The Canadian Journal of Neurological Sciences (2024), **51**, 734–754
doi:10.1017/cjn.2024.16

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Review Article

Canadian Consensus Guidelines for the Diagnosis and Treatment of Autoimmune Encephalitis in Adults

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ABSTRACT: Autoimmune encephalitis is increasingly recognized as a neurologic cause of acute mental status changes with similar prevalence to infectious encephalitis. Despite rising awareness, approaches to diagnosis remain inconsistent and evidence for optimal treatment is limited. The following Canadian guidelines represent a consensus and evidence (where available) based approach to both the diagnosis and treatment of adult patients with autoimmune encephalitis. The guidelines were developed using a modified RAND process and included input from specialists in autoimmune neurology, neuropsychiatry and infectious diseases. These guidelines are targeted at front line clinicians and were created to provide a pragmatic and practical approach to managing such patients in the acute setting.

RÉSUMÉ : Consensus canadien en ce qui a trait aux lignes directrices pour le diagnostic et le traitement de l'encéphalite auto-immune. L'encéphalite auto-immune (EAI) est de plus en plus reconnue comme une cause neurologique de modifications aiguës de l'état mental dont la prévalence est semblable à celle de l'encéphalite infectieuse. Malgré une sensibilisation accrue, les approches diagnostiques demeurent incohérentes et les preuves garantissant un traitement optimal sont limitées. Les lignes directrices canadiennes représentent une approche consensuelle fondée sur des données probantes (lorsque ces dernières sont disponibles) en vue du diagnostic et du traitement de patients adultes atteints d'EAI. Elles ont été élaborées selon un processus RAND modifié et ont bénéficié de l'apport de spécialistes en neurologie auto-immune, en neuropsychiatrie et en maladies infectieuses. Ces lignes directrices s'adressent aux cliniciens de première ligne et ont été créées pour offrir une approche pragmatique et pratique de prise en charge des patients dans un contexte de soins aigus.

Keywords: Autoimmune encephalitis; paraneoplastic encephalitis; treatment guidelines

(Received 25 October 2023; final revisions submitted 23 January 2024; date of acceptance 25 January 2024; First Published online 5 February 2024)

Introduction

Autoimmune encephalitis (AIE) is an inflammatory disease of the brain that classically presents with subacute-onset neurological symptoms. The symptoms associated with specific AIE entities are reflective of selective involvement of central nervous system (CNS) structures by the inflammatory process. AIE has been demonstrated to be at least equal in prevalence to infectious encephalitis with an incidence of 0.2–0.8 per 100,000-person years.[1,2,3] AIE is increasingly being considered in the differential diagnosis of patients presenting with subacute onset of psychiatric symptoms, cognitive decline, and seizures, although misdiagnosis remains common[4].

Unfortunately, there is a paucity of clinical trial data to guide the diagnosis and treatment of AIE, and a lack of formally trained autoimmune neurologists both globally and in Canada. As a result, challenges persist in ensuring patients are accurately diagnosed in a timely manner, undergo complete evaluation, and are rapidly initiated on appropriate therapy when indicated. International best practice recommendations have been published to help address this gap,[5] but lack in regional specificity and contain more detail

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Cite this article: Hahn C, Budhram A, Alikhani K, AlOhaly N, Beecher G, Blevins G, Brooks J, Carruthers R, Comtois J, Cowan J, de Robles P, Hébert J, Kapadia RK, Lapointe S, Mackie A, Mason W, McLane B, Muccilli A, Poliakov I, Smyth P, Williams KG, Uy C, and McCombe JA. (2024) Canadian Consensus Guidelines for the Diagnosis and Treatment of Autoimmune Encephalitis in Adults. *The Canadian Journal of Neurological Sciences* **51**: 734–754, https://doi.org/10.1017/cjn.2024.16

than may be relevant for non-neuroimmunologists. The following guideline document has been developed as a practical and rapid reference for front line neurologists, internal medicine physicians, psychiatrists and other health care workers caring for patients with AIE in hospitals in Canada, while emphasizing throughout that input from a specialist in autoimmune neurology is valuable and should be sought when possible. Additionally, whenever applicable, this document has been tailored to reflect the reality in Canada around access to testing and treatment.

Patients with AIE can consume a disproportionate amount of healthcare resources.[6] As with stroke, we believe that early and effective treatment gives patients the best possible chance of recovery and early data suggests that delays in immunotherapy treatment result in a poor prognosis.[7–9] Neurologists, in conjunction with patients and their families, can play an important role when advocating for prompt access to treatments.

Methodology

Canadian Consensus Guidelines for the Diagnosis and Treatment of Autoimmune Encephalitis in Adults were developed with input from neurologists and psychiatrists with interest and/or training in the field of neuroimmunology from across Canada, as well as an infectious disease physician where relevant. Physicians were identified through the Anti-NMDA Receptor Encephalitis Foundation Directory and Canadian Consortium of MS Clinics. Participants were divided into primary and secondary panels with the primary panel responsible for the comprehensive literature review and drafting of each section and the secondary panel providing initial section review. For diagnosis and management decisions that lack evidence, consensus was attempted using a modified RAND method (see appendix). Areas where consensus was not obtainable are indicated. The guidelines were additionally reviewed by a member of the public previously diagnosed with AIE and endorsed by the leadership of the Anti-NMDA Receptor Encephalitis Foundation.

Diagnosis of autoimmune encephalitis

Epidemiologic considerations

The prevalence of AIE is increasing, likely related to increasing recognition of the diagnosis.[1,2] AIE occurs in people of all ages; however, there are antibody-specific age predilections. For example, N-methyl-d-aspartate receptor (NMDAR) antibody encephalitis occurs more frequently in children and young women[2,3] while leucine-rich glioma-inactivated 1 (LGI1) antibody encephalitis predominates in older men.[3,10] A personal or family history of autoimmune disease may also be a predisposing factor.[12] Other known risk factors for AIE include preceding herpes simplex encephalitis and other forms of infectious encephalitis.[13–17] Immune checkpoint inhibitors (ICIs), used in the treatment of a growing number of malignancies, have also been identified as conferring increased risk for diverse neurological autoimmune complications, including AIE.[18]

Presenting symptoms

AIE typically presents with a subacute onset of symptoms, however, certain neural antibody-associated syndromes may have a more indolent course, such as LGI1 antibody, contactin-associated protein-like 2 (CASPR2) antibody, glutamic acid decarboxylase-65 (GAD65) antibody and dipeptidyl-peptidase-like protein 6 (DPPX) antibody encephalitis.[19–22] An infectious prodrome often occurs days to weeks preceding neuropsychiatric manifestations. Other non-specific prodromal symptoms can include headache, fever, fatigue, sleep disturbance, weight loss, and early psychiatric manifestations.[9]

A detailed history and physical examination are critical to achieving a timely diagnosis of AIE. In one retrospective series examining diagnoses at hospital admission in patients subsequently confirmed as having AIE, only a third were initially thought to have encephalitis; more than 50% of those were initially felt to be of infectious origin.[23] This is reflective of the heterogeneity of clinical presentations of AIE. Misdiagnosis is also not uncommon; a recent study of patients referred to AIE specialty clinics reported a misdiagnosis rate of 27% among patients with an original referral diagnosis of AIE.[4] Factors associated with misdiagnosis include overreliance on isolated serum antibody positivity, and classification of encephalopathy based on non-specific cognitive, psychiatric and/or functional symptoms.[4]

The most common presenting symptoms of AIE are reflected by diagnostic criteria (see below) and consist of acute mental status changes (including cognitive decline and working memory deficits), seizures, and psychiatric symptoms (commonly paranoia, agitation, personality changes and/or hallucinations).[24–26] Other symptoms may be seen depending on the phenotype/antibody association and common phenotypes of AIE include, but are not limited to, limbic encephalitis, cerebellar or brainstem syndromes, and encephalomyelitis.[26] While significant overlap exists in the diverse phenotypes of AIE, certain features should prompt suspicion for a particular antibody. Faciobrachial dystonic seizures, for example, are strongly associated with LGI1 antibody encephalitis.[27]

Diagnostic criteria

Diagnostic criteria for AIE were first proposed by Graus et al. in 2016 (Figure 1).[28] An AIE diagnosis can be classified according to the degree of diagnostic certainty including possible, probable, and definite. While the diagnostic criteria can be helpful in identifying patients in whom a diagnosis of AIE should be considered, they also serve to identify those patients in whom AIE is less likely. In cases where criteria are met only for "possible" AIE after investigations including neural antibody testing are complete, early involvement of a specialist in autoimmune neurology is important. This is especially true if considering a trial of immunotherapy.

Based on the above diagnostic criteria, transition from "possible" to "probable" AIE can be achieved by meeting more specific phenotypic criteria for NMDAR antibody encephalitis or antibody-negative AIE. A diagnosis of definite AIE requires neural specific antibody positivity or meeting specific criteria for limbic encephalitis/acute disseminated encephalomyelitis (ADEM)/Bickerstaff's encephalitis in addition to the criteria for "possible" AIE (Figure 2).

While psychiatric symptoms are common in AIE[9] caution must be exercised in cases of isolated psychiatric manifestations. Some studies report the identification of NMDAR antibody in patients with schizophrenia and psychotic disorders, as well as in healthy control subjects; however, antibody detection in these series

https://doi.org/10.1017/cjn.2024.16 Published online by Cambridge University Press

Diagnosis can be made when all three of the following criteria are 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:**
   a. **New focal CNS findings**
   b. **Seizures not explained by a previously known seizure disorder**
   c. **CSF pleocytosis (white blood cell count of more than five cells per mm^3)**
   d. **MRI suggestive of encephalitisł**
3. **Reasonable exclusion of alternative causes**

***Altered mental status defined as decreased or altered level of consciousness, lethargy or personality change. łBrain 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.**

Reprinted from Lancet Neurology, Vol.15, Graus et al, 'A clinical approach to diagnosis of autoimmune encephalitis', p393, Copyright (2016), with permission from Elsevier. CNS = central nervous system; CSF = cerebral spinal fluid; MRI = magnetic resonance imaging (of the brain); WBC = white blood cell

Figure 1: Diagnostic criteria for possible autoimmune encephalitis.

