2022 Alberta Consensus Guidelines for Diagnosis and Treatment of Autoimmune Encephalitis

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Initial Investigations and Diagnostic criteria of Autoimmune Encephalitis

Encephalitis is a relatively common disease with hospitalization rates estimated around 5-10 per 100 000 population in North America[1,2]. Although viral causes of encephalitis were historically considered the most common, autoimmune encephalitis may match its prevalence[3]. As such, it is increasingly important to recognize autoimmune encephalitis to allow for early treatment, given significant risk for morbidity and mortality with significant potentially for reversibility earlier in the disease course.

Features important to consider surrounding the diagnosis and initial investigations of a person suspected to have autoimmune encephalitis are as follows: (1)as with infectious encephalitis, the presentation is acute and a precipitous decline which requires care in an intensive care setting is common; (2)patients with autoimmune encephalitis can present with fever and a CSF leukocytosis which can be very similar to infectious encephalitis. However, both of these features can also be absent; (3)aside from CSF findings, other paraclinical tests can be normal, have non-specific findings, or are subject to false positive findings; (4) some paraclinical tests can take weeks to be completed and reported. This is particularly relevant when considering the diagnosis and the goal of providing treatment quickly[4,5], and lastly; (5) patient outcomes, especially those that are occurring in the acute setting, are largely clinical in nature. There is a lack of paraclinical tests that accurately prognosticate remission of encephalitis. As a result, the diagnosis and treatment of people with autoimmune encephalitis is predominantly directed by their clinical evaluation.

The first and most important step in the diagnosis of autoimmune encephalitis is a detailed neurological history and neurological examination. The time course is typically acute to subacute in nature, chronic evolution is unusual and would suggest a degenerative cause, while hyper acute presentations are suggestive of a vascular cause. History of an underlying malignancy may suggest a paraneoplastic cause of autoimmune encephalitis, though many patients with paraneoplastic autoimmune encephalitis will have no preceding history of malignancy. Idiopathic autoimmune encephalitis may have history of a preceding viral illness, herpes encephalitis, or use of TNF alpha antagonists, alemtuzumab, daclizumab or checkpoint inhibitors. Although in patients using checkpoint inhibitors, paraneoplastic causes need also be considered. Many patients however will have none of these associations in their preceding history.

Neurological exam findings can include alterations in mental status and memory, as well as focal neurological deficits, with the presentation depending on the anatomical structures involved. Clinical presentations involved with a specific anti-neural antibody can have stereotypical features, but there is commonly overlap of phenotypes among multiple anti-neural antibodies. As a result, a clinical phenotype is not necessarily predictive of the associated antibody, if discovered[6].

Diagnostic criteria for autoimmune encephalitis have been proposed, with categories of possible, probable and definite autoimmune encephalitis. The practical application of these criteria is to consider clinical and paraclinical tests which evolve over time for every individual patient, and to then apply that information to further refine or refute the diagnostic category of the patient. The diagnosis of possible autoimmune encephalitis is provided in Table 1.

Table 1. Diagnostic criteria for possible autoimmune encephalitis.
(adapted from Graus et al., 2016[7]).

Diagnosis can be made when all three of the following criteria have been met:
1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms 2. At least one of the following: • New focal CNS findings • Seizures not explained by a previously known seizure disorder • CSF pleocytosis (white blood cell count of more than five cells per mm^3) • MRI features suggestive of encephalitis† 3. Reasonable exclusion of alternative causes *Altered mental status is defined as decreased or altered level of consciousness, lethargy, or personality change. †Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

Table 1 describes the clinical background that should raise initial suspicion for a diagnosis of autoimmune encephalitis. In all criteria for autoimmune encephalitis, alternative diagnoses need always be excluded. Potential alternative diagnoses are extensive. In further refining or refuting the diagnosis of autoimmune encephalitis, the next steps are typically central nervous system imaging, usually MRI of brain (and potentially spinal cord, depending on the clinical presentation). Spinal fluid examination is undertaken early to look for supportive findings of autoimmune encephalitis but also importantly to exclude other causes, especially infectious encephalitis.

Laboratory Testing

Once the diagnosis of AIE is suspected, serologic investigations should be targeted at both ruling out potential mimics as well as confirming antibody positivity. Tables 3 and 4 below provide suggested laboratory studies for patients with suspected AIE. For autoantibody testing, we recommend samples be sent locally to Mitogen laboratory first given the significant costs associated with international reference labs such as the Mayo Clinic. Mitogen's testing catalog includes the following antibody targets: NMDA, VGKC, DPPX, GABAB, AMPA, GAD65, Amphiphysin, Ri (NOVA-1), Yo, Hu, PNMA2 (Ma2/Ta), CV2.1, Recoverin, SOX1, Titin, Zic4 and Tr (DNER).

However, given the differences in techniques between individual laboratories' assays (see table 2 for details of different assay types) as well as the limited scope of antibody testing offered locally, consideration should be given for use of more than one reference laboratory to analyze samples. This is particularly true when the suspicion for autoimmune encephalitis is high and initial analysis returns negative or if any antibody test returns positive that does not match the patient's clinical phenotype, especially at a low titre.

For detection of anti-neural antibodies, studies should be performed in both CSF and serum to improve the yield and diagnostic accuracy. Testing certain antibodies in serum alone can have relatively high false negative rates, while other antibodies may be more likely detected in serum than CSF[8–11].

Table 2. Lab assay techniques for detection of anti-neural antibodies[12,13]

Testing Technique	Description	Comments relating to Neuroimmunology Practice
Tissue based assay/Immunohistochemistry (IHC)	Patient serum or CSF applied to mouse/rat brain sections; staining detected via indirect immunofluorescence (IIF)	- Has the potential to detect novel antibodies - Interpreter dependent
Western blot/Immunoblotting	Patient serum or CSF sample is applied to membrane containing antigen/protein of interest	- Specific testing for intracellular antibody targets (many classical paraneoplastic antibody syndromes) - Results need to be interpreted with caution when used independently
Cell Based Assay (CBA)	A cell line is transfected with DNA encoding the antigen/protein of interest, subsequently expressing that antigen. Patient serum and CSF	- Used for detection of synaptic/cell surface antigen targets - Allows detection of an antibody recognizing the antigen of interest

	applied to the cell based assay and detected via IIF.	in its native conformation

Table 3. Initial Work-up of suspected AIE

Routine Bloodwork	• CBC, liver enzymes, creatinine, urea, extended electrolytes • Ferritin • SPEP • Vitamin B12
Metabolic	• TSH, anti-TPO antibodies, anti-Thyroglobulin antibodies
Systemic Autoimmune	• ANA/ENA panel, anti-dsDNA • C3, C4 • CRP
Infectious Diseases	• HIV, syphilis, EBV serology • Hep B/C* • TB skin test/Quantiferon*
Autoantibody Testing through Mitogen	• Autoimmune Encephalitis Panel (NMDA, VGKC, DPPX, GABAB, AMPA) • GAD65 (not part of the encephalitis panel – may be done through Dynalife depending on location) • Paraneoplastic disease profile • Consider MOG in the appropriate clinical context (see table 4)
Other	• Urinalysis • Nasopharyngeal swab for respiratory viruses

