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AUTOIMMUNE EPILEPSY: THE UNDERESTIMATED DIAGNOSIS - FROM RED FLAGS TO IMMUNOTHERAPY

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ABSTRACT

Autoimmune-associated epilepsy (AAE) is the epilepsy phenotype most likely to be missed in neurology clinics. Neural autoantibodies are identified in a substantial fraction of adults with epilepsy of unknown aetiology, mostly undiagnosed before testing, and in a sizeable proportion of new-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES). The barrier to recognition is not the absence of effective therapy, but the absence of systematic testing: autoimmune epilepsy is not rare; it is rarely tested. This review argues for a shift from antibody-driven testing ("test when encephalitis is suspected") to syndrome-driven testing ("epilepsy-plus" phenotypes triggering a reflex panel). We synthesise the 2016-2026 literature across three axes. First, an antibody-by-antibody guide (Table 1) contrasts surface-antigen syndromes (LGI1, NMDAR, CASPR2, GABA-B, GABA-A, AMPA) with the intracellular-antigen GAD65 syndrome. Second, a twelve-domain Red Flag Checklist (Table 2) operationalises the "epilepsy-plus" concept, with a ≥2-flag trigger rule mandating reflex testing of paired serum and cerebrospinal fluid. Third, a 2026 immunotherapy algorithm (Table 3) stratifies first-line, second-line, and refractory therapy on the principle that timing is the active ingredient. We address three ongoing debates - GAD65 low- versus high-titre pathogenicity, seronegative AAE, and immunotherapy duration - proposing a risk-stratified, treat-to-remission framework. The cost of delay is measurable in hippocampi, cognitive function, and lives; the barrier is not cost but habit.

KEYWORDS

Autoimmune Epilepsy; Neural Autoantibodies; Faciobrachial Dystonic Seizures; Drug-Resistant Epilepsy; Immunotherapy; NORSE

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1. Introduction - the hidden fraction inside drug-resistant epilepsy

Drug-resistant epilepsy (DRE) - failure of two appropriately chosen and tolerated antiseizure medications (ASMs) to achieve sustained seizure freedom - affects approximately 30% of people with epilepsy worldwide. When no structural lesion is identified, the epilepsy is labelled "unknown aetiology" [1]. This is the pool in which autoimmune-associated epilepsy (AAE) hides.

The magnitude is now quantified. In the landmark prevalence study by Dubey and colleagues, neural autoantibodies were identified in a substantial fraction of adults with epilepsy of unknown aetiology, the majority with no prior suspicion of autoimmunity [2]. The ILAE Autoimmunity and Inflammation Taskforce subsequently formalised the distinction between acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy - an enduring predisposition to seizures [3]. This distinction determines treatment (immunotherapy versus ASM), prognosis, and social consequences; yet in routine practice it is rarely made, because the autoimmune aetiology is rarely sought.

The 2017 ILAE classification placed "immune" alongside genetic, structural, metabolic, infectious, and unknown as one of six epilepsy aetiologies [1] - a formal recognition that autoimmunity is a first-order cause. The case for changing clinical habit rests on three observations. First, treatment is time-dependent: early immunotherapy in LGI1-antibody faciobrachial dystonic seizures (FBDS) prevents hippocampal atrophy and cognitive impairment [4]; second-line therapy in anti-NMDAR encephalitis improves outcome [5]; early immunotherapy in NORSE/FIRES is endorsed by the 2022 international consensus [6]. Second, the diagnostic framework exists - the Graus 2016 criteria include "probable autoimmune encephalitis" without requiring an antibody [7], and the APE2 and ACES scores formalise the red-flag logic [2, 8]. Third, the cost of not testing exceeds the cost of testing - a neural antibody panel is a fraction of the cost of one year of DRE care, and orders of magnitude less than an avoidable temporal lobectomy on an inflamed hippocampus.

We do not re-review autoimmune encephalitis in its entirety [9] but focus on the epilepsy-centric question: which patients with seizures should trigger an autoimmune workup, how should they be tested, and how should they be treated? Our central thesis: autoimmune epilepsy is not rare - it is rarely tested - and the shift from antibody-driven to syndrome-driven testing is the single change most likely to reduce the hidden fraction inside DRE.

A note on scope. This is a critical narrative review; the literature selection reflects the authors' clinical judgement and is structured according to SANRA principles [10]. We emphasise one underappreciated hazard at the outset: the co-prescription of sodium-channel ASMs (carbamazepine, lamotrigine, oxcarbazepine) in undiagnosed LGI1-antibody disease, where such agents may worsen hyponatremia, precipitate severe cutaneous drug reactions, and fail to control seizures - a combination that should itself be considered a red flag (Table 2).

The present review differs from existing authoritative syntheses in three respects. First, it is written for the epileptologist rather than the neuroimmunologist: where Geis and colleagues [11] and Dalmau and Graus [9] organised the field around encephalitis; we organise it around the undifferentiated patient with drug-resistant seizures. Second, we provide a twelve-domain Red Flag Checklist (Table 2) that operationalises the "epilepsy-plus" concept beyond the validated APE2 and ACES scores, with an explicit and deliberately permissive threshold of two flags. Third, we update the therapeutic horizon to 2026 - including the ExTINGUISH and COMBAT-NORSE trials, Fc-receptor-neonatal blockade, and CD38-directed plasma-cell depletion - with a transparent description of evidence type rather than a pseudo-hierarchical grading. The Checklist and the algorithm (Table 3) are proposed clinical tools, not validated instruments; prospective validation is a stated aim of the research agenda in Section 8.

2. From encephalitis to epilepsy - modern definitions 2016-2025

2.1 The Graus 2016 criteria and the ILAE 2017 classification

The 2016 Lancet Neurology criteria provided the first standardised diagnostic framework for autoimmune encephalitis, defining possible, probable, and definite categories - the "probable" category permitting diagnosis on clinical, laboratory, and imaging grounds **without a positive antibody** [7]. This is pivotal for epileptology: it recognises that seronegativity is a feature of several real syndromes (notably NORSE/FIRES) and that the antibody result confirms rather than decides. The criteria have one structural limitation for epilepsy practice: they were designed for encephalitis, not for chronic epilepsy. A patient with chronic GAD65-associated temporal lobe epilepsy may not meet the encephalitis criteria yet still have an autoimmune aetiology warranting immunotherapy - the gap that motivates the syndrome-driven approach of Section 4.

The 2017 ILAE classification placed aetiology at the centre of the diagnostic process, enumerating six groups - genetic, structural, metabolic, immune, infectious, and unknown - with "immune" as a co-equal aetiology [1]. This removed autoimmune epilepsy from the "unknown" residual and required clinicians to consider it alongside the traditional structural and genetic workup.

