NORSE (including FIRES) DIAGNOSTIC EVALUATION

Disclaimer: This is a sample of suggested tests to investigate patients with unexplained new-onset refractory status epilepticus (NORSE) or its subset febrile infection related epilepsy syndrome(FIRES). It does not claim to be a complete list of tests to be done nor does it claim that most or all tests should be done on all patients. It mostly serves as a reminder of the many possible etiologies to consider, but requires individualization, as with any medical algorithm. The NORSE Institute is grateful to its Medical Advisory Board for developing this NORSE Diagnostic Evaluation. (Last update: 9/3/2020)

Within first 24 hours:

- Initiate institutional status epilepticus protocol (see algorithm on NORSE Institute website)
- Obtain history, especially regarding immunosuppression, medications and supplements, recent illness, recent vaccinations, recent travel, accidental or occupational exposure to animals, insects, pathogens, drugs or toxins
- Consider treatment for possible HSV encephalitis
- Triage for appropriate cardiopulmonary support
- MRI brain with and without contrast, consider MRA and MRV head
- Initiate continuous video EEG monitoring, regardless of cessation of convulsive activity (unless patient wakes up and follows commands).
- Serologic/imaging tests (see below)

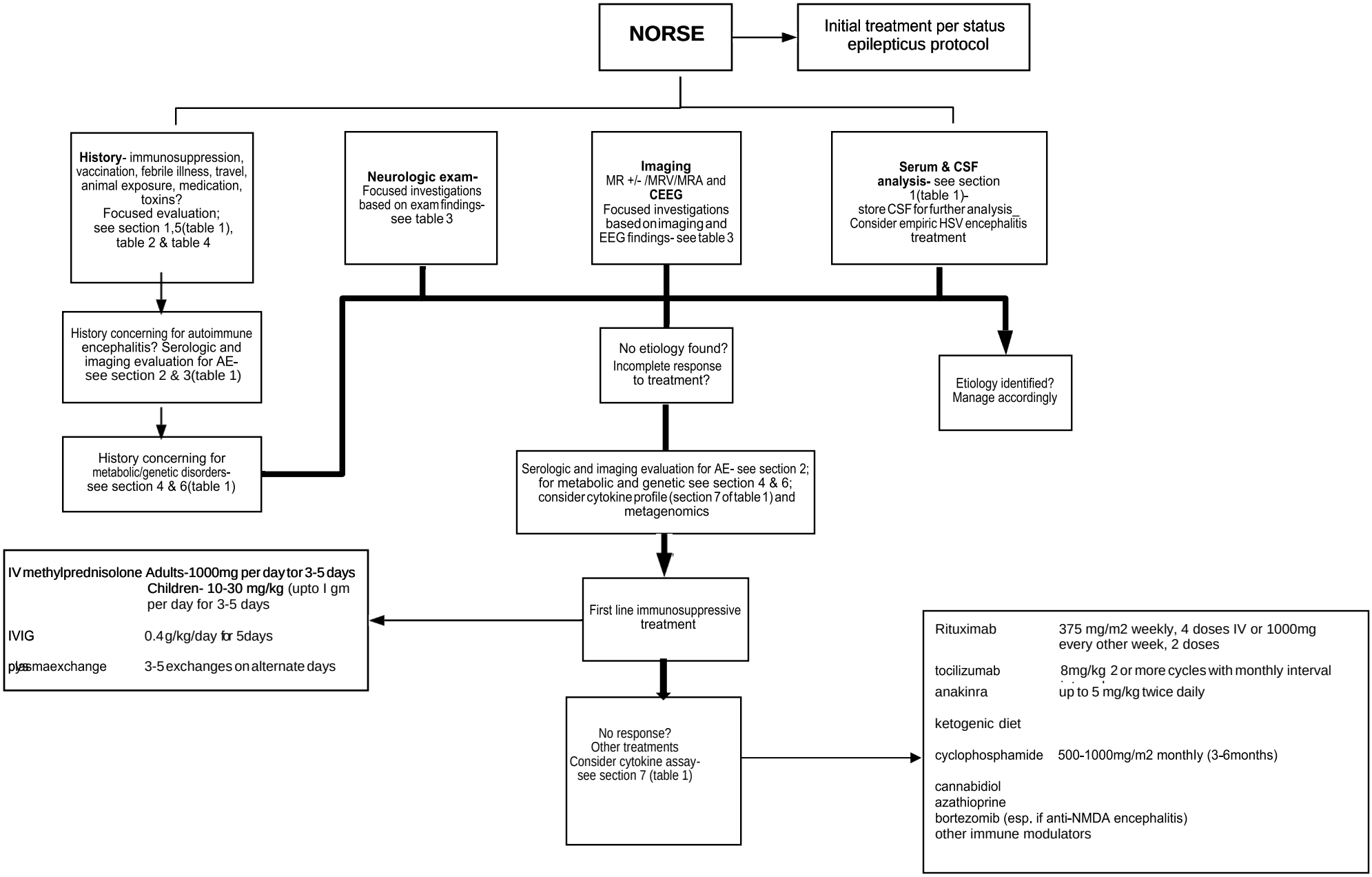
NORSE
Initial treatment per status epilepticus protocol
History- immunosuppression, vaccination, febrile illness, travel, animal exposure, medication, toxins?
Focused evaluation; see section 1,5(table 1), table 2 & table 4
Neurologic exam- Focused investigations based on exam findings- see table 3
Imaging
MR +/- /MRV/MRA and CEEG
Focused investigations based on imaging and EEG findings- see table 3
Serum & CSF analysis- see section 1(table 1)-
store CSF for further analysis_
Consider empiric HSV encephalitis treatment
History concerning for autoimmune encephalitis? Serologic and imaging evaluation for AE- see section 2 & 3(table 1)
History concerning for metabolic/genetic disorders- see section 4 & 6(table 1)
No etiology found?
Incomplete response to treatment?
Etiology identified?
Manage accordingly
Serologic and imaging evaluation for AE- see section 2; for metabolic and genetic see section 4 & 6; consider cytokine profile (section 7 of table 1) and metagenomics
First line immunosuppressive treatment
IV methylprednisolone Adults-1000mg per day tor 3-5 days
Children- 10-30 mg/kg (upto I gm per day for 3-5 days
IVIG 0.4 g/kg/day for 5days
plasmaexchange 3-5 exchanges on alternate days
No response?
Other treatments
Consider cytokine assay- see section 7 (table 1)
Rituximab 375 mg/m2 weekly, 4 doses IV or 1000mg every other week, 2 doses
tocilizumab 8mg/kg 2 or more cycles with monthly interval
anakinra up to 5 mg/kg twice daily
ketogenic diet
cyclophosphamide 500-1000mg/m2 monthly (3-6months)
cannabidiol
azathioprine
bortezomib (esp. if anti-NMDA encephalitis)
other immune modulators

