

Autoimmune Encephalitis in Critical Care: Optimizing Immunosuppression

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Abstract

Autoimmune diseases affecting the nervous systems are a common cause of admission to the intensive care unit (ICU). Although there exist several well-described clinical syndromes, patients more commonly present with progressive neurologic dysfunction and laboratory and radiographic evidence of central nervous system (CNS) inflammation. In the critical care setting, the urgency to intervene to prevent permanent damage to the nervous system and secondary injury from the systemic manifestations of these syndromes often conflicts with diagnostic uncertainty. Furthermore, treatment is limited by current therapeutic agents that remain non-specific for individual diseases, especially for those whose pathophysiology remains unclear. Primary autoimmune, paraneoplastic, parainfectious, and iatrogenic neurologic disorders all share the common underlying pathophysiology of an adaptive immune response directed against an antigen within the nervous system. Several different mechanisms of immune dysfunction are responsible for pathogenesis within each of these categories of disease, and it is at this level of pathophysiology that the most effective and appropriate therapeutic decisions are made. In this review, we outline the basic diagnostic and therapeutic principles in the management of autoimmune diseases of the nervous system in the ICU. We approach these disorders not as lists of distinct clinical syndromes or molecular targets of autoimmunity but rather as clusters of syndromes based on these common underlying mechanisms of immune dysfunction. This approach emphasizes early intervention over precise diagnosis. As our understanding of the immune system continues to grow, this framework will allow for a more sophisticated approach to the management of patients with these complex, often devastating but frequently reversible, neurologic illnesses.

Keywords

- ▶ autoimmune neurology
- ▶ paraneoplastic disorder
- ▶ limbic encephalitis
- ▶ neurologic disorder

Autoimmune and noninfectious inflammatory disorders of the central and peripheral nervous systems encompass a group of diseases increasingly encountered in the intensive care unit (ICU).¹ Traditionally, these disorders are reviewed as a list of diseases with corresponding diagnostic guidelines

and treatment options. However, this approach is less relevant in fulminant disorders presenting to an ICU, when a comprehensive diagnostic workup cannot feasibly be completed prior to the need for intervention to prevent further neurologic injury. Additionally, despite having the clinical,

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laboratory, and radiographic markers of autoimmunity, some patients elude formal diagnosis.

In recent years, research into the basic immunological processes underlying many of these syndromes has revealed several common pathophysiologic mechanisms. At the most basic level, all autoimmune disorders of the nervous system are caused by an adaptive immune response directed against an antigen within the nervous system. Several overlapping categories of autoimmune neurological disease—including primary autoimmune, paraneoplastic, and parainfectious—are mediated by the abnormal adaptive immune response. The pathologic response is induced by either autoantigens (self-antigens) or foreign antigens. Autoantigens recruit the adaptive immune system in autoimmune and paraneoplastic disorders. In paraneoplastic disorders, which occur in the context of a neoplasm, the immune response is directed against neuronal antigens that are ectopically expressed by the tumor (e.g., limbic encephalitis caused by the expression of the ANNA-1 (Hu) antigen by small cell lung cancer).² Parainfectious conditions are mediated by an abnormal or enhanced immune response triggered by a foreign antigen (e.g., Guillain-Barré syndrome caused by molecular mimicry resulting in the production of antiganglioside antibodies).³ Some conditions, such as anti-NMDA receptor encephalitis, can be autoimmune (without an associated neoplasm), paraneoplastic (related to ovarian teratoma),⁴ or parainfectious (as in post-HSV anti-NMDA receptor encephalitis).⁵ Although the source of the inciting antigen may vary, the underlying mechanism of immune dysfunction is likely the same in each of these settings. Iatrogenic autoimmune neurologic disorders are now garnering increased recognition, given the rise in the incidence of these disorders as a result of powerful immune-activating therapies for oncologic indications.⁶ With the increasing use of immune checkpoint inhibitors and chimeric antigen receptor (CAR) T cells for the treatment of cancer, the incidence of these disorders is likely to continue to rise in coming years.

As such, many of these disorders are better classified not by the specific autoantigen involved but rather by their common underlying pathogenic mechanisms of immune dysfunction. This is important because the presence of certain autoantibodies, such as anti-GAD65 or anti-ANNA-1 (Hu), can often be observed in several different autoimmune neurologic syndromes^{3,7} and in certain cases may simply be a marker for an autoimmune process with an unknown pathologic target (e.g., anti-thyroid peroxidase [TPO] in Hashimoto's encephalopathy^{8,9}). Additionally, as described earlier, more than one pathogenic mechanism can give rise to the same clinical syndrome.³ As an example, limbic encephalitis can be caused by autoantibodies against NMDA receptor and T-cell-mediated cytotoxicity associated with anti-ANNA1 (Hu) antibodies. Ultimately, though, the key to this classification scheme, based on mechanism of underlying immune dysfunction, is that it emphasizes early disease-modifying treatment above definitive diagnosis. Furthermore, clinical syndromes that elude formal diagnosis can at the very least be characterized immunologically to guide a rational approach to empiric therapy in the ICU.

Immune mechanisms and related pathology that are implicated in autoimmune disorders of the nervous system can be classified into disorders of T-cell-mediated pathology, autoantibody-mediated pathology, granulomatous inflammation, autoinflammatory pathology, and iatrogenic activation of a specific immune process or target (→ **Table 1**).

Iatrogenic Autoimmunity

Iatrogenic autoimmunity is not a novel concept. Drug-induced lupus is a well-established adverse effect of several nonimmunomodulatory drugs, including procainamide, hydralazine, and minocycline. The incidence of iatrogenic autoimmunity has risen with the introduction of immunomodulatory therapeutics, including interferon- α , tumor necrosis factor- α (TNF α) inhibitors and, most recently, checkpoint inhibitors and genetically altered CAR-T cells.⁶ Despite the risk of development of systemic and CNS autoimmune disorders, the use of immunomodulatory therapies has become the standard of care in patients with autoimmune disorders and for many oncologic indications, such as advanced melanoma. Thus, understanding and early recognition of their CNS-related adverse effects will be imperative. For example, interferon- α has been linked to the exacerbation of psoriasis and sarcoidosis¹⁰ and the development of autoimmunity manifesting as vasculitis, inflammatory arthritis, and drug-induced lupus, among others. TNF α inhibitors, which are typically used for the management of rheumatoid arthritis and inflammatory bowel disease, carry an increased risk for CNS and peripheral nervous system demyelination^{11,12} and drug-induced lupus.^{13,14}