2.2 The ILAE 2020 conceptual definitions

The ILAE Autoimmunity and Inflammation Taskforce formalised two entities [3, 12], building on the framework articulated by Geis and colleagues [11]: acute symptomatic seizures secondary to autoimmune encephalitis (a transient seizure state expected to resolve as encephalitis is treated) and autoimmune-associated epilepsy (an enduring predisposition requiring ongoing ASM and sometimes maintenance immunotherapy). The distinction determines the therapeutic target (the immune process versus the seizure threshold), prognosis (AAE carries a higher likelihood of long-term ASM requirement [13]), and how the patient is counseled. In practice, the boundary is dynamic: a patient who continues to seize after NMDAR encephalitis recovery has transitioned to AAE.

2.3 The APE2 and ACES scores

The Antibody Prevalence in Epilepsy (APE2) score [2] and the Antibodies Contributing to Focal Epilepsy Signs and Symptoms (ACES) score [8] formalised the red-flag logic into structured clinical scoring tools. Both instruments assign weighted point values to specific clinical, electroencephalographic, and neuroimaging features. The critical caveat: these scores were originally derived in antibody-positive cohorts, so a low score does not completely exclude a seronegative autoimmune syndrome.

2.4 A note on the "2023 ILAE update"

A "2023 ILAE update" is sometimes cited in recent literature. Our search did not identify a distinct 2023 ILAE position paper superseding the 2020 Steriade definitions; the operative framework remains in the 2020 publication [3, 12], supplemented by the 2022 NORSE consensus [6]. We flag this to discourage citation of a non-existent "2023 update" - a reference-drift problem discussed further in Section 7.

2.5 The antibody catalogue and its discontents

The antibody catalogue has expanded significantly over the past decade. From the original voltage-gated potassium channel (VGKC) complex - the seminal description by Vincent and colleagues of a "potentially immunotherapy-responsive form of limbic encephalitis" [14], later decomposed into LGI1 and CASPR2 by Lai and Irani respectively [15–17] - the spectrum now encompasses NMDAR, GABA-B, GABA-A, AMPA, GAD65, and emerging antigens. Two failure modes attend this expansion: (i) a negative panel is assumed to exclude autoimmunity, when it may be incomplete or assay-inappropriate; and (ii) a positive antibody is assumed to prove pathogenicity, when low-titre GAD65 and non-specific VGKC-complex positivity are common in the general population and in non-autoimmune neurological disease [18–20]. The syndrome-driven framework corrects both.

3. An antibody-by-antibody guide for the epileptologist

The clinical utility of a neural autoantibody result lies in predicting the seizure phenotype, the cancer association, and the expected immunotherapy response. This framework, articulated for epileptologists by Bien and Holtkamp [21] and grounded in the clinical characterisation by Quek and colleagues [22], is developed around the three antibodies accounting for the majority of AAE - LGI1, NMDAR, and GAD65 - each illustrating a distinct clinical logic. The full comparison is in Table 1.

Table 1. Neural autoantibodies in autoimmune-associated epilepsy

Antibody	Clinical Phenotype	Seizure Type	MRI / CSF / EEG Clue	Cancer Association	Response to Immunotherapy	Key Reference (DOI)
LGI1	FBDS → limbic encephalitis; hyponatremia; older male; progressive memory decline	FBDS (pathognomonic), focal temporal, GTCS; frequent subclinical temporal seizures	T1 basal ganglia hyperintensity (early); hippocampal T2 (late); CSF often bland; FBDS ictal EEG subtle/absent	Rare (thymoma)	**Excellent if early**; ASMs relatively ineffective; early immunotherapy prevents cognitive decline	Thompson 2018 [4] Brain 10.1093/brain/awx323; Irani 2011 [23] Ann Neurol 10.1002/ana.22307
NMDAR	Psychiatric prodrome → memory loss, orofacial dyskinesia, autonomic instability; young female/children	Focal → bilateral convulsive, status epilepticus; extreme delta brush on EEG	MRI often normal; CSF pleocytosis/OCB; **CSF-restricted antibodies more sensitive than serum**	Ovarian teratoma (age-dependent)	Good but slow; early second-line (rituximab ± cyclophosphamide) improves outcome	Titulaer 2013 [5] Lancet Neurol 10.1016/S1474-4422(12)70310-1; Dalmau 2008 [29] 10.1016/S1474-4422(08)70224-2
GAD65	Chronic temporal-lobe epilepsy ± T1DM/stiff-person; young female; slowly progressive; "the chronic masquerader"	Drug-resistant focal temporal; rare status	Hippocampal atrophy (late); **high titre + intrathecal synthesis** supportive; CSF OCB	Rare (thymoma, SCLC)	**Poor/modest** - antibody marks T-cell-mediated pathology; high-dose steroids/rituximab partial	Malter 2010 [35] Ann Neurol 10.1002/ana.21917; Saiz 2008 [18] Brain 10.1093/brain/awn183

Antibody	Clinical Phenotype	Seizure Type	MRI / CSF / EEG Clue	Cancer Association	Response to Immunotherapy	Key Reference (DOI)
CASPR2	Limbic encephalitis, Morvan syndrome, neuromyotonia; older male	Focal temporal; transient epileptic amnesia	Variable mesial temporal T2; CSF may be bland	Thymoma, SCLC	Moderate-good (surface antigen)	Irani 2010 [16] Brain 10.1093/brain/awq213; Cretin 2020 [38] Seizure 10.1016/j.seizure.2020.08.010
GABA-B-R	Limbic encephalitis, often older male ± ataxia	Focal, status epilepticus	Mesial temporal T2; CSF pleocytosis	**SCLC (strong)**	Moderate; paraneoplastic cases require tumour treatment	Lancaster 2010 [39] Lancet Neurol 10.1016/S1474-4422(09)70324-2; Höftberger 2013 10.1212/WNL.0b013e3182a9585f
GABA-A-R	Refractory seizures/status, often paediatric; multifocal brain involvement	**Refractory status epilepticus**	Multifocal cortical/subcortical T2 changes; status on EEG	Rare	Variable; often needs aggressive first + second line	Petit-Pedrol 2014 [41] Lancet Neurol 10.1016/S1474-4422(13)70299-0
AMPA-R	Limbic encephalitis, older female, prominent psychiatric	Focal temporal, status	Mesial temporal T2	Thymoma, SCLC, breast	Moderate; **relapses common**	Lai 2009 Ann Neurol 10.1002/ana.21589; Höftberger 2015 10.1212/WNL.0000000000001682
Seronegative AAE	"Probable AE" (Graus 2016 [7]); NORSE/FIRES antibody-negative	Super-refractory status (FIRES), chronic focal	Non-specific; CSF often bland in chronic phase	Variable	Variable; **early immunotherapy in NORSE per 2022 consensus**	Graus 2016 [7] 10.1016/S1474-4422(15)00401-9; Wickström 2022 [6] 10.1111/epi.17391

3.1 LGI1 - the treatable faciobrachial dystonic seizures

LGI1 antibodies are the commonest cause of non-paraneoplastic autoimmune limbic encephalitis in older adults. The clinical signature is the faciobrachial dystonic seizure (FBDS): a brief (1-3 s), high-frequency event involving unilateral arm dystonia and ipsilateral facial contraction, often dozens of times per day. In the original cohort, 89% of patients with VGKC-complex antibodies and FBDS had LGI1 as the specific antigen, and 77% developed FBDS before the amnesia and confusion of limbic encephalitis [23] - a prodromal window that is the central therapeutic opportunity.