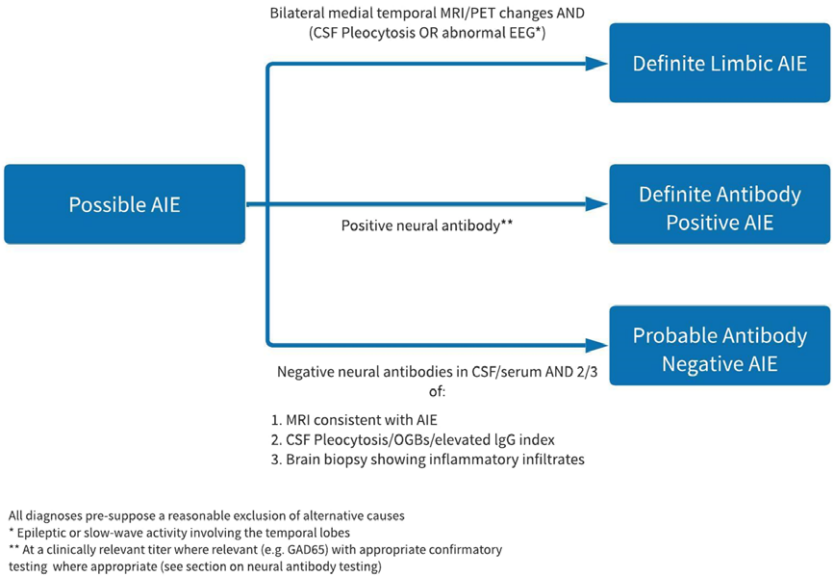

Figure 2: Diagnostic progression in autoimmune encephalitis (excluding ADEM, Bickerstaff's). ADEM = Acute disseminated encephalomyelitis; CNS = central nervous system; CSF = cerebral spinal fluid; EEG = electroencephalography; GAD65 = glutamic acid decarboxylase-65; IgG = immunoglobulin G; MRI = magnetic resonance imaging (of the brain); OGBs = oligoclonal bands; PET = positron emission tomography (of the brain).

typically relied on serum testing alone or evaluated antibody subtypes/sub-classes which are not known to be pathogenic.[29–31] More recent studies have confirmed that NMDAR antibodies are highly specific for AIE when detected in CSF in addition to serum.[32] In recognition of this, while balancing the desire to not miss any patient with an autoimmune cause of psychiatric symptoms, it has been suggested that certain factors should prompt further workup in patients with a first psychotic episode. This includes rapid progression, the presence of concurrent neurological symptoms, fluctuating catatonia, refractoriness to antipsychotic medications, or abnormal paraclinical investigations.[33]

Practical Tips on Diagnosis:

1. AIE can have variable clinical presentations, and a thorough history and physical exam are essential in making an accurate diagnosis.
2. Caution must be taken when undertaking treatment in patients who only meet criteria for "Possible AIE" despite completion of investigations.

Initial investigations

Once AIE is suspected, clinicians need to: 1) work towards obtaining evidence supporting this diagnosis and; 2) exclude mimics. This is an evolving process in which tests are processed in parallel with decisions on acute therapies. Recommended for all patients are cerebrospinal fluid (CSF) examination, brain magnetic resonance imaging (MRI), electroencephalography (EEG), and panel-based neural antibody testing.[5,28] Other paraclinical tests should also be considered in certain cases as detailed below.

Laboratory testing

Cerebrospinal fluid and serum

Please see Table 1 for an outline of suggested CSF and serum investigations for AIE.[5,28,34] CSF examination is of vital importance in the workup of AIE. Infectious pathogens should be ruled out. Evidence of inflammation can be found by evaluating the protein, cellular profile, oligoclonal banding, and IgG index. Paired CSF and serum samples must be tested to identify CSF-specific

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Table 1: Initial laboratory investigations of suspected AIE. Tests **in bold** are strongly recommended to establish the diagnosis and exclude common mimics. Optional tests are also listed if clinically indicated by presenting history

	Blood Draw	Cerebrospinal Fluid Obtain >= 12 ml
Routine	**Complete blood count** **Electrolytes, creatinine** **Liver function tests** **Glucose** **Serum along with CSF protein electrophoresis to identify CSF-specific oligoclonal bands** **Serum along with CSF IgG and albumin to calculate IgG index**	**Cell count and differential** **Protein** **Glucose** **Serum along with CSF protein electrophoresis to identify CSF-specific oligoclonal bands** **Serum along with CSF IgG and albumin to calculate IgG index** **Cytology** **Hold >= 3 ml for future testing**
Metabolic	**TSH** **Vitamin B12** Toxicology	
Systemic Autoimmune	**ANA and ENA panels** **CRP** Anti-dsDNA, C3, C4, ANCA panel	
Infectious Diseases *Immunocompromised or travel history in italics*	**HIV, Syphilis screening** Respiratory viral panel Arboviruses serology, Lyme serology **Hepatitis B/C**, TB skin test/QuantiFERON**** *Fungal, parasitic, helminthic, amoebic tests. Consider infectious disease consultation.*	**HSV, VZV, enterovirus PCR** **Bacterial culture and sensitivity** Mycobacterial culture, AFB smear Cryptococcus testing Syphilis VDRL (if serum testing positive) *CMV, HHV-6* *Fungal cultures* *JCV PCR*
Specialized Autoantibody Testing (Centre dependent)	**Comprehensive neural antibody testing**	**Comprehensive neural antibody testing**
Other Antibody Testing Based on Clinical Phenotype	MOG antibody, aquaporin-4 antibody, GQ1b ganglioside antibody	
Malignancy suspected or leptomeningeal involvement	Flow Cytometry	Flow Cytometry ***

AFB = acid-fast bacillus; ANA = anti-nuclear antibody; ANCA = anti-nuclear cytoplasmic antibody; C3 = complement component 3; C4 = complement component 4; CMV = cytomegalovirus; CRP = C-reactive protein; CSF = cerebrospinal fluid; dsDNA = double stranded DNA; EBV = Epstein-Barr virus; GAD65 = glutamic acid decarboxylase-65; GFAP = glial fibrillary acidic glycoprotein; HHV-6 = human herpesvirus-6; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IgG = immunoglobulin G; IgLON5 = IgLON Family Member 5; JCV = John Cunningham virus; MOG = myelin oligodendrocyte glycoprotein; PCR = polymerase chain reaction; SSA = Sjögren's-syndrome-related antigen A; SSB = Sjögren's-syndrome-related antigen B; TB = tuberculosis; TPO = thyroid peroxidase; TSH = thyroid stimulating hormone; VDRL = venereal disease research laboratory; VZV = varicella zoster virus.
**Hepatitis and tuberculosis testing is important for future treatment planning and should be obtained before use of steroid or IVIg whenever possible.
***Yield of flow cytometry without a history of hematological malignancy nor leptomeningeal gadolinium enhancement has been shown to be extremely low.[34]

oligoclonal bands. CSF findings most consistent with AIE include mild to moderate lymphocytic leukocytosis (generally <100 white blood cells), presence of CSF-specific oligoclonal bands, increased IgG index, and/or elevated protein.[35] A significant proportion of people with AIE have normal CSF studies[36] and inclusion of testing for oligoclonal bands significantly increases sensitivity.[37] Glucose is typically normal in AIE although low glucose can be seen in autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy.[38,39] Testing for CJD should be sent only if there is high clinical suspicion. Repeat CSF examination can be considered if diagnostic uncertainty remains, as CSF findings may evolve with evolution of AIE.[40]

Serum screening should incorporate a broad differential, excluding infectious, metabolic, and systemic autoimmune causes of encephalopathy. Of note, some systemic clues may exist to suggest underlying cause; for example, hyponatremia can be seen in 65% of cases of LGI1 antibody encephalitis.[22]

Neural antibody testing

Neural antibody testing in patients with suspected AIE is invaluable to patient diagnosis and management.[28,41,42] While rare clinical features are virtually pathognomonic for an individual neural antibody, many clinical and neuroimaging features of AIE can occur with various neural antibodies (e.g., memory deficits, psychiatric symptoms, seizures, medial temporal lobe T2-hyperintensities on MRI brain).[5,27,28,43] Because of the potential for phenotypic overlap across antibody-associated presentations, comprehensive panel-based neural antibody testing in patients with suspected AIE is generally recommended over sequential antibody testing to maximize sensitivity and facilitate prompt diagnosis.

Sensitivity of serum is higher than CSF for some antibodies (e.g., LGI1 and CASPR2 antibodies) while sensitivity/specificity of CSF is higher than serum for others (e.g., NMDAR and GFAP antibodies).[44–47] Furthermore, for rare/novel antibodies, the preferred specimen to test may not be well-established. For these reasons, testing both serum and CSF optimizes sensitivity and specificity. Assays commonly used for neural antibody detection include tissue indirect immunofluorescence/immunohistochemistry (TIIF/IHC), immunoblots, cell-based assays, radioimmunoassays and enzyme-linked immunosorbent assays (Table 2). Incorporation of TIIF/IHC is recommended to optimize sensitivity and specificity of neural antibody testing for patients with suspected AIE and should be considered standard of practice.[63]

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Table 2: Test methodologies employed for neural antibody detection in patients with suspected autoimmune encephalitis