Immune checkpoint inhibitors are a novel class of therapeutics designed to target the inhibitory pathways in the immune system that maintain self-tolerance and modulate the immune response.¹⁵ Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) was the first clinically targeted immune checkpoint receptor and functions by regulating the central expansion of T cells. The interaction of T-cell-expressed CTLA-4 with CD80 or CD86 on antigen-presenting cells blocks T-cell costimulation and abrogates an activated T-cell response. Inhibition of CTLA-4 thus overcomes a block in costimulatory signals that are required for activation of both naive T cells and resting clones, harnessing the host's native immune response against cancer.^{15,16} Another clinically relevant immune checkpoint receptor, programmed cell death protein 1 (PD-1), and its ligand (PD-L1) have been targeted to prevent the inhibition of cytotoxic T cells via upregulated ligands PD-L1 and PD-L2 in the tumor microenvironment.¹⁵ The checkpoint inhibitors ipilimumab (human antibody to CTLA-4) and pembrolizumab and nivolumab (PD-1 antagonists) and combination strategies with immunotherapy have offered cancer patients durable disease control. However, they have also unmasked unique neurological toxicities that can range from minor headaches and confusional states to severe disabling demyelinating disorders and immune-mediated encephalitis.¹⁷ The incidence of immune-related neurological adverse events with the use of checkpoint inhibitors is reported to be as high as 1%.¹⁸ Checkpoint inhibitors may trigger the immune response against the pituitary gland¹⁹ and specific neuronal antigens, leading to autoimmune

Table 1 Autoimmune CNS diseases and treatments classified by mechanism of underlying immune dysfunction

Predominant pathophysiology	T cell mediated	B cell (autoantibody) mediated	Granulomatous disorders	Autoinflammatory disorders	NOS	Iatrogenic
Disorders	Multiple sclerosis	SLE	Sarcoidosis	Behçet's disease	Susac's syndrome	Checkpoint inhibitors
	ADEM	Demyelinating disorders associated with anti-AQP4 (NMO) and anti-MOG antibodies	GCA	Monogenic periodic fever syndromes	Hashimoto encephalopathy (steroid-responsive encephalopathy associated with autoimmune thyroiditis)	CAR-T
	PACNS (PCNSV)	Miller-Fisher syndrome (anti-GQ1b antibodies)	Granulomatosis with polyangiitis (Wegener's granulomatosis)		Transverse myelitis NOS	
	Aβ-related angiitis	Bickerstaff encephalitis (anti-GQ1b antibodies)				
	IgG4-RD	Antiphospholipid syndrome				
	Sjögren's syndrome	Antibodies against cell-surface synaptic receptors and ion channels: NMDA, AMPA, LGI1, CASPR2, GABA-A GABA-B, glycine receptor, mGluR1, mGluR5, DR2, DPPX, VGCC, AChR				
	Antibodies against intracellular antigens: ANNA-1 (Hu), ANNA-2 (Ri), ANNA-3, Ma1/Ma2, CV2/CRMP5, PCA-1 (Yo), PCA-2, GFAP amphiphysin, ^a GAD65 ^a					
	CLIPPERS					
	Glucocorticoids	Glucocorticoids	Glucocorticoids	Glucocorticoids	Glucocorticoids	Anti-IL-6R (tocilizumab), anti-IL6 (siltuximab)
	Cyclophosphamide	Plasma exchange	TNFα inhibitors (GCA does not respond)	TNFα inhibitors	Cyclophosphamide	NSAIDs
Treatments	Anti-CD20 targeting therapies	IVIg	Anti-CD20 targeting therapies		Anti-CD20 targeting therapies	Glucocorticoids
	Natalizumab	Anti-CD20 targeting therapies	Cyclophosphamide			
		Anti-C5 (eculizumab)	Anti-IL-6R (tocilizumab)			
		Anti-IL-6R (tocilizumab)				

Abbreviations: ADEM, acute disseminated encephalomyelitis; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; GCA, giant cell arteritis; IgG4-related disease; NMOSD, neuromyelitis optica spectrum disorders; NOS, not otherwise specified; PACNS, primary angiitis of the central nervous system; PCNSV, primary CNS vasculitis; SLE, systemic lupus erythematosus.

^aAutoantibodies to intracellular synaptic antigens GAD65 and amphiphysin are probably not pathogenic.

Table 2 CNS disorders associated with immune-mediated treatments

Treatment class	Medication	Clinical syndrome
Anti-TNF α	Adalimumab Etanercept Infliximab	Demyelinating disorders ¹³ (CNS, including optic neuritis, ⁷⁵ PNS)
Anti-IL-6R	Tocilizumab	Demyelinating disorders, multiple sclerosis ⁷⁶ Cognitive impairment with leukoencephalopathy ⁶
Anti-PD1/L1	Nivolumab Pembrolizumab	Myasthenia gravis ⁷⁷ Encephalitis ¹⁷ Demyelinating disorders ⁷⁸ PRES Stiff-person syndrome ⁷⁹
Ant CTLA-4	Abatacept Belatacept Ipilimumab	Hypophysitis ¹⁸ Ischemic stroke ⁷⁸ PRES ⁷⁸ Myasthenia gravis ⁷⁸ Guillain-Barré syndrome ¹⁷

Abbreviations: CNS, central nervous system; PNS, peripheral nervous system; PRES, posterior reversible leukoencephalopathy syndrome.

encephalitis,²⁰ even associated with anti-NMDA receptor antibodies reported in a single case.²¹ Ongoing development and use of checkpoint inhibitors will necessitate clinicians to become even more vigilant in their evaluation of adverse neurologic events and assessing for induced autoimmunity, especially given the broad spectrum of possible clinical syndromes (►Table 2).

CAR-T cells are genetically modified T cells that have a fabricated antigen receptor from multiple sources engineered to a specific target cell antigen. A patient's own cells are isolated, genetically modified, cloned, and reinfused to redirect T-cell specificity to a specific tumor-associated antigen.²² New generations of CAR-T cells have incorporated a costimulatory domain that offer a potentially durable treatment response but leave patients susceptible to potential side effects for years following therapy. Cytokine release syndrome (CRS) is the most common side effect encountered with CAR-T-cell therapy, and results from T-cell activation, proliferation, and production of endogenous cytokines.²³ Symptoms can span fever and flu-like syndromes to systemic shock and multiorgan failure including profound neurotoxicity. These neurologic symptoms may range from headache and confusion to frank delirium, aphasia, seizures, and, in severe cases, coma.^{23,24} The mechanism for these immune-mediated side effects are still being elucidated, but organ damage may occur by autoimmune mechanisms when CAR-T cells cross-react with native host antigens.^{25,26} Early recognition of side effects from CAR-T-cell therapy is essential. A grading scale for severity of CRS ranging from 1 to 5 has been employed to ensure adequate monitoring, with 1 and 2 representing symptoms that are non-life-threatening and 3 and 4 representing life-threatening symptoms usually requiring ICU level care.²³

T-Cell-Mediated Autoimmunity

It should be noted that not all autoantibodies associated with neuroinflammatory conditions have a direct pathogenic role. Autoantibodies against intracellular cytoplasmic antigens, such as ANNA-1 (Hu), ANNA-2 (Ri), CV2/CRMP5, PCA-1 (Yo), and GFAP, are biomarkers of disease that are probably T cell mediated (►Table 1).³ Effector T cells uniformly cause cell death, which implies that such T-cell-mediated damage is irreversible and response to treatment is unfavorable.