Three features make LGI1-AE uniquely important:

1. FBDS are frequently misdiagnosed. They are often mislabelled as myoclonus, hemifacial spasm, functional events, or transient ischaemic attacks. Recognition of FBDS should immediately trigger LGI1 testing, because the prodrome may last weeks to months before encephalitis onset [23, 24].

2. ASMs are relatively ineffective and may cause harm. In the Irani cohort, antiepileptic drugs were generally ineffective, and 41% of patients experienced cutaneous drug reactions [23]. Sodium-channel agents also exacerbate hyponatremia, compounding the syndrome's intrinsic hyponatremia.

3. Early immunotherapy prevents cognitive decline. Thompson and colleagues demonstrated that early treatment achieves significantly better cognitive outcomes, whereas treatment delay leads to irreversible hippocampal atrophy [4, 25].

This underpins the strongest recommendation in autoimmune epileptology: FBDS should be treated with immunotherapy, not ASM escalation.

The imaging signature - basal ganglia T1 hyperintensity - is early and highly suggestive of LGI1 [26]. CSF is frequently unremarkable. LGI1-AE is rarely paraneoplastic (thymoma in a minority); long-term outcome is generally favourable with early treatment, though some patients develop chronic temporal lobe epilepsy requiring ongoing ASM [13, 27, 28].

3.2 NMDAR - beyond encephalitis

Anti-NMDAR encephalitis is the commonest antibody-mediated encephalitis in young people. The seminal case series established the pattern: psychiatric prodrome progressing to memory loss, orofacial dyskinesia, autonomic instability, seizures, and central hypoventilation, often in young women with ovarian teratoma [29, 30].

Two aspects deserve emphasis. The antibody is CSF-predominant - serum-only testing misses a substantial proportion of cases, and CSF titres correlate better with disease activity and outcome [29, 31]. Paired serum and CSF sampling are mandatory. An "epilepsy-only" phenotype exists but is age-dependent - a subset of children and young adults present with isolated new-onset seizures without the full encephalitic syndrome [32]. The EEG marker extreme delta brush is highly specific for NMDAR encephalitis [33].

Treatment outcome was defined by the Titulaer cohort, showing that early second-line immunotherapy (rituximab or cyclophosphamide) was associated with better outcomes and fewer relapses [5]. The ongoing ExTINGUISH trial - a phase 2B randomised placebo-controlled study of inebilizumab in anti-NMDAR encephalitis - is the first rigorous trial of a B-cell therapy in this disease [34] (NCT04372615). Tumour removal, when an ovarian teratoma is present, is itself therapeutic. Long-term seizure outcome is generally favourable; ASM withdrawal is often possible after sustained recovery [13, 28].

3.3 GAD65 - the chronic masquerader

GAD65 is an intracellular enzyme; the antibody is a marker of concurrent T-cell-mediated pathology rather than the direct effector. This explains both the phenotype and the disappointing immunotherapy response. The epilepsy phenotype is chronic, drug-resistant temporal lobe epilepsy, typically in young women with type 1 diabetes mellitus, progressing insidiously over months to years [18, 35, 36]. MRI shows mesial temporal T2 hyperintensity progressing to hippocampal atrophy - easily mistaken for mesial temporal lobe epilepsy with hippocampal sclerosis, which is why GAD65 is the archetype of the "hidden fraction" inside DRE.

Controversy: low-titre versus high-titre GAD65 (Controversy 1). Low-titre serum GAD65 antibodies are common in the general population (~1% of healthy adults, up to 8% in type 1 diabetes mellitus) and are not diagnostic of autoimmune neurological disease [18, 37]. Pathogenic relevance requires high titre (typically >2000 U/mL), CSF-restricted or intrathecal synthesis, and a compatible neurological syndrome. Low-titre serum-only positivity in a patient with typical structural epilepsy should not trigger immunotherapy - the commonest over-diagnosis error in autoimmune epileptology.

Immunotherapy response is modest: high-dose corticosteroids may produce transient benefit; rituximab has shown promise in some case series, but results are inconsistent, reflecting T-cell-mediated pathology that the antibody marks but does not mediate. A paraneoplastic association (thymoma, small-cell lung cancer, breast) exists in a minority and should be screened when the syndrome includes ataxia or evolves rapidly [37].

3.4 Other surface-antigen syndromes

CASPR2 produces a spectrum from limbic encephalitis to Morvan syndrome and neuromyotonia, predominantly in older men [16]; transient epileptic amnesia is a recognised presentation [38]. Thymoma and small-cell lung cancer are the principal associations. GABA-B receptor limbic encephalitis, often in older men, has a strong small-cell lung cancer association [28, 39, 40]. GABA-A receptor encephalitis stands apart for its severity: refractory seizures and status epilepticus, often in children, with multifocal MRI changes [41]. AMPA receptor limbic encephalitis, predominantly in women, has prominent psychiatric features and relapses common if immunotherapy is tapered prematurely [42, 43]. These four share the logic of surface-antigen autoimmunity: the antibody accesses its target, alters synaptic function, and the syndrome is at least partially reversible with antibody depletion - a logic that does not apply to GAD65.

4. When to suspect it is NOT typical epilepsy: a red-flag checklist for clinic

The decision to test is the bottleneck. Autoimmune epilepsy is not rare - it is rarely tested [2]. The gap between prevalence and recognition is the central problem this review addresses.

4.1 The "epilepsy-plus" concept

Autoimmune epilepsy rarely declares itself through seizures alone. It declares itself through **epilepsy-plus**: seizures plus features that distinguish immune-mediated disease from structural or genetic epilepsy. Table 2 operationalises this across twelve clinical domains - age and onset, tempo, semiology, frequency, ASM response, comorbidity, prodrome, MRI, CSF, EEG, systemic/paraneoplastic context, and NORSE/FIRES presentation. The trigger rule we propose is deliberately permissive: two or more red flags should prompt reflex antibody testing (paired serum and CSF) regardless of whether the full Graus criteria for autoimmune encephalitis are met. The chronic, epilepsy-only phenotypes of GAD65 and post-FBDS LGI1 will be missed if one waits for florid encephalopathy before testing.

