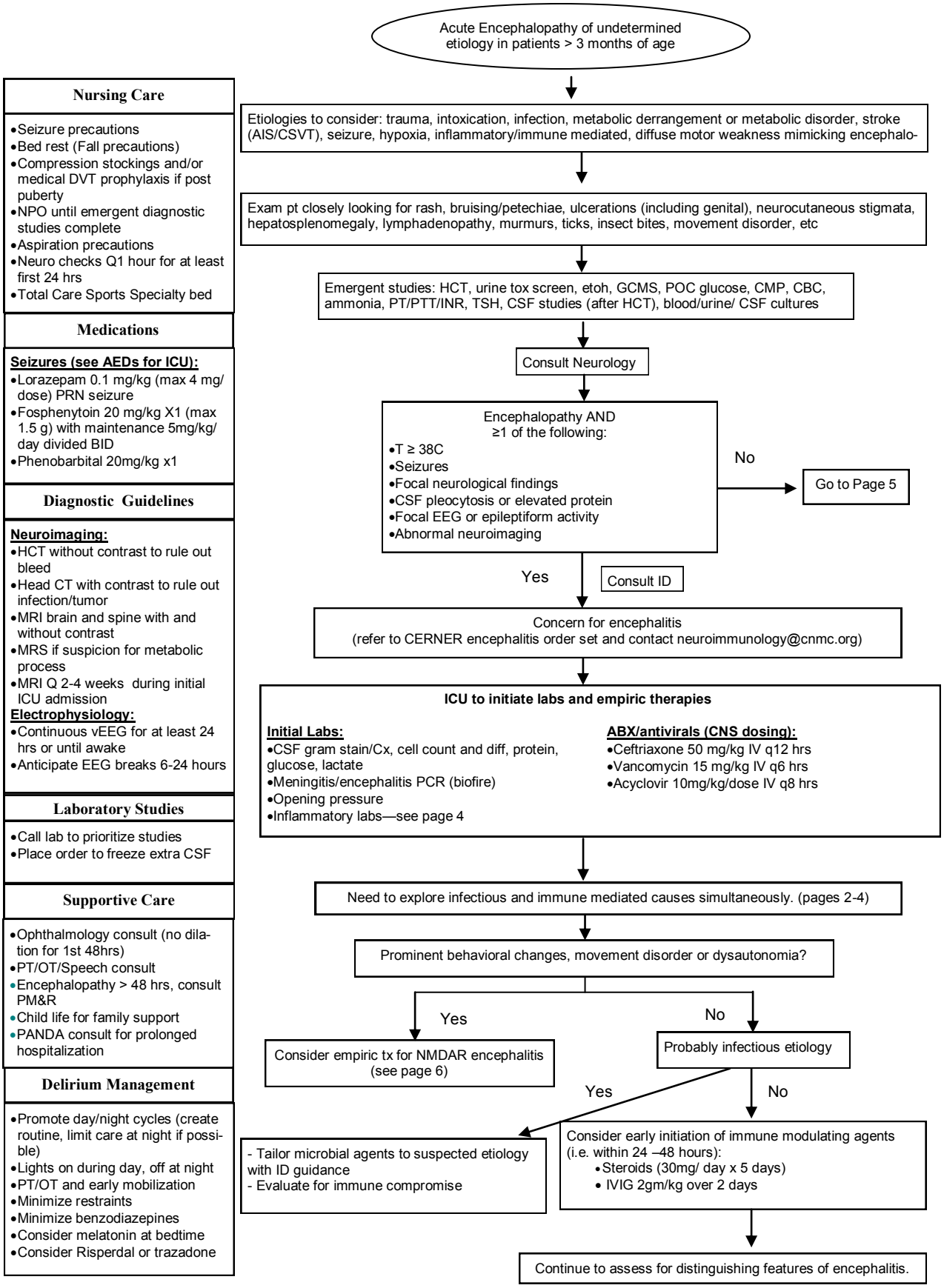
Pediatric Acute Encephalopathy/Encephalitis Diagnostic Pathway