Autoantibody-Mediated Autoimmunity

Autoantibodies have a pathogenic role when targeting surface antigens, such as AQP4, MOG, NMDA receptor, AMPA receptor, LGI1, CASPR2, and acetylcholine receptor (AChR) (►Table 1). They cause cellular dysfunction or injury through several different mechanisms, including receptor agonist or antagonist effect, antigen (receptor) internalization, activation of the complement, and antibody-dependent cell-mediated cytotoxicity (ADCC).^{27,28} Receptor agonist and antagonist effect as well as receptor internalization is reversible and effects of rapidly instituted immunotherapy are commonly very favorable.

Other Mechanisms of Autoimmunity and Neuroinflammation

Granulomatous inflammation is a form of chronic inflammation defined by the presence of histiocytes (activated macrophages), which engage in interaction with CD4+ T cells. The histiocytes may coalesce to form multinucleated giant cells. Examples of granulomatous diseases include sarcoidosis and giant cell arteritis (GCAs; ►Table 1). Auto-inflammatory disorders are driven by dysregulated innate rather than adaptive immunity.²⁹ In certain conditions, the mechanism of autoimmunity cannot be elucidated and is reported here as not otherwise specified (NOS).³⁰

Autoantigens in the Nervous System and Associated Disorders

Antigens targeted by autoantibodies and T cells in primary neurologic autoimmune disorders are expressed by glia or neuronal cells. Examples of diseases characterized by glial autoimmunity include neuromyelitis optica spectrum disorders (NMOSD) mediated by antibodies to aquaporin-4 (AQP4),³¹ conditions mediated by antibodies to myelin oligodendrocyte glycoprotein (MOG),³² and a steroid-responsive meningoencephalomyelitis associated with antibodies to glial fibrillary acidic protein (GFAP).³³ The spectrum of conditions associated with neuronal autoimmunity is much wider and depends on the cell types that are targeted, function of the targeted antigen, and immunopathogenic mechanisms that are recruited by T cells or autoantibodies.^{3,34–36} Clinically recognizable autoimmune syndromes include limbic encephalitis, Bickerstaff brainstem encephalitis, Miller Fisher syndrome, neuromyelitis optica (NMO), subacute cerebellar degeneration, opsoclonus-myoclonus, stiff-person syndrome, Morvan syndrome, sensory neuronopathy

Table 3 Well-characterized (“classic”) autoimmune syndromes of the CNS

Classic syndromes	Etiologies
Limbic encephalitis	Paraneoplastic or primary autoimmune, HSV, HHV6, syphilis
With faciobrachial dystonic seizures, hyponatremia	Anti-LGI1 antibodies
With abnormal behavior (psychiatric manifestations), movement disorder (dyskinesias), dysautonomia	Anti-NMDAR antibodies
Cerebellar ataxia (subacute cerebellar degeneration)	Paraneoplastic [anti-PCA1 (Yo)], autoimmune (mGluR1, GAD65), parainfectious and infectious (VZV, EBV, CJD), toxic/metabolic [ethanol, phenytoin, lithium, chemotherapy (cytarabine), vitamin E deficiency], genetic [(spino) cerebellar ataxias] etiologies
Opsoclonus-myoclonus(-ataxia)	Anti-ANNA-2 (Ri), anti-ANNA1 (Hu) antibodies
Neuromyelitis optica	Anti-AQP4, anti-MOG antibodies
Miller-Fisher syndrome	Anti-GQ1b antibodies
Stiff-person syndrome	Anti-GAD65, anti-amphiphysin, anti-glycine receptor antibodies
Morvan syndrome (myokymia or neuromyotonia, dysautonomia, sleep disturbance, encephalopathy with visual hallucinations)	Anti-CASPR2 antibodies
Sensory ganglionopathy (neuronopathy)	Paraneoplastic [anti-ANNA-1 (Hu) antibodies], Sjögren syndrome, pyridoxine intoxication, platinum-based chemotherapy
Myasthenia gravis	Anti-AChR, anti-MuSK antibodies
Lambert-Eaton myasthenic syndrome	Anti-VGCC antibodies

Abbreviations: CJD, Creutzfeldt–Jakob disease; EBV, Epstein–Barr virus; HHV6, human herpesvirus 6; HSV, herpes simplex virus; VZV, varicella zoster virus.

(ganglionopathy), myasthenia gravis (MG), and Lambert-Eaton myasthenic syndrome (→ **Table 3**). The majority of the listed conditions have been associated with several autoantibodies. Conversely, the same antibody can cause different syndromes; for example, anti-ANNA-1 (Hu) antibody has been associated with limbic encephalitis and sensory ganglionopathy.

As our understanding of the basic pathologic mechanisms underlying autoimmunity continues to grow, it is very likely that this approach will become of increasing importance in the treatment of acute neuroinflammatory disorders. At present, this approach will hopefully be of help in guiding treatment decisions in these otherwise seemingly “data-free” zones of critical care medicine. For this reason, we will organize our discussion of these disorders on the pathophysiology of the underlying immune dysfunction, workup strategies, and available interventions. While there is an attempt to cluster these groups of disorders based on immunological processes involved, we do recognize that frequently multiple immunological pathways are implicated and multiple classes of interventions may be effective. Treatment strategies will focus on the spectrum of potential risk/benefit ratios for currently available immunologic therapies. Unfortunately, these disorders frequently remain untreated or undertreated because of difficulties with establishing the diagnosis, especially in cases when histopathological evaluation is essential. We suggest organizing these disorders based on the predominant pathophysiology of the underlying immune dysfunction, diagnostic strategies, and available interventions. This approach allows for the possibility of rapid interventions with empiric therapies in cases where diagnosis remains elusive.

