Pediatric Autoimmune Encephalitis Care Guideline

Inclusion Criteria:
- Previously healthy and age ≥ 3 years old
- At least 2 or more clinical features of neurologic dysfunction* (See box to right)

Exclusion Criteria:
- < 3 years old, hyperacute or chronic

***Clinical Features of Neurologic Dysfunction**
- AMS/level of consciousness or EEG with slowing or epileptiform activity (focal or generalized)
- Focal neurologic deficits
- Cognitive difficulties
- Acute developmental regression
- Movement disorder (except tics)
- Psychiatric symptoms
- Seizures not explained by a previously known seizure disorder or other condition

Hyperacute < 24h
- Consider vascular and toxic-metabolic etiologies
- Follow Acute Stroke Guideline

Onset

Chronic > 3 mo
- Consult on call Neurology
- Off Guideline

Acute/Subacute ≤ 3 mo

Admit patient and initiate workup [b]
1. MRI brain w/wo (including T1 axial and sagittal, T2 axial, T2 FLAIR axial and sagittal, and DWI/ADC axial, T1 post contrast axial)
2. Routine EEG/VTM
3. Lumbar puncture
4. Consider screening for neoplasm in > 12 year old or patients with risk factors (CT chest/abdomen/pelvis or pelvic/ testicular US)

Other Recommended Workup [b]

Blood:
- CBC with differential; CMP
- Lactate
- ESR; CRP
- Mycoplasma Antibody (MP)
- Acute hepatitis panel
- TSH; Free T4
- Vitamin B12 level; Vitamin D level
- Analyzer 1000
- QuantiFERON Gold
- Lymphocyte subset panel – TBNK analysis
- Immunoglobulin pane – A, G, MIGGAM
- Multiple sclerosis (MS) profile (collect with CSF)
- Neopterin, Serum (NEOP)
- Neurofilament Light Chain, Plasma
- Cytokine Panel 13, Serum
- Pediatric Autoimmune Central Nervous system disorders evaluation- *Peds Autimm Enceph CNS, S*
- Gamma-Amino Butyric Acid Type A (GABA-A) Receptor Antibody by Cell Binding Assay - *GABA-A-R Ab CBA, S*
- Pregnancy, Serum, Qual (if female age ≥ 10 years)
- Coma Panel, Blood (COMAP)
- MD to RN Lab Communication: Save 1 extra read top tube with serum before treatment initiation

Send Out Labs
- Misc Lab: Stratify JCV Antibody (with Index Reflex to Inhibition Assay – Serum (send to Quest, Test ID: 91665)

Urine:
- Urine pregnancy (if female) age (≥ 10yo)
- Coma Panel, Urine (COMAPU)
- Rapid Urine Drug Screen

Respiratory/Viral Cultures:
- Respiratory Panel PCR 2.1; Ureaplasma and Mycoplasma Species by PCR
- Viral Culture (VC) – Routine, Nasopharynx
- Routine Rectal and Throat swabs

CSF (obtain at least 15cc):
- Reminder to obtain opening/closing pressure for proceduralist
- Cell Count / Diff, CSF (CCCSF)
- Total Protein, Spinal Fluid (TPCSF
- Glucose, CSF (GLUCSF)
- CSF Culture
- Lactic Acid, CSF (LACCSF)
- Mycoplasma Pneumo AB, CF CSF (MYCOP)
- EBV Quantitative PCR (CSF only)
- Meningitis/Encephalitis PCR Panel
- Multiple sclerosis (MS) profile (collect with serum)
- T & B Cell QN by Flow Cytometry
- Cytology Request
- Neopterin, CSF
- Pediatric Autoimmune Central Nervous system disorders evaluation - Peds Autoimm Enceph CNS, CSF
  - Gamma-Amino Butyric Acid Type A (GABA-A) Receptor Antibody by Cell Binding Assay – GABA-A-R Ab CBA, CSF
  - N-methyl-D-Aspartate Receptor Antibody, IgG, CSF with Reflex to Titer – NMDA IgG Reflex to Titer, CSF
- Save 5-10 cc of CSF for future testing

*See supplemental table with diagnostic criteria for AE on Page 3.