Nursing Care

- Seizure precautions
- Bed rest (Fall precautions)
- Compression stockings and/or medical DVT prophylaxis if post puberty
- NPO until emergent diagnostic studies complete
- Aspiration precautions
- Neuro checks Q1 hour for at least first 24 hrs
- Total Care Sports Specialty bed

Medications

Seizures (see AEDs for ICU):

- Lorazepam 0.1 mg/kg (max 4 mg/ dose) PRN seizure
- Fosphenytoin 20 mg/kg X1 (max 1.5 g) with maintenance 5mg/kg/ day divided BID
- Phenobarbital 20mg/kg x1

Diagnostic Guidelines

Neuroimaging:

- HCT without contrast to rule out bleed
- Head CT with contrast to rule out infection/tumor
- MRI brain and spine with and without contrast
- MRS if suspicion for metabolic process
- MRI Q 2-4 weeks during initial ICU admission

Electrophysiology:

- Continuous vEEG for at least 24 hrs or until awake
- Anticipate EEG breaks 6-24 hours

Laboratory Studies

- Call lab to prioritize studies
- Place order to freeze extra CSF

Supportive Care

- Ophthalmology consult (no dilation for 1st 48hrs)
- PT/OT/Speech consult
- Encephalopathy > 48 hrs, consult PM&R
- Child life for family support
- PANDA consult for prolonged hospitalization

Delirium Management

- Promote day/night cycles (create routine, limit care at night if possible)
- Lights on during day, off at night
- PT/OT and early mobilization
- Minimize restraints
- Minimize benzodiazepines
- Consider melatonin at bedtime
- Consider Risperdal or trazadone

Table 1– Diagnostic Tests for Infectious Causes of Encephalitis (use ACUTE ENCEPHALOPATHY order set)

Priority may change based on history, exposures and clinical exam. Please confirm priority with ID and Neurology consultants prior to ordering

Organism	Blood	CSF	Other
Tier 1 Infectious Panel			
Meningitis/Encephalitis PCR **(biofire)**		Enterovirus E. coli Haemophilus influenza Listeria Neisseria meningitides Strep agalactiae Strep pneumo Cytomegalovirus HSV 1 and 2 HHV 6 Parechovirus VZV Cryptococcus	Ophtho exam if suspected CMV
HSV		CSF	**Please send separately even though Included in the biofire**
CMV	serology	*Included in biofire*	
VZV	serology	*Included in biofire*	
EBV	PCR	PCR	**EBV PCR (CSF) must be ordered misc**
Enterovirus	PCR	*Included in biofire*	
Arbovirus (West Nile, La Crosse, EEE, WEE, SLE)**	WNV serology***, arboviral serology,	WNV serology*** Arboviral serology	**Arboviral IgM (CSF) must be ordered misc**
Respiratory viruses			Nasal Respiratory Viral PCR, CXR
Mycoplasma	serology	PCR	NP PCR, CXR
Tier 2 Infectious Panel			
Bartonella	serology		Ophtho exam if suspected
HIV	serology and DNA PCR	DNA PCR	**HIV DNA PCR (CSF)**
Lyme	EIA screen serology with reflex WB	EIA screen serology with reflex WB	Ophtho exam if suspected
Mycobacterium TB		PCR, AFB smear and culture	PPD, CXR, PCR and culture of respiratory secretions **PCR (CSF) must be ordered misc**
Rickettsia**– RMSF, Ehrlichia, Anaplasma	RMSF serology, Ehrlichia serology, anaplasma serology	CSF PCR's all low yield	Review blood smear for morula if suspected anaplasma

List continues on page 3...