CSF Studies (ideally collect >= 10 ml CSF)	• Cell count, differential, protein
	• Oligoclonal bands
	• Bacterial C+S, Viral panel (VZV, HSV)
	• Mitogen Testing
	  ○ Autoimmune Encephalitis Panel (NMDA, VGKC, DPPX, GABAB, AMPA)
	  ○ GAD65 (not part of the encephalitis panel)
	  ○ Paraneoplastic disease profile
	• CSF Cytopathology
	• Reserve >= 2 ml of CSF for future testing

Imaging/Electrophysiology	• MRI with gadolinium of brain +/- spinal cord (if myelitis is clinically suspected) • CT Chest/Abdo/Pelvis + sex specific malignancy screening. Expanded testing recommend if NMDA is suspected - see Table 10 for details. • Consider PET BODY when suspicion of underlying malignancy is high as this can increase the diagnostic yield for cancer by 18%[14] • EEG if any suspicion of seizure or altered LOC

* Hepatitis and tuberculosis testing is important for future treatment planning and should be obtained before use of steroid or IVIg whenever possible

Table 4. Additional work-up for select phenotypes

Clinical/Imaging Phenotype	Additional Testing
Optic neuritis/transverse myelitis or cortical/brainstem lesions	• NMSOD Profile (Mitogen lab)
Brainstem restricted disease	• Serum anti-GQ1b antibodies (Mitogen Neurological Disease Profile) • NCS/EMG if there is suspicion of Bickerstaff's • AFB in CSF
Prominent sleep disturbance or movement disorder	• Serum/CSF for igLON5 (Mitogen)
Immunocompromised state, unusual travel history, recent immigration	• ID consult
Positive rheumatologic symptom screen or positive systemic autoimmune work-up	• Rheumatology consult

Table 5. Testing not routinely recommended for work-up of AIE

Test	Comments
CSF Flow Cytometry	Yield of flow cytometry in patients without a known history of hematological malignancy has been shown to be extremely low and approaches zero if additionally no gadolinium enhancement is seen on MRI[15]. The Calgary zone hematopathology lab no longer performs flow cytometry unless the above history is present or cytopathology is abnormal
Outside laboratory anti-neural antibody panels (e.g Mayo Clinic, Athena labs)	Send out to external labs should be reserved for cases where the initial screen is negative and clinical suspicion of AIE is very high or if any antibody test returns positive that does not match the patient's clinical phenotype, especially at a low titer
FDG-PET Brain	Can be considered in MR negative cases to help confirm AIE but should be interpreted with caution as specificity of some PET findings is unclear.

MRI Imaging

Patients with autoimmune encephalitis can be classified anatomically according to their presentation. These can be divided into presentations that are predominantly limbic, cortical/subcortical, striatal, diencephalic, cerebellar, encephalomyelitis or meningoencephalitis. As an extension to the neurological history and examination that divides patients into these groups, MRI can be used to demonstrate the appropriate focal or multifocal pathology. However, it is important to note that MRI can often be normal, especially early in the time course of the illness. Repeat imaging can be considered at 2-4 weeks if the initial study is normal. For example, in a common form of autoimmune encephalitis, NMDA receptor

associated encephalitis, over half of patients will have normal imaging in the initial presentation and in some forms of autoimmune encephalitis, MRI is expected to be normal[6,16–18].

Just as different clinical phenotypes with different anti-neural antibodies can co-exist, so too can appearances of pathology on MRI brain. However, there are MRI features that are thought to be characteristic of specific antibodies. Table 6 summarizes some of these associations.

Table 6. Anatomical-MRI findings in association with anti-neural antibodies

(modified from Abboud et al., 2021[19]).

Anatomical classification of autoimmune encephalitis	Corresponding clinical syndromes	Initial MRI Features	Possible associated antibodies
Limbic encephalitis	- Cognitive presentation - Psychiatric presentation - Epileptic presentation	Multiple findings possible, including T2 hyperintensities in the frontal lobe, mesiotemporal, thalamic, basal ganglia, and cerebellum	Hu, CRMP5/CV2, Ma2, NMDAR, AMPAR, LGI1, CASPR2, GAD65, GABABR, DPPX, mGluR5, AK5, Neurexin-3α antibodies
Cortical/subcortical encephalitis	- Cognitive presentation - Epileptic presentation	As for limbic encephalitis, sometimes extensive associated with GABA A antibodies	PCA-2 (MAP1b), NMDAR, GABA A/B R, DPPX, MOG antibodies
Striatal encephalitis	- Movement disorder presentation	Involvement of basal ganglia, sometimes with mesial temporal lobes.	CRMP5/CV2, DR2, NMDAR, LGI1, PD10A antibodies
Diencephalic encephalitis	- Autonomic presentation - Sleep disorder presentation	Bilateral involvement of thalamus and hypothalamus	Ma 1–2, IgLON5, DPPX, AQP4 antibodies
Brainstem encephalitis	- Cognitive presentation - Movement disorder presentation - Cranio-bulbar presentation	Focal involvement of brainstem.	Ri, Ma 1–2, KLHL11, IgLON5, DPPX, AQP4, MOG, GQ1b antibodies
Cerebellitis or cerebellar degeneration	- Ataxic presentation	Often normal MRI of cerebellum	Hu, Ri, Yo, Tr, CASPR2, KLHL11, NIF, mGluR1, GAD65, VGCC antibodies
Meningoencephalitis	- Cognitive presentation - Seizure presentation - Meningeal presentation	Perivascular periventricular radial enhancement	GFAP antibody or seronegative AE
Encephalomyelitis	- Movement disorder presentation including PERM and SPS - Spinal presentation - Opticospinal presentation	Can be normal imaging or involvement of optic nerves and spinal cord	GAD65, amphyphysin, glycine receptor, PCA-2 (MAP1B), GABA A/B R, DPPX, CRMP5/CV2, AQP4, MOG antibodies

AchR, Acetyl Choline Receptor; AE, autoimmune encephalitis; AK5, Adenylate kinase 5 Ab ; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor ; AQP4, aquaporin-4; CASPR, Contactin-associated protein-like ; CRMP5, Collapsin response mediator protein 5 ; DPPX, Dipeptidyl-peptidase-like protein 6 ; GABAR, Gamma-Amino butyric acid Receptor ; GAD65, Glutamic acid decarboxylase 65 ; GFAP, glial fibrillary acidic protein; GQ1b, ganglioside Q1B antibody; IgLON5, immunoglobulin-like cell adhesion molecule 5; KLHL11, kelch-like protein 11 ; LGI1, Leucine-rich glioma inactivated ; mGluR1, Metabotropic glutamate receptor 1 ; mGluR5, Metabotropic glutamate receptor ; MOG, myelin oligodendrocyte glycoprotein; NIF, Neuronal intermediate filament ; NMDAR, N-Methyl D-Aspartate Receptor ; PCA2, Purkinje Cell Cytoplasmic Ab Type 2 ; PERM, progressive encephalomyelitis with rigidity and myoclonus; SPS, stiff person syndrome ; VGCC, voltage gated calcium channel.