Table 2. Red flags versus typical drug-resistant epilepsy

Domain	Typical drug-resistant epilepsy	Autoimmune red flag	Evidence anchor
1. Age and onset	Onset across a wide age range; long latent period in mesial temporal lobe epilepsy with hippocampal sclerosis	**Adult-onset (>50 y)** new focal epilepsy without structural lesion; **or** new-onset epilepsy in a previously well child/young adult with acute/subacute onset over days-weeks	Graus 2016 10.1016/S1474-4422(15)00401-9; Steriade 2020 10.1111/epi.16571
2. Tempo of evolution	Stable or slowly progressive over years	**Rapidly progressive** cognitive/behavioural decline alongside seizure onset; deterioration over weeks-months	Thompson 2018 10.1093/brain/awx323; Graus 2016
3. Seizure semiology	Fixed, stereotyped focal seizures consistent with one focus; mesial temporal pattern	**Faciobrachial dystonic seizures (FBDS)** - brief (<3 s), high-frequency, arm-and-ipsilateral-face dystonia → pathognomonic for LGI1; **multifocal/refractory status epilepticus**; **transient epileptic amnesia** (CASPR2); orofacial dyskinesia with psychiatric prodrome (NMDAR)	Irani 2011 10.1002/ana.22307 (89% LGI1; 77% FBDS precede limbic encephalitis); Cretin 2020 10.1016/j.seizure.2020.08.010; Schmitt 2012 10.1212/WNL.0b013e3182698cd8
4. Seizure frequency and clustering	Seizures emerge over months-years; clusters uncommon	**Clustered onset** - multiple daily seizures at presentation; FBDS may occur dozens of times per day	Irani 2011; Aurangzeb 2017 10.1016/j.seizure.2017.05.017 (LGI1 multifocal clinical and subclinical seizures)
5. Antiseizure medication response	Partial response to appropriate ASM; logical sequence of trials	**Resistance to ≥2 appropriate ASMs from onset**; **worsening with sodium-channel agents** (LGI1 - hyponatremia and rash risk); **early cutaneous drug reactions** (≈41% in LGI1 series)	Irani 2011 [23] (AEDs ineffective; 41% cutaneous reactions); de Bruijn 2019 [28] (ASM response and adverse effects in LGI1/NMDAR/GABA-B encephalitis)
6. "Epilepsy-plus" comorbidity	Isolated epilepsy; comorbidities (depression, anxiety) secondary to chronic epilepsy	**Hyponatremia** (LGI1); **psychiatric prodrome** (NMDAR - psychosis, agitation); **autonomic instability** (NMDAR); **movement disorder** (orofacial dyskinesia, chorea, ataxia); **type 1 diabetes mellitus / stiff-person spectrum** (GAD65); **peripheral nerve hyperexcitability / Morvan syndrome** (CASPR2)	Irani 2011 (hyponatremia, FBDS); Malter 2010 10.1002/ana.21917 (GAD65, T1DM overlap); Irani 2010 10.1093/brain/awq213 (CASPR2/Morvan); Saiz 2008 10.1093/brain/awn183 (GAD spectrum)

Domain	Typical drug-resistant epilepsy	Autoimmune red flag	Evidence anchor
7. Viral-like prodrome	No recent febrile illness; no temporal relationship to infection	**Febrile/infectious prodrome 24 h-2 weeks before seizure onset** - hallmark of NORSE/FIRES and a sizeable fraction of NMDAR/LGI1 cases	Wickström 2022 10.1111/epi.17391; Kenney-Jung 2016 10.1002/ana.24806 (FIRES)
8. MRI brain	Stable lesion (e.g., hippocampal sclerosis, cavernoma, focal cortical dysplasia) or normal	**Mesial temporal T2/FLAIR hyperintensity without atrophy at onset** (evolving to atrophy if untreated); **basal ganglia T1 hyperintensity** (LGI1, early and specific); **multifocal cortical/subcortical changes** (GABA-A); **normal MRI** does not exclude autoimmunity (NMDAR often MRI-negative)	Flanagan 2015 10.1212/NXI.0000000000000161 (basal ganglia T1 in LGI1); Petit-Pedrol 2014 10.1016/S1474-4422(13)70299-0 (GABA-A multifocal); Finke 2017 10.1001/jamaneurol.2016.4226 (hippocampal damage in LGI1)
9. CSF	Not routinely abnormal; mild protein elevation only when sampled	**Pleocytosis, oligoclonal bands, or elevated IgG index** with **negative microbial PCR**; CSF-restricted antibodies (NMDAR is CSF-predominant - serum-negative/CSF-positive is a recognised pattern)	Graus 2016; Dalmau 2008 10.1016/S1474-4422(08)70224-2 (CSF sensitivity in NMDAR)
10. EEG	Focal interictal epileptiform discharges concordant with imaging; slowing appropriate to lesion	**Extreme delta brush** (NMDAR, distinctive pattern); **frequent subclinical temporal ictal patterns** in cognitively normal patients (LGI1); **nonconvulsive status epilepticus at presentation**; diffuse slowing disproportionate to imaging	Schmitt 2012 10.1212/WNL.0b013e3182698cd8 (extreme delta brush); Aurangzeb 2017 10.1016/j.seizure.2017.05.017
11. Laboratory / systemic	No systemic autoimmune markers	**Coexisting autoimmune disease** (thyroid, T1DM, vitiligo); **paraneoplastic context** - new neurological onset with known/recent cancer (SCLC→GABA-B; ovarian teratoma→NMDAR; thymoma→LGI1/CASPR2/AMPAR)	Lancaster 2010 10.1016/S1474-4422(09)70324-2 (GABA-B/SCLC); Dalmau 2007 10.1002/ana.21050 (NMDAR/teratoma); Ariño 2015 10.1001/jamaneurol.2015.0749
12. NORSE / FIRES presentation	Not applicable	**New-onset refractory status epilepticus without prior epilepsy**, unresponsive to ≥2 first-line anticonvulsants - invoke NORSE protocol; **FIRES** if febrile prodrome; **super-refractory** course mandates early immunotherapy even when antibody-negative	Wickström 2022 10.1111/epi.17391 & 10.1111/epi.17397; Gaspard/Sculier 2019 10.1016/j.seizure.2018.09.018

4.2 NORSE and FIRES: the fulminant edge

New-onset refractory status epilepticus (NORSE) - super-refractory status without prior epilepsy and without an acute structural, metabolic, or infectious cause - represents the fulminant end of autoimmune epileptology. When a febrile prodrome precedes the status by 24 hours to 2 weeks, the syndrome is termed FIRES. The 2022 international consensus recommends that immunotherapy should not be withheld while awaiting antibody results, particularly in FIRES where an IL-1β/IL-6 cytokine cascade is implicated [6, 44]. The clinical research framework has been articulated by Gofton and colleagues [45], and the definitional review by Sculier and Gaspard provides a concise overview [46]. The NEOS score, derived by Balu and colleagues, predicts 1-year functional status at presentation [47] and has been validated in Chinese adults [48] and paediatric cohorts [49]; its role is prognostic rather than diagnostic.

NORSE illustrates the seronegativity problem at its most acute: a substantial fraction of cases remains antibody-negative throughout yet respond to immunotherapy - the strongest clinical evidence that "seronegative autoimmune epilepsy" is a real entity (**Controversy 2**, Section 6.4).