Tissue indirect immunofluorescence/immunohistochemistry (TIIF/IHC)	Various	Requires expertise in interpretation of neural antibody tissue staining patterns Can be used to screen for rare/novel neural antibodies against intracellular/extracellular antigens to maximize sensitivity(48-58) Can be used to corroborate positive immunoblot or CBA results to maximize specificity(59-64)
Cell-based assays (CBA)	Anti-NMDAR, LGI1, CASPR2, GABA(B)R, AMPAR, DPPX, GAD65, IGLON5, MOG, GLYR	CBA reported to have higher sensitivity than TIIF/IHC for certain neural antibodies (e.g., LGI1, CASPR2); however, higher sensitivity may come at cost to specificity(46,21) Specificity of isolated positivity by CBA varies across analytes and is lower in the absence of corresponding positivity by second assay (e.g., TIIF/IHC); for weak/low isolated serum positivity by CBA, discuss further evaluation with testing laboratory (e.g., testing at higher dilution for anti-CASPR2)(63,65-67) Note that CBAs for anti-MOG and anti-GlyR are not routinely incorporated in neural antibody panels for autoimmune encephalitis, but should be ordered in patients with compatible disease phenotypes (e.g., ADEM and unilateral cerebral cortical encephalitis/FLAMES for anti-MOG, PERM for anti-GlyR); restricting testing of these antibodies to patients with compatible disease phenotypes reduces proportion of false-positives, which usually occur as low levels of positivity in serum(68-74)
Immunoblots	Anti-Hu, Yo, Ri, amphiphysin, CV2/CRMP5, Ma2/Ta, SOX1, Zic4, Tr/DNER, GAD65	Specificity of isolated positivity by immunoblot varies across analytes and is lower in the absence of corresponding positivity by second assay (e.g., TIIF/IHC)(59-64)
Radioimmunoassays (RIA)	Anti-GAD65 Anti-VGKC	Serum cutoffs for what constitutes high levels of anti-GAD65 by RIA have been published (>20 nmol/L or>2,000 U/mL); demonstrating intrathecal production of anti-GAD65 may aid in diagnosis of GAD65 neurologic autoimmunity (63,75-78) Detection of anti-VGKC in the absence of anti-LGI1/CASPR2 lacks specificity for neurologic autoimmunity (79,80)
Enzyme-linked immunosorbent assays (ELISA)	Anti-GAD65	Serum and CSF cutoffs for what constitutes high levels of anti-GAD65 by ELISA have been published (>10,000 IU/mL for serum, >100 IU/mL for CSF); demonstrating intrathecal production of anti-GAD65 may aid in diagnosis of neurologic autoimmunity(63,78)

ADEM = acute disseminated encephalomyelitis; AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2 = contactin-associated protein-like 2; CRMP5 = collapsin response-mediator protein 5; DNER = delta/Notch-like epidermal growth factor-related receptor; DPPX = dipeptidyl-peptidase-like protein 6; FLAMES = FLAIR-hyperintense Lesions in Anti-MOG-associated Encephalitis with Seizures; GABA(B)R = γ-aminobutyric acid type B receptor; GAD65 = glutamic acid decarboxylase-65; GlyR = glycine receptor; IGLON5 = IgLON Family Member 5; LGI1 = leucine-rich glioma-inactivated 1; MOG = myelin oligodendrocyte glycoprotein; NMDAR = N-methyl-D-aspartate receptor; PERM = progressive encephalomyelitis with rigidity and myoclonus; SOX1 = SRY-box transcription factor 1; VGKC = voltage-gated potassium channel.

In Canada however, many centers rely on commercial laboratories that do not incorporate TIIF/IHC in their testing algorithms. As such, the results reported are not confirmed with 2 testing methodologies, which may result in a high proportion of false-positive results.[60–62,65] Similarly, more limited testing can miss antibodies that are not included in, or are sub-optimally detected by, standard commercially available panels; such antibodies may only be detected if TIIF/IHC along with confirmatory assays available at specialized centers are used.[81,82] As such, it is highly recommended to involve a specialist in autoimmune neurology when a positive neural antibody result is found in a patient with an atypical clinical presentation or when no antibody is detected in a patient in whom AIE is strongly suspected, so they can review results and direct further testing at specialized laboratories.

Importantly, awaiting neural antibody results should not delay consideration of empiric immunotherapy if there is a high index of suspicion for AIE and reasonable exclusion of alternative diagnoses. Once available, a positive neural antibody result can serve to confirm the diagnosis, inform malignancy screening, and support escalation of immunotherapy in cases where there is incomplete response.

Special mention must be given to testing for thyroid antibodies, which are found in 11% of healthy controls and as high as 20% of adults over 60 years.[83] Accordingly, testing for thyroglobulin antibodies or thyroid peroxidase antibodies is of limited value in the evaluation of AIE, may contribute to AIE misdiagnosis, and should not be routinely performed.[4,84,85] Similarly, detection of voltage-gated potassium channel (VGKC) antibodies without LGI1 or CASPR2 antibodies lacks specificity for neurologic autoimmunity, so testing of VGKC antibodies is not recommended.[79,80]

Imaging

Magnetic resonance imaging

MRI brain with and without gadolinium should be obtained for all patients with suspected AIE. Imaging can reveal evidence of focal or multifocal involvement. Subtypes of AIE can preferentially affect certain anatomical structures, aiding in classifying type of AIE, in addition to directing a more focused differential diagnosis.[86,87] With respect to particular MRI findings, T2/FLAIR hyperintensities restricted to the medial temporal lobes are classical of autoimmune limbic encephalitis and are central to its diagnostic criteria[28]. Cortical-subcortical T2/FLAIR-hyperintense lesions are characteristic of GABA(A)R antibody encephalitis, and have also been reported with several other neural antibodies including those targeting Hu.[88–93] Unilateral cortical T2/FLAIR-hyperintense lesions with hypointensity of the adjacent subcortical white matter have been described in patients with encephalitic presentations of MOG antibody-associated

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disease.[73,74,94,95] T2/FLAIR hyperintensities restricted to the claustrum have been reported to be useful markers of seizures related to autoimmune encephalitis.[96] Importantly, however, these findings have varying specificity for AIE and similar neuroimaging abnormalities may be observed in patients with a broad array of alternative diagnoses, underscoring the need to interpret their presence in the clinical context of the patient. Additionally, MRI can be normal in AIE, particularly when imaging is obtained early.[97–100] Imaging changes can develop over time, therefore repeat imaging should be considered when the diagnosis is unclear.[97–100] MRI of the spinal cord should be obtained in cases with symptoms and signs localizing to the spinal cord. MRI can also be utilized for anatomy-specific malignancy screening as appropriate (e.g., pelvic MRI for ovarian teratoma).

Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET) imaging

There is increasing evidence for the utility of FDG-PET in the diagnosis of AIE. FDG-PET is more sensitive than MRI (87% and 25-50% respectively) and shows changes earlier.[97] Medial temporal lobe hypermetabolism has been reported in patients with limbic encephalitis and normal-appearing temporal lobes on MRI, indicating a higher sensitivity of FDG-PET for active inflammation that may be of benefit to the diagnosis and monitoring of patients with this condition.[28,101] Various other metabolic patterns have been described, involving regions correlating to clinical findings. For example, NMDAR antibody encephalitis can demonstrate an anteroposterior gradient with frontotemporal hypermetabolism and parieto-occipital hypometabolism; but not in all cases.[97] Findings should be interpreted with caution though, as PET findings, especially hypometabolism, are influenced by medications or concurrent neurodegeneration and the specificity of PET findings in the context of suspected AIE is unknown.[97,98]

FDG-PET should not be used alone for diagnosis, rather to complement other evidence of AIE inflammation and notably is not relied upon in commonly used diagnostic criteria and consensus statements.[5,102] Additionally, PET scans are not widely available in all Canadian provinces and use may be restricted to oncologic indications only.

Whole-body FDG-PET is a sensitive test for occult malignancy,[103] with particularly high yield in AIE associated with neural antibodies that are intermediate-risk or high-risk for underlying tumor.[104,105]

Electroencephalography (EEG)

EEG can provide evidence of focality when MRI is normal, occasionally shows findings that may help identifying specific subtypes of AIE and is part of the diagnostic criteria for definite limbic AIE[28,106,107] (Figure 2). Common findings include slowing and epileptiform changes, but these are not specific.[70,108] Extreme delta brush is seen in up to 30% of cases of NMDAR antibody encephalitis but is not unique to this disorder.[106,109,110] Hyperventilation induced focal seizures may also be a marker of AIE.[111]

Other ancillary tests

Biopsy is not typically necessary in AIE, and the presence of inflammatory cells alone is not specific.[40] The utility of brain biopsy is for confirmation of alternate pathologies. Nerve conduction studies and electromyography can be helpful in cases of CASPR2 antibody encephalitis, Bickerstaff's encephalitis, and stiff person spectrum disorders.[112,113]

Practical Tips on Investigations:

1. Due to phenotypic overlap, neural antibody testing for suspected AIE should generally be performed using comprehensive panels instead of sequential single-antibody testing to maximize sensitivity and facilitate prompt diagnosis.
2. Paired CSF/serum neural antibody testing should be performed, when feasible, to optimize sensitivity and specificity.
3. Incorporation of TIIF/IHC in neural antibody testing optimizes sensitivity and specificity, and is considered standard of laboratory practice in many regions around the world; neural antibody testing should be performed at laboratories with expertise in TIIF/IHC whenever possible.
4. When encountering unexpectedly positive or negative neural antibody results, contacting the testing laboratory to review test methodology (e.g., use of comprehensive panel-based testing, confirmatory testing with TIIF/IHC) as well as discussion with a specialist in autoimmune neurology is recommended.
5. Follow-up MRI of brain should be considered in cases with an initial negative MRI and a strong suspicion for a diagnosis of AIE.
6. Brain PET is more sensitive than MRI but specificity of findings is unknown; as such PET findings alone should not be used to make a diagnosis of AIE.
7. Thyroglobulin antibody and Thyroid peroxidase antibody testing are of limited value in the evaluation of patients meeting criteria for autoimmune encephalitis and should not be routinely performed.

First-line treatment

Defining severity of AIE

Defining the clinical severity of autoimmune encephalitis can be helpful in guiding treatment. While clinical scales do exist (e.g., Clinical Assessment Scale in Encephalitis[114]) we propose a rapid and practical approach to stratify disease severity based on functional impairment.

i. Severe – All patients requiring non-elective admission (including ICU) or any patient with significant and/or progressive functional impairment defined as inability to perform basic ADLs.
ii. Mild/Moderate – all others (mostly applicable to outpatients).

Recommendations for first-line treatment

The treatment of autoimmune encephalitis (AIE) is predominantly based on case series/retrospective data[115–117] and expert consensus apart from one positive randomized controlled trial for intravenous immunoglobulin (IVIg) in LGI1/CASPR2 antibody seropositive patients.[118] A clinical presentation consistent with the diagnosis of AIE with exclusion of an infectious cause are the key elements to initiate first-line treatment without delay. Studies suggest that early immunotherapy is associated with better outcome.[7–9] Early tumor removal in paraneoplastic encephalitis is crucial to consider in parallel with first-line therapeutic agents.

For patients who have acute presentations (like are typical of viral encephalitides) or subacute/chronic presentations with clinical or ancillary test findings concerning for infection (e.g., bacterial, fungal or parasitic infections of the CNS), antimicrobial treatment for a possible infectious cause of encephalitis as well as infectious disease consultation as appropriate should be pursued prior to empiric administration of immunotherapy.