Consider other diagnosis

No

Criteria for probable AE met*

Yes

Start empiric treatment

See page 4

Consults
- Neurology
- Infectious Disease if concern for infection
- Psychiatry for management of agitation/ catatonia
- Rheumatology (if escalating treatment to tocilizumab)
- Social Work for support
- Hematology for plasma exchange (PLEX). Will need double lumen central line. Avoid groin.
- Rehabilitation (PT, OT, ST) once patient stabilized

Notes:

[a] based on modified Rankin Scale

[b] refer to supplemental table for treatment regimen and doses

Approved Evidence Based Medicine Committee
Original: 7/16/2025

Pediatric Autoimmune Encephalitis Care Guideline

Probable AE, or definite antibody-positive AE

Start treatment

Standard disease [a]

If none of the ICU criteria met then admit to Neuroscience Unit.

Consider placing on "Watcher Status"

Severe disease [a]

ICU criteria:
- Refractory status epilepticus
- Severe dysautonomia [d]
- Respiratory failure

First line therapy [b]
1. IV corticosteroid
and/or
2. IVIG
3. **Plasma Exchange** (PLEX)

- First line therapy for patients *NOT* in the ICU
- Initiate one of the therapies, can escalate to a different first line if no improvement within 1 week

Combined first line therapies
1. IVIG + IV corticosteroid
2. IV corticosteroid + PLEX*

*If **Autonomic Dysfunction** (AD), respiratory failure, etc.

Improvement?

Yes

Consider maintenance first line:

- Monthly IV steroid or IVIG depending on response [c]

No

Second line therapy:

Rituximab
See page 4

Improvement?

Yes

No

Consider other second line therapies:

- Cyclophosphamide (Cytoxan)
- IL-6 inhibitors (Tocilizumab)

Notes:

[a] based on modified Rankin Scale
[b] refer to supplemental table for treatment regimen and doses
[c] refer to supplemental table for immunotherapy response
[d] refer to supplemental table for management

Pediatric Autoimmune Encephalitis Care Guideline

Supplemental Tables

Pediatric Autoimmune Encephalitis Diagnostic Criteria		Diagnostic Categories		
Categorical features of Autoimmune Encephalitis (AE)	**Specific diagnostic features**	**Possible AE**	**Probable Ab neg AE**	**Definite Ab + AE**
1. *Evidence of acute or subacute symptom onset*	Onset of neurologic and/or psychiatric symptoms over ≤ 3 mo in a previously healthy child	Yes	Yes	Yes
2. *Clinical evidence of neurologic dysfunction*	Features include: a) Altered Mental Status/Level of Consciousness or EEG w/ slowing or epileptiform activity (focal or generalized) b) Focal neurologic deficits c) Cognitive difficulties d) Acute developmental regression e) Movement disorder (except tics) f) Psychiatric symptoms g) Seizures not explained by a previously known seizure disorder or other condition	≥ 2	≥ 2	≥ 2
3. *Paraclinical evidence of neuroinflammation*	Features include: a) Cerebral Spinal Fluid (CSF) inflammatory changes (leukocytosis > 5 cells/mm^3 and/or oligoclonal bands (OCB) b) MRI features of encephalitis c) Brain biopsy showing inflammatory infiltrates and excluding other disorders	Not available	≥1	≥ 1[a]
4. *AE serology*	Presence in serum and/or CSF of well-characterized autoantibodies associated with AE	Not available	No	Yes
5. *Exclusion of other etiologies*	Reasonable exclusion of alternative causes, including other causes of central nervous system (CNS) inflammation	Yes	Yes	Yes

a When antibodies against NMDA receptor, gamma-aminobutyric acid A receptor, or glutamic acid decarboxylase 65 are present in CSF, further paraclinical markers of neuroinflammation are not required to diagnose definite AE. When only serum AB are present, one or more paraclinical markers of neuroinflammation required.

Adapted from Celluci et al. Neurol Neuroimmunol Neuroinflamm 2020.