Epidemiology

Autoimmune disorders of the nervous system are generally diagnosed at a younger age than other disorders of the nervous system warranting ICU level care, such as infectious or vascular injuries. However, all age groups can be equally affected. Certain disorders are well known to have a preponderance for a particular sex; NMO, multiple sclerosis (MS), Susac's syndrome, younger patients with MG, Sjögren's syndrome,³⁷ Behçet's disease in the United States and northern Europe,^{31,38} and GCA are all more common in women than in men, whereas older patients with MG, chronic inflammatory demyelinating polyneuropathy, acute disseminated encephalomyelitis,³⁹ Guillain-Barré syndrome, and IgG4-related disease (IgG4RD)⁴⁰ are all slightly more common in men. No gender predilection exists in sarcoidosis or primary angiitis of the central nervous system (PACNS).^{41,42}

Diagnostic Strategy

The differential diagnosis of new-onset neurologic dysfunction in the ICU is almost always first described generically as toxic/metabolic, infectious, neoplastic, primary vascular, or inflammatory (autoimmune/parainfectious/paraneoplastic). Autoimmune disorders are suspected when the disease course is subacute (progression over a course of <3 months); there is evidence of inflammation; and toxic, metabolic, hereditary disorders (e.g., mitochondrial diseases, inborn errors of metabolism), infectious, and primary neoplastic processes are less likely or have been excluded.⁷ The course of autoimmune neurologic disease may be monophasic, relapsing-remitting,

or chronic progressive. Parainfectious disorders may present either acutely or subacutely, typically within weeks of the presentation of an inciting antigen (either an infectious disease or vaccination), and, unlike paraneoplastic and autoimmune conditions, more commonly have a monophasic course. Iatrogenic autoimmunity should be considered in patients undergoing therapy with immunomodulatory therapies such as immune checkpoint inhibitors or CAR-T cells.

Autoimmune disorders of the nervous system may be limited to (e.g., isolated neurosarcoidosis) and/or specific for the nervous system (e.g., MS) or may be a manifestation of a systemic disease (e.g., Sjögren syndrome).⁴³ They can affect any neurological domain and frequently have multifocal presentations. Occasionally, well-defined clinical syndromes can be identified and these are extremely helpful; examples are listed in ►Table 3. More frequently though, the clinical findings are nonspecific and additional evidence is sought through diagnostic testing.

All patients in the ICU should undergo a routine laboratory workup to rule out alternative, noninflammatory conditions, and to look for evidence of systemic medical conditions that may be associated with or underlying the presenting neurologic syndrome.^{37,43,44} For example, patients with neurosarcoidosis with hypothalamic involvement may have evidence of hormonal dysfunction, and a normocytic anemia may be seen as a consequence of chronic systemic inflammation in several different rheumatologic disorders.²⁹ These medical conditions may also affect the treatment decisions. ►Table 4 lists a set of basic screening laboratories that can be helpful to rule out alternative diagnoses or support the diagnosis of autoimmune dysfunction. There is an ongoing effort to establish immunologic biomarkers that could serve as an aid in the early identification of iatrogenic complications of immune checkpoint inhibitors and CAR-T cells.

One of the first diagnostic studies obtained in most cases is some form of neuroimaging. Although head computed tomography (CT) is often the most rapidly attainable neuroimaging study, the diagnostic yield of this study in evaluating suspected neuroinflammatory disorders is very poor. CT angiography and postcontrast scans are somewhat more useful, particularly for cases of suspected CNS vasculitis. Magnetic resonance imaging of the brain (and often spine) with and without gadolinium has become the cornerstone of advanced neurological workup in the ICU. Patterns of T2/FLAIR abnormalities, restricted diffusion, contrast enhancement, and perfusion sequences may be specific for certain infectious, toxic, or inflammatory conditions (►Table 5).^{30,31,39,41,42,45,46} More advanced neuroimaging, including spectroscopy and fluorine-18-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/CT (FDG-PET/CT) of the brain, may also help establish a definitive diagnosis or to narrow down the differential diagnosis. Several studies in patients with paraneoplastic encephalitis have indicated PET-based glucose metabolism patterns that extend beyond limbic areas (e.g., frontotemporal *hyper-* and occipital *hypometabolism* in NMDAR encephalitis⁴⁷).⁴⁸ Further studies are still needed to validate the positive and negative predictive value of abnormalities of glucose metabolism in FDG-PET/CT for the diagnosis of autoimmune

Table 4 Suggested clinical and laboratory tests in patients with suspected autoimmune disorders of the nervous system

Alternative pathologies	Markers of inflammation and/or autoimmunity
CBC w/diff ^a	ESR ^a
Electrolytes, glucose ^a	CRP ^a
BUN/Cr ^a	ANA ^a
LFTs ^a	Anti-dsDNA ^a
Ammonia	Extractable nuclear antigens (ENA)—anti-Ro/La ^a
Vitamin B12	ANCA ^a
Coagulation panel ^a	RF, ACPA (anti-citrullinated peptide antibodies)
Thyroid function	Antiphospholipid antibodies
Cortisol	Myositis-specific antibodies
Toxicology screen ^a	Complement levels
Urinalysis and culture ^a	Cryoglobulins
Blood culture	IgG4 level
Serologies for syphilis	Anti-TPO antibodies
SPEP with immunofixation	ACE
Serum-free light chains	HLA-B51
Serum flow cytometry	Anti-AQP4 antibodies
β2 microglobulin	Paraneoplastic antibodies

Abbreviations: ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; BUN, blood urea nitrogen; CBC, complete blood cell count; Cr, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LFTs, liver function tests; RF, rheumatoid factor; SPEP, serum protein electrophoresis; TPO, thyroperoxidase; w/diff, with differential.

^aBasic laboratory evaluations.

encephalitis.⁴⁹ ►Table 6 describes additional imaging modalities and possible diagnostic conclusions to which these studies may lead.

An important test in the workup of inflammatory disorders of the nervous system is the lumbar puncture, and the diagnostic value of cerebrospinal fluid (CSF) analysis in CNS dysfunction cannot be emphasized enough. ►Table 7 lists initial CSF studies that should be requested in all patients with suspected inflammatory neurologic disorders. CSF inflammation is most frequently defined by the presence of one or more of the following: pleocytosis (>5 white blood cells), elevated protein (>50 mg/dL), the presence of oligoclonal bands (OCBs; >1 or higher dependent on local laboratory thresholds), and an elevated IgG index (>0.66). Hypoglycorrhachia (glucose <45 mg/dL) is typically seen in infectious (bacterial, fungal) and neoplastic conditions (leptomeningeal carcinomatosis), but can be observed in some inflammatory disorders (typically neurosarcoidosis, and also in PACNS and neuro-Behçet's disease).⁵⁰ CSF cytology and flow cytometry may provide further insight into the pathogenesis of the underlying disease process, and can be helpful in identifying neoplastic or therapeutically induced etiologies.⁵¹⁰