We recommend that patients with severe AIE be treated with a combination of high dose steroids (1 g IV methylprednisolone daily for 5 days, or equivalent), AND IVIg (2 g/kg over 2–5 days) or

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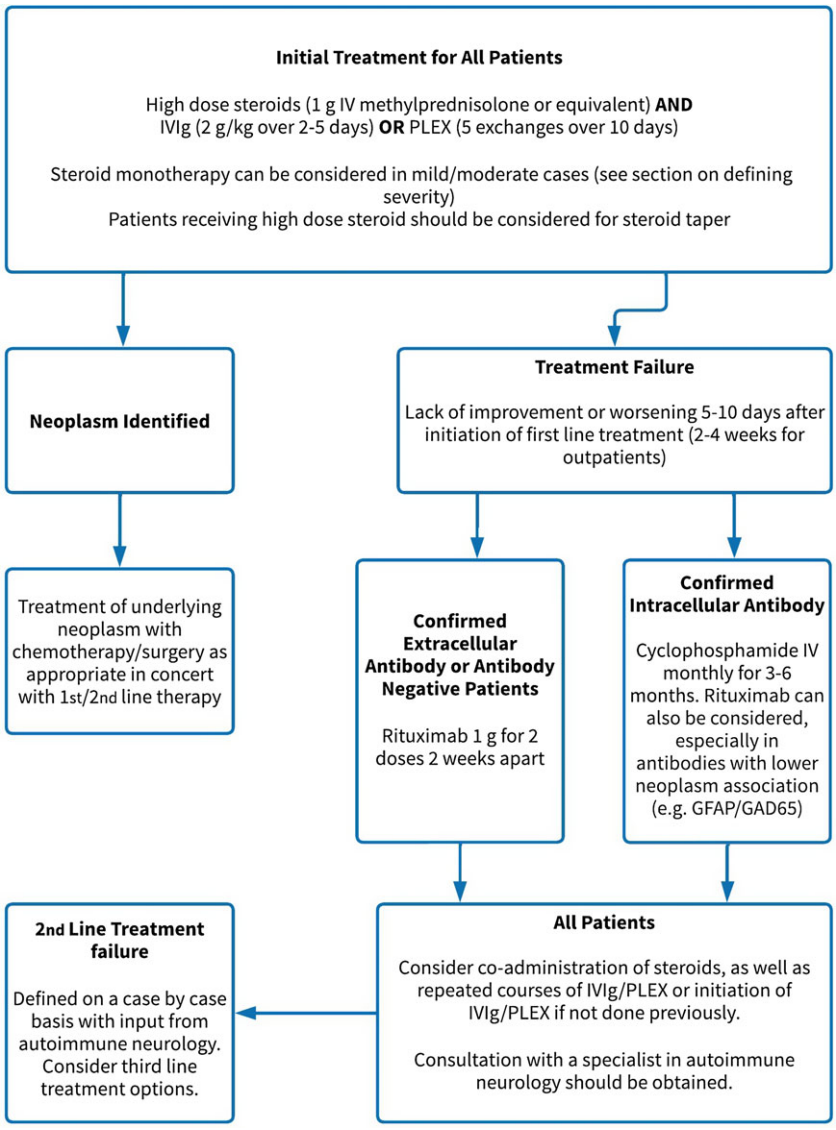

Figure 3: Proposed treatment algorithm for AIE. PLEX = plasma exchange; IVIg = intravenous immunoglobulin; GAD = glutamic acid decarboxylase; GFAP = glial fibrillary acidic protein.

plasma exchange (PLEX) (5 exchanges every other day over 10 days) (Figure 3). Treatment with steroid monotherapy can be considered in mild/moderate cases, such as in patients with anti-LGI1 encephalitis who are assessed in the outpatient setting with seizures in relative isolation, but input from a specialist in autoimmune neurology is recommended. If an associated neoplasm is found, treatment of the neoplasm must be part of the first-line protocol.

Although some studies suggest that PLEX might induce a more rapid effect by removing autoantibodies and other inflammatory substances in the plasma.[119] there is currently no definite evidence to suggest the superiority of IVIg versus PLEX. Additionally, there are some concerns that antibody mediated diseases associated with pathogenic IgG4 antibodies (e.g., LGI1, CASPR2) may not respond as well to IVIg.[120] It should be noted, that treatment with IVIg can affect autoantibody testing in serum and may result in a CSF pleocytosis and increased CSF IgG,[121,122] and so completion of investigations is necessary prior to initiation of IVIg.

In addition to the recommendation for early and appropriate treatment, we recommend early consideration for the transfer of any patient with moderate to severe AIE to a center with experience in the management of such patients and access to PLEX.

Use of corticosteroids after initial treatment

Current evidence for or against the use of corticosteroid taper is limited, although use of a taper may help prevent early relapse.[5,123,124] We recommend that corticosteroid taper be considered in most patients treated with any first-line treatment protocol which includes high dose IV steroids, particularly in patients with severe disease, unless a clear medical contraindication exists (including the risk of exacerbating neuropsychiatric symptoms). This is in keeping with other expert recommendations.[5,125]

If a steroid taper is used, we recommend 0.5–1 mg/kg/day of oral prednisone, tapering over 4–12 weeks depending on risk of side effects and comorbidities. An alternate (and possibly better tolerated regimen) of pulse steroids (1 g IV methylprednisolone or PO equivalent) weekly initially for 6 weeks followed by every 2 weeks for the next 6 weeks may also be considered.

Longer tapers may be helpful in some diseases (e.g., LGI1 antibody encephalitis).[123] For NMDAR antibody encephalitis, if

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ongoing corticosteroids are administered in the first months of disease then IV pulses rather than oral taper may be preferable, although guidance for adult cases is limited.[126] Input from a specialist in autoimmune neurology may be helpful in guiding taper.

Treatment trials in patients meeting criteria only for "Possible" AIE

Patients meeting only possible AIE criteria after completion of investigations merit special consideration. Importantly, these were not intended to be used as standalone criteria, but rather as the minimum requirements to suspect AIE.[127] In patients who only meet criteria for possible AIE but in whom alternative diagnoses have reasonably been excluded, a controlled immunotherapy trial with predefined distinct and objective treatment measures of efficacy can be considered with involvement of a specialist in autoimmune neurology.

Defining treatment failure

There is no widely accepted definition of treatment failure or refractory disease in autoimmune encephalitis. Second-line therapies are felt to be relatively safe and effective in managing AIE.[9] They are also associated with better outcomes when compared to those who receive additional first-line treatment or no further treatment.[9] Accordingly, we suggest a low threshold to escalate immunotherapy, particularly in patients with severe AIE.

We define treatment failure in patients with AIE as lack of improvement or worsening 5–10 days after initiation of first-line treatment in severe AIE and 2–4 weeks after initiation of first-line treatment in mild/moderate AIE. The shorter time period in severe AIE is to encourage earlier consideration of second-line therapy (discussed below). Whenever possible, lack of improvement or worsening of objective measures (e.g., seizure frequency, cognitive testing scores) should be used to define treatment failure.

In patients who experience treatment failure, particularly those who are antibody-negative, care should be taken to ensure that the diagnosis of autoimmune encephalitis is correct.

Second-line treatment

Second-line therapy is recommended for anyone who fails first-line treatment as defined above. Choice of second-line therapy is influenced by antibody associations and presence of neoplasm. Involvement of a specialist in autoimmune neurology is recommended in patients undergoing consideration for second-line therapy.

Acute second-line treatment in patients with cell surface antibodies or negative antibodies

Patients with autoimmune encephalitis who have antibodies targeting cell surface antigens (Table 3) should preferentially receive rituximab as second-line therapy due to possible better efficacy and more favorable safety profile[5,128] (Figure 3). In antibody-negative AIE, rituximab is preferable over cyclophosphamide due to its more favorable safety profile.[5,128,129] In general, however, input from a specialist in autoimmune neurology is recommended prior to administering second-line immunotherapies given their prolonged immunosuppressive effect and unique toxicities (e.g., infertility with cyclophosphamide, discussed later on). For ease of administration, rituximab may be administered as two intravenous infusions of 1 g, two weeks apart, rather than four 375 mg/m^2 infusions for 4 weeks.[128] Administration of monthly cyclophosphamide infusions of 600–1000 mg/m^2 for 3–6 months have commonly been described.[128] Myeloablative cyclophosphamide protocols can be considered in severe disease with input from a specialist in autoimmune neurology with experience in their use.

Consideration should also be given to repeated high dose pulse steroids, concurrent steroid taper, and repeated PLEX/IVIg (if initial PLEX/IVIg was effective) or initiation of PLEX/IVIg (if one of these were not applied during first-line treatment).[5] This should be strongly considered when there is potential for delays in treatment, for example if insurance/administrative approval is needed for use of rituximab.

Table 3: Anti-neural antibodies associated with encephalitis

Antibody Target/Type	Examples
Antibodies against Extracellular Targets	NMDAR-IgG, AMPAR, LGI1, CASPR2, GABA-A/BR, mGLUR1, Glycine, mGLuR5, DPPX, Neurexin-3a
Antibodies against Intracellular Targets	Hu (ANNA-1), Yo (PCA-1), Ma1/2, CRMP5/CV2, Amphiphysin, KLHL11, PCA-2, Ri (ANNA-2)
Antibodies against Intracellular Targets with lower association with malignancy	GAD65, GFAP

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA = antineuronal nuclear antibody; CASPR2 = contactin-associated protein-like 2; CRMP5 = collapsin response-mediator protein 5; DNER = Delta/notch-like epidermal growth factor-related receptor; DPPX = dipeptidyl-peptidase-like protein; $GABA_AR$ = gamma-aminobutyric acid-a receptor; $GABA_BR$ = gamma-aminobutyric acid-b receptor; GAD = glutamic acid decarboxylase; GFAP = glial fibrillary acidic protein; GlyR = glycine receptor; LGI1 = leucine-rich glioma-inactivated protein 1; LKLHL11 = Kelch-like protein 11; mGluR1 = metabotropic glutamate receptor type 1; mGluR5 = metabotropic glutamate receptor type 5; NMDAR = N-methyl-D-aspartate receptor; PCA-1 = Purkinje cell cytoplasmic antibody type 1; PCA-2 = Purkinje cell cytoplasmic antibody type 2; References: 63,130.

