2024加拿大指南|成人自身免疫性脑炎的诊断和治疗

摘要

认为自身免疫性脑炎是引起急性精神状态改变的神经系统原因的呼声近年越来越大，其发病率与感染性脑炎相似。尽管人们的认识不断提高，但诊断方法仍然不一致，而且寻求最佳治疗的证据也有限。国外神经内科相关专家，包括自身免疫性神经病学、神经精神病学和传染病专家，于2024年02月05日在期刊《The Canadian Journal of Neurological Sciences》发布**《2024 加拿大指南：成人自身免疫性脑炎的诊断与治疗》**。该指南是使用改进的RAND过程制定的，主要针对一线临床医生，目的是为了提供一种务实且实用的方法对急性期患者进行管理。

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Review Article

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

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01 前言

自身免疫性脑炎（AIE）：一种表现为亚急性起病的神经系统炎症性疾病，与特定自身免疫性脑炎结构相关的症状反映了炎症过程对中枢神经系统（CNS）结构的选择性侵润。

- 流行病学：AIE的发病率与感染性脑炎相似，为每年每10万人中会发生0.2-0.8例。
- 诊断挑战：尽管对AIE的认识增加，但诊断方法仍不一致，最佳治疗方案的证据有限。

02 自身免疫性脑炎的诊断

◆ 流行病学考虑：AIE的患病率在增加，疾病可以发生在各个年龄段，但是不同抗体相关的AIE在不同年龄段的患病率是不同的。

◆ 临床表现：AIE通常表现为亚急性起病的症状，且某些抗体相关的综合征可能病程更缓慢，**如LGI1抗体、抗CASPR2抗体、抗GAD65抗体和抗DPPX抗体脑炎。**感染性前驱症状通常发生在神经精神症状出现前几天到几周，其他非特异性的前驱症状可能包括头痛、发热、疲劳、睡眠障碍、体重减轻和早期精神症状。

◆ 诊断标准：根据Graus等人于2016年首次提出的标准，AIE的诊断可以根据诊断的确定性程度分为可能、可能和确定三个级别。诊断标准有助于确定可能得AIE的患者，同时们也有助于确定患AIE不太可能的患者。在完成包括神经抗体检测在内的检查后，确定符合“可能的”AIE标准的情况下，自身免疫性神经病学专家的早期参与是非常重要的，尤其是考虑进行免疫治疗试验的情况。

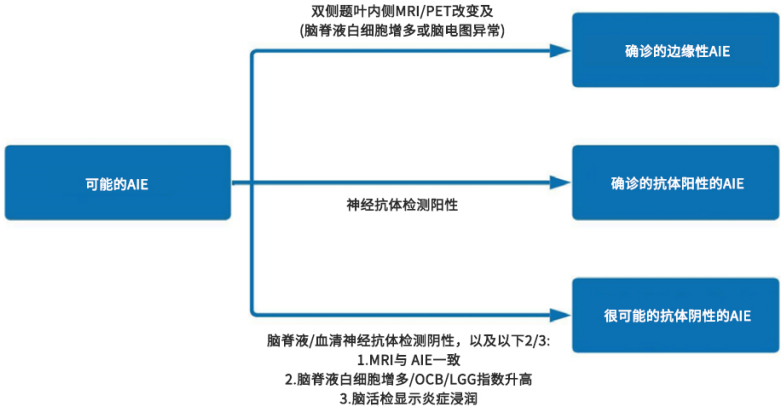
Diagnosis can be made when all three of the following criteria are met:

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 mm³)**
   d. **MRI suggestive of encephalitis‡**
3. **Reasonable exclusion of alternative causes**

***Altered mental status 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.**

(1) 亚急性病起病(小于3个月)的工作记忆下降、意识状态改变或精神症状;
(2) 至少存在以下1条:新发局灶性中枢神经系统症状;不能用既往病史解释的癫痫发作;
脑脊液有核细胞数增多;脑 MRI 提示脑炎样改变;
(3)排除其它诊断。