Treatment Regimens and Doses		
Immunotherapies	**Type of use**	**Dosing**
IV methylprednisolone	1) First-line immunotherapy 2) Prolonged first-line immunotherapy	1) 30 mg/kg/day (max dose – 1 g/day) for 3-5 days 2) 30 mg/kg/day (max dose – 1 g/day) for 3 days, monthly
Therapeutic plasma exchange	First-line immunotherapy	• One course is typically 3-5 exchanges over 3-7 days
IV immunoglobulin	1) First-line immunotherapy 2) Prolonged first-line immunotherapy	1) 2 g/kg over 2 days 2) 1 g/kg, monthly
IV rituximab[a]	Second-line immunotherapy	• 750 mg/m^2 (max dose – 1g) given twice separated by 2 weeks ***Or***
	Maintenance (>6mo) immunosuppression	• 750 mg/m^2 (max dose - 1g) every 6 months or sooner if repopulation of CD19 occurs
IV tocilizumab	Second-line immunotherapy *Consult Rheumatology prior to initiation*	• < 30kg: 12 mg/kg/dose ***or*** • ≥ 30kg; 8 mg/kg/dose (max dose - 800mg) Given monthly over 6mo or more (duration of required immunosuppression)
IV cyclophosphamide	Escalation second-line immunotherapy *Consult Oncology prior to initiation*	• 500 - 1,000 mg/m^2 (max dose - 1,500 mg) monthly pulses for up to 6mo

[a] Rituximab dosing protocols were all equally accepted as there are no data to support one protocol over another.

Definition of Response to Immunotherapy	
Best responder: These patients, regardless of severity, improve rapidly after immunotherapy (within weeks) and are clearly making functional gains in the first 2 months after treatment and by 3 months are returning to normal function.	Typically require 3 – 6 months of 1st line therapy (prolonged/ maintenance)
Average responder: These patients, regardless of severity, may not make any clear functional improvements in the first month after treatment commencement, but in the second and third month start to make clear functional gains. By 6 months, the patient is home and may still have deficits, but continues to make slow improvements.	Typically require 6 – 12 months 1st line therapy +/- 2nd line (prolonged/maintenance)
Poorest responder: These patients fail to make substantial and functionally useful improvements in the first 3 months after treatment commencement, remained impaired, and have significant care needs. Require prolonged rehabilitation and inpatient care, often > 3 months.	Typically require 12 – 24 months 1st line therapy + additional 2nd line (prolonged/maintenance)

Nosadini et al. Neurol Neuroimmunol Neurinflamm 2021.

Pediatric Autoimmune Encephalitis Care Guideline

Symptomatic Management of Autoimmune Encephalitis
Treating the underlying disease is first-line treatment

	Definition	Treatment
Delirium/ neuropsychiatric symptoms secondary to autoimmune encephalitis	Acute onset of deficits in attention, awareness, and cognition that fluctuate in severity over time. May include perceptual disturbances like hallucinations/paranoia.	• *Quetiapine IR 0.5 mg/kg q8hours • *Chlorpromazine IM for severe agitation * Psychiatry evaluates and treats There is increased comorbidity between anti-NMDA receptor encephalitis and catatonia and should avoid high potency anti-dopaminergic agents (i.e. risperidone).
Catatonia	Psychomotor disorder featured by marked decrease or excitability in reactivity to the environment. The diagnosis of catatonia is a clinical diagnosis. May use the Bush-Francis Catatonia Rating Scale (BFCRS) or Pediatric Catatonia Rating Scale (PCRS) for screening and tracking symptoms improvement/ worsening. The BFCRS is more easily accessible.	• *IV Lorazepam 0.05 mg/kg (max 2 mg per dose) initial trial dose. ○ If positive, start maintenance lorazepam. ○ Typically require high doses of IV lorazepam for treating catatonia, may range up to 6mg-24mg or even higher. Avoid dopamine blocking drugs. * Psychiatry evaluates and treats.
Secondary Movement Disorders	• Orofacial dyskinesia • Tremors • Dystonia • Choreoathetosis • Ballism	• Clonidine 0.025 to 0.05 mg/day, daily or divided BID • Lorazepam 0.05 mg/kg (max 2 mg per dose) • Anticonvulsants (i.e. phenobarbital, sodium valproate, and carbamazepine) • Tetrabenazine • Trihexyphenidyl Baclofen and amantadine have no effect (Mohammad et al).
Severe Dysautonomia	• Central hyperthermia or hypothermia • Arrhythmia • Abnormal blood pressure • Central hypoventilation or hyperventilation • Hypersecretion • Urinary incontinence	• Minimize parasympathetic stimulation by utilizing foley catheter, bowel regimens to prevent constipation, and careful suctioning of the endotracheal tube. • Evaluate infectious etiologies for hypothermia/hyperthermia. Only use antimicrobials if indicated. • Administer antipyretics, environmental cooling, and cooling blankets as indicated for hyperthermia.