Table 5 Magnetic resonance imaging findings and patterns of contrast enhancement

Location and pattern	Possible etiologies
FLAIR hyperintensity in the subarachnoid space	Elevated CSF protein/cells—meningitis, carcinomatosis; artifact (hyperoxygenation, propofol exposure, contrast extravasation)
Mesiotemporal T2/FLAIR hyperintensities	Limbic encephalitis of autoimmune or paraneoplastic etiology, HSV, syphilis, HHV-6
White matter T2/FLAIR hyperintensities (without contrast enhancement) ^a	Multiple sclerosis (classically causes periventricular T2/FLAIR hyperintensities, i.e., “Dawson’s fingers”) Other inflammatory/demyelinating conditions (NMO, ADEM, neurosarcoidosis, Behçet’s disease, Sjögren’s syndrome) Vascular pathologies (vasculitis, migraine, microvascular changes, CAA-related inflammation, Susac’s syndrome, CADASIL, postradiation changes) Arboviruses (classically causes T2/FLAIR hyperintensities of the basal ganglia and deep nuclei) Other viral infections (PML, HIV encephalopathy) Primary neoplasms (glioma, gliomatosis cerebri, lymphomatosis cerebri, intravascular lymphoma) Toxic exposures (methotrexate, cytarabine, toluene, heroin, alcohol) Leukodystrophies and mitochondrial diseases
Cortical DWI “ribboning”	Creutzfeldt–Jacob disease, hypoxic-ischemic brain injury, focal seizures, mitochondrial disease
Microhemorrhages (SWI susceptibility hypointensities)	CAA, CAA-related inflammation, amyloid- β -related angiitis, CADASIL, disseminated intravascular coagulation, H1N1 influenza, ITP, and TTP
Intra-axial rim enhancement ^a	“MAGIC DR”: metastasis, abscess, glioma, infarction, contusion, demyelination (usually “open” ring), radiation necrosis
Pachymeningeal enhancement ^a	Infectious and inflammatory, granulomatous diseases (syphilis, tuberculosis, fungal infections, neurosarcoidosis, granulomatosis with polyangiitis) Other inflammatory conditions (IgG4-related disease, idiopathic hypertrophic pachymeningitis, Tolosa-Hunt, rheumatoid arthritis) Neoplasms (meningioma, lymphoma, metastasis, histiocytic disorders, including Rosai-Dorfman disease)
Leptomeningeal enhancement ^a	Intracranial hypotension, meningitis, leptomeningeal carcinomatosis, neurosarcoidosis, amyloid- β -related angiitis, CAA-related inflammation
Nerve root enhancement ^a	External compression, Guillain-Barré syndrome, Elsberg syndrome, metastasis, neurofibroma, schwannoma, granulomatous disease, Lyme disease, CMV, schistosomiasis

Abbreviations: ADEM, acute disseminated encephalomyelitis; CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CMV, cytomegalovirus; HHV6, human herpesvirus 6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; ITP, idiopathic thrombocytopenic purpura; NMO, neuromyelitis optica; PML, progressive multifocal leukoencephalopathy; TTP, thrombotic thrombocytopenic purpura.

^aContrast enhancement, which results from the breakdown of blood–brain barrier, is indicative of active inflammation.

It is important to recognize that often the only marker of CNS inflammation is the presence of autoantibodies or OCBs, and that even in the absence of elevated protein or pleocytosis, these findings may be signs of pathology.⁵² The classic example is MS; however, OCBs in the CSF are not unique to MS and are simply a marker of the intrathecal production of immunoglobulins. Importantly, whenever CSF is sent for OCB analysis, there should be a parallel investigation of serum with a report on the relative band patterns in the CSF and serum to confirm the presence of intrathecal oligoclonal immunoglobulin production.⁵³ Quantitative IgG analysis (i.e., IgG index) is an informative complementary test but is not considered a substitute for qualitative IgG assessment (OCBs), which has higher sensitivity and specificity. In addition to CSF cell counts with differential, cellular responses can be evaluated by analysis of

T-cell subsets and their CD4/CD8 ratio.⁵⁴ This is, however, of limited value, and the normal values are not standardized (► **Table 8**). As discussed earlier, many autoantibodies serve as biomarkers of disease mediated by T cells.

Electroencephalography is rarely specific but often very informative diagnostically in evaluating patients with altered level of consciousness or localizing pathologic regions within the brain. Occasionally, certain findings may be suggestive of specific disease processes (see ► **Table 6** for details).^{2,9} Additional investigations may be required to narrow down the differential diagnosis, establish a definitive diagnosis, or determine the extent of a systemic disease (► **Table 6**). Whole-body PET/CT may also be used to determine appropriate sites for diagnostic biopsy in patients with multisystem involvement.

Table 6 Imaging and diagnostic studies for evaluation of patients with suspected autoimmune disorders of the nervous system

Diagnostics	Finding	Potential diagnosis
CT/CTA head	Vascular beading	Vasculitis
	Venous engorgement	AVM, fistula, VST
	Atrophy	Neurodegenerative process
CT of the chest, abdomen/pelvis	Mass	Malignancy
MRI spectroscopy	Lactate peak	Metabolic abnormalities
Brain ¹⁸ F-FDG-PET/CT		
	Medial temporal lobe hypermetabolism (patterns of cerebral glucose metabolism described in NMDAR and VGKC encephalitis) ⁴⁷	Limbic encephalitis
	Hypometabolic brain regions (not validated) ⁴⁸	Other forms of autoimmune encephalitis
Whole-body ¹⁸ F-FDG-PET/CT	Areas of FDG avidity	Malignancy, inflammation
EEG	Extreme delta brush	NMDAR encephalitis
	PSWC	CJD
	Periodic temporal discharges	HSV
	Diffuse slowing with triphasic	Metabolic encephalopathy
Mammogram	Breast lesion (cancer)	Conditions associated with several antineuronal antibodies, including anti-amphiphysin
Transvaginal US	Ovarian mass	NMDAR encephalitis
Testicular US	Testicular mass (cancer)	Brainstem, limbic encephalitis, cerebellar degeneration
Dilated fundoscopic examination and fluorescein angiography	Branch retinal artery occlusions with hyperfluorescence of the vessel wall	Susac's syndrome
	Uveitis	Sarcoidosis, Behçet disease, other rheumatologic conditions
	Vitreous opacities, sub-retinal pigment epithelial infiltrates	Intraocular-central nervous system lymphoma
Temporal artery biopsy	Granulomatous inflammation	Giant cell arteritis
Labial salivary gland biopsy	Focal lymphocytic sialadenitis	Sjögren syndrome

Abbreviations: AVM, arteriovenous malformation; CAA, cerebral amyloid angiopathy; CJD, Creutzfeldt–Jakob disease; HSV, herpes simplex virus; ¹⁸F-FDG-PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography; PSWC, periodic sharp wave complexes; US, ultrasound; VST, venous sinus thrombosis.