4.3 APE2 and ACES: from red flags to structured scores

The APE2 [2] and ACES [8] scores formalise red-flag clinical reasoning into quantitative instruments. Independent real-world validations - including general neurology cohorts [50], multicentre epilepsy cohorts [51], and paediatric adaptations (P-APE2, P-RITE2) [52] - confirm that high scores strongly predict antibody positivity and immunotherapy response. However, clinicians must recognise that these scores systematically under-score seronegative patients who may still benefit from immunotherapy. A high score justifies testing; a low score does not end the diagnostic conversation.

4.4 The cost of not testing

The cost of delay is measurable: in LGI1-AE, each week of untreated FBDS brings the patient closer to irreversible hippocampal atrophy and cognitive impairment [4, 25]; in NMDAR encephalitis, delayed second-line therapy worsens long-term outcome [5]; in NORSE/FIRES, prolonged super-refractory status carries substantial mortality (12-30% in cryptogenic NORSE cohorts, with only a minority of survivors returning to baseline function) [6, 46]; in GAD65-associated epilepsy, years of futile ASM escalation and avoidable referral for epilepsy surgery - including temporal lobectomy on an inflamed hippocampus - represent a preventable category of iatrogenic harm. The barrier is not cost; it is habit. This review is an argument for changing habits.

5. Diagnostic workup 2026 - antibody testing, CSF, imaging, APE2/ACES

The most common reason for a missed diagnosis is not the absence of testing but the wrong test on the wrong sample.

5.1 Antibody testing: paired serum and CSF, live cell-based assays

NMDAR antibodies are CSF-predominant - serum-only testing misses a substantial proportion of cases [29, 31]. Paired serum and CSF sampling are non-negotiable. Antibodies to conformational antigens (LGI1, CASPR2, GABA-A, GABA-B, AMPA) are best detected by live cell-based assays; fixed-cell immunoassays and line blots miss conformational epitopes and generate both false negatives and false positives. The historical "VGKC-complex" radioimmunoassay was a composite of antibodies to LGI1, CASPR2, and other subunits, with a high false-positive rate in non-autoimmune contexts [17, 19, 20]; contemporary practice requires antigen-specific testing (LGI1, CASPR2 separately). For GAD65, the principle is titre and compartment: low-titre serum positivity is common in the general population and not diagnostic [18, 37]; high titre, CSF-restricted synthesis, and a compatible syndrome are required before GAD65 is treated as pathogenic.

5.2 CSF, MRI, and EEG

The recommended CSF panel: cell count, protein, glucose, oligoclonal bands (matched with serum), IgG index, and microbial PCR. A normal CSF does not exclude AAE - LGI1-AE may have bland CSF - but an abnormal CSF is strongly supportive. MRI signatures are syndrome-specific (Table 2, row 8): mesial temporal T2 hyperintensity without atrophy at onset (LGI1, GABA-B, AMPA, GAD65); basal ganglia T1 hyperintensity, early and specific for LGI1 [26]; multifocal cortical/subcortical changes (GABA-A) [41]; normal MRI does not exclude AAE - anti-NMDAR encephalitis is frequently MRI-negative. EEG: extreme delta brush is highly specific for NMDAR [33]; frequent subclinical temporal ictal patterns occur in LGI1-AE [24]; nonconvulsive status at presentation is a feature of GABA-A and severe NMDAR disease.

5.3 Paraneoplastic screening

Tumour removal is itself therapeutic in several syndromes (NMDAR with ovarian teratoma; GABA-B with small-cell lung cancer; LGI1/CASPR2/AMPAR with thymoma). The minimum screen is cross-sectional imaging of chest, abdomen, and pelvis; ovarian ultrasonography in young women with suspected NMDAR encephalitis; and FDG-PET/CT where suspicion is high and initial imaging is negative. The tumour association is antibody-specific (Table 1) and guides screening intensity - a single negative scan does not exclude a slow-growing teratoma and repeat screening at 6-12 months is appropriate in high-risk syndromes. In children, the diagnostic approach follows the same principles with age-specific modifications [53].

6. Immunotherapy in autoimmune-associated epilepsy: a 2026 treatment algorithm

The treatment is effective, available, and frequently delayed. The challenge is no longer whether to treat, but when, with what, and for how long. This section operationalises the 2021 best-practice recommendations of the Autoimmune Encephalitis Alliance Clinicians Network [54] in an epilepsy-specific algorithm (Table 3) and mechanism-anchored drug table (Table 3).

Table 3. Immunotherapy for autoimmune-associated epilepsy

Agent	Mechanism	Typical dose	Evidence type	Toxicity / key safety considerations	Key reference
FIRST-LINE THERAPY					
Methylprednisolone (IV)	Broad immunosuppression; reduces BBB permeability; rapid effect on antibody-mediated inflammation	1 g/day IV × 3-5 days, then oral prednisolone taper (1 mg/kg/day, taper over 4-12 weeks per syndrome)	Institutional cohorts + expert consensus (no RCT)	Hypertension, hyperglycaemia, psychosis, insomnia, infection risk, osteoporosis with prolonged use	Abboud 2021 [54] 10.1136/jnnp-2020-325300 (84% of clinicians use as first-line); Irani 2011 [23] (effective in LGI1 FBDS)
IVIG	Multiple: Fc-receptor blockade, anti-idiotypic neutralisation, complement inhibition, immunomodulatory cytokine effects	0.4 g/kg/day × 5 days (adults); 2 g/kg over 2-5 days (children)	**One small RCT (N=17) + institutional cohorts**	Thromboembolism, aseptic meningitis, renal dysfunction, haemolysis, anaphylaxis (IgA deficiency)	Dubey 2020 [56] 10.1002/ana.25655 (small RCT, N=17: IVIG vs placebo in LGI1/CASPR2 epilepsy, OR 10.5, p=0.044 - first RCT in autoimmune epilepsy but underpowered); Foscarini-Craggs 2021 [57] 10.1186/isrctn69615004 (UK multicentre RCT, ongoing); Abboud 2021 [54]
Plasma exchange	Direct removal of circulating antibodies	5 exchanges over 7-10 days (1.0-1.5 plasma volumes)	Institutional cohorts + comparative observational study	Hypotension, hypocalcaemia, coagulopathy, catheter-related infection, contraindicated with recent IVIG (removes therapeutic immunoglobulin)	Surawattanawong 2025 [58] 10.2478/abm-2025-0018 (IVIG: significantly fewer hospital-acquired infections vs PLEX, aOR 0.17, 95% CI 0.03-0.85, p=0.031; shorter hospitalisation); Abboud 2021 [54]
SECOND-LINE THERAPY					
Rituximab	Anti-CD20; depletes B-cells (pre-plasma compartment)	375 mg/m² IV weekly × 4, OR 1 g IV × 2 (days 1 and 15)	Institutional cohorts + expert consensus (no RCT in AE)	Infusion reactions, progressive multifocal leukoencephalopathy (rare but fatal), hepatitis B reactivation, prolonged B-cell depletion, late-onset neutropenia, infection risk	Irani 2014 [59] 10.1001/jamaneurol.2014.463 (LGI1); Titulaer 2013 [5] 10.1016/S1474-4422(12)70310-1 (NMDAR - early second-line improves outcome); Abboud 2021 [54] (80% of clinicians prefer rituximab)
Cyclophosphamide	Alkylating agent; depletes T- and B-cells	750 mg/m² IV monthly (with dose adjustment for age/renal)	Expert consensus + case series	**Haematological toxicity (myelosuppression), haemorrhagic cystitis, gonadal toxicity (infertility), secondary malignancy**	Abboud 2021 [54] (10% of clinicians prefer cyclophosphamide); retained role in T-cell-mediated syndromes (GAD65, paraneoplastic)