基于上述诊断标准，可以通过满足NMDAR抗体脑炎或抗体阴性AIE的更特异性的表型标准来实现从“可能”到“很可能”AIE的过渡。明确的AIE诊断需要神经特异性抗体阳性或符合边缘性脑炎/急性播散性脑脊髓炎（ADEM）/Bickerstaff脑炎的特定标准，除此之外还需符合“可能的（possible）”的AIE的标准（所有诊断都假定合理排除其他原因）。



03 初步检查

一旦怀疑患有AIE，临床医生需要:1）获取支持这一诊断的证据；2）合理排他。疾病是一个不断演变的过程，在这个过程中，在急性期检查应与治疗决策并行，推荐患者进行脑脊液（CSF）检查，脑磁共振成像（MRI）、脑电图（EEG）和**神经抗体检测。**在某些情况下也应考虑其他辅助临床检测，详情如下；

◆ 实验室检查

建议的脑脊液和血清检查见下表

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 ***

AIE脑脊液检查至关重要，在AIE的诊断中应排除病原体感染。通过评估脑脊液中蛋白质可以找到炎症的证据，除此之外还可检查**细胞形态、寡克隆带和IgG指数。**
血清筛查应包括广泛的差异，排除感染性、代谢性和全身性自身免疫性脑病的原因。值得注意的是，可能存在一些系统性的线索来提示潜在的原因；例如，在65%的LGI1抗体脑炎病例中可出现低钠血症。

◆ **神经抗体检测**

疑似AIE患者进行神经抗体检测对患者的诊断和管理是非常重要的。虽然少数的临床特征可以作为单个神经抗体的病理标志，但AIE的许多临床和神经影像学特征可以与各种神经抗体同时出现（如记忆障碍、精神症状、癫痫发作、MRI颞叶内侧T2高强度）。由于抗体相关表现之间可能存在表型重叠，通常建议对疑似AIE患者进行全面的的神经抗体组合检测，而不是进行单个抗体检测，最大限度地提高灵敏度并加快诊断效率。

某些抗体（如LGI1和CASPR2抗体）的血清敏感性高于CSF，而CSF对其他抗体（如NMDAR和GFAP抗体）的灵敏度/特异性高于血清。此外，对于罕见/新型抗体，优选样本可能并不确定。由于这些原因，同时检测血清和CSF可以优化灵敏度和特异性。**通常用于神经抗体检测的检测方法包括间接免疫荧光法/免疫组化（TIIF/IHC）、免疫印迹法、CBA、放射免疫沉淀和酶联免疫吸附试验。建议TIIF/IHC并用来提高疑似AIE患者神经抗体检测的敏感性和特异性，并应被视为标准检测。**

TIP

TBA（Tissue-based Assay，基于组织的检测方法）是一个广泛的概念，它包括了多种使用组织样本来检测抗体的方法。TIIF（Tissue Indirect Immunofluorescence，组织间接免疫荧光）是TBA的一种形式，特别用于检测自身免疫性疾病中的自身抗体。
TBA可以包括但不限于以下几种方法：
TIIF：使用已知的抗体（一抗）与组织样本孵育，然后使用荧光标记的二抗来检测一抗的结合情况，通过荧光显微镜观察。**海默医学神经免疫抗体常用验证方法为TBA中的TIIF，与CBA结合使用验证结果。**
直接免疫荧光（DIF）：直接使用荧光标记的一抗与组织样本孵育，观察抗体与组织中抗原的直接结合。
免疫组化（IHC）：使用酶标记的一抗或二抗来检测组织切片中的抗原，通过颜色变化来可视化抗原的位置。

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)

TIIF技术可以用于筛选针对胞细内/外抗原的罕见/新型神经抗体，以最大化检测的敏感性，并且可以用来确认免疫印迹或基于细胞的检测（CBA）结果的阳性，以最大化特异性。

