivation with anticholinergics or botulinum toxin (21, 31). Many clinicians find it helpful to treat the dysautonomia similar to other forms of paroxysmal sympathetic hyperactivity (sympathetic storm) with β blockade, opioids, α-2 agonists, benzodiazepines, baclofen, and gabapentin.

Benzodiazepines remain first-line treatment for catatonia. Electroconvulsive therapy (ECT), which may enhance NMDA receptor expression, may be considered as a last resort in refractory or malignant cases although data in this setting are lacking. Status epilepticus, arrhythmias, and dysautonomia are relative contraindications to ECT and should be ruled out first (32).

Sedatives and anesthetics may be necessary to facilitate management in the ICU and the operating room. For patients not requiring deep levels of sedation, dexmedetomidine or clonidine may be useful to provide general comfort and assist with control of dysautonomia (33). In the absence of convincing clinical data, it is assumed that agents with NMDA antagonist properties, for example, ketamine, nitrous oxide, and volatile anesthetics, should be avoided (2, 34). Propofol may antagonize the NMDA receptor, and although one case noted worsening of dyskinesia, it has been used without complications in other cases for sedation, agitation, and dyskinesia (17, 34, 35). Reports indicate that effects vary based on receptor subunit isoforms or distribution and may influence drug utility. Because seizures are a common occurrence, using agents with gamma-aminobutyric acid stimulating properties achieves several therapeutic goals (antiepileptic, treat agitation, improve patient-ventilator synchrony). Enhanced understanding of the drug-receptor interaction based on receptor distribution and composition could improve therapeutic decision-making for symptom management.

DISEASE-MODIFYING TREATMENT

Steroids are the cornerstone of the initial therapy and are often used concomitantly with immunotherapy. However, the most effective strategy remains undefined, particularly in the ICU. Many clinicians have followed an approach of steroids (methylprednisolone 1 g/d for 5 d) with either IV immune globulin (IVIG 0.4 g/kg/d for 5 d) or plasmapheresis, followed by second-line immunotherapy (rituximab and/or cyclophosphamide) after failure (lack of improvement in 10–14 d) of the former (2, 3, 6). Plasma exchange and immunoadsorption can be used to treat ANRE; both modalities appear to be equally effective although immunoadsorption may be better tolerated (36). Hypotension, hypocalcemia, coagulopathies, and catheter-associated infections are concerns with plasma exchange, which may make it difficult to perform in children and patients with dysautonomia or severe agitation (37). IVIG is logistically easier to implement than plasma exchange. **Table 5** summarizes the standard immunotherapies used for ANRE in the ICU.

Early case series describing the use of glucocorticoids, IVIG, or plasmapheresis has defined "first-line" treatment (21, 25). Combined immunotherapy, steroids + immunoglobulin, administered early (before or within 8 d of ICU admission) was associated with positive outcomes defined as a modified Rankin Scale (mRS) of 0–2, with an odds ratio of 16.2 (3.3–78.6) compared with later initiation. Early immunoglobulin or steroids alone was not statistically superior to late immunotherapy with odds ratios of 3.3 (0.7–16.8) and 5.0 (0.8–32.2), respectively. Single-agent therapy was used in a small number of patients resulting in low statistical power, but the magnitude of the odds ratio for good outcome was also smaller than combined immunotherapy (3).

Although first-line therapies may eliminate or reduce serum anti-NMDA antibodies, currently available second-line therapies arrest further antibody production. Rituximab and cyclophosphamide are most often used: both target antibody-producing B cells. Selection and timing of therapy following failure of first-line treatment are controversial. An often accepted strategy is to consider second-line therapy if an insufficient response is observed after 10–14 days of first-line treatment (2, 3, 40). In one series of 74 ICU patients with ANRE who received first-line immunotherapy, 61% received rituximab, cyclophosphamide, or both with a median administration time of 34 days (3). For each regimen, about half of patients had a good neurologic outcome (mRS, 0–2) at 6 months. The authors note that the rate of second-line therapy was high compared with previously published data and suggest that this is likely due to the severity or refractory nature of ANRE requiring intensive care. The impact of initiating early B-cell–depleting immunotherapies concurrently with traditional strategies in critically ill ANRE patients remains unknown but may be beneficial since most severe cases fail first-line therapy. The reduction in relapse observed with these second-line therapies may further support more routine incorporation into treatment regimens (2, 40).