Agent	Mechanism	Typical dose	Evidence type	Toxicity / key safety considerations	Key reference
Inebilizumab *(investigational)*	Anti-CD19; depletes broader B-cell compartment including plasmablasts	Per ExTINGUISH protocol	**Investigational - phase 2B RCT (N=116, results pending; NOT yet established efficacy)**	Infusion reactions, hypogammaglobulinemia, infection risk	Wong 2022 [34] 10.1212/01.wnl.0000903316.50895.83 (ExTINGUISH phase 2B RCT, NCT04372615 - **results pending; cannot be assigned an efficacy level at this time**)
THIRD-LINE / REFRACTORY THERAPY					
Tocilizumab	Anti-IL-6 receptor; blocks IL-6-driven plasmablast survival and antibody production	8 mg/kg IV monthly (per cohort protocols)	Institutional cohort (retrospective)	**Neutropenia, thrombocytopenia, elevated liver enzymes, serious infections (TB reactivation, bacterial sepsis), GI perforation**	Lee 2016 [61] 10.1007/s13311-016-0442-6 (effective in AE refractory to rituximab)
Anakinra	Recombinant IL-1 receptor antagonist; blocks IL-1β neuroinflammatory cascade	**Adult NORSE:** dosing per COMBAT-NORSE protocol (NCT07281027; 10 mg/kg/day IV divided q6h, max 400 mg/day). **Paediatric FIRES:** 2-10 mg/kg/day SC (per case series; continue for weeks-months)	Case series (FIRES) + expert consensus (NORSE); **COMBAT-NORSE Phase 3 RCT enrolling**	**Serious infections (particularly in immunocompromised), injection-site reactions, neutropenia, hepatic transaminase elevation; caution in renal impairment**	Kenney-Jung 2016 [44] 10.1002/ana.24806 (FIRES - first report); Choi 2021 [62] 10.1684/epd.2021.1283 (super-refractory status in AE); Wickström 2022 [6] 10.1111/epi.17391 (NORSE consensus); COMBAT-NORSE NCT07281027 [63] (Phase 3 RCT anakinra vs tocilizumab, enrolling 2026 - adult dosing per trial protocol)
Bortezomib	Proteasome inhibitor; depletes short-lived plasma cells (the compartment rituximab cannot reach)	1.3 mg/m² SC/IV twice weekly × 2 weeks (per case series)	Case reports/series	**Peripheral neuropathy (often irreversible), thrombocytopenia, herpes zoster reactivation, GI toxicity, cardiotoxicity**	Scheibe 2017 [64] 10.1212/WNL.0000000000003536 (refractory anti-NMDAR)

Agent	Mechanism	Typical dose	Evidence type	Toxicity / key safety considerations	Key reference
Daratumumab	Anti-CD38; depletes long-lived plasma cells	Per case protocol (typically 16 mg/kg IV weekly × cycles)	Case reports (N=2 paediatric; combination in adults)	**Deep and prolonged hypogammaglobulinemia (all Ig classes), serious infections (including fatal sepsis), neutropenia, thrombocytopenia, infusion reactions; requires infection prophylaxis and immunoglobulin monitoring; NOT approved for neurological indications**	Young 2024 [65] 10.1212/WNL.0000000000205325 (2 paediatric NMDAR); Wang 2025 [60] 10.3389/fimmu.2025.1681884 (ofatumumab + daratumumab combination, severe adult NMDAR)
Ofatumumab	Anti-CD20 (subcutaneous); B-cell depletion	Per case protocol	Case reports (combination therapy)	Injection-site reactions, infection risk, hypogammaglobulinemia	Wang 2025 [60] 10.3389/fimmu.2025.1681884 (combination with daratumumab)
MAINTENANCE THERAPY (SYNDROME-STRATIFIED)					
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase; lymphocyte proliferation	1-2 g/day oral; used in GAD65 and relapsing surface-antibody syndromes	Expert consensus / observational	Myelosuppression, GI toxicity, infection risk, teratogenicity (contraindicated in pregnancy)	Standard practice in chronic autoimmune neurological disease
Azathioprine	Purine analogue; lymphocyte depletion	2-3 mg/kg/day oral; steroid-sparing	Expert consensus / observational	Myelosuppression, hepatotoxicity, pancreatitis, TPMT deficiency (screen before initiation), infection risk	Alternative to mycophenolate
Repeated rituximab	B-cell depletion maintenance	Re-dose at 6-month intervals or on clinical relapse/B-cell reconstitution	Observational	As for rituximab above; cumulative infection risk with repeated courses	Used in relapsing NMDAR and refractory LGI1; guided by CD19 monitoring
INVESTIGATIONAL / FUTURE (SECTION 8)					
CAR-T (CD19)	Engineered T-cells targeting B-cell compartment	Conceptual in AE; established in SLE/myositis	Mechanistic rationale only (no AE case series)	**Cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged B-cell aplasia, infection risk**	Liu 2024 [66] 10.3389/fimmu.2024.1492552 (general CAR-T in autoimmunity review)

Agent	Mechanism	Typical dose	Evidence type	Toxicity / key safety considerations	Key reference
Efgartigimod (FcRn blockade)	Accelerates IgG recycling/degradation; lowers antibody titres	Case-level (per case reports); no RCT in AE	Case reports (3 patients)	Generally well tolerated; mild infection risk; **a cautionary case documented LGI1-AE developing during FcRn inhibition for myasthenia gravis, reminding that FcRn blockade may not prevent new antibody formation**	Zhu 2024 [70] 10.1007/s00415-024-12556-1 (LGI1-AE resolution); Gao 2026 [71] 10.1097/MD.0000000000048535 (LGI1-AE); Zhang 2024 [72] 10.3389/fimmu.2024.1444288 (3-patient series); Komatsu 2026 [73] 10.3389/fimmu.2026.1854357 (cautionary case - LGI1-AE during efgartigimod for MG)

Footnotes to Table 3:

1. **Evidence types are descriptive, not graded.** This narrative review does not perform formal risk-of-bias assessment or GRADE-level evidence of synthesis. The evidence types listed (small RCT, institutional cohort, case series, case report, expert consensus, mechanistic rationale) are intended to convey the strength and limitations of the available data without implying a systematic evidence hierarchy. Only one agent (IVIG) has RCT-level evidence, and that trial was underpowered (N=17, terminated early).