CSF Analysis

CSF sampling is the most important investigation in the diagnosis of autoimmune encephalitis. While often helpful in producing evidence to support the diagnosis; of even greater importance is exclusion of infectious encephalitis. As a result, CSF examination often takes place before MRI. CSF should be sent for cells and differential, total protein and glucose content as well as IgG index and oligoclonal bands. Viral studies need be completed including HSV, VZV and others depending on the patient's history. Bacterial, fungal, treponemal and mycobacterial studies should all be considered. For carcinomatous and lymphomatous causes, cytology should be performed. Flow cytometry has very low yield in cases without gadolinium enhancement on MRI or history of hematological malignancy[15]. Occasionally consideration is given for a prionopathy and in the appropriate clinical context CSF should be sent for prion panels including RTQuIC. This however should not be done routinely.

It is important to note that CSF analysis can be abnormal in autoimmune encephalitis, but often is normal and for some syndromes it is rare to have CSF abnormalities. If abnormalities are seen, there may be a mild to moderate leukocytosis. There can be an elevation of protein, but glucose content is typically normal and low CSF glucose should trigger strong consideration for infectious etiologies or leptomeningeal spread of malignancy. IgG index can be elevated and oligoclonal bands can be present, but often this is not the case[20].

EEG

A normal EEG does not absolutely exclude autoimmune encephalitis, although an EEG that is otherwise normal with normal background rhythm, other than non-pathological rhythms such as beta rhythm which can be associated with medication effects, can be helpful to provide further evidence supporting a primary psychiatric disorder, rather than autoimmune encephalitis.

EEG can sometimes provide highly supportive paraclinical information for the diagnosis of autoimmune encephalitis, especially the finding of delta brush in NMDA receptor associated autoimmune encephalitis. More commonly, EEG can be helpful for excluding other presentations such as non-convulsive status epilepticus as the primary presentation of the patient. EEG can have a role in excluding the existence of frequent seizures that are concurrent with autoimmune encephalitis. In the appropriate clinical setting, EEG with periodic sharp wave complexes can be helpful for further support of the diagnosis of Creutzfeld Jacob Disease.

Brain Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

In the absence of focal structural abnormalities on MRI brain, FDG-PET can potentially be used, and has been incorporated into suggested diagnostic criteria for limbic encephalitis, as shown in Table 7. A common pattern seen in FDG-PET is bitemporal hypermetabolism and bilateral parietal-occipital hypometabolism. Studies have demonstrated that FDG-PET can detect changes when MRI brain does not demonstrate structural abnormalities and may also be able

to do this earlier in the course of the disease[21,22]. It is important to note these studies are retrospective, with patients that have been determined to have autoimmune encephalitis.

Further investigation is needed to determine the specificity of FDG-PET findings for autoimmune encephalitis compared to identifying other neurodegenerative, psychiatric or infectious diseases. Also, it is important to consider that immune therapies, anaesthetic agents, psychiatric medications and anti-seizure medication can affect brain metabolism which in turn can affect findings on FDG-PET. Caution should be taken in relying on FDG-PET as a paraclinical test in both refining and refuting the diagnosis of autoimmune encephalitis. It should never be used in isolation but potentially can be helpful in combination with history, neurological examination and remaining paraclinical tests.

Brain Biopsy

Brain biopsy is typically not required for the diagnosis of autoimmune encephalitis. Brain biopsy would be undertaken when a diagnosis other than autoimmune encephalitis is thought to be likely, and done under appropriate indications.

Antibody and Anatomically Specific Diagnosis

The diagnosis of autoimmune encephalitis should initially be suspected in patients based on suggestive features as shown in table 1. Once the diagnosis is considered, it can then be further refined or refuted based on the history, neurological exam and paraclinical tests as above.. As shown in table 6, different subtypes of encephalitis can be categorized according to their anatomical localization. In the same way, the differential diagnosis of autoimmune encephalitis is independently determined by first determining the anatomical localization within the nervous system, as each localization will have its own potential differential diagnosis.

Limbic encephalitis remains one of the more common presentations of AIE and so separate diagnostic criteria for autoimmune limbic encephalitis have been proposed (table 7). These criteria may provide increased diagnostic surety in the context of absent anti-neural antibodies although specificity is unknown. On the other hand, patients that meet the criteria for possible AIE (table 1) and have anti-neural antibodies specific to their appropriate clinical syndrome would then fulfill a diagnosis of that specific antibody-associated autoimmune encephalitis.

One of the more common autoimmune encephalitides is NMDA receptor-associated encephalitis which not uncommonly lacks suggestive changes on MRI. Given the limited sensitivity of MRI in NMDA receptor associated AIE, most NMDA patients would not meet criteria for definite limbic encephalitis. Accordingly, separate criteria for possible and definite NMDA receptor-associated autoimmune encephalitis have also been suggested, as shown in Table 8.

Table 7. Diagnostic criteria for definite autoimmune limbic encephalitis.
(adapted from Graus et al., 2016[7]).

Diagnosis can be made when all four* of the following criteria have been met:
1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system 2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes† 3. At least one of the following: • CSF pleocytosis (white blood cell count of more than five cells per mm3) • EEG with epileptic or slow-wave activity involving the temporal lobes 4. Reasonable exclusion of alternative causes *If one of the first three criteria is not met, a diagnosis of definite limbic encephalitis can be made only with the detection of antibodies against cell-surface, synaptic, or onconeural proteins. †^{18}Fluorodeoxyglucose (^{18}F-FDG) PET can be used to fulfil this criterion. Results from studies from the past 5 years suggest that ^{18}F-FDG-PET imaging might be more sensitive than MRI to show an increase in FDG uptake in normal-appearing medial temporal lobes.

Table 8. Diagnostic criteria for anti-NMDA receptor encephalitis.
(adapted from Graus et al., 2016[7]).

Probable anti-NMDA receptor encephalitis*
Diagnosis can be made when all three of the following criteria have been met:

1. Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:

- Abnormal (psychiatric) behaviour or cognitive dysfunction
- Speech dysfunction (pressured speech, verbal reduction, mutism)
- Seizures
- Movement disorder, dyskinesias, or rigidity/abnormal postures
- Decreased level of consciousness
- Autonomic dysfunction or central hypoventilation

2. At least one of the following laboratory study results:

- Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
- CSF with pleocytosis or oligoclonal bands

3. Reasonable exclusion of other disorders

4. Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,† after reasonable exclusion of other disorders

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis).
†Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay).

There are patients that fit the diagnosis of possible autoimmune encephalitis but do not have anti-neural antibodies and do not meet criteria for definite limbic encephalitis. Once other explainable causes have been excluded, they can be classified as autoantibody-negative but probable autoimmune encephalitis based on the suggested criteria shown in Table 9.

Table 9. Criteria for autoantibody-negative but probable autoimmune encephalitis.
(adapted from Graus et al., 2016[7]).