TABLE 1: DIFFERENTIAL DIAGNOSES TO BE CONSIDERED

Screen	Disease/agent tested

Section.1
 	
Initial workup
	Recommended in most or all patients:
	• **Whole blood/Serum**: CBC, bacterial and fungal cultures, RPR-VDRL, HIV-1/2 immunoassay with confirmatory viral load if appropriate.
	• **Serum**: IgG and IgM testing (acute and convalescent) for chlamydia pneumoniae, bartonella henselae, mycoplasma pneumonia, coxiella burnetii, shigella species and chlamydia psittaci
	• **Nares or nasopharyngeal swab (the latter preferred)**: Respiratory viral DFA panel; SARS-CoV2 PCR
	• **CSF**:
	  ○ Cell counts, protein, and glucose, Bacterial and fungal stains and cultures.
	  ○ RT-PCR for HIV, PCR for HSV1, HSV2, VZV, EBV, M.Tb; consider WNV, VDRL, encephalitis panel,
	  ○ PCR for chlamydia pneumoniae and psittaci, bartonella henslae, mycoplasma pneumonia, coxiella burnetti and Shigella species,
	  ○ Autoimmune epilepsy panel (see section 2);
	  ○ Consider metagenomics for any non-human nucleic acid material,
	  ○ Consider cytokine profile (section 7).
	  ○ Consider cytology and flow cytometry.
	