Detailed definitions of movement disorders:
Orofacial dyskinesia: involuntary repetitive movements of the mouth and face.
Tremors: "a rhythmic back-and-forth or oscillating involuntary movement about a joint axis".
Dystonia: sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
Chorea: random-appearing sequence of one or more discrete involuntary movements or movement fragments.
Athetosis: "a slow, continuous, involuntary writhing movement that prevents maintenance of a stable posture".
Ballism: "large amplitude movements of the limbs, sometimes with a flinging or flailing quality".

Pediatric Autoimmune Encephalitis Care Guideline

Anatomical classification	Serological classification	Etiological classification
1. Limbic 2. Cortical/subcortical 3. Striatal 4. Diencephalic 5. Brainstem 6. Cerebellar 7. Encephalomyelitis 8. Meningoencephalitis 9. Combined	1. Antibodies to intracellular antigens (classical onconeural antibodies) [a] 2. Antibodies to surface antigens and other antigens with high clinical relevance (e.g., NMDAR, AMPAR, LGI1, CASPR2, GABAR A/B, DPPX, glycine receptor, AQP4, MOG, GFAP)[b] 3. Antibodies to surface antigens with low clinical relevance (e.g., VGKC, VGCC)	1. Idiopathic 2. Paraneoplastic 3. Postinfectious 4. Iatrogenic (e.g., ICI or other immune-modulating agents)

a= GAD65 Ab is directed against an intracellular antigen but in high titers, it mediates an autoimmune encephalitis phenotype similar to surface antibodies with high clinical relevance, and in low titers is usually clinically irrelevant to neurological symptoms

b= GFAP is a cytoplasmic antigen associated with intermediate filaments. Considered clinically relevant in patients presenting with typical radiological findings (perivascular radial enhancement).

Adapted from: Abboud H, et al. J Neurol Neurosurg Psychiatry 2021.

Anatomical classification of AE	Clinical syndrome	Associated Ab
Limbic encephalitis	Cognitive, psychiatric, epileptic presentation	Hu, CRMP5/CV2, Ma2, NMDAR, AMPAR, LGI1, CASPR2, GAD65, GABABR, DPPX, mGluR5, AK5, Neurexin-3a
Cortical/subcortical encephalitis	Cognitive, seizure presentation	PCA-2 (MAP1b), NMDAR, GABA A/B R, DPPX, MOG
Striatal encephalitis	Movement disorder presentation	CRMP5/CV2, DR2, NMDAR, LGI1, PD10A
Diencephalic encephalitis	Autonomic, sleep disorder presentation	Ma 1-2, IgLON5, DPPX, AQP4
Brainstem encephalitis	Cognitive, movement disorder, cranio-bulbar presentation	Ri, Ma 1-2, KLHL11, IgLON5, DPPX, AQP4, MOG, GQ1b
Cerebellitis or cerebellar degeneration	Ataxic presentation	Hu, Ri, Yo, Tr, CASPR2, KLHL11, NIF, mGluR1, GAD65, VGVV
Meningoencephalitis	Cognitive, seizure, meningeal presentation	GFAP or seronegative
Encephalomyelitis	Movement disorder, spinal and optico spinal involvement	GAD65, amphyphysin, glycine receptor, PCA-2 (MAP1B), GABA A/B R, DPPX, CRMP5/CV2, AQP4, MOG

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