Diagnosis can be made when all four of the following criteria have been met:
1. Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. Exclusion of well defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)
3. Absence of well characterized autoantibodies in serum and CSF, and at least two of the following criteria: • MRI abnormalities suggestive of autoimmune encephalitis* • CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both* • Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)**
4. Reasonable exclusion of alternative causes
*Some inherited mitochondrial and metabolic disorders can present with symmetric or asymmetric MRI abnormalities and CSF inflammatory changes resembling an acquired autoimmune disorder. **Please note the section on Brain biopsy in the text of this article.

It is important to note that suggested diagnostic criteria provide guidance for directing the diagnosis but do not serve as a specific indication as to when to start immune therapy. For instance, immune system-associated therapies may be indicated very early in the stage of information gathering where patients may only partially fit the diagnosis of possible autoimmune encephalitis. This is especially relevant as early and aggressive treatment has been associated with improved outcome in autoimmune encephalitis[9,23,24]

In terms of the performance of suggested criteria for autoimmune encephalitis, subsequent studies demonstrate need for ongoing revisions, particularly when considering paraclinical tests in the diagnosis of autoimmune encephalitis. In recent retrospective studies that examine

patients that have a final diagnosis of autoimmune encephalitis, in applying suggested criteria, the large majority of patients do not fulfil criteria for definite autoimmune encephalitis, or in one study, none at all. A significant number of patients do not fit probable or even for some patients, possible criteria for autoimmune encephalitis[25–27]

First Line Treatment Algorithm for Autoimmune Encephalitis

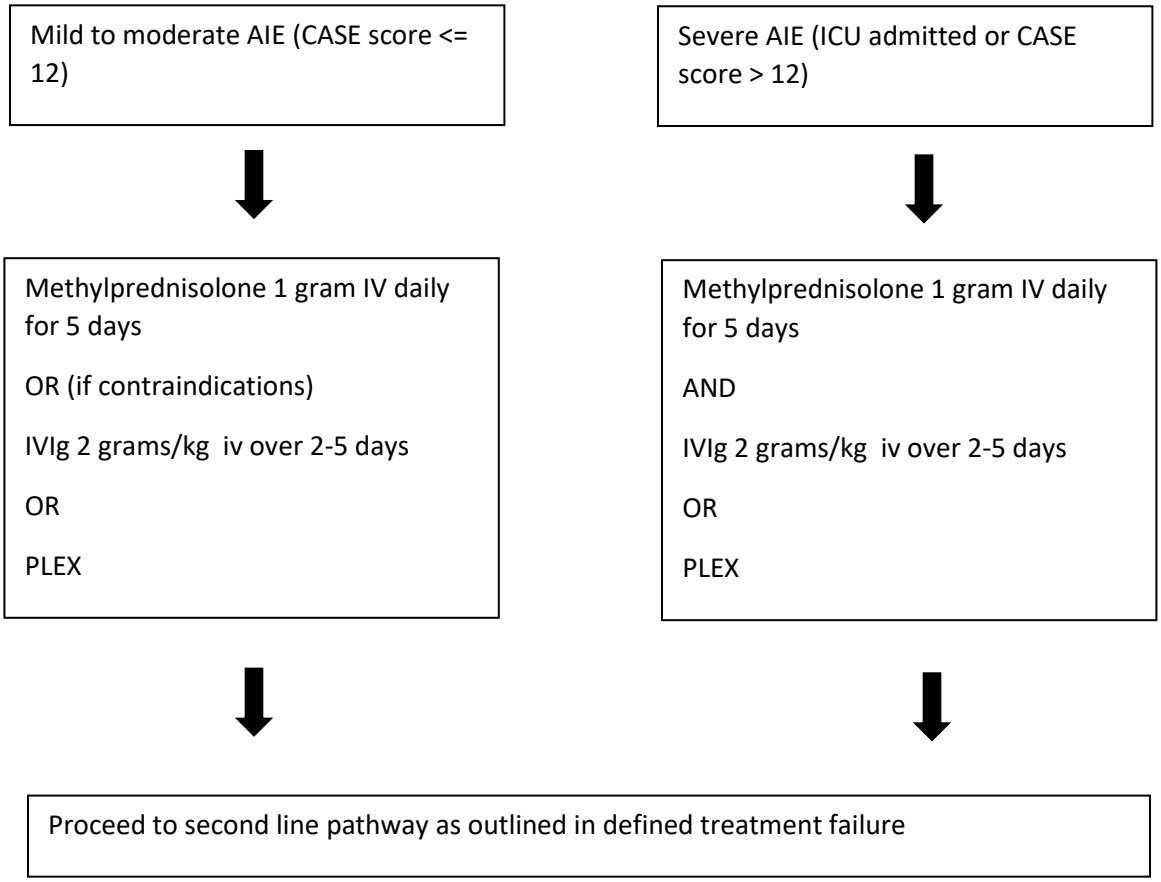
The treatment of autoimmune encephalitis (AIE) is based on anecdotal evidence and expert consensus. The algorithm below (figure 1) pertains to patients with a probable or definite diagnosis of AIE as outlined in the preceding section. Patients with possible AIE should undergo a controlled therapeutic trial as outlined following this section, so as to decide whether to pursue additional 2nd line therapies.

Proposed best practice recommendations have recently been published based on a review of existing literature and expert opinion from 68 members of the Autoimmune Encephalitis Alliance Clinicians Network located in 17 countries[19].

The principles recommended from these guideline include:

1. Early and aggressive therapy is recommended and has been demonstrated to improve outcome[7,9]
2. Consider involving a neurologist with expertise in the management of autoimmune neurological diseases early in the course of disease.
3. Consider transfer of a patient with AIE to a center with experience in the management of patients with AIE and access to PLEX.

Figure 1 - First Line Treatment Algorithm for Autoimmune Encephalitis



AIE: autoimmune encephalitis; iv: intravenous; IVIg: intravenous Ig; PLEX: plasma exchange.

Chronic Use of Corticosteroids

Currently there is no evidence for the use of steroid taper, including if or how a steroid taper should occur or for how long. Expert groups recommend some sort of taper either in the form of high dose oral steroids (0.5 – 1 mg/kg) tapered over 6-12 weeks or ongoing pulse steroids (1 g IV methylprednisolone) weekly initially for 6 weeks followed by every 2 weeks for the next 6 weeks[28,29].

Whether or not to use a steroid taper and the choice of steroid taper should be made on an individual basis. This may depend on the severity of the disease, whether 2nd line therapies are used, and the risk to the patient depending on comorbidities such as cardiovascular risk factors, diabetes, age and risk for infection. Consider involving a neurologist with expertise in the management of autoimmune neurological conditions to aid in clinical decision making.

Possible Autoimmune Encephalitis

Patients presenting with possible autoimmune encephalitis as per the diagnostic criteria merit special consideration. We recommend a controlled immunotherapy trial with distinct and objective pre and post treatment measures of efficacy. For example, should the patient present with frequent seizures, we recommend a reduction in seizure frequency by at least 50% with the immunotherapy trial, while maintaining without alteration if possible, other interventions such as concomitant anti-epileptic therapies. If a person presents with cognitive decline, a predetermined increase in objective cognitive measures should occur in order to determine the efficacy of the trial.