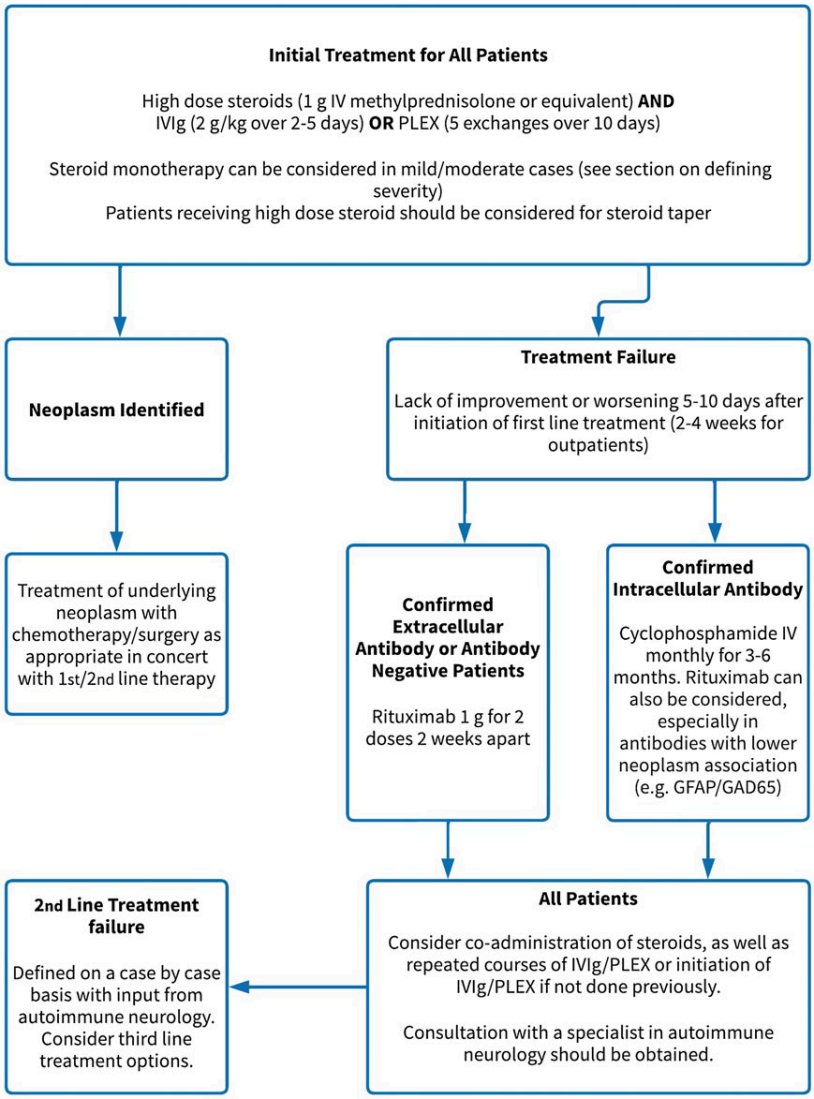
04 影像学检查

◆ 磁共振成像（MRI）：所有疑似AIE患者应进行脑部MRI检查，有助于发现局部或多灶性受累。

◆ 正电子发射断层扫描（PET）成像：FDG-PET在AIE的诊断中越来越有用，比MRI更敏感。

05 治疗

◆ 一线治疗：AIE的治疗主要基于病例系列/回顾性数据和专家共识。建议在排除感染性原因后立即开始一线治疗。



◆ 二线治疗：对于一线治疗失败的患者，推荐进行二线治疗，选择受抗体关联和肿瘤存在的影响。

对细胞表面抗体或阴性抗体患者的急性二线治疗

具有针对细胞表面抗原的抗体的自身免疫性脑炎患者应优先接受利妥昔单抗作为二线治疗，因为可能有更好的疗效和更有利的安全性（图3）。在抗体阴性的AIE中，利妥昔单抗的安全性优于环磷酰胺。然而，一般来说，由于长期免疫抑制，在给予二线免疫治疗之前，推荐自身免疫神经学专家的意见