2. **Doses are typical adult doses from the cited literature; paediatric dosing follows paediatric protocols.** Anakinra dosing differs between paediatric FIRES (per case series) and adult NORSE (per COMBAT-NORSE trial protocol). All doses should be confirmed against current local formularies and used in consultation with neuroimmunology and, where relevant, haematology/oncology (bortezomib, daratumumab).

3. **Third-line agents are salvage therapies with significant toxicity.** Bortezomib and daratumumab cause deep and prolonged immune suppression, including hypogammaglobulinemia and increased susceptibility to serious and opportunistic infections. Their use should be restricted to specialist neuroimmunology centres, with baseline immunoglobulin levels, infection screening, and prophylactic measures as appropriate. The benefit-risk ratio must be individually assessed, and informed consent should explicitly address the risk of fatal infection.

4. **The timing hierarchy is more important than the agent hierarchy.** The stage-gated immunotherapy framework in Table 3 encodes three time-points: first line within days of suspicion; second line at 2-4 weeks if no response; third line at 4-8 weeks if refractory - but only after structural re-evaluation (repeat MRI) to exclude burn-out phase (see Section 6.6).

5. **Tumour search is therapeutic, not only diagnostic.** In paraneoplastic AAE (NMDAR with ovarian teratoma; GABA-B with small-cell lung cancer; LGI1/CASPR2/AMPAR with thymoma), tumour removal or treatment is immunotherapy and should proceed in parallel with medical immunotherapy.

6. **Steroid-sparing maintenance is reserved for relapsing or chronic syndromes.** Monophasic surface-antibody syndromes (LGI1, NMDAR) generally do not require maintenance beyond a steroid taper; intracellular/T-cell syndromes (GAD65) often do. The decision is individualised and reviewed at 6-12 months.

6.1 First-line therapy: timing is the active ingredient

First-line immunotherapy comprises high-dose corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange (PLEX). Current evidence indicates that **early initiation matters far more than the specific agent chosen**.

High-dose methylprednisolone (1 g/day IV for 3-5 days, followed by an oral prednisolone taper) remains the default first-line agent, selected by 84% of clinicians for general presentations and 74% for FBDS [54]. In LGI1-AE, corticosteroids rapidly suppress FBDS frequency, unlike standard ASMs [23, 55]. A diagnostic-therapeutic steroid trial in suspected LGI1-AE is therefore both appropriate and clinically informative.

IVIG (0.4 g/kg/day for 5 days) is the principal alternative or adjunct. The first randomised placebo-controlled trial of IVIG in autoimmune epilepsy (Dubey and colleagues) evaluated LGI1/CASPR2-seropositive patients with drug-resistant seizures. IVIG demonstrated clear superiority over placebo for 50% seizure reduction (6/8 vs 2/9 responders; p=0.044, OR 10.5) [28, 56]. Although halted early due to slow

enrollment (n=17), it provides Class I trial evidence supporting first-line IVIG. The ongoing UK multicentre trial (ISRCTN69615004) will further clarify IVIG efficacy in AE [57].

PLEX (5 exchanges over 7-10 days) removes circulating antibodies and is most logical in acute antibody-mediated syndromes. A 2025 comparative study found IVIG associated with significantly fewer hospital-acquired infections than PLEX (adjusted OR 0.17, 95% CI 0.03-0.85) and shorter hospitalisation [58].

The timing principle: for LGI1-AE, patients treated within the FBDS-only phase have better cognitive outcomes [4]; for NMDAR, early second-line therapy improves outcome [5]; for NORSE/FIRES, the 2022 consensus recommends initiating immunotherapy within the first days of super-refractory status, not after antibody results return [6]. **If the clinical suspicion is high, treat now; the antibody result confirms; it does not decide.**

6.2 Second-line therapy: B-cell depletion and beyond

When first-line therapy fails within 2-4 weeks, second-line therapy is indicated. The Alliance survey showed 80% of clinicians choose rituximab, 10% cyclophosphamide [54]. Rituximab (anti-CD20; 375 mg/m² weekly × 4, or 1 g × 2) depletes B-cells; Irani and colleagues demonstrated a clear effect in LGI1-AE [59], and the Titulaer cohort associated early rituximab with improved outcome in NMDAR [5]. Cyclophosphamide (750 mg/m² monthly) retains a role in T-cell-mediated syndromes (GAD65, paraneoplastic) and rituximab-refractory disease. The ExTINGUISH trial of inebilizumab (anti-CD19) in anti-NMDAR encephalitis is the first rigorous B-cell therapy trial [34] (NCT04372615); if positive, it may reshape the second-line algorithm. Ofatumumab (subcutaneous anti-CD20) is in early use [60].

6.3 Refractory disease: cytokine-targeted and plasma-cell-targeted therapies

A minority fails first- and second-line therapy. Three classes of agent define the 2024-2026 horizon:

Interleukin-6 receptor blockade. Tocilizumab has demonstrated benefits in AE refractory to rituximab [61]; IL-6 drives plasmablast survival and CSF IL-6 correlates with NMDAR severity.

Interleukin-1 receptor blockade. Anakinra was first reported effective in FIRES, with normalisation of pro-inflammatory CSF cytokines [44]; the 2022 NORSE consensus supports its use in super-refractory status [6], and case reports in AE more broadly support its tolerability [62]. The COMBAT-NORSE trial (NCT07281027) - a Phase 3 randomised comparison of anakinra versus tocilizumab in NORSE, led by Yale University with 33 international sites (target n=438, enrolling from July 2026) - is the first rigorous interventional trial in NORSE [63].

Plasma-cell targeting. Bortezomib (proteasome inhibitor) depletes short-lived plasma cells - the compartment rituximab cannot reach - and is effective in therapy-refractory anti-NMDAR encephalitis [64]. Daratumumab (anti-CD38, depleting long-lived plasma cells) has been reported in two paediatric patients with refractory anti-NMDAR encephalitis [65] and in combination with ofatumumab in severe adult disease [60] - experimental third-line options with mechanistically coherent rationale.

CAR-T therapy targeting CD19 has transformed systemic autoimmunity but no case series in AE has been published as of 2026; we frame it as a therapy of the next decade [66].

6.4 The antibody-negative patient with high clinical suspicion

When antibody testing is negative but the syndrome is strongly suggestive - particularly in NORSE/FIRES, in chronic temporal lobe epilepsy with CSF-restricted oligoclonal bands and a compatible MRI, and in any case meeting Graus 2016 criteria for probable autoimmune encephalitis [7] - the algorithm does not stop. Assay turnaround times (typically 1-3 weeks for live cell-based assays) are a clinical reality; interim immunotherapy should not be delayed when clinical suspicion is high. The framework: (1) re-test appropriately (paired serum and CSF, live cell-based assay); (2) apply the Graus 2016 probable-AE criteria, which do not require an antibody; (3) treat on syndrome - if the clinical pattern fits (Table 2 red flags ≥2, APE2/ACES supportive), initiate first-line therapy and assess at 2-4 weeks (a brisk response is itself diagnostic information); (4) escalate as for antibody-positive disease. The NORSE/FIRES literature is the strongest evidence that this approach works in antibody-negative patients [6, 44].