There is no evidence to direct which immunotherapy should be chosen; decision should be made on an individual basis depending on patient factors related to side effects, accessibility, and comorbidities. Options include (1) pulse steroids given for 3 days IV followed by weekly for 6 weeks and every 2 weeks for the subsequent 6 weeks, (2) IVIg 2 grams/kilogram divided over 5 days followed by maintenance therapy for a total of 12 weeks, or (3) plasma exchange in select patients, with a protocol developed in concert with the apheresis team. If there is a significant and objective improvement in clinical measures following immunotherapy trial, we would recommend consideration of a 2nd line immunotherapy. Depending on the choice of immunotherapy, a taper in the first-line medication may be required. Consider involving a neurologist with expertise in the management of autoimmune neurologic conditions to aid in clinical decision making and medication management.

Cancer screening in Autoimmune or Paraneoplastic Encephalitis

The following recommendations consist of expert opinion only as robust evidence for a specific screening protocol does not exist. We suggest the following approach (see Table 10 below) depending on whether or not a specific neoplasm is suspected based on antibody type, medical history or specific clinical presentation.

Table 10. Screening algorithm based on suspected neoplasm[14,19,30]

Suspected Neoplasm	Initial Screen	If Initial Screen Negative	If Second Line Screen Negative
SCLC/Thymoma	Enhanced CT Chest	FDG-PET or Integrated FDG-PET/CT	n/a
Breast Cancer	Mammography	MRI Breast	FDG-PET/CT
Ovarian Teratoma	Transvaginal US	CT or MR pelvis/abdomen	CT-Thorax (for extra pelvic teratoma)
Ovarian Carcinoma	Transvaginal US	Enhanced CT pelvis/abdomen	FDG-PET/CT
Testicular Tumor	Testicular US	Enhanced CT pelvis	Unclear if FDG-PET is of value[31,32]
No specific neoplasm suspected[19,32]	Enhanced CT Chest/Abdomen/Pelvis	Mammogram or breast MR Transvaginal US or MRI pelvis Testicular ultrasound	Full body FDG-PET/CT

Ongoing Screening

If initial screening is negative in a patient with high risk phenotype along with high risk or intermediate-risk antibodies (see table 11), screening should be repeated every 3–6 months for 2-4 years[33]. For patients with intermediate-risk phenotypes and lower-risk or negative antibodies (see table 11) a comprehensive screening for cancer by the time of initial diagnostic assessment is sufficient. Re-screening could be considered in patients who are refractory to treatment or with relapsing neurological disease[33].

Table 11. Risk of Malignancy based on clinical phenotype and antibody status

Malignancy Risk	High	Intermediate	Low
Clinical Phenotype	• Encephalomyelitis • Limbic encephalitis • Rapidly progressive cerebellar syndrome • Opsoclonus-myoclonus	• Encephalitis other than well-defined limbic encephalitis • Brainstem encephalitis, • Morvan syndrome • Stiff-person syndrome	
Confirmed Antibody	• Hu • CV2/CRMP • SOX1 • PCA2/MAP1B • Amphiphysin • Ri/ANNA2 • Yo/PCA-1 • Ma2/Ma • Tr/DNER • KLHL11	• AMPAR • GABAbR • mGLUR5 • P/Q VGCC • NMDAR • CASPR2	• mGLUR1 • GABAaR • CASPR2 • GFAP • GAD65 • LGI1 • DPPX • GlyR • MOG

Definition of Treatment Failure

Defining failure of initial therapy in AIE may be difficult due to symptom fluctuation, transient deficits related to post ictal changes and delayed improvement in some neurologic signs and symptoms, especially cognitive impairment. However, use of second line therapy may be associated with better outcomes so identifying patients who have failed initial treatment remains important[9].

Assessing for improvement remains a clinical determination. We do not recommend using antibody titres as correlates for disease activity as they can fluctuate independent of clinical status[10,34]. Similarly, radiologic worsening can lag behind clinical improvement[35–37] or represent a post-ictal phenomenon and should be interpreted with caution if no clinical worsening is also apparent. Repeating a PET scan of the brain can sometimes be helpful in demonstrating objective improvement (e.g. resolution of focal hypermetabolism). This may be most useful in circumstances where clinical assessment is made difficult due to functional overlay or persistence of some neurological symptoms/signs worrisome for active disease.

We suggest defining treatment failure as one of depending on the severity of presentation:

1. ICU admitted/severely affected patients (CASE score >= 12):
    a. Lack of significant improvement or ongoing worsening in signs/symptoms of AIE (including ongoing uncontrolled seizures) after completion of initial induction therapy
2. Mild to moderately affected patients (CASE Score < 12):
    a. Lack of significant improvement in signs/symptoms of AIE (including ongoing uncontrolled seizures) 5-7 days after completion of initial induction therapy
    OR
    b. Continued progression in signs/symptoms of AIE (including increasing seizure frequency without other cause) after completion of first line induction therapies.

Antibody status ideally should be determined by the time second line therapy is being considered as it may help guide specific treatments or investigations for a neoplastic cause. However, this is not always practical due to lab processing times; lack of antibody testing results should not preclude the use of second line therapies.

Second Line Agents

If the patient meets criteria for treatment failure as above we recommend use of a second line agent, either rituximab or cyclophosphamide (see figure below).

For non-paraneoplastic AIE, we suggest starting with rituximab (2 divided doses of 1 g, 2 weeks apart or 375 mg/m2 weekly for 4 weeks)[19,38].

For probable paraneoplastic cases, treatment and/or resection of the tumor and input from oncology and/or neuro-oncology is strongly recommended in patients who fail first line therapy. Cyclophosphamide could be considered in cases when tumor resection is not possible if supported by oncology but evidence for efficacy is limited.[28]

Protocols for cyclophosphamide vary and little evidence exists to guide optimum therapy. For mild to moderately affected patients monthly infusions of 750 mg/m2 for 3-6 months are suggested[39,40]. For

critically ill patients a myeloablative protocol of 600 mg/m2 with G-CSF support, 5 doses over 8 days can be considered.

Similar to the case of induction treatment, there is a lack of evidence for specific protocols to guide use of corticosteroids during/after second line therapy. A steroid taper should be considered in severe cases to potentially reduce risk of early relapse[28]. Possible options include oral steroids (starting at 1 mg/kg) with a taper over 3-6 months, a second pulse of 1g IV methylprednisolone for 3-5 days during second line therapy followed by weekly pulses for 6-8 weeks or a more rapid taper of oral prednisone over 2-4 weeks.

A repeat course of apheresis could be considered if the patient did show improvement or stabilization with the initial course of apheresis or if apheresis has not been previously attempted. If patients continue to progress after rituximab infusions despite ongoing steroid use and/or apheresis then consideration should be given for cyclophosphamide infusions or tocilizumab[41].