Acute second-line treatment in patients with intracellular antibodies

In confirmed or probable paraneoplastic cases, treatment and/or tumor resection is strongly recommended in all patients in consultation with oncology and/or neuro-oncology (Figure 3). Paraneoplastic encephalitis with autoantibodies against intracellular targets may be immunotherapy-resistant, in contrast to autoimmune encephalitis with autoantibodies against extracellular targets.[129] However, this is not universal and so trials of immunotherapy (both first line and second line if initial treatment fails) should still be considered in these cases.[130] Patients with encephalitis associated with antibodies targeting intracellular antigens, and in particular those with high-risk paraneoplastic antibodies (e.g., anti-Hu, anti-Yo), should preferentially receive cyclophosphamide due to its broader immunosuppressive effect.[131,132] There is little evidence regarding optimum cyclophosphamide therapy or dosing regimens in this setting.

Despite B-cell depletion being the main mechanism of action for rituximab, there is also indirect suppression of T-cell activity through changes in B- and T-cell signaling pathways.[133] Rituximab can be considered in circumstances where contraindications to cyclophosphamide exist.

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For patients with encephalitis associated with antibodies targeting intracellular antigens that have a lower cancer association (e.g., anti-GFAP, anti-GAD65), either cyclophosphamide or rituximab may be considered for second-line immunotherapy.

Additionally, if they have not been given previously, trial of IVIg or PLEX may be considered when other immunotherapies are unavailable or contraindicated, given their relatively low risk and rare reports of benefit attributed to their use even in patients with AIE who harbor antibodies against intracellular targets.[134–136] It should be acknowledged, however, that in general their efficacy is likely to be lower than in those with AIE in the setting of extracellular antibodies, which are considered to be pathogenic, as opposed to intracellular antibodies, which are not considered to be pathogenic.

Second-line therapy in patients with neoplasm

Second-line therapy can be undertaken in concert with treatment of the underlying neoplasm. Guidance from oncology in cases where surgery is not expected to be curative is essential and delaying second-line therapy may or may not be necessary based on oncology input.

Choice of second-line therapy should be guided by antibody type as above.

Treatment failure after second-line therapy

Defining treatment failure after second-line therapy is challenging due to variations in onset of action of second-line therapies depending on dose/regimen used as well as the co-administration of PLEX/IVIg/repeat IV steroids. As a result, we suggest the determination of treatment failure after second-line therapy be done in consultation with a specialist in autoimmune neurology.

Third-line/alternative immunotherapy

There are a number of third-line and experimental immunotherapies (tocilizumab, bortezomib) which have been employed in cases refractory to second-line immunotherapy.[5,128,137,138] Involvement of a specialist in autoimmune neurology is essential to discuss additional therapeutic options in cases when a patient fails second-line therapy.

Special considerations for refractory NMDAR-IgG AIE

NMDAR antibody encephalitis is associated with underlying teratoma in 11–36% of cases.[9,139–141] Microteratomas (occult or imaging negative) are rarely reported[142,143] and true incidence is unknown.

In cases of severe refractory NMDAR antibody encephalitis, evidence for bilateral "blind" oophorectomy for removal of potential occult ovarian teratoma is limited.[144] The existing evidence is predominantly based on case series/case reports, many of which were published before options for third-line treatment were available. Given the permanent effects on fertility/iatrogenic menopause and the fact that most patients with refractory NMDAR antibody encephalitis would be unable to provide informed consent due to their underlying disease, such procedures should only be undertaken as a last resort and with informed consent through a surrogate decision maker.

Accordingly, we strongly recommend these procedures be limited to patients with persistently life-threatening disease who fail second (rituximab and/or cyclophosphamide), and third-line therapy (tocilizumab or bortezomib) and who have had multiple imaging modalities to investigate for teratoma including endovaginal ultrasound and MRI pelvis as well as CSF confirmation of NMDAR antibodies. Given the poor level of evidence for "blind" oophorectomy and permanent effects on fertility some authors involved in this guideline strongly believe that this procedure should not be offered.

Teratomas are rare in patients younger than 18 or older than 45[9] and blind oophorectomy is not recommended outside of this age range.

Involvement of specialists in autoimmune neurology and gynecology is essential in such cases given permanent impacts to fertility and iatrogenic menopause.

Immune checkpoint inhibitor related autoimmune encephalitis

A detailed discussion of treatment of ICI related AIE is outside the scope of this article and oncology guidelines exist elsewhere.[145] In general, first-line treatment remain similar to other forms of AIE. Rituximab may be used in antibody positive cases although concerns exist around persistent immunosuppression in active malignancy, and oncology input is essential.[145,146]

Practical Tips on Treatment:

1. Early initiation of appropriate treatment is essential to optimize outcomes.
2. Awaiting neural antibody results should not delay consideration of empiric immunotherapy if there is a high index of suspicion for AIE, after reasonable exclusion of alternative diagnoses.
3. All patients with severe AIE should receive high dose corticosteroids with IVIg or PLEX as initial therapy; treatment with steroid monotherapy can be considered in mild/moderate cases but input from a specialist in autoimmune neurology is recommended (Figure 3).
4. Treatment of underlying neoplasm (if found) should occur in concert with first-line treatment when possible.
5. Second-line therapy should be offered to all patients with severe AIE who fail to improve or worsen 5-10 days after initiation of first-line therapy (2-4 weeks for mild/moderate cases).
6. Proposed differences in the approach to treatment of patients with severe AIE compared to those with mild/moderate disease include the routine initiation of dual first-line immunotherapies and the more rapid determination of treatment failure, to encourage earlier escalation to second-line immunotherapy in those with severe disease.
7. Early involvement of a specialist in autoimmune neurology is strongly recommended for all patients who fail first-line treatment.

Screening for neoplasm

While initially described as consequences of paraneoplastic syndromes, AIE has been increasingly recognized as a non-paraneoplastic phenomenon.[5] Still, all subtypes of AIE may be associated with an underlying neoplasm at varying frequencies.[5,147] A paraneoplastic AIE cannot be ruled out clinically; hence, neoplasm screening is recommended for all initial adult AIE presentations and should also be considered at the time of AIE relapse.[5,148–150]

Initial neoplasm screening is imaging based and can be formulated as a three-step process, terminated early if neoplasm is identified or if three steps are exhausted without a neoplasm identified.[148] Conventional CT imaging of the body, focused sex-specific imaging (ectopic germ cell tumors would be covered by the prior step), and finally a whole-body PET scan (in patients with intermediate or high-risk antibodies or some cases of antibody-negative AIE – see below)

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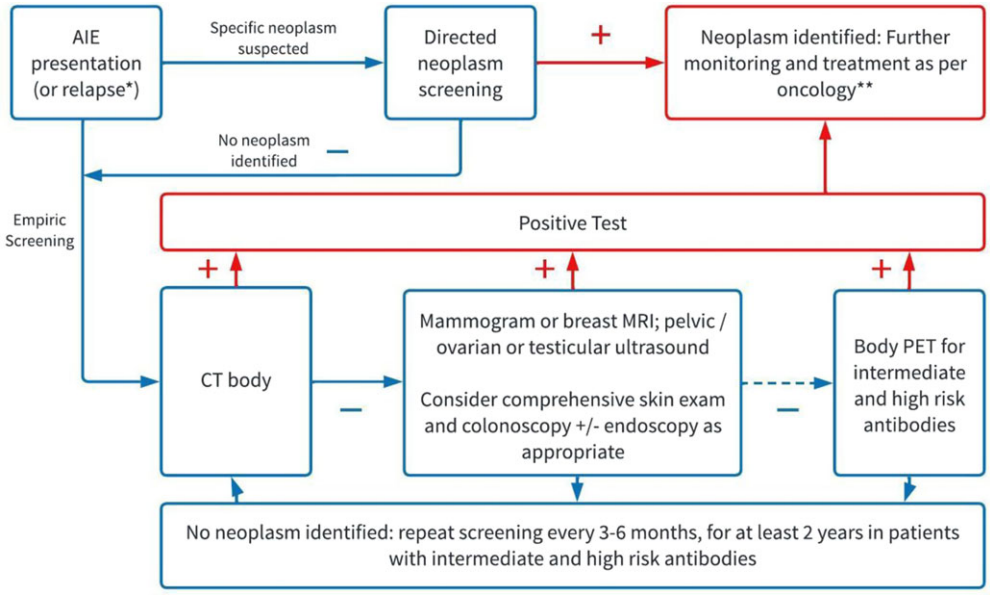

Figure 4: Neoplasm screening protocol. AIE: autoimmune encephalitis, CT: computed tomography, MRI: magnetic resonance imaging, PET: positron emission tomography. *Can be considered in a relapse, especially in patients with intermediate or high-risk antibodies. **For benign neoplasms oncology involvement may not be necessary as treatment is typically surgical.

comprise the three imaging modalities recommended for occult cancer screening in cases of AIE. First-line use of whole-body PET CT can be considered in cases where there is a strong antibody-neoplasm association. This may not be feasible in all areas of Canada and we do not encourage delaying neoplasm screening if there is a prolonged wait for antibody testing results. Of note, sensitivity of PET for ovarian teratoma is felt to be low, and pelvic US or MRI is preferred.[151]

Optimal screening for antibody-negative AIE is unknown. Some authors propose considering definite LE as a higher risk phenotype meriting PET scan and regular follow-up screening similar to intermediate and/or high-risk antibodies.[148] This can also be considered in patients with antibody-negative AIE and poor response to immunotherapy or other significant risk factors for malignancy.

Imaging is recommended even in patients with a known neoplasm that is not strongly associated with AIE, as it may identify a second, more likely relevant neoplasm.[152] In cases with a strong paraneoplastic association, directed testing can be started immediately (e.g., immediate ovarian ultrasound for NMDAR antibody encephalitis in a young woman to rule out a teratoma, testicular ultrasound in a man with KLHL11 antibody encephalitis to rule out testicular neoplasm). Screening for classic tumor markers (e.g., carcinoembryonic antigen (CEA)) is of little benefit in identifying neoplasm in patients with AIE.[153] A neoplasm screening flowchart is shown in Figure 4[5].