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

◆ 三线/替代免疫治疗：对于对二线治疗无反应的患者，可以考虑第三线和实验性免疫治
疗。

◆ 关于治疗的实践提示

✓ 尽早开始适当的治疗对于优化治疗效果至关重要。

✓ 在合理排除其他诊断后，如果高度怀疑是 AIE，则不应因为等待神经抗体的结果而推迟考虑经验性免疫疗法。

✓ 所有重度 AIE 患者都应接受大剂量皮质类固醇联合 Ig或 PLEX作为一线治疗;轻度/中度病例可考虑单用类固醇治疗。治疗潜在肿瘤(如果发现)应尽可能与一线治疗同时进行。

✓ 所有在开始一线治疗 5-10 天后(轻度/中度病例为 2-4周)病情未见好转或恶化的重度 AIE 患者都应接受二线治疗。

✓ 与轻度/中度疾病患者相比，重度 AE患者的治疗方法计划有所不同，包括常规启动一线免疫疗法，以及更快速地确定治疗失败以鼓励重度疾病患者更早地升级到二线免疫疗法。

✓ 强烈建议所有一线治疗失败的患者尽早接受自身免疫性神经病学专家的治疗。

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.

06 难治性NMDAR-IgG AIE的特殊注意事项

◆ 难治性NMDAR-IgG AIE：NMDAR抗体脑炎与潜在的畸胎瘤相关，治疗选择包括手术切除肿瘤。如果没有发现肿瘤，随访肿瘤筛查则非常依赖于高或中风险抗体的存在，以及在较小程度上的高风险表型（LE，外周受累的脑脊髓炎）。

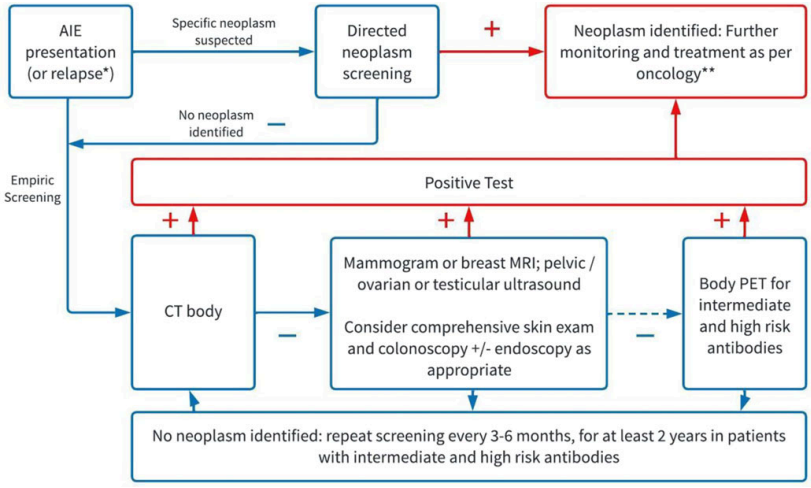
Table 4: Antibody type and malignancy risk

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%)

◆ 免疫检查点抑制剂相关的AIE：治疗与AIE类似，但需要肿瘤学专家的参与。

07 肿瘤筛查

◆ 筛查建议：所有成人AIE患者在诊断时应进行肿瘤筛查，初始筛查应基于影像学。



◆ 关于肿瘤筛查的实践提示

✓ 所有出现 AIE 的成年患者在确诊时都应接受恶性肿瘤筛查。

✓ 在等待神经抗体检测结果时，不应延迟初步筛查。

✓ 如果初筛结果为阴性，则应进行性别特异性检测。

✓ 对于低风险抗体和初始阴性筛查的患者，没有必要进行随访筛查，但应该对具有中等或高风险抗体的患者进行随访鎦查。

✓ 对于抗体阴性患者，随访筛查的最佳方法尚不清楚，但应考虑在某些患者中进行重复筛查(例如，那些具有高风险表型的患者,如 LE、难治性/复发性疾病和/或恶性肿瘤的重大风险因素)。

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)

08 其他疾病表现的治疗

◆ 癫痫管理：推荐结合抗癫痫药物（ASMs）和免疫抑制治疗AIE相关的癫痫。

◆ 神经精神症状：AIE患者常见的神经精神症状应通过一线和二线治疗改善，但可能需要症状性治疗。

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

09 康复/预后

◆ 预后：AIE的预后因具体亚型和相关癌症而异，早期治疗与改善长期功能和认知预后相关。

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).