Disease Specific Considerations

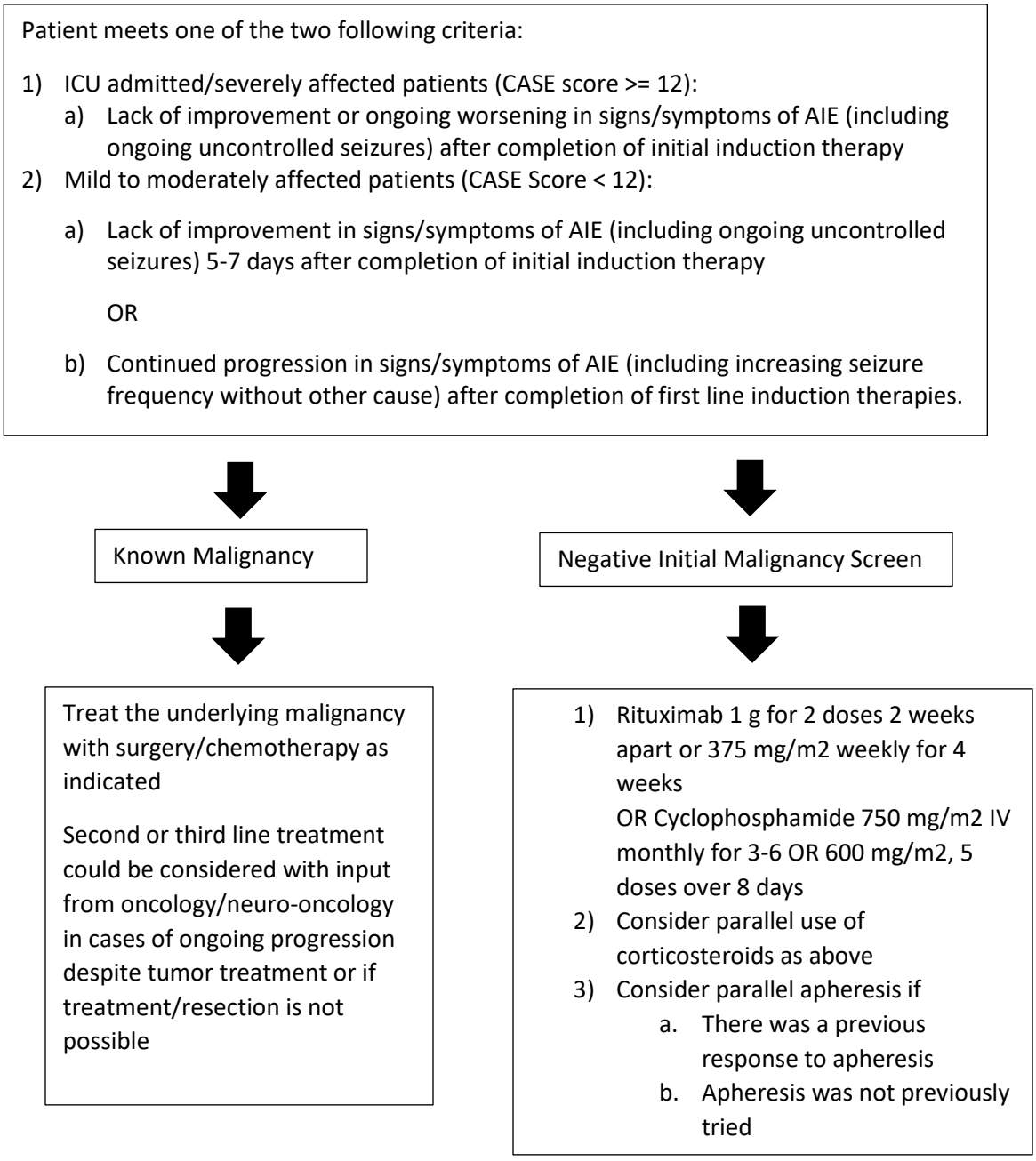
Patients with refractory NMDA receptor encephalitis despite use of second line therapy should be considered for exploratory laparotomy/oophorectomy even in the absence of clear imaging abnormalities[42–44]. Additionally, both tocilizumab (see above) and bortezomib have been shown to be effective in some small case series in refractory NMDA patients and can be considered as a 3rd line treatments[45–47].

Use of Disability and Prognostic Scores

The Clinical Assessment Scale in Encephalitis (CASE) is a disability score designed to measure the severity of AIE (see appendix)[48]. It has not been validated as a longitudinal assessment tool but sequential scoring may be considered to help quantify clinical improvement and/or worsening.

The anti-NMDAR Encephalitis One Year Functional Status (NEOS) score is a disability score specific to NMDAR[49] which is predictive of the functional outcome at one year. Scoring must be done at least 4 weeks after onset of symptoms. While useful for predicting outcome, it has not been validated for guiding treatment decisions and due to the need to wait 4 weeks after onset it may not be practical to use for this purpose.

Figure 2 - Second Line Treatment Algorithm for Refractory Autoimmune Encephalitis



Disease Specific Considerations for NMDA Encephalitis

1) Consider exploratory laparotomy/oophorectomy in patients who failed 2nd line therapy even in the absence of clear findings on pelvic imaging.
2) Bortezomib and Tocilizumab are additional 3rd line options.

Mitigating Risks of Immunosuppression

A general approach to mitigating risks and side effects when prescribing immunosuppressive treatments to patients with autoimmune encephalitis will be discussed here. However, a comprehensive discussion of the risks of individual immunosuppressive drugs noted in this document is beyond the scope of this guideline. Rather this can serve as a brief overview to aid in patient counseling regarding the risks of immunosuppression and provide some insight into minimizing these risks. This section will likely be most relevant to patients undergoing second line therapy or those instituted on chronic immunosuppressive therapies.

While most guidance relating to the use of immunosuppression draws from literature surrounding the clinical contexts of post-transplantation, hematological malignancies, and rheumatological disease, several excellent reviews on the topic of immunosuppression for neurologists have been previously published[50,51].

The risks of immunosuppressive therapies can be broadly grouped into the following categories:

1. Infectious risk (primary infections and reactivated infections)
2. Reproductive health (risk of infertility and/or teratogenic effects)
3. Increased cancer risks
4. Metabolic risks (e.g. bone health)

Defining level of immunosuppression

In 2014, the Infectious Disease Society of America (IDSA) published a clinical practice guidelines regarding vaccinations in immunocompromised patients that defined 'high level immunosuppression' as patients receiving cancer chemotherapy (such as cyclophosphamide), prednisone doses greater or equal to 20mg per day for greater than 14 days, and rituximab, among other clinical contexts[52].This would apply to all patients with AIE who undergo second line therapies but not those on first line therapy alone.

Infectious reactivation

Patient undergoing immunosuppressive treatment are at risk of reactivated infections including hepatitis B, hepatitis C, latent tuberculosis infection (LTB), HIV, and varicella zoster virus (VZV). Strongyloides stercoralis screening (serology and stool sample for ova and parasites) should be considered in patients with epidemiological risk factors including refugees and immigrants coming from endemic areas (Africa, Latin America, Oceania and Asia)[53]. This risk is likely minimal in patients only on first line therapy for AIE; however, early screening at or before first line therapy remains recommended given the difficulty in predicting who might require treatment escalation and the possibility of falsely positive infectious serology in the context of recent IVIg administration[54].

Screening of hepatitis B should include liver enzymes and liver function tests, hepatitis B surface antigen (HBsAg), hepatitis B core (HBc) IgM and IgG, anti-hepatitis B surface antibody (anti-HBsAg) and hepatitis B viral loads in the setting of suspected acute or chronic infection[51]. Patients without evidence of immunity to hepatitis B should be offered immunization if practical, and patients with serological findings suggesting acute or chronic infection should undergo consultation with hepatology.