** Repeat serologic testing recommended 10-21 days after initial presentation

*** WNV is not included in the arboviral panel (although it

Tier 3 Infectious Panel	Blood	CSF	Other
Malaria	Thin and Thick Smears		
Rotavirus			Stool/rectal rotavirus antigen
Parvovirus	serology and PCR	PCR	Highest risk in neonates
Rabies			Conjunctiva and Saliva PCR
Syphilis	VDRL or RPR w/ FTA-ABS if +	CSF VDRL	
Endemic Fungi- Histoplasma, Coccidioides		Histo antigen and serology	Urine Histo antigen
Amoeba– Naegleria, Balamuthia	Balamuthia serology (IFA) via CDC	Naegleria wet prep	**Balamuthia, Naegleria (Cx), Amoeba Wet Prep must be ordered misc**
Immunocompromised Host			
HHV-6		*Included in biofire*	
West Nile Virus		PCR	
Cryptococcus	Cryptococcal Antigen	*Included in biofire*	CXR
JC-Virus		JCV PCR	
Toxoplasma	Toxoplasma serology	Toxo PCR	Ophtho exam
Amoeba– Acanthamoeba		Wet prep	**Must be ordered as misc test**

Labs to obtain PRIOR to IVIG

Infectious studies with titers

* Labs to be determined based on presentation

**** Obtain ID recommendations prior to administering IVIG** (e.g. HIV, Lyme, Arbovirus, EBV, coxsackie)

Inflammatory studies with titers

SERUM

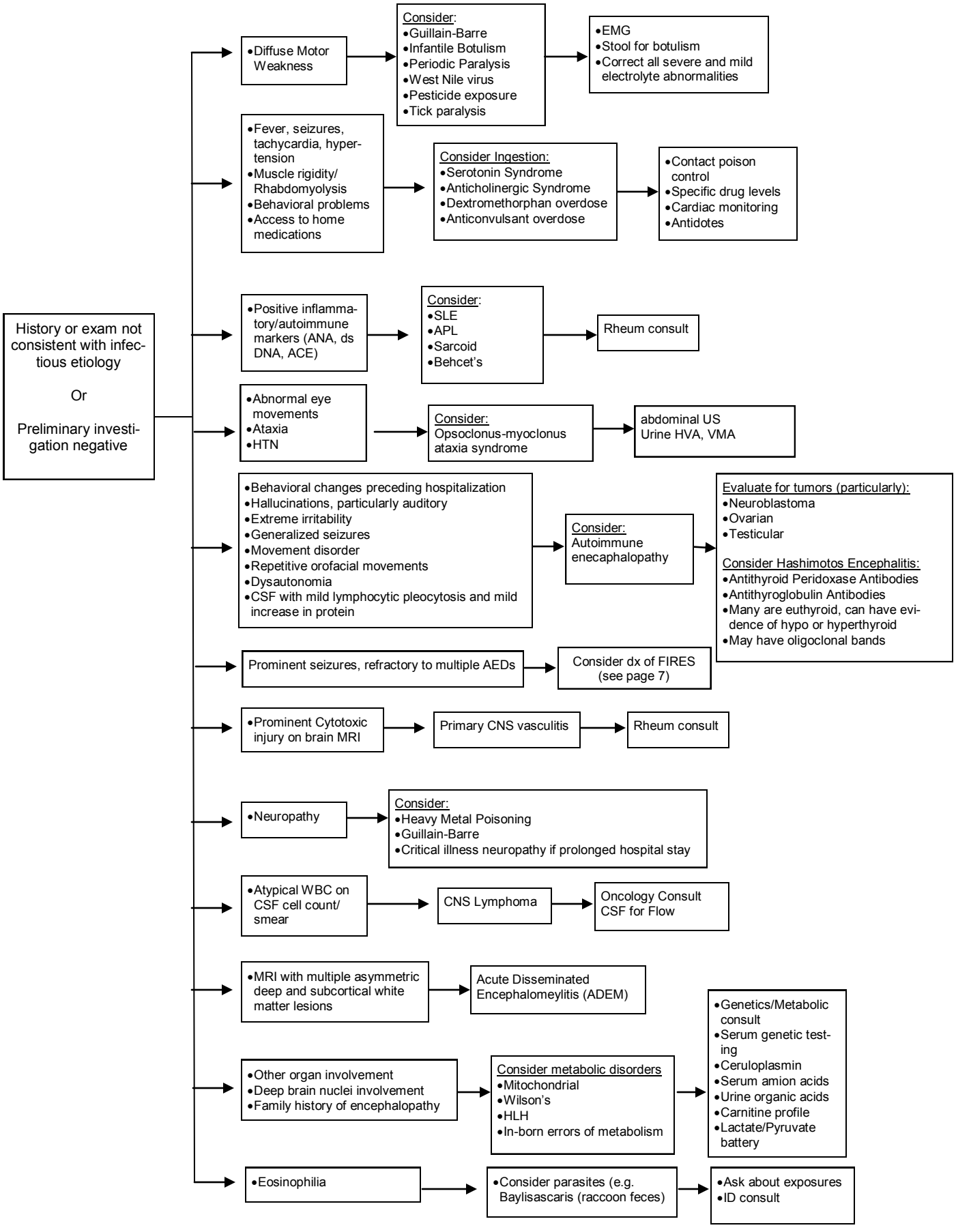
ANA
ds- DNA,
TPO/ anti-thyroglobulin
Encephalopathy, Autoimmune Evaluation (ENS1)
NMO Ab (AQP4)
Anti MOG Ab
Antiphospholipid Ab
Oligoclonal bands
IgG synthesis
Immunoglobulins (IGAM)