10 慢性管理

◆ 复发：AIE复发率在不同亚型间存在显著差异，复发的治疗应根据一线和/或二线治疗方案进行。

◆ 长期免疫抑制：长期免疫治疗的决策缺乏数据，建议在复发形式的AIE中考虑三年或更长时间的维持免疫治疗。

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 $1^{st}/2^{nd}$ line treatment algorithms as above unless a particular therapy is known to be ineffective for the patient.

11 减轻免疫抑制治疗风险的重要考虑因素和策略

◆ 潜伏感染筛查：

✓ 建议尽早进行广泛的测试，以识别任何潜伏感染，如水痘-带状疱疹病毒（VZV）、HIV、乙型/丙型肝炎和结核病。

✓ 一旦识别出感染，应尽早开始适当的预防性或决定性治疗，并建议咨询传染病专家。

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.

◆ 疫苗接种：

✓ 应考虑为开始免疫抑制治疗的患者接种年龄适宜和背景适宜的疫苗。

✓ 疫苗接种计划可能需要根据免疫治疗的紧迫性进行调整或推迟，并且在非活疫苗治疗期间接种疫苗的效力可能会降低。

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

◆ 生殖健康/妊娠风险：

✓ 一线免疫疗法通常在妊娠期间是安全的，类固醇和IVIg/PLEX被认为是安全的选择。

✓ 像利妥昔单抗这样的二线药物在治疗和受孕/分娩之间的延迟时间有不同的指南，一些报告表明即使在分娩后6个月内治疗也是安全的，尽管它通常会导致婴儿的CD19/20短暂耗竭。

✓ 环磷酰胺在妊娠期间不应使用，并且可能带来不孕风险，需要讨论并可能探索在允许的情况下进行配子的采集/储存。在这种情况下强烈建议涉及自身免疫神经病专家。

◆ 肺孢子虫（PJP）预防：

✓ 对于接受免疫治疗的患者来说，PJP预防至关重要，但确切的应用仍有争议。

✓ 甲氧苄啶-磺胺甲恶唑（TMP-SMX）是PJP预防的标准，对于轻微反应的TMP-SMX，可以考虑进行脱敏和随后的使用，而不是使用阿托伐醌、达普松或喷他脒治疗。

✓ 推荐的PJP预防方案包括在以下情况下提供预防。

◆ 糖皮质激素使用的并发症

糖皮质激素在短期疗程中（例如，胃溃疡/出血，骨坏死）很少引起持久的副作用，但长期使用的后果可能会破坏治疗努力。常见问题包括代谢综合征恶化（即体重指数增加、高血压、高脂血症、糖耐量减退）、骨质疏松症、感染以及愈合受损/皮肤变薄。神经精神表现可能是最棘手的问题，因为它们可能与脑炎症状重叠。如果副作用非常严重，则可能需要更快地减量/停药，但存在几种减轻策略（表9）。

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.

12 临床和多学科护理

◆ 护理建议：建议早期转诊至有AIE管理经验的中心，特别是对一线治疗无反应的患者。

13 结论

自身免疫性脑炎越来越被认识到是亚急性神经系统症状和意识状态变化的原因。尽管如此，关于诊断和管理的高质量证据仍然缺乏。在这种情况下，这些共识指南可能有助于帮助一线临床医生识别、适当调查和治疗自身免疫性脑炎（AIE）患者，目的是标准化护理。在加拿大，护理方面的差距存在并将会继续存在；不仅在获取一线和二线治疗（特别是血浆置换（PLEX）和利妥昔单抗）的途径上，还在获取诊断和管理AIE专业知识的临床医生和中心的途径上。此外，作者希望建立指南可能有助于在省和国家层面争取公平的治疗机会。

幸运的是，增加的认识也导致了最近针对AIE的临床试验和治疗的发展。这些发展为AIE的新基于证据的治疗提供了希望，并持续改善患者的预后。