Often the workup of neurologic disease yields only non-specific markers of inflammation without providing a specific diagnosis, in which case stereotactic brain biopsy may be required to further narrow the pathologic process and guide treatment. When considering CNS biopsy, the potential diagnostic benefit must be weighed against the risk of permanent neurologic injury. With that said, in patients with rapidly progressive neurologic deterioration of uncertain etiology, often the value is sufficiently high and morbidity sufficiently low to justify the use of biopsy.⁵⁵ In general, targets for biopsy should be in regions of active disease involvement on neuroimaging. When the area of active involvement is inaccessible, the potential diagnostic yield of biopsy drops considerably and the utility of such an intervention should be further considered. When feasible, brain and/or meningeal biopsy yields invaluable information regarding the nature of the inflammatory response, the

underlying cellular/immune process, and the microstructural distribution of the inflammation, all of which can have significant impact on the choice of therapy. Demonstration of characteristic histopathological findings is the method of choice for making definitive diagnosis of vasculitis, sarcoidosis, IgG4RD, and neoplasm.^{29,40–42,56}

Treatment Options

In the ICU setting, the clinical examination and diagnostic workup must be focused on identifying specific pathophysiologic processes that allow for early targeted treatment, rather than solely aimed at securing a specific diagnosis. The balance between diagnostic confidence, the risk of disease progression, and the risks of treatments will ultimately define individual patient care. No large randomized controlled trials have been performed in patients with neuroinflammatory conditions,

Table 7 CSF studies consistent with inflammation of the CNS

CSF study	Result
Glucose	Normal
Protein	Elevated
WBCs	5–100
IgG index	>0.66
Oligoclonal bands	>1 (laboratory-dependent value)
Paraneoplastic panel	Positive
New generation sequencing of microbial DNA	Negative
Flow cytometry	Normal
Cytology	Normal
HSV1/HSV2 PCR	Negative
VZV PCR and Ab	Negative
β2 microglobulin	Normal
IgH gene rearrangement	Absent

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; WBCs, white blood cells.

except for MS. The initial therapy often serves both as an initial treatment and a diagnostic test. It should be kept in mind that patients with autoimmune disorders might not respond to initial immunotherapeutic agent or could need intensive and prolonged therapies; conversely, patients with other disorders, such as primary CNS lymphoma, may respond to immunotherapy. ► **Table 1** lists categories of autoimmune pathophysiology and associated disorders as well as potential acute interventions. Glucocorticoids, intravenous immunoglobulin (IVIG), and plasma exchange (plasmapheresis) should be reserved for induction (management of active disease to induce remission), primarily because of their rapid onset and nonspecific effects on the immune system.^{1,57–60} Maintenance immunotherapy includes various agents that modulate immune response more specifically.^{1,59,61} The risk of these interventions is real and may significantly contribute to secondary sequelae such as

opportunistic infections. It is important to realize that this is true for other widely accepted indications for these medications including immune suppression in organ transplantation.

The treatment of immunologic diseases of the brain is not limited to immunomodulation but includes the supportive management of associated secondary symptoms. The clinical course of patients with autoimmune neurologic disorders is frequently complicated by periods of both agitation and paroxysmal sympathetic hyperactivity, each of which may be superimposed on a backdrop of often-profound encephalopathy.^{62,63} There is little data available to guide clinicians about the most appropriate ways to manage these difficult and often refractory symptoms, which frequently lead to major morbidity and mortality for otherwise reversible disorders. Our recommendations for pharmacological interventions are based mainly on experiences with patients who have suffered traumatic brain injury, stroke, and subarachnoid hemorrhage.^{64–66} Overall, we advocate for nonpharmacologic measures, such as promoting the presence of family at the bedside, reinforcement of appropriate cues to promote a normal circadian rhythm, keeping familiar sights and sounds with personal pictures and music in the room, and other delirium precautions. In the event these environmental interventions are insufficient, pharmacological interventions are instituted. Our recommended treatment options are presented in ► **Table 9**. The interventions are grouped into three different sections, which are at times difficult to separate clinically: paroxysmal sympathetic hyperactivity, agitation, and shivering control during aggressive temperature management.^{64–69}

Finally, many of these disorders are paraneoplastic, occurring in the setting of neoplasia (malignant or benign tumors). These lesions are frequently small but need to be identified and treated rapidly to decrease the antigen load.² Testing can often take weeks to occur, whereas neurologic deterioration can occur over hours. For example, surgical resection of an ovarian teratoma identified on imaging in a patient with a clear-cut clinical syndrome of anti-NMDA receptor encephalitis should not be delayed while awaiting the results of serology. Cases of paraneoplastic autoimmune neurologic disorders require multidisciplinary therapy plans developed by neurologists, oncologists, radiation therapists, and surgeons.

Table 8 Selected markers of adaptive immune response in CSF

CSF constituents	Differential diagnosis
Oligoclonal bands > 1 (number of bands for positive result is defined by each laboratory; comparison with serum is mandatory)	Autoimmune diseases with intrathecal immunoglobulin production (MS, ADEM, neurosarcoidosis, Behçet's disease, SLE, Sjögren's syndrome, paraneoplastic or autoimmune disorders caused by antineuronal antibodies) CNS infections (neurosyphilis, neuroborreliosis, HIV encephalitis) Lymphoma
IgG index = (CSF IgG/CSF albumin)/(serum IgG/serum albumin) >0.66 (laboratory-dependent value)	Immunoglobulin targeting antigens within CNS
Autoantibodies	Detection of antineuronal autoantibodies strongly supports the diagnosis of autoimmune encephalitis

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; CSF, cerebrospinal fluid; MS, multiple sclerosis; SLE, systemic lupus erythematosus.

Table 9 Pharmacologic management of sympathetic hyperactivity, agitation, and shivering

Sympathetic hyperactivity		Agitation		Shivering	
Agent	Maximum dose	Agent	Maximum dose	Agent	Maximum dose
Propranolol	520 mg/d	Propranolol	520 mg/d	Acetaminophen	4 g/d
Clonidine	1.2 mg/d	Pindolol	100 mg/d	Buspirone	90 mg/d
Morphine	20 mg/d	Dexmedetomidine	1 mg/kg/h	Magnesium	1 g/h
Methadone	40 mg/d	Benzodiazepines	NA	Meperidine	400 mg/d
Benzodiazepines	NA	Propofol	83 µg/kg/min	Fentanyl	25 µg/h
Gabapentin	4,800 mg/d	Ketamine	0.5 mg/kg/h	Dantrolene	2.5 mg/kg
Dantrolene	10 mg/kg/d	Quetiapine	300 mg/d	Clonidine	1.2 mg/d
Baclofen (PO/IT)	80 mg/d	Olanzapine	20 mg/d	Dexmedetomidine	1 mg/kg/h
Bromocriptine	40 mg/d	Ziprasidone	80 mg/d	Propofol	83 µg/kg/min
Chlorpromazine	60 mg/d	Loxapine	250 mg/d	Neuromuscular paralysis	N/A
Propofol	83 µg/kg/min	Haloperidol	100 mg/d		
		Clozapine	750 mg/d		
		Valproate	2,250 mg/d		
		Lamotrigine	50 mg/d		
		Phenobarbital	240 mg × 1		
		Carbamazepine	800 mg/d		
		Buspirone	20 mg/d		
		Amitriptyline	75 mg/d		
		Sertraline	200 mg/d		
		Lithium	900 mg/d		
		Amantadine	400 mg/d		
		Methylphenidate	30 mg/d		