If a neoplasm is identified, anti-neoplastic therapy and follow-up monitoring are dependent on neoplasm type and should be directed by an oncologist. In cases of benign neoplasm, oncologist involvement may not be needed as surgical removal may be the only treatment required. Paraneoplastic AIE is most commonly associated with neoplasms of the lung (especially SCLC), breast, thymus, ovaries or testicles, as well as neuroblastoma and Hodgkin's lymphoma.[5] Paraneoplastic antibodies do not correlate with tumor bulk, and so do not reflect neoplasm treatment response, which should be dictated by neoplasm specific guidelines.[153]

If no neoplasm is found, the need for follow-up oncologic screening is most dependent on the presence of a high or intermediate-risk antibodies, and to a lesser extent high-risk phenotype (LE, encephalomyelitis with peripheral involvement), age, incomplete treatment response, smoking status, and other cancer risk factors.[48,147,154] A list of high, intermediate, and low-risk antibodies associated with AIE is in Table 4.[63,155]

While paraneoplastic neurological disorders may precede a neoplasm diagnosis, a tumor is found within 1 year of presentation in >90% of cases with solid tumors.[154] In cases associated with intermediate and high-risk antibodies, repeat screening every 3–6 months for at least 2 years is recommended.[5,147-149,154,156,157] While there is no firm consensus on the exact frequency and duration of neoplasm surveillance, one should consider frequent and prolonged screening for cases with multiple risk factors. Patients with antibody-negative disease and high-risk phenotypes such as LE, poor response to immunotherapy, relapsing disease and/or significant risk factors for malignancy should also be considered for follow-up neoplasm screening as defined in these guidelines.

Practical Tips on Neoplasm Screening

1. All adult patients presenting with AIE should undergo screening for malignancy at the time of diagnosis.
2. Initial screening should not be delayed while awaiting neural antibody test results.
3. Sex-specific testing should be undertaken if the initial screen is negative (Figure 4).
4. Follow-up screening is not necessary in patients with a low-risk antibody and initial negative screening but should be done in patients with intermediate or high-risk antibodies.
5. For antibody-negative patients, the optimal approach to follow-up screening is unknown but repeat screening should be considered in certain patients (e.g., those with high-risk phenotypes such as LE, refractory/relapsing disease, and/or significant risk factors for malignancy)

Treatment of other disease manifestations

Seizure management

The International League Against Epilepsy nomenclature of "acute symptomatic seizures secondary to autoimmune encephalitis" (ASSAE) and "autoimmune-associated epilepsy" are helpful conceptually when classifying patients AIE with seizures,[158]

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Table 4: Antibody type and malignancy risk

High-risk Antibodies (>70%)
Hu (ANNA-1), CV2/CRMP5, PCA-2 (MAP1B), SOX1, Amphiphysin, Ri (ANNA-2), Ma2/Ma, KLHL11, Yo (PCA-1), TR (DNER)
Intermediate Risk (30-70%)
AMPAR, $GABA_BR$, mGLUR5, NMDAR, CASPR2*, $GABA_AR$
Low Risk (<30%)
GFAP, GAD65, LGI1, CASPR2, DPPX, GlyR, MOG, AQP4, mGLUR1

*CASPR2 is only considered intermediate risk when in the context of Morvan syndrome.
AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor;
ANNA = antineuronal nuclear antibody; CASPR2 = contactin-associated protein-like 2;
CRMP5 = collapsin response-mediator protein 5; DNER = Delta/notch-like epidermal growth factor-related receptor; DPPX = dipeptidyl-peptidase-like protein; $GABA_AR$ = gamma-aminobutyric acid-a receptor; $GABA_BR$ = gamma-aminobutyric acid-b receptor;
GAD = glutamic acid decarboxylase; GFAP = glial fibrillary acidic protein; GlyR = glycine receptor; LGI1 = leucine-rich glioma-inactivated protein 1; LKLHL11 = Kelch-like protein 11; MAP1B = microtubule-associated protein 1B; mGluR1 = metabotropic glutamate receptor type 1; mGluR5 = metabotropic glutamate receptor type 5; MOG = myelin oligodendrocyte glycoprotein; NMDAR = N-methyl-D-aspartate receptor; PCA-1 = Purkinje cell cytoplasmic antibody type 1; References: 63,155.

although the modified term "autoimmune encephalitis-associated epilepsy" (AEAE) serves to make explicit the link between AIE and seizures in all cases.[159] The proportion of patients with AIE who develop seizures has been estimated at 50–70%.[159] AIE associated with autoantibodies targeting extracellular antigens – especially $GABA_AR$,[59] $GABA_BR$,[161] NMDAR,[162] and LGI1[46] – are a more commonly encountered cause of seizures than AIE associated with those targeting intracellular antigens. GAD65 antibody is a notable exception.[159,77,163] There is a paucity of data on the overall incidence and risk factors associated with the development of AEAE. Relatively small retrospective cohort studies of patients treated for seizures related to AIE reported that, at a two-year follow-up, 2-42% of patients developed AEAE.[164–166]

We recommend a combined initial treatment approach with anti-seizure medications (ASMs) and immunosuppression for the treatment of seizures related to AIE. Some patients (in particular those with antibodies against extracellular targets) may respond to immunosuppression alone, indicating ASSAE.[118,148,165,167] Patients who receive immunosuppression, and who receive it quickly, have a higher chance of achieving seizure freedom.[118,165,167,168] Sodium-channel blockers are possibly more effective for the treatment of seizures related to AIE, especially in patients with LGI1 antibody encephalitis, but are associated with higher risks of side effects.[140,167,169] Enzyme-inducing ASMs should be avoided in patients treated with chemotherapy due to risk of lowering drug levels.[170] In the patient who is no longer in the acute phase of AIE and has become seizure-free a gradual wean from ASMs can be considered after discussing the importance of vigilance for signs or symptoms of seizure recurrence that would merit prompt clinical re-assessment.[148,165]

Neuropsychiatric symptoms

Neuropsychiatric symptoms are common in AIE and are expected to improve with first- and second-line treatments.[8,171] To our knowledge, there are no randomized controlled trials investigating treatment of neuropsychiatric symptoms in patients with AIE; management therefore relies on observational studies and expert opinion, usually with conventional psychiatric treatments.[172] Psychiatric symptoms in patients with AIE improve less frequently with symptomatic treatments compared to patients with psychiatric conditions, and patients are more likely to experience side effects.[173–175]

Regarding acute agitation and psychosis, special caution is required with antipsychotic medications.[173,176] Patients face a higher risk of drug induced movement disorders, worsening agitation, rhabdomyolysis, and neuroleptic malignant syndrome, especially with medications with high affinity for the D2 dopamine receptor, such as haloperidol.[177] If required, atypical antipsychotics are preferred.[172,178] Options are detailed in Table 5 including strategies to target sleep disturbance.

Electroconvulsive therapy has been used for severe psychosis and catatonia in AIE[171–173,179] with some success, especially when the catatonia is treatment resistant, and immunotherapy has failed.[180] Catatonia can be treated with benzodiazepines, with caution in patients with hypoventilation and decreased arousal.[178]

Even with treatment, recovery can take many years and is often incomplete with cognitive, and neuropsychiatric symptoms persisting in 50% of patients.[175,181–183] Behavioral agitation, emotional lability, posttraumatic stress disorder symptoms, anxiety, and depression are common. Selective serotonin reuptake inhibitors, pindolol and valproic acid have been used for agitation and disinhibition[173] in those with chronic symptoms.

Persistent cognitive symptoms include deficits in attention, memory, executive function, and processing speed, and are associated with poor psychosocial outcomes.[173] Supervision, rehabilitation, and family-centered care are important.[171,184] Non-pharmacological management borrowed from the TBI literature includes reducing overstimulation, clustering care, minimizing physical restraint as well as assessing the environment and sleep wake cycles.[185]

Rehabilitation/prognosis for recovery

Prognostication in AIE is challenging due to lack of long-term evidence, and variability in outcomes based on specific AIE subtype and associated cancer.[186,187] For example, 75–85% of patients with NMDAR antibody encephalitis achieve good functional outcomes (modified Rankin Score of 0-2)[140,162] compared with only 43% of patients with GAD65 antibody encephalitis.[77] Approximately half of patients with AIE may continue to experience cognitive impairment after the acute onset of disease.[8] Earlier initiation of treatment has been associated with improved long-term functional,[186,187] cognitive[8] and psychiatric[188] outcomes across a variety of AIE subtypes. Once patients are no longer in the acute phase of AIE, they should be routinely screened for residual neuropsychiatric impairment and be offered a combination of psychiatric care[189] and neuropsychological rehabilitation.[148,189]

Practical Tips on Secondary Management

1. Patients who receive prompt immunosuppression are more likely to obtain seizure freedom.
2. A combined initial approach of immunosuppression and use of anti-seizure medications is strongly recommended for most patients with AIE and seizures.
3. Neuropsychiatric symptoms are common in AIE and are expected to improve with first- and second-line treatments but symptomatic therapy may still be required (Table 5).