Screening for hepatitis C should include a hepatitis C antibody, followed by a hepatitis C viral load if the antibody tests results as positive. Hepatology consultation is recommended for patients with suspected active hepatitis C infection.

Reactivation of LTBI is common concern in the setting of immunosuppressive treatments, with highest risk in patients treated with prolonged and high dose corticosteroids, rituximab, and TNF alpha inhibitors. Patients being considered for immunosuppression should preferentially undergo interferon gamma release assay (IGRA) testing, or tuberculin skin testing (TST) if IGRA is not readily available).

Vaccine Preventable Illnesses

Addressing vaccine preventable diseases is an important pillar of reducing infectious risks associated with immunosuppression. In general, where safe, feasible and practical, vaccines should be administered prior to the start of planned immunosuppression with live vaccines given four or more weeks prior and inactivated vaccines given at least 2 or more weeks prior[52]. Live vaccines should be avoided in patients already undergoing immunosuppression. Unfortunately, due to the acute nature of AIE, immunization before institution of first line therapy or even second line therapy is rarely practical. This may be most applicable to patients where chronic immunosuppression is being considered.

As per the IDSA guidelines for vaccination of patients with "chronic inflammatory disease on immunosuppressive medications", recommended vaccinations include the following inactivated vaccines:

a) Pneumococcal conjugate vaccine (PCV-13)
b) Pneumococcal polysacharride vaccine (PPSV-23; initial dose should be given 8 weeks after PCV-13, and a second dose 5 years later[52])
c) Annual immunization with inactivated influenza vaccine
d) Varicella vaccine should be given to patients without evidence of varicella immunity greater than 4 weeks prior to starting immunosuppression
e) Administration of 2 doses of recombinant zoster vaccine (RZV) are recommended in patients aged 18 and over[4]
f) Hepatitis A/B vaccination should be offered for those planning to travel to endemic areas
g) Human Papilloma Virus (HPV) vaccination is recommended for patients 26 years old or younger; a 3 dose regimen is suggested in the immunocompromised. Benefit of vaccination in older adults is unclear[55].
h) In uncertain clinical situations, an infectious disease consultation should be considered.

Vaccination against COVID-19 including updated booster doses is recommended where practical. Worse outcomes have been reported in patients infected with COVID-19 who are exposed to potent immunosuppressive agents although it remains unclear how prior vaccination may alter that risk[56].

Reproductive health/Pregnancy Risk

The effects of immunosuppressive therapy on a patient's reproductive health must be carefully considered and discussed especially given the relatively young patient population affected by autoimmune encephalitis and the nature of treatments often used. The main consideration relates to the likelihood of male or female infertility, and the risk of teratogenicity. Cyclophosphamide (CYC), an alkylating chemotherapeutic, is likely highly teratogenic and is contraindicated in pregnancy although

use in later trimesters may have less risk[57]. Patients receiving cyclophosphamide should be counselled to use contraception and should be appraised of the high likelihood of teratogenicity. CYC is also highly associated with infertility in both men and women, in an age and dose dependent fashion[58]. Fertility consultation should be offered to patients at risk of infertility in this clinical setting if practical.

Management of patients with AIE who are pregnant is outside of the scope of this document but ideally should be undertaken with input from maternal-fetal medicine/obstetrics. In general, plasmapheresis and IVIg are considered safe in pregnancy[59,60]. Older literature suggested that steroids should be avoided in the first trimester due to risk of cleft palate; however more recent studies argue against such an association and obstetrical guidelines support their use in pregnant patients with autoimmune disease, even in early pregnancy[57]. There are no controlled studies addressing the risks associated with rituximab use in pregnancy. Several recent case series/cohort studies are reassuring, although transient b-cell depletion in infants has been seen and there may be an increased risk of pre-term labor[61,62].

Malignancy risk

Of the acute therapies for autoimmune encephalitis, CYC carries the highest risk of future malignancies in a dose dependent fashion. In patients with granulomatosis with polyangiitis undergoing CYC therapy, those receiving >36g cumulative dose had a higher risk of developing non-melanoma skin cancers (NMSC), bladder cancer, and myeloid leukemia. Patients receiving lower doses, had an elevated risk of NMSC only[63,64]. Other patients receiving long term immunosuppression should be referred for age appropriate cancer screening and annual skin checks through their family physician.

Pneumocystis jirovecii (PJP) prophylaxis during corticosteroid use

Pneumocystis jirovecii pneumonia is a well known opportunistic infection complicating HIV-AIDS and immunosuppression therapy for organ transplantation, hematological malignancies and rheumatological disorders. Trimethoprim/sulfamethoxazole (TMP-SMX) is the antibiotic of choice used in prophylaxis of PJP in patients with rheumatic disease receiving high dose glucocorticoids[65,66]. Dapsone (100 mg oral daily) and atovaquone (1500 mg oral suspension daily) are alternate options in those with a contraindication or allergy to TMP-SMX[66]. Prophylaxis should be continued while patients are receiving prednisone equivalent doses >= 15mg/day for more than 4 weeks[65]. Prophylaxis for patients receiving lower doses of prednisone should be considered in patients with other risk factors for developing PJP including advanced age, lymphopenia, or concomitant use of cyclophosphamide/rituxmab[65,66].

Metabolic risk

Short term and prolonged corticosteroid use are complicated by a variety of metabolic challenges including diabetes, hypertension, osteonecrosis, and osteoporosis. Age appropriate cardiovascular risk reduction can be considered for patients undergoing immunosuppression in conjunction with their family physician. All patients receiving 2.5 mg of oral prednisone per day or more, for greater than 3 months, should be considered for measures to mitigate the risk of osteoporosis or for additional investigations and management[67]. General principles for reducing risk include minimizing glucocorticoid dose and duration, utilization of steroid sparing agents, vitamin D and calcium supplementation, and yearly clinical fracture risk assessments. Algorithms for additional testing (bone mineral density, BMD) and treatments (i.e. bisphosphonate therapy) have been published elsewhere[67]. Endocrinological consultation should be sought for patients with multimorbid or complex disease.

Suggested General Pre-Immunosuppression Investigations

Table 12 below lists recommended laboratory studies to be done when considering initiation of immunosuppression in patients with AIE. Ideally, the infectious disease studies should be completed before IVIg or steroid treatment to maximize sensitivity and reduce risk of false positive serologies.

Table 12. Screening lab work to be completed before immunosuppression

Routine Labs	• Complete blood counts • Creatinine • Electrolytes • Liver enzymes and liver function tests • Urinalysis • Hemoglobin A1c • Lipid panel
Infectious disease studies	• Latent tuberculosis screening (tuberculin skin test (TST) or interferon gamma release assay (IGRA); Chest X-ray) • HIV testing • Varicella zoster serology (to confirm immunity) • Hepatitis C serology. If positive, hepatitis C viral load • Hepatitis B serology (hepatitis B core antibody IgM, IgG (HBc IgM, HBc IgG); hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg) • Strongyloides stercoralis serology and stool sample for ova and parasites (in patients from endemic areas or who have resided for more than a year in an endemic area)

Chronic immunosuppression in patients with autoimmune encephalitis and treatment of suspected relapses

Following the acute/initial presentation and treatment of autoimmune encephalitis, many additional decisions are required, which will be discussed below. There is a paucity of data to guide long term management of patients with autoimmune encephalitis and the recommendations below represent the consensus practice of the authors.