Table 10 Suggested pretreatment screening studies and baseline evaluations before initiating immunosuppressive agents

Infection screens	Other diagnostic studies
Hepatitis B screening (HBsAg, anti-HBs, anti-HBc) ^a	CBC ^a
Hepatitis C screening (anti-HCV) ^a	BUN/Cr ^a
HIV antibodies, ^a PCR; T-cell CD4 count	LFTs ^a
TB testing (PPD/IGRA) ^a	hCG
JC virus antibody index	25-hydroxycholecalciferol (vitamin D) level
<i>Strongyloides stercoralis</i> , serology	Bone densitometry
<i>Trypanosoma cruzi</i> , serology	TMPT genotype
	CXR
	Ophthalmologic evaluation
	Immunoglobulin levels (IgM, IgG, IgA)

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; Cr, creatinine; CXR, chest X-ray; HCV, hepatitis C virus; IGRA, interferon-gamma release assay; LFTs, liver function tests; PPD, purified protein derivative; TMPT, 5-thiopurine-methyltransferase.

^aObtained from all patients.

Iatrogenic autoimmune complications of checkpoint inhibitors and CAR-T-cell therapy should always be managed in collaboration with the primary oncologist. Treatment of immune-related adverse events (irAEs) of checkpoint inhibitors includes interruption or permanent discontinuation of their use and may require corticosteroids and possibly even additional immunosuppressants, such as TNFα inhibitors and mycophenolate mofetil.⁷⁰ As described earlier, the most prominent irAE of CAR-T-cell therapy is CRS, which is treated with the recombinant IL-6 receptor antagonist tocilizumab. The neurologic toxicities of CAR-T-cell therapy are generally also treated with corticosteroids, which have a superior blood-brain barrier penetration to tocilizumab and may also act on pathologic immune pathways unrelated to CRS.²⁵

Treatment Risks

Treatment with immunomodulatory agents incurs a significant risk for infection and other systemic side effects. The potential risks of adverse reactions can be minimized by screening evaluations, patient monitoring, and preventative measures. Baseline and screening laboratory testing that should be obtained before introducing immunomodulatory agents is listed in ►Table 10, and preventative measures for infectious and noninfectious complications are outlined based on specific toxicities of individual medications in ►Table 11.⁷¹

Table 11 Immunomodulatory therapies: dosing regimens, key risks and adverse effects, and suggested monitoring and prophylactic strategies

Immunotherapy (mechanisms of action)	Dosing	Major risks	Prophylaxis	Monitoring parameters
Glucocorticoids (genomic effects, nongenomic effects: leukocyte adhesion and cytokine modulation)	Methylprednisolone 1 g IV QD for 3–5 d Prednisone start 1 mg/kg/d (60–80 mg QD) Dexamethasone 1–40 mg Q6H	Hyperglycemia, psychiatric events, infections, adrenal suppression, osteoporosis, osteonecrosis, myopathy, glaucoma, cataracts	PPI, Vitamin D + calcium ± bisphosphonates and alternatives TMP/SMX/ atovaquone/ dapsone	Lipid profile Ophthalmologic evaluation Bone densitometry Q12 months
IVIG (autoantibodies, passive immunization, complement downregulation, cytokine modulation)	2 g/kg over 3–5 d	Hypersensitivity reactions, thromboembolic events, renal failure, aseptic meningitis, hemolytic anemia, neutropenia	Acetaminophen Diphenhydramine	VS during infusion BUN/Cr within 10 d after initiation of IVIG treatment
Plasma exchange (removal of pathogenic antibodies from vascular compartment, cytokine modulation)	1–1.5 plasma volumes, typically 5 exchanges allowing for vascular compartment equilibration between treatments (QOD)	IV access complications; hypocalcemia, hypotension, arrhythmia, coagulopathy; medication removal	Calcium carbonate, fluids, albumin, FFP	CBC, electrolytes, Ig levels, coagulation panel
Cyclophosphamide (DNA alkylation, Th1 suppressor, and Th2 enhancer)	Partners MS: 800 mg/m ² IV Q4 wk × 6 EULAR: 15 mg/kg IV Q2 wk × 3 SLE NIH: 0.5–1 g/m ² Q4 wk × 6 EURO lupus: 500 mg IV Q2 wk × 6	Cytopenias, infections, hemorrhagic cystitis, malignancies (particularly bladder cancer), gonadal toxicity	Aggressive IVF Mesna Antiemetics TMP/SMX/atovaquone/dapsone Fertility preservation measures	CBC w/ diff on days 7, 10, 14, 27–28 after IV, Q2 wk while on PO BUN/Cr Q2 wk UA Q3–6 mo (continue after discontinuation)
Anti-CD20 antibodies (B-cell and plasmablast depletion)	Rituximab 1,000 mg Q2 wk × 2 or 375 mg/m ² Q week × 4 (usually Q6 mo)	Hypersensitivity reactions, hypogammaglobulinemia, CVID, infections, PML	HBV reactivation prophylaxis Acetaminophen Diphenhydramine Methylprednisolone	VS ± telemetry during infusion CBC w/ diff Q2–4 mo, CD19/20 counts IgG/IgM levels
TNFα inhibitors (inhibition of macrophage activation via decrease in TNFR1/2 stimulation)	Infliximab IV 5 mg/kg at 0, 2, 6 wk, then Q4–8 wk Adalimumab SC 40 mg Q2 wk	Hypersensitivity reactions, hepatotoxicity, CNS and PNS demyelination, including optic neuritis, TB reactivation	Treat latent TB HBV reactivation prophylaxis Consider TMP/SMX/atovaquone/dapsone Acetaminophen	VS during infusion CBC w/ diff Q ≥ 6 mo LFTs Q ≥ 6 mo
Azathioprine (DNA intercalation, inhibition of purine synthesis)	Start 1 mg/kg/d (50–100 mg QD), then increase by 50 mg/wk to 2–3 mg/kg/d	Hepatotoxicity, leukopenia and other cytopenias, infections, GI toxicity (nausea, diarrhea)	None	TMPT genotype pretreatment Q1–2 wk while adjusting dose, then Q4–12 wk: CBC w/diff LFTs
Methotrexate (inhibition of thymidylate and purine synthesis)	PO: start 7.5 mg Q wk, then increase to 15–25 mg Q wk SC: start 7.5 mg Q wk, then increase to 10–25 mg Q wk	Nausea, diarrhea, mucositis, cytopenias, hepatotoxicity, (hypersensitivity pneumonitis)	Folic acid QD or folinic acid Q wk Sun protection	CXR pretreatment CBC w/diff Q2–4 wk for first 12 wk, then Q8–12 wk LFTs Q8 wk
Mycophenolate mofetil (inhibition of guanosine synthesis)	Start 250 or 500 mg BID, then increase by 500 mg/d every 1–2 wk to 1,000–1,500 mg BID	Nausea, diarrhea, abdomen pain, hepatotoxicity, cytopenias, hypertension, nephrotoxicity, cough, dyspnea, infections, headache, tremor	Sun protection	Q1–2 wk for first 12 wk, then Q6–8 wk: CBC w/diff BUN/Cr LFTs
Ecilizumab (anti-C5 antibody)	Ecilizumab 400–1,200 mg IV Q2 wk	Hypersensitivity reactions, hypertension, anemia	Acetaminophen Diphenhydramine	Cr, CBC, LDH up to 12 wk after last treatment
Tocilizumab (anti-IL6R antibody)	Tocilizumab 4–8 mg/kg IV Q4 wk or 162 mg SC Q wk	Hypersensitivity reactions, GI perforation, hepatotoxicity, neutropenia, thrombocytopenia, TB reactivation	Acetaminophen Diphenhydramine	CBC, LFTs Q4 wk
Natalizumab (anti-α4-integrin antibody)	300 mg IV Q4 wk	PML, hypersensitivity reactions	Acetaminophen Diphenhydramine	VS during infusion CBC, LFTs Q6 mo, anti-JCV antibodies in seronegative patients Q6 mo