CSF

Encephalopathy, Autoimmune Evaluation (ENC1)
Oligoclonal bands
IgG synthesis

Diagnostic studies for inflammatory causes of encephalopathy /encephalitis

Serum	CSF
General screening labs for consideration of non-infectious encephalitis (primary and/or secondary)	
Immunoglobulins, ESR, CRP, ANA, ds- DNA, C3/4, ACE, TPO/ anti-thyroglobulin lactate/pyruvate battery, carnitine (free and total) Oligoclonal bands and IgG Index (to be done at the same time as CSF)	Neopterin Lactate Cytology Oligoclonal bands and IgG Index (to be done at the same time as serum) Encephalopathy, Autoimmune Evaluation (ENC1) ****If unable to tap, send** Serum Encephalopathy, Autoimmune Evaluation (ENS1) (send before IVIG)
Specific diagnoses based on clinical presentation and course	
Demyelinating brain or spine lesions, visual impair-ment - NMO Ab (AQP4)	- NMO Ab (AQP4)
Demyelinating lesion brain or spine (including ADEM) - Anti MOG Ab	- Anti MOG
Brainstem lesions or GBS like symptoms - GQ1B	- GQ1B
Acute psych disease, movement d/o, dysautonomia - NMDA Ab	- NMDA Ab
FIRES or prominent seizures - genetic epilepsy panel	- Cytokines CSF 1mL (Cincinnati Childrens test #5863724)
Multiorgan failure in FIRES TG Ferritin HLH screening (Cincinnati) Soluble IL2 –R	
Prominent cerebral edema, necrotizing lesions, prominent thalamic lesions and/or flu positive. - RANBP2 gene (ANE)	
Rash, autoimmune disease, suspect vasculitis Personalized gene sequencing panel for vasculitis Antiphospholipid Ab Beta 2 glycoprotein ANCA panel ENA (RNP, Sm) ENA 1 (SSA/SSB)	