Despite targeted therapy, some patients may fail treatment, which is often associated with insufficient CSF anti-NMDA antibody titer reduction. This is possibly attributable to inadequate CNS penetration of traditional therapies. The CNS penetration of rituximab is debated with most reports describing low penetration through the intact BBB. However, it still appears to decrease CNS concentrations of CD20+ B

TABLE 5. Acute Immunotherapies for Anti-N-Methyl-D-Aspartate Receptor Encephalitis in the ICU (2, 38, 39)

Agent	Dosage	Adverse Effects	Pearls
Glucocorticoids	Acute: methylprednisolone 1 g daily × 3–5 d Maintenance: prednisone 60–80 mg (≈1 mg/kg) daily, followed by prolonged taper	Infection, weight gain, hyperglycemia, hypertension, osteoporosis, cataracts, insomnia, psychosis, myopathy, peptic ulcers	Maintenance indication and duration not defined
Plasmapheresis (PLEX)	30–40 mL/kg (1–1.5 plasma volumes)/cycle Typically five cycles per treatment (may be repeated)	Hypotension, coagulopathy (replace factors with fresh frozen plasma)	Avoid angiotensin-converting inhibitors during PLEX Schedule concomitant drugs to minimize removal
IVIG	0.4 g/kg daily × five doses (may be repeated)	Infusion reactions, aseptic meningitis, deep vein thrombosis, kidney injury	Premedicate to minimize infusion reactions May cause positive anti-HBV antibodies (product specific)
Rituximab	375 mg/m^2 weekly × 4 wk	Infusion reactions, cytopenias, infection	Premedicate to minimize infusion reactions Obtain baseline HBV status (preferably before IVIG); if positive, consider antiviral prophylaxis to minimize risk of reactivation
Cyclophosphamide	750 mg/m^2 every 4 wk (may delay based on blood counts) × 4–6 mo	Nausea, vomiting, myelosuppression, infection, malignancy, infertility	Infertility less likely in this treatment scenario (higher risk if cumulative dose > 50 g) Low risk of cystitis with low doses Monitor for leukopenia
Bortezomib	1.3 mg/m^2 on 21-d cycle (given on days 1, 4, 8, and 11) × 1–6 cycles	Infusion reactions, cytopenias, neuropathies, heart failure exacerbation, infection, herpes reactivation	Premedicate to minimize infusion reactions Monitor for cytopenias If history of herpes simplex virus, consider antiviral prophylaxis to minimize risk of reactivation Consider subcutaneous injection to minimize risk of adverse events

HBV = hepatitis B virus, IVIG = IV immunoglobulin, PLEX = plasma exchange.

cells (41, 42). Intrathecal therapy with methotrexate or rituximab has been attempted to overcome low CNS penetration (43). The lack of consistent clinical response even with direct delivery to the CNS is suggestive of a potential role of long-lived plasma cells that continue to secrete anti-NMDA antibodies (44). Bortezomib is a proteasome inhibitor that predisposes both short- and long-lived plasma cells to apoptotic death. Similar to rituximab, it has low CNS penetration but still appears to decrease CNS plasma cell concentration. In one series, the addition of bortezomib after failure of first-line and second-line therapies resulted in clinical improvement and antibody decline in four of five patients (44). In one case of refractory ANRE, addition of bortezomib to tocilizumab and cyclophosphamide resulted in improvement (45). Additionally, bortezomib may impact ANRE via activation of presynaptic NMDA receptors mediated by changes in protein kinase C (46). Given the clinical success of bortezomib in refractory ANRE, this combination may offer an attractive early strategy for severe cases.

PROGNOSIS

Early detection and optimal management of ANRE may herald positive outcomes although recovery may be delayed. In ICU-specific ANRE cases, good neurologic outcomes were observed in 57% (at 6 mo) and in 88% (at 24 mo), which is comparable to all patients with ANRE (2, 3). Low initial CSF inflammation (WBC, < 50 cells/mm^3) and early immunotherapy predict good outcome in ICU patients, the latter factor also being consistent with the general population of ANRE patients (2, 3). In a large case series of patients with ANRE, combining analysis of adults and children, lower severity of symptoms and admission to a general ward (as opposed to the ICU) carried good prognosis (47). However, a more recent study with patients admitted to an ICU reported that concomitant organ failure, status epilepticus, and the identification of a tumor did not influence outcome (3). The explanation for the contradictory findings is not clear, but it is possible that the latter study reflects the intensivists' increasing experience, familiarity, and prompt treatment of ANRE. The importance of early treatment is supported by the finding that patients with ANRE treated during the first episode of encephalitis have better outcome than those treated during subsequent episodes (47). The recognized clinical phenotypes (Table 4) also appear to have prognostic significance; children with persistent catatonia tend to have worse outcomes and prolonged encephalopathy (14).

SUMMARY/CONCLUSIONS

ANRE may masquerade as many other neurologic, systemic, or psychiatric illnesses. Erroneous diagnosis may often lead to intensivists being the first clinicians to encounter ANRE. Intensivists should be familiar with the clinical presentation because early recognition, aggressive critical care, systemic steroids, IVIG or plasma exchange, tumor removal, and immunotherapy can significantly impact outcome. The role of second-line immunotherapies in early or refractory disease requires further study. Autonomic and neuropsychiatric findings and possible idiosyncratic reactions to treatment may adversely affect patients with ANRE and the clinician needs to be aware of these important issues. Future areas of research should concentrate on the selection and timing of initiation of second-line therapies and the implementation of prolonged immunosuppression.

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