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood cell count; Cr, creatinine; CVID, common variable immunodeficiency; CXR, chest X-ray; FFP, fresh frozen plasma; HBV, hepatitis B virus; IVF, intravenous fluids; IVIG, intravenous immunoglobulin; JCV, JC virus; LDH, lactate dehydrogenase; LFTs, liver function tests; PML, progressive multifocal leukoencephalopathy; PPI, proton pump inhibitor; TB, tuberculosis; Th1/Th2, T helper cell type 1/type2; TMP/SMX, trimethoprim/sulfamethoxazole; TMPT, 5-thiopurine-methyltransferase; TNFR1/2, tumor necrosis factor receptor 1/2; UA, urinalysis; VS, vital signs.

Complications related to chronic immune suppression are due to opportunistic infections or noninfectious etiologies, including cancer; despite these, treatment is generally necessary as the autoimmune disease may lead to permanent neurologic injury. Vaccinations play a significant role in prevention against opportunistic infections in patients who are chronically immune suppressed, and vaccinations should be administered according to established guidelines (e.g., 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host⁷²). However, routine vaccinations against influenza, *Streptococcus pneumoniae*, and zoster are frequently avoided during the period of acute illness, as they may conceivably worsen immunologic disease.

Glucocorticoids and many immunomodulators increase the risk for *Pneumocystis jiroveci* pneumonia (PJP); this risk is more relevant in chronically immune suppressed patient, but antibiotic prophylaxis is frequently considered, in particular as patients started on steroids in the ICU often will require a prolonged taper.

► **Table 11** lists available acute immunomodulatory regimens and associated prophylaxis. It is important to recognize that, while there are limited data guiding the use of these medications, the risk of withholding potentially efficacious treatment may outweigh risks associated with therapeutic agents for rapidly deteriorating patients.

Frequently, screening laboratory tests are positive, but immunologic treatment is still given; in these cases, additional antimicrobials, an infectious disease consultation, or additional discussions with the family regarding relative risks and benefits may be warranted. For example, JC virus (JCV) serologies are often positive prior to initiation of immunemodifying therapy, in which case the JCV antibody index may be useful to assess the relative risk of progressive multifocal leukoencephalopathy (PML) in the individual patient (JCV antibody index >1.5 indicates an increased risk for PML).⁷³ The risk-benefit ratio of any immunosuppressive drug should be discussed with each patient and their family. Given their potential for significant toxicity, obtaining informed consent is required for certain immunosuppressants, such as cyclophosphamide, rituximab, and natalizumab.

Autoimmune neurologic disease is common in the younger people, and family planning should be addressed in each patient of reproductive age. Fertility preservation measures should be instituted in every patient in whom cyclophosphamide use is considered. Adjustment or discontinuation of immunosuppression should be considered before a planned pregnancy. Certain treatments are compatible with pregnancy, including glucocorticoids, IVIG, plasmapheresis, and azathioprine up to 2 mg/kg/day.⁷⁴ TNF α inhibitors are considered reasonably safe within first and second trimester and during lactation. Methotrexate, mycophenolate mofetil, and cyclophosphamide must be discontinued before conception due to proven teratogenicity (pregnancy category D and X). Most biologic agents have limited documentation on safe use in pregnancy and should be discontinued or replaced by other medication before conception.

Immunologic interventions may counteract the primary treatment goal in cases of iatrogenic autoimmune CNS

disorders, where the initial treatment with CAR-T-cell therapy produces a robust tumor lysis response at the cost of CNS toxicity. In these cases, anti-IL-6 therapies such as tocilizumab may be employed first, but ultimately corticosteroids may be required to dampen and, as a result, potentially eliminate the therapeutic CAR-T-cell response.²⁵

Finally, it should be recognized that immunologic interventions often affect the yield of future diagnostic studies. For example, treatment with IVIG will make the interpretation of future serologic studies particularly difficult, and treatment with glucocorticoids can significantly decrease the diagnostic yield of tissue biopsy of certain inflammatory and neoplastic lesions. For this reason, it is reasonable to collect extra serum and necessary tissue biopsies prior to the initiation of therapy.

Conclusion

Autoimmune neurologic disorders in the critical care unit often cause significant morbidity and mortality, and are associated with prolonged and expensive ICU stays. Fortunately, if treated rapidly, these are potentially reversible disorders. Focusing early interventions on appropriate mechanism-based therapy centered on suspected etiology with currently available immunomodulatory agents is essential to prevent irreversible neurologic injury and secure the best chance of a good outcome. Research aimed at expanding our understanding of the basic pathophysiology of these diseases will hopefully allow for more targeted interventions in years to come.

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