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Table 5: Recommended agents for neuropsychiatric symptoms

Medication Class/ Treatment Modality	Medication	Target Symptoms	Specific benefits in context of AIE	Specific risks in context of AIE	Reference
Benzodiazepine	Most common midazolam, lorazepam, clonazepam	Agitation, catatonia		Adverse cognitive profile, risk of worsening, hypoventilation	173,178,185
Mood stabilizing anti-seizure medications	Valproic acid	Agitation, mood lability	Also treats seizures	Teratogenicity	173
	Carbamazepine	Agitation, mood lability	Also treats seizures	Hyponatremia	173
	Lamotrigine	Agitation, mood lability, theoretically may target psychosis	Also treats seizures		185
Alpha agonist	Clonidine	Agitation, cognitive impairment, sleep disturbance		Hypotension, bradycardia in patients with autonomic symptoms	185
	Guanfacine	Agitation, cognitive impairment, sleep disturbance		Hypotension, bradycardia in patients with autonomic symptoms	185
Antidepressant	Trazodone	Sleep disturbance		Orthostatic hypotension in patients with autonomic symptoms	173
	Mirtazapine	Sleep disturbance, depression		Orthostatic hypotension in patients with autonomic symptoms	185
	Selective Serotonin Reuptake Inhibitor	Depression, anxiety		SIADH (hyponatremia)	185
Beta blocker	Propranolol, pindolol	Agitation		Hypotension, bradycardia in patients with autonomic symptoms	173,185
Typical antipsychotic	Haloperidol	Delirium, agitation, psychosis		Drug induced movement disorders	173,187
	Chlorpromazine	Agitation, psychosis, sleep disturbance		Drug induced movement disorders	173
Atypical antipsychotic	Olanzapine	Agitation, psychosis, sleep disturbance		Drug induced movement disorders	173,178,185
	Quetiapine	Agitation, psychosis, sleep disturbance		Drug induced movement disorders	173,185
	Risperidone	Agitation, psychosis, sleep disturbance		Higher risk of drug induced movement disorders than other atypical antipsychotics	173,185
	Aripiprazole	Agitation, psychosis		Drug induced movement disorders	173,185
	Clozapine	Psychosis, sleep disturbance		Highest risk of all antipsychotics for inducing seizures	173,185
Stimulant	Methylphenidate or amphetamine formulations	Cognitive impairment, daytime sedation, low energy		Lowers seizure threshold, may worsen psychosis, hypertension	185
Miscellaneous	Amantadine	Cognitive impairment, daytime sedation, low energy		May worsen motor or neuropsychiatric symptoms	185
	Melatonin	Insomnia			185
Electroconvulsive therapy		Catatonia		Requires anesthetic (limited risk of long-term memory impairment)	171-173, 179, 180
Sedative/hypnotics	Zolpidem, zopiclone	Insomnia			185
Anxiolytic	Buspirone	Anxiety			185
NMDA Antagonist	Ketamine	Agitation		Requires intravenous access, hypertension, theoretical worsening of psychosis	176
Anticholinergic	Benztropine, trihexyphenidil	Drug induced movement disorders		Delirium, can worsen cognitive impairment	185

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Chronic management

Relapse in autoimmune encephalitis

Relapse in AIE is not uncommon, and characteristics demonstrate significant variability between AIE subtypes.[9,21,22,42,128,190] Retrospective observational studies of NMDAR, LGI1, and CASPR2 antibody encephalitis indicate relapse rates ranging from 10 to 41% and symptoms may be identical to the index episode (e.g., LGI1 antibody encephalitis re-presenting with seizures), similar but milder (e.g., NMDAR antibody encephalitis presenting with behavioral symptoms after previous severe ICU admission) or a different distinct core clinical syndrome (e.g., CASPR2 antibody encephalitis presenting with cerebellar ataxia after previous seizure presentation). Reliable data is however hard to obtain as rates and characteristics are confounded by small cohort sizes with limited follow-up duration and a lack of consensus on the definition of relapse in autoimmune encephalitis. Resultantly, relapse attributes are not fully known for all AIE subtypes (e.g., the relapse rate for antibody-negative AIE is unknown).

For the purposes of these guidelines, we define relapse in AIE as a clear objective worsening of symptoms after initial improvement or plateau, preferably supported by evidence of inflammation on MRI or in CSF, and usually occurring at a minimum of 2–3 months from original presentation. PET scan findings are often non-specific[102] and isolated PET abnormalities should be interpreted with caution if they are the only objective marker of relapse. Antibody titers are typically not helpful in defining relapse due to their imperfect correlation with disease activity.[47,191]

For acute treatment of relapse, we suggest following the first-line and/or second-line treatment algorithm as appropriate unless a patient is known to have failed a particular therapy in the past. Long-term immunosuppression may be appropriate and consultation with a specialist in autoimmune neurology is recommended in cases of relapse both to confirm relapse and guide long-term treatment.

Long-term immunosuppression

Data to guide long-term immunosuppression decisions in AIE are lacking. Given uncertainty and variability of relapse rates, long-term therapy is not routinely recommended for all patients at first presentation of AIE, although we acknowledge substantial variability in practice even among experts. One to two years of immunotherapy may be justified for patients with more severe disease. In relapsing forms of AIE, three or more years of maintenance immunotherapy has been proposed.[148] We recommend involvement of a specialist in autoimmune neurology when considering initiation of long-term immunosuppression.

Practical Tips on Chronic Management:

1. Risk of relapse in AIE differs depending on specific antibody positivity and ranges from 10-41%.
2. Long-term immunosuppressive therapy is not routinely recommended for all patients at first presentation of AIE, although we acknowledge there is substantial variability in practice even among experts.
3. Relapses should be treated according to the 1st/2nd line treatment algorithms as above unless a particular therapy is known to be ineffective for the patient.

Mitigation of risks of immunosuppression

Latent infection screening

Although risks of recrudescent infection vary by pathogen and immunotherapy, early broad testing to expedite appropriate prophylactic or definitive treatment is advised. Screening should routinely include testing for VZV, HIV, Hepatitis B/C, and tuberculosis. When abnormalities are found, immunotherapy can often be started soon after implementing appropriate monitoring/treatment (Table 6). When active or latent infections are identified, consultation with an infectious disease specialist is advised.

Vaccination

Age appropriate and risk context appropriate vaccinations (e.g., meningococcal vaccination in military recruits) should be considered for all patients embarking on immunosuppression (Table 7).[200,203–206] Although delaying immunotherapy 4–6 weeks after a vaccine series is completed is typically recommended, this is not practical in acute autoimmune encephalitis presentations. Often vaccination may be delayed pending treatment conclusion (Table 8)[207,208] or, if therapy is prolonged, be taken during treatment with non-live vaccines, recognizing efficacy of vaccines may be reduced.

Reproductive health/pregnancy risks

First-line immunotherapies are generally safe in pregnancy.[211] Steroids can be administered, including high dose IV pulse therapy.[212–214] When used, decision makers should be advised of mild increased infection risk including those more relevant to pregnancy (e.g., endometritis). Treatment with IVIg and PLEX are considered safe in pregnancy although additional hypercoagulability should be discussed.[215,216]

Some second-line agents can also be used safely. Guidelines for rituximab vary with regards to advisable delay of 6 to 12 months between treatment and conception/delivery.[217] Reports have demonstrated safety when treatment occurs within 6 months of delivery even if an ability to cross the placenta routinely leads to transient CD19/20 depletion in the infant.[218,219] Cyclophosphamide should never be used in pregnancy and its use in men or women requires discussion of infertility risk, and potential gamete harvesting/storage (acuity permitting) should be explored. Involvement of a specialist in autoimmune neurology in such cases is strongly recommended.

Pneumocystis jirovecii (PJP) prophylaxis

PJP prophylaxis is crucial but precise application is debated for those on immunotherapy. Guidelines exist for those with rheumatologic/hematologic conditions but relevance in neurological illness is unknown.

Trimethoprim-sulfamethoxazole (TMP-SMX) is the gold standard for PJP prophylaxis. If a prior minor reaction to TMP-SMX is reported (i.e., no respiratory or mucosal membrane involvement or fever) then desensitization and subsequent use is preferable to therapy with atovaquone, dapsone, or pentamidine.[220,221]

Overall, we recommend providing PJP prophylaxis in the following scenarios[220,222].

1. All patients on high dose corticosteroids (20 mg of prednisone for 2 weeks or more, alone or in combination with other medications).

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Table 6: Overview of screening response by pathogen

Pathogen	Context	Screen	Approach
Hepatitis B[192,193]	Agent: Cyclophosphamide, Prednisone, Rituximab, Infliximab/ TNF alpha inhibitors	Serology (Anti-HBs Ab, anti-HBc Ab), Other (HBsAg, HBV DNA)	**HBsAg +ve:** Treat Hepatitis infection. **Anti-HBs -ve/anti-HBc +ve:** Monitor ALT, HBV DNA, and HBsAg every 1–3 months or treat prophylactically. **Anti-HBs -ve/anti-HBc -ve:** Immunize when possible.
Hepatitis C[194,195]	Agents: Pulsed Corticosteroids, Rituximab†	Serology	**Anti-HCV +ve:** Test HCV DNA. If positive, treat. If negative, monitor transaminases periodically while on immunosuppressive treatment.
HIV[196,197]	General	Serology	**HIV+:** Consult ID for consideration of ART
Strongyloidiasis[198–201]	Agent: Prednisone Other: Visitor / Resident of Endemic Region, Eosinophilia	Serology, Stool Ova and Parasites	Treat if positive test or high suspicion exists with Ivermectin 200 µg/kg per day orally × 1 or × 2 given 2 weeks apart. **Contraindications to Ivermectin:** *Loa loa* filarial exposure (West or Central Africa travel), pregnancy, weight <15 kg.
Tuberculosis (TB)[202]	General	QuantiFERON Gold (esp. where patient has received tuberculosis vaccination), Mantoux Skin test	Initiate treatment 2–4 weeks prior to immunosuppression if possible (minimum lead time is the confirmation of tolerance of antimicrobials).
VZV‡	Agents: Effective lymphocyte depletors (esp. where prolonged lymphopenia is anticipated / realized)*	Serology	May consider anti-viral prophylaxis versus vaccination if titer does not reflect immunity.

†Rituximab and cyclophosphamide can be used to treat the immunological complications of Hepatitis C but a risk of severe hepatitis exists beyond risk posed by hepatitis C.
‡VZV testing is to ascertain if sufficient immunity remains to reduce the risk of emergent singles.
Ab: Antibody, Ag: Antigen, cART: combined antiretroviral therapy, CD: Cell differentiation factor, CNS: Central Nervous System, CSF: Cerebrospinal Fluid, DNA: Deoxyribonucleic Acid, esp: especially, HB: Hepatitis B, HC: Hepatitis C, HIV: Human Immunodeficiency Virus, HBs Ag: Hepatitis B surface antigen, HBc Ab: Hepatitis B core antibody, ID: Infectious disease.