Upon completion of acute treatment of autoimmune encephalitis, a bridging treatment or an immunotherapy (typically prednisone) weaning protocol is frequently instituted by expert clinicians. However there is no clear evidence that "bridging treatment" or a prednisone taper reduces subsequent risk of relapse or early recurrence[28]. Ultimately, patients diagnosed with autoimmune encephalitis should be referred to a clinician with expertise in neuro-immunological diseases or to a dedicated multidisciplinary multiple sclerosis (MS)/neuro-immunology clinic for consideration of further clinical and radiological follow-up and detection of clinical relapses. The early use of long-term immunosuppression remains an unanswered question in treating autoimmune encephalitis, however, some initial data suggests early initiation and treatment with rituximab may improve clinical outcomes and reduce relapse rates for certain antibody mediated forms of AIE[68].

In patients who experience recurrent disease, clinical relapses should be treated in a similar matter to the initial presentation of autoimmune encephalitis (discussed elsewhere) followed by consideration of long-term immunosuppression. A relapse rate of 10-35% is reported in the setting of autoimmune encephalitis[69–73], but these rates are highly dependent on specific clinical antibody syndromes. The decision to begin long term immunosuppression is patient and clinical context specific, taking into consideration the following i) relapse risk based on antibody if known ii) type of antibody detected (neuronal cell surface versus intracellular target) iii) autoimmune (likely higher risk of relapse) versus paraneoplastic (likely lower relapse risk)(8) iv) severity of initial attack and residual disability/deficits v) patient risk profile to immunosuppression vi) occurrence of clinical relapse(s)[9].

There is no evidence to support the use of a particular immunosuppressive agent in long term immunosuppression management of autoimmune encephalitis. The decision is patient and clinical context specific and often made on a case by case basis. Patient factors (medical co-morbidities, side effects, family planning) and disease factors (specific antibody related syndrome versus seronegative, putative humoral versus cell mediated mechanism) should be considered. Immunosuppressive agents that are frequently used in this setting include azathioprine, mycophenolate mofetil (MMF), methotrexate, IVIG maintenance therapy, and rituximab[74].

The optimal duration of long term immunosuppression remains another unanswered question and there is currently no evidence to guide duration of long-term immunosuppression in the treatment of autoimmune encephalitis. A duration of 2-3 years is commonly proposed and instituted[28].

While data and evidence are lacking for each of the above decision points, these considerations were the focus of a recent international and collaborative review by clinicians of the Autoimmune Encephalitis Alliance Clinicians Network (AEACN).[28]

Appendix

Clinical Assessment Scale in Encephalitis (CASE) Score

Category	Status	Score
Seizure	None	0
	Controlled seizures	1
	Intractable seizures	2
	Status epilepticus	3
Memory dysfunction	None	0
	Mild (does not affect daily activities)	1
	Moderate (interferes with daily activities)	2
	Severe (no recent memory or unable to communicate)	3
Psychiatric symptoms (delusion, hallucination, disinhibition, aggression)	None	0
	Mild (no need for medical intervention because it does not affect daily activities)	1
	Moderate (need for medical intervention because it interferes with daily activities)	2
	Severe (needs continuous care or admission because of psychiatric symptom) or unable to check	3
Consciousness	Alert (opens eyes spontaneously)	0
	Drowsy (opens eyes to voice)	1
	Stupor (opens eyes to pain)	2
	Comatose (does not open eyes)	3
Language problem	None	0
	Mild (slow but able to express sentences)	1
	Moderate (unable to express full sentences)	2
	Severe (unable to communicate)	3
Dyskinesia/dystonia	None	0
	Mild dyskinesia (does not affect daily activities)	1
	Moderate dyskinesia (interferes with daily activities)	2
	Severe dyskinesia causing secondary medical problems (self-injury, rhabdomyolysis, requires restraint, damages IV lines)	3
Gait instability and ataxia	Normal	0
	Mild, able to walk unassisted	1
	Moderate, assisted walking	2
	Severe, unable to walk	3
Brainstem dysfunction (number of symptoms)	None	0
	Gaze paresis	1
	Tube feeding	1
	Ventilator care due to central hypoventilation	1
Weakness (the mean motor power of all limbs, rounded off)	Normal (grade V)	0
	Mild (grade IV)	1
	Moderate (grade III)	2
	Severe (≤grade II)	3
Total Score		/27

Adapted from Lim et al., 2019[48]

Figure 3 – Summary Diagram for Initial Diagnosis and Treatment of AIE

Suspicion of diagnosis of AIE based on (with exclusion of other causes):

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms

2. At least one of the following: (a) new focal CNS findings, (b) Seizures not explained by a previously known seizure disorder, (c) CSF pleocytosis, (d) MRI features suggestive of encephalitis

↓ Begin initial work-up

Labs
- ☐ CBC, liver enzymes, creatinine, urea, extended electrolytes, CRP, Ferritin, SPEP
- ☐ TSH, anti-TPO antibodies, anti-Thyroglobulin antibodies*
- ☐ ANA/ENA panel, C3, C4
- ☐ HIV, syphilis, EBV serology, VZV titers
- ☐ Mitogen testing - autoimmune encephalitis panel, GAD65, paraneoplastic disease profile
- ☐ Urinalysis, nasopharyngeal swab for respiratory viruses

CSF
- ☐ Cell count, differential, protein, oligoclonal bands
- ☐ Bacterial C+S, Viral panel (VZV, HSV)
- ☐ Mitogen Testing - autoimmune encephalitis panel, GAD65, paraneoplastic disease profile
- ☐ CSF Cytopathology
- ☐ Consider holding >= 2 mls CSF for future testing

Other
- ☐ MRI with gadolinium
- ☐ CT Chest/Abdo/Pelvis + sex specific malignancy screening (testicular US, mammogram, pelvis US/MRI especially if NMDA AIE suspected)◊
- ☐ EEG if any suspicion of seizure or altered LOC

*Keep in mind thyroid antibodies are elevated in 13% of healthy individuals

◊See table 4 for additional work-up depending on specific clinical phenotypes

↓ Initial treatment trial (in parallel with ongoing work-up)

Mild to moderate AIE (CASE score<= 12)
- ☐ Methylprednisolone 1 gram IV daily for 5 days OR (if contraindications) IVIg 2 grams/kg over 2-5 days OR PLEX
- ☐ PJP prophylaxis if on steroid taper

Severe AIE (ICU admitted or CASE score > 12)
- ☐ Methylprednisolone 1 gram IV daily for 5 days AND
- ☐ IVIg 2 grams/kg over 2-5 days OR PLEX
- ☐ Consider steroid taper
- ☐ PJP prophylaxis if on steroid taper

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