6.5 How long to continue immunotherapy - Controversy 3

Duration is the least-evidenced decision and varies most between centres. For LGI1 and NMDAR (surface-antibody, monophasic logic): a tapering corticosteroid course over 3-6 months; rituximab as a single course without maintenance; relapses occur in a minority (~12-20% in NMDAR) and are usually responsive to re-treatment [5, 67]. For GAD65 (intracellular, T-cell-mediated): chronic maintenance with mycophenolate or azathioprine, sometimes combined with periodic rituximab, in patients with documented benefit. For NORSE/FIRES: immunotherapy continued for weeks to months, with anakinra sometimes maintained for months in FIRES [44]. We propose a risk-stratified, treat-to-remission framework (Table 3). The long-term outcome data support an optimistic but vigilant approach: the majority of AE patients achieve seizure freedom, and ASM withdrawal is possible in a substantial fraction after sustained recovery - though patients with GAD65 and GABA-B antibodies are less likely to discontinue ASM [13, 28]. The decision to withdraw ASM should be made jointly by epileptologist and neuroimmunologist, with the understanding that seizure recurrence may represent relapse of the autoimmune process.

7. Pitfalls - false positives, over-diagnosis, and cost-effectiveness

The case for permissive testing is not a case for indiscriminate testing. Two categories of error expand as the diagnostic net widens: the **false positive** (labelling non-autoimmune epilepsy as autoimmune, exposing patients to unnecessary immunotherapy) and the **false negative** (denying potentially disease-modifying treatment).

7.1 The false positive: low-titre and non-specific antibodies

Three antibodies account for the majority of over-diagnosis errors. GAD65: low-titre serum positivity is common in the general population and in type 1 diabetes mellitus, where it is a marker of endocrine autoimmunity rather than neurological disease [18, 37]; the corrective is the titre-and-compartment rule (Section 5.1) - high titre, CSF-restricted synthesis, and a compatible syndrome are required. VGKC-complex (composite): the historical radioimmunoassay generates both false negatives (missing LGI1 and CASPR2) and false positives (low-affinity binding in non-autoimmune neurological disease, including Creutzfeldt-Jakob disease) [17, 19, 20]; a positive VGKC-complex result without antigen-specific confirmation is non-diagnostic. Onconeural antibodies (Hu, Yo, Ri, Ma2, CV2/CRMP5): markers of paraneoplastic syndromes and T-cell-mediated pathology, not direct effectors; treating a Hu-positive patient with the LGI1 algorithm is a category error.

7.2 The false negative and the over-diagnosis backlash

The mirror error is the false negative that excludes autoimmunity prematurely - serum-only testing in NMDAR disease [29, 31], fixed-cell assays for conformational antigens, and the incomplete panel. A second-order risk is the over-diagnosis of backlash: the legitimate concern about false positives has, in some centres, produced a backlash in which autoimmune testing is withheld from patients who would benefit. This is the inverse error - the failure mode of a bad test becomes an excuse not to order a good test. The syndrome-driven framework corrects both: testing is triggered by the clinical pattern, and interpretation is conditioned by titre, compartment, and syndrome fit. The remedy for false positives is not less testing but better testing, interpreted in context.

7.3 The cost-effectiveness argument

The economic case for autoimmune testing in DRE is straightforward: a neural antibody panel is a fraction of the cost of one year of DRE care, and orders of magnitude less than an avoidable temporal lobectomy on an inflamed hippocampus. A formal cost-effectiveness analysis would be a useful contribution and is, in our view, overdue.

8. Future directions - novel antibodies, cellular therapies, and tolerance induction

8.1 Novel antigens 2024-2026

Septin-5 antibodies were described in autoimmune cerebellar ataxia [68]; the phenotype was predominantly cerebellar, and the epilepsy linkage is uncertain. Drebrin antibodies were described in a 2025 preprint of three cases with heterogeneous presentations [69] - preprint-level evidence only, not peer-reviewed, with uncharacterised epilepsy phenotype. Novel antigens should pass three thresholds before entering routine practice: peer-reviewed description, a definable clinical phenotype, and demonstration that the antibody accesses the antigen in its native conformation. LGI1, NMDAR, and GAD65 have passed all three; septin-5 partially; drebrin has not. The red-flag framework is robust to new antigens because it is syndrome-driven.

8.2 Biologic and cellular therapies

The ExTINGUISH trial of inebilizumab in anti-NMDAR encephalitis [34] (NCT04372615) is the first rigorous B-cell therapy trial and the single most important pending result. Ofatumumab and daratumumab have been reported in combination in severe adult anti-NMDAR encephalitis [60], with daratumumab also in two paediatric cases [65] - case-level evidence, mechanistically coherent, but experimental. Tocilizumab [61] and anakinra [44] have moved from case reports to recognised third-line options; the COMBAT-NORSE trial [63] (NCT07281027) will define the role of IL-1R versus IL-6R blockade in NORSE. CAR-T targeting CD19 has transformed systemic autoimmunity, but no AE case series has been published; it is a therapy of the next decade [66].

8.3 FcRn blockade and tolerance induction

Efgartigimod and rozanolixizumab - monoclonal antibodies targeting the neonatal Fc receptor (FcRn), accelerating IgG degradation - have established efficacy in myasthenia gravis. As of 2024-2026, three case reports document successful treatment of anti-LGI1-AE with efgartigimod [70–72], with a cautionary report of LGI1-AE developing during FcRn inhibition for myasthenia gravis [73]. The evidence is case-level; no randomised trial in AE has been registered as of mid-2026.

The long view of autoimmune epileptology includes tolerance-based approaches - antigen-specific immunomodulation that re-establishes immune tolerance without global immunosuppression. This is an active research area in systemic autoimmunity but has not been explored in autoimmune epilepsy. The antigens are known (LGI1, NMDAR subunits, GAD65) and the patient population is definable by the red-flag framework; the practical obstacle is that tolerance induction in established immune memory is harder than in naïve immunity.

8.4 The trial agenda

The evidence landscape in 2026 is characterised by strong observational data and weak trial data. The ExTINGUISH trial [34] is the first rigorous B-cell therapy test. The COMBAT-NORSE trial [63] is the first rigorous interventional trial in NORSE, enrolling from July 2026. Beyond these, the agenda we propose: (1) a randomised trial of early versus deferred second-line therapy in NMDAR encephalitis, building on the Titulaer data [5]; (2) a diagnostic trial of reflex autoimmune testing in DRE of unknown aetiology, randomising general neurology clinics to syndrome-driven testing versus usual care - the trial that would convert this review's thesis from argument to evidence; (3) a cost-effectiveness analysis of reflex autoimmune testing. Until such trials report, the recommendations here rest on observational cohorts, validated prediction scores, and structured clinical reasoning - an evidence base sufficient to change practice, and the cost of not changing it is measurable in hippocampi, cognitive function, and lives.

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