Table 7: Vaccination recommendations – adapted from CDC 2022 and Canadian guidelines (Rubin et al. 2014; Government of Canada 2021; CDC 2022)

Vaccine	Administration	Context
IIV4 / RIV4	Annual dose	Universal
LAIV4	Contraindicated	
TD or Tdap[Tox]	Primary series if unimmunized; booster q10 years	Universal
MMR [LV]	Contraindicated	
RZV	Consider 2 doses (min interval 4 weeks)	Patients with no evidence of immunity
HPV [RV]	3 doses up to age 26	Consider as age appropriate
Pneumococcal (PCV13, PCV15, PCV20, PPSV23)	1 dose of PCV13 then 1 dose of PPSV23 (min interval 8 weeks) with PPSV23 booster 5 years later	Universal
Hepatitis A / B [InV / RV]	Administration dependent on vaccine brand	Consider in groups that would be high risk in the event of infection (B-Cell agents, prednisone 10 mg or greater for 4 or more weeks)
COVID19	Annual dose	Universal

HPV: Human Papilloma Virus; InV: Inactivated vaccine; LV: Live vaccine; MMR: Measles, Mumps, Rubella; PCV15: 15-valent pneumococcal conjugate vaccine; PCV20: 20-valent pneumococcal conjugate vaccine; Pneumococcal polysaccharide vaccine (PPSV23); RIV4: recombinant influenza vaccine; LAIV4: live attenuated influenza vaccine; RV: Recombinant Vaccine; RZV: Recombinant Varicella Vaccine; SRPCV: Subunit, recombinant, polysaccharide, and conjugate vaccines; TD: Tetanus, Diphtheria; Tdap: Tetanus, Diphtheria, Acellular Pertussis, Tox: Toxoid; IIV4: inactivated influenza vaccine.

2. Overlapping rituximab/cyclophosphamide therapy until the resolution of either CD19/20 cell counts (if rituximab is discontinued) or lymphopenia/neutropenia (if cyclophosphamide is discontinued).
3. Patients on 5 mg prednisone equivalent or more in combination with cyclophosphamide.

Practical Tips on Mitigation of Risks of Immunosuppression:

1. All patients with AIE should be routinely screened for VZV, HIV, Hepatitis B/C, and tuberculosis, ideally prior to initiation of immunosuppression.
2. IVIg can result in false-positive Hepatitis B core antibody results leading to unnecessary use of anti-viral medications.
3. First-line therapies (IVIg, PLEX, corticosteroids) are generally considered safe in pregnancy.
4. All patients receiving 20 mg prednisone equivalent or more for more than 2 weeks should receive PJP prophylaxis.

Complications of corticosteroid use

Corticosteroids infrequently cause lasting side effects during brief courses (e.g., gastric ulcer/bleeding, avascular necrosis), but the consequences of long-term use can undermine therapeutic efforts. Common issues include worsening metabolic syndrome (i.e., increased body mass index, hypertension, hyperlipidemia, glucose intolerance), osteoporosis, infections, and impaired wound healing/skin thinning.[223–225] Neuropsychiatric manifestations are perhaps the most problematic as they can overlap with encephalitic symptomatology. If side effects are extreme, more rapid tapering/ discontinuation may be required however several mitigation strategies exist (Table 9).[226,227]

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Table 8: Recommendations for treatment related vaccine delays

Agent	Approach
Cyclophosphamide[209]	**Vaccination post-treatment:** Wait a minimum of one month after treatment and until lymphocyte and neutrophil counts have normalized. **Vaccination during treatment:** Plan vaccinations 1 week prior to the next IV infusion.
Prednisone[207]	**Vaccination post-treatment:** Wait one month after high dose immunosuppression (i.e., prednisone of 20 mg or more when administered for 2 weeks or more; 10 mg or more when administered for 4 weeks or more). **Vaccination during treatment:** No special consideration.
Rituximab[210]	**Vaccination post-treatment:** Wait 6–12 months after the final infusion. **Vaccination during treatment:** Plan 4–6 weeks prior to subsequent infusion.

Table 9: Steroid side effect mitigation[226]

Item	Approach
Adrenal Insufficiency	**Investigations:** Cosyntropin stimulation testing if suspected.[228] **Management:** Raise steroids and/or slow / arrest wean; in patient who have received 5 mg of prednisone or more refer to relevant presurgical guidelines as necessary.[227] Consider endocrinology referral.
Avascular Necrosis	**Investigations:** X-ray, MRI, radionucleotide scan. **Treatment Options:** Wean steroids, orthopedic referral
Glaucoma[229]	**Monitoring (For patients receiving 10 mg of prednisone or more):** Consider referring to optometry for IOP monitoring at 1, 3, and 6 months and every 6 months thereafter. **Treatment Options:** Refer to ophthalmology
Upper Gastrointestinal Bleed/Gastric Ulcer	Consider use of proton pump inhibitor in patients on concomitant NSAID and/or all hospitalized patients[205]
Metabolic syndrome	**Traditional approach:** Standard therapy, diet / activity encouragement / counseling
Osteoporosis	**All:** Calcium 1000–1500 mg, Vitamin D 800–2000 IU[226], monitor with BMD at a maximum of one year then every 1–3 years depending on FRAX score. **Medium+ FRAX or prolonged therapy (>3 months at 7.5+ mg):** Bisphosphonate, expedite steroid wean when possible. **3–5 years on bisphosphonate:** consider drug holiday / rotate to teriparatide.[231]
Psychosis	**Traditional approach:** Atypical antipsychotics, taper steroids. **Neuroleptic sensitivity:** Long-acting benzodiazepines,[232] Lithium.[233]

BMD: Bone mineral density; IOP: Intraocular pressure; FRAX: Fracture risk assessment tool; MRI: Magnetic resonance imaging.

Considerations for clinical and multidisciplinary care

Given the complexities in both the acute and chronic management of AIE, early referral to a center with expertise in managing AIE and access to PLEX is recommended, especially in patients who do not respond to first-line therapy. A link to an updated list of centers and clinicians with interest and expertise in AIE is provided in the appendix. Early involvement of psychiatry in patients with prominent and/or persistent neuropsychiatric symptoms is also warranted. Rheumatology, oncology and infectious disease consultations should be considered in patients with features of systemic autoimmune disease, known malignancy or immunocompromised state and/or features suggestive of CNS infection respectively.

Conclusion

Autoimmune encephalitis has been increasingly recognized as a cause of subacute neurological symptoms and mental status changes. Nonetheless, high quality evidence for diagnosis and management remains lacking. In this context, these consensus guidelines may be helpful in aiding front line clinicians to recognize, appropriately investigate, and treat patients with AIE with the aim of standardizing care. Gaps in care exist and will continue to exist in Canada; not only around access to first- and second-line treatments (notably PLEX and rituximab) but also in access to clinicians and centers with expertise in diagnosing and managing AIE. Additionally, the authors hope that establishment of guidelines may be helpful when advocating for equitable access to treatment at the provincial and national level.

Increased recognition has fortunately also resulted in the recent development of clinical trials and therapeutics specific to AIE. These developments provide hope for new evidence-based treatments for AIE and ongoing improvement in outcomes for patients.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2024.16.

Acknowledgements. We would like to thank Dr Alexandra Olmos-Perez for her valuable input in the ethical considerations around blind oophorectomy as well as Brooke Hahn for her help with the graphic design of the figures and tables.

We would also like to thank Gary Sarohia and Nesrin Shaheen for their input and review from the patient/family member perspective along with the support of the anti-NMDA Receptor Encephalitis Foundation.

Author contribution. CH was responsible for the overall design of the guidelines and administration of the RAND process.

CH and JM provided overall editorial review and editing of the draft manuscript.

AB additionally provided overall editorial review.

The primary panel members included NA, AB, JB, JC, RC, JH, AM, BM, IP, KW and CU.

Secondary panel members were KA, GB, GB, JB, JC, PD, RK, SL, AM, WM and PS.

RAND Process voting participants were KA, NA, AB, GB, JB, RC, JH, RK, JM, IP, PS, KW and CU.

Funding statement. This manuscript was unfunded.

Competing interests. AB reports that he holds the London Health Sciences Centre and London Health Sciences Foundation Chair in Neural Antibody Testing for Neuro-Inflammatory Diseases, and receives support from the Opportunities Fund of the Academic Health Sciences Centre Alternative Funding Plan of the Academic Medical Organization of Southwestern Ontario.

AM reports honoraria from Alexion, Biogen, EMD Serono, and Novartis.

CH reports grant funding from the Alberta Neurosciences, Rehabilitation and Vision Strategic Clinical Network as well as honoraria from Alnylam, Akcea and Pfizer.

CU reports a paid committee position on the British Columbia Provincial Blood Coordinating Board "IVIG for Central Nervous System Indications Task Force" and speaker's fee from the Northwest Rheumatism Society.

IP reports honoraria from Biogen, Novartis, Roche and EMD Serono.

JB reports remuneration from Alexion, Atara Phramaceutics, Bayer Healthcare, Beigene, BMS (Celgene), EMD Inc., Hoffmann-La Roche, Jansen (J&J), Merck Serono, Novartis, Sanofi-Genzyme, and Teva Canada innovation for work as a clinical trial EDSS rater.

JC reports educational honoraria from Takeda

JH received salary support during his work on this manuscript through a grant from the American Epilepsy Society.

JM reports grant funding from the University of Alberta Department of Medicine, consulting fees from Novartis, educational honoraria from the American Academy of Neurology and participation in an advisory board for Horizon

KM reports educational funding from the University of Calgary, membership on the executive of the Federation of Medical Women of Canada, membership on the Nominations Committee of the Royal College of Physicians and Surgeons of Canada and is the co-founder of Kolabo.

NA reports educational honoraria from Biogen

PS received speaking honoraria and honoraria from serving on the scientific advisory boards of: Biogen-Idec Pharmaceuticals; Roche Pharmaceuticals; EMD Serono Canada Pharmaceuticals; Novartis Pharmaceuticals, and honoraria for serving as an expert reviewer for the Short Term Exceptional Drug Therapy program in Alberta, Canada. She is a co-investigator in receiving an unrestricted research grant for a prospective pregnancy registry cohort project in Canada from Biogen-Idec Canada.

RC reports grants for Roche/Genentech, Roche and Teva Innovation, consulting fees from Roche, Serono, Sanofi, Biogen, Novartis, Alexion and Teva and travel support from Serono.

RK reports honoraria from Horizon Therapeutics

SL reports consulting fees from Bayers, educational honoraria from UdeM Neuro-Oncology Course, Medlink, Le Medecin du Quebec and Neurodiem, payment for expert testimony from MD Analytics, as well as participation in scientific advisory board meetings for Alexion and Novocure

WM Reports consulting fees from Servier, Novocure, AnHHeart and Boeringher Inggelheim as well as participation as the chair of the data monitoring committee for Ono Therapeutics.

The remaining authors have no competing interests to declare.

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