History or exam not consistent with infectious etiology
Or
Preliminary investigation negative
•Diffuse Motor Weakness
Consider:
•Guillain-Barre
•Infantile Botulism
•Periodic Paralysis
•West Nile virus
•Pesticide exposure
•Tick paralysis
•EMG
•Stool for botulism
•Correct all severe and mild electrolyte abnormalities
•Fever, seizures, tachycardia, hypertension
•Muscle rigidity/ Rhabdomyolysis
•Behavioral problems
•Access to home medications
Consider Ingestion:
•Serotonin Syndrome
•Anticholinergic Syndrome
•Dextromethorphan overdose
•Anticonvulsant overdose
•Contact poison control
•Specific drug levels
•Cardiac monitoring
•Antidotes
•Positive inflammatory/autoimmune markers (ANA, ds DNA, ACE)
Consider:
•SLE
•APL
•Sarcoid
•Behcet's
Rheum consult
•Abnormal eye movements
•Ataxia
•HTN
Consider:
Opsoclonus-myoclonus ataxia syndrome
abdominal US
Urine HVA, VMA
•Behavioral changes preceding hospitalization
•Hallucinations, particularly auditory
•Extreme irritability
•Generalized seizures
•Movement disorder
•Repetitive orofacial movements
•Dysautonomia
•CSF with mild lymphocytic pleocytosis and mild increase in protein
Consider:
Autoimmune enecaphalopathy
Evaluate for tumors (particularly):
•Neuroblastoma
•Ovarian
•Testicular
Consider Hashimotos Encephalitis:
•Antithyroid Peridoxase Antibodies
•Antithyroglobulin Antibodies
•Many are euthyroid, can have evidence of hypo or hyperthyroid
•May have oligoclonal bands
Prominent seizures, refractory to multiple AEDs
Consider dx of FIRES (see page 7)
•Prominent Cytotoxic injury on brain MRI
Primary CNS vasculitis
Rheum consult
•Neuropathy
Consider:
•Heavy Metal Poisoning
•Guillain-Barre
•Critical illness neuropathy if prolonged hospital stay
•Atypical WBC on CSF cell count/ smear
CNS Lymphoma
Oncology Consult
CSF for Flow
•MRI with multiple asymmetric deep and subcortical white matter lesions
Acute Disseminated Encephalomeylitis (ADEM)
•Other organ involvement
•Deep brain nuclei involvement
•Family history of encephalopathy
Consider metabolic disorders
•Mitochondrial
•Wilson's
•HLH
•In-born errors of metabolism
•Genetics/Metabolic consult
•Serum genetic testing
•Ceruloplasmin
•Serum amion acids
•Urine organic acids
•Carnitine profile
•Lactate/Pyruvate battery
•Eosinophilia
•Consider parasites (e.g. Baylisascaris (raccoon feces)
•Ask about exposures
•ID consult

NMDA Management

TIMELINE: Presumed antibody mediated encephalopathy including NMDA

WEEK 1:

Day 1 and 2: EEG monitoring for at least 24 hours to confirm presence/absence of seizures
MRI brain with and without contrast
Start pulse steroids (see page 8 for dosing after screening for TB risk)
Start IVIG (see page 8 for dosing)
** SEND antibody LABS prior to IVIG **
** Confirm all antibody labs are received with the lab (call for any order not in process in CERNER)
Minimize sedation
Assess for and treat dysautonomia, sleep disturbance and/or delirium
If symptoms severe consider PLEX prior to IVIG (e.g. if dysautonomia)

WEEK 2: Repeat MRI brain (+/- spine) with and without contrast
If no significant improvement and/or moderate to severe impairment, start Rituximab (see page 8 for dosing)

WEEK 4: If no significant improvement and/or moderate to severe impairment, start Cytoxan

* *Once NMDAR encephalitis confirmed, begin tumor surveillance*

FIRES Management

FIRES criteria

SRSE (must have failed wean of 3rd line agent)
Age 3-17
Seizures preceded by febrile illness
No alternative diagnosis despite comprehensive evaluation for infectious and inflammatory causes of seizures

Strategies for weaning infusion medications

Phenobarbital with goal levels ~ 100
Felbamate with goal levels > 50 *(fosphenytoin drives level down)*
Avoid propofol (due to concerns for secondary mitochondrial injury and propofol infusion syndrome)
Start metabolic supplements *(see page 8)*
Start ketogenic diet
Start aggressive bowel regimen (if being fed enterally).
* ILEUS IS NOT COMPATIBLE WITH ENTERAL AED ADMINISTRATION
Attend to parental inquiries regarding cannabadiols.
Bolus ketamine 1 mg/kg and begin infusion 1 mg/kg/hr (titrate to max of 10 mg/kg/hr)
Avoid polypharmacy, limit background AEDs to 4

Strategies for reducing inflammation

Begin pulse dose steroids (see page 8 for dosing)
Begin IVIG 2g/kg div 2 days as soon as labs sent (must confirm they are received in the lab and being processed)
Begin Anakinra (5 mg/kg/dose BID) once FIRES suspected
Consider PLEX if hemodynamically stable (will need to get AED labs post PLEX and bolus immediately after infusion) - anticipate timing for line placement and transfusion team preparation.
Consider Cytoxan if seizures continue to be refractory beyond week 3

Monitoring

Switch EEG to double distance once burst suppressed
Scalp breaks should be given every 4 days (minimum 4 hours)
Daily am trough for AED levels (phenobarbital, phenytoin, VPA)
Felbamate and Topiramate levels Monday and Thursday
High index of suspicion for DRESS (monitor for rash), HLH (multiorgan failure, increased TG and ferritin), dysautonomia (including gut dysmotility)
MRI brain every 2-4 weeks during initial PICU admission

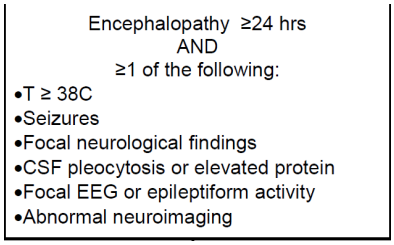
Immune Modulating Therapies

Medication	Dose	Side Effects	Miscellaneous
IVIG	1g/kg IV Q day x 2 days, then once monthly x 6 months	Hypersensitivity/infusion reactions, hypotension, headache, aseptic meningitis	**Order all titer studies prior to administration.**
MethylPREDnisolone	30 mg/kg/day daily x 5 days (max: 1 gm daily)	HTN, immunosuppression, hyperglycemia, gastritis	• Consider risk factors for TB and HSV • Avoid if lymphoma included in DDX • Concurrent admin of GI prophylaxis
Plasma exchange (PLEX)	Typically 5 rounds, every other day	Hemodynamic instability, bleeding (large catheter), possible drug removal	• Requires catheter placement • If young child or agitated need sitter for line safety • **Consider repeat IVIG after PLEX finished**
RiTUXimab	750mg/m2/dose Q 2 weeks x 2 (max: 1000mg/dose)	Immune suppression, hypersensitivity/infusion reactions, PML (rare)	Counsel family on rare risk for PML **Lymphocyte subset panel #1 pre and 3 months post infusion**
Anakinra	3-5mg/kg SQ BID (max: 200mg/day)	Injection site reactions	Send CSF and serum cytokines to Cincinnati
Cyclophosphamide (Cytoxan)	500mg/m2 monthly x 6 months (max: 2500mg)	Immune suppression, nausea, vomiting, hemorrhagic cystitis	• Abx prophylaxis • Counsel family on theoretical risk for infertility (females)

Metabolic Supplements for FIRES or similar presentation

Medication	Indication	Dose
Levocarnitine	Secondary mitochondrial dysfunction	50 mg/kg/day divided Q6 hours
Thiamine	Secondary mitochondrial dysfunction	100 mg daily
CoenzymeQ	Secondary mitochondrial dysfunction	5 mg/kg/day divided Q12 hours
Pyridoxine	Pyridoxine responsive seizures suspected	100 mg daily

Clinical Documentation Recommendations



Diagnostic criteria met: Y/N

History:

Prodrome: Fever or illness within 10 days of presentation Y/N
Developmentally normal prior to presentation: Y/N

Clinical findings:

Fever during the first 24 hours of admission (≥ 38) Y/N
Rash Y/N Date noted _____

Course:

Seizure during hospitalization Y/N Date first _____ Date last _____
ICU admission Y/N
G tube Y/N
Trach Y/N
Pacemaker Y/N

Diagnostic work up:

CSF: Y/N Dates _____
EEG Y/N Dates _____
Genetic labs (any) Y/N
MRI brain Y/N Date _____

Treatment:

Acyclovir administered: date started _____ c Number of days of therapy ____
Immune modulating therapy:
IVIG Y/N date _____
Steroids Y/N date _____
PLEX Y/N date _____
Anakinra Y/N date ____
Rituximab Y/N date ____