	Recommended in immunocompromised patients:
	• **Serum**: IgG cryptococcus species, IgM and IgG histoplasma capsulatum, IgG toxoplasma gondii
	• **Sputum**: M Tb Gene Xpert
	• **CSF**: eosinophils, silver stain for CNS fungi, PCR for JC virus, CMV, EBV, HHV6, EEE, enterovirus, influenza A/B, HIV, WNV, parvovirus. listeria Ab, measles (rubeola),
	• **Stool**: adenovirus PCR, enterovirus PCR
	
	Recommended if geographic/seasonal/occupational risk of exposure:
	• Serum buffy coat and peripheral smear
	• Lyme EIA with IgM and IgG reflex
	• Hepatitis C immunoassay and viral load if appropriate
	• Send further serum and CSF samples to CDC DVBID Arbovirus Diagnostic Laboratory, CSF and serum rickettsial disease panel, flavivirus panel, bunyavirus panel
	• Serum testing for acanthamoeba spp., balamuthia mandrillaris, baylisascaris procyonis
	• Other
	
	Consider **CSF Metagenomics** for any infectious genetic material

	Optional: See attached **table 2** for further geographical/zoonotic risk factors

Section.2 **Auto-immune/ paraneoplastic**	Recommended: • **Serum and CSF paraneoplastic and autoimmune epilepsy antibody panel.** To include antibodies to: LGI-1, CASPR2, Ma1, Ma2/TaDPPX, GAD65, NMDA, AMPA, GABA-B, GABA-A, glycine receptor, Tr, amphiphysin, CV-2/CRMP-5, Neurexin-3alpha, adenylate kinase, anti-neuronal nuclear antibody types 1/2/3 (Hu, Yo and Ri), Purkinje cell cytoplasmic antibody types 1,2, GFAP- alpha, anti-SOX1, N-type calcium Ab, PQ-type calcium channel, Acetylcholine receptor (muscle) binding Ab, Ach-R ganglionic neuronal Ab, AQP4, MOG Ab, IgLON5 Ab, D2R Ab • **Additional serologic studies-Serum** (likely not pathogenic but hint towards an autoimmune etiology) ANA (detection and identification), ANCA, anti-thyroid antibodies (anti-thryoglobulin, anti-TPO), anti-endomysial, ESR, CRP, SPEP, IFE, RA, ACE., cold and warm agglutinins, tests for MAS/HLH (serum triglycerides and sIL2-r, ferritin)
	Suggestion: Store extra frozen CSF and serum for possible further autoimmune testing in a research lab.
Section.3 **Neoplastic**	Recommended: CT chest/abdomen/pelvis, pelvic or scrotal ultrasound, mammogram, CSF cytology, flow cytometry, cancer serum markers. Pelvic MRI. Whole body PET-CT if above tests are not conclusive.
	Optional: Bone marrow biopsy
Section.4 **Metabolic**	Recommended: **Whole blood/Serum:** BUN/Cr, LDH, liver function tests, electrolytes, Ca/Mg/Phos, ammonia, **Urine:** Porphyria screen (spot urine), UA with microscopic urinalysis
	Consider: Vitamin B1 level, B12 level, homocysteine, folate, lactate, pyruvate, CK, troponin; tests for mitochondrial disorder (lactate, pyruvate, MR spectroscopy, muscle biopsy),
Section.5 **Toxicological**	Recommended: benzodiazepines, amphetamines, cocaine, fentanyl, alcohol, ecstasy, heavy metals, synthetic cannabinoids, bath salts
	Consider: Extended opiate and overdose panel, LSD, heroin, PCP, marijuana

Section. 6 Genetics	Consider: obtain genetics consult, if possible. Genetic screens for mitochondrial disorders (MERRF, MELAS, POLG1, SURF1, MT-ATP6) and VLCFA screen. Consider ceruloplasmin and 24-hour urine copper. Consider mendeliome or whole exome sequencing (also look for gene polymorphisms in IL 1B, IL6, IL10, TNF-alpha, HMBG1, TLR4, IL1RN, SCN1A and SCN2A), mitochondrial genome sequencing and CGH array
Section.7 Cytokine Assay	**Serum and CSF**: cytokine assay for quantitative measure of IL-1β, IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-17, granulocyte-macrophage colony stimulating factor, tumor necrosis factor-α, HMGB1, CCL2, CXCL8, CXCL9, CXCL10, CXCL11

At 48 hours:

- Assess returned test results, initiate appropriate treatments
- If patient continues to have refractory status epilepticus or coma, transfer to higher level of care for appropriate further treatment of NORSE at a center with experience in these cases, including continuous video EEG monitoring.

At 72 hours:

- Consider initiation of high dose parenteral corticosteroids. Transfer to higher level of care for consideration of IVIG, plasmapheresis, or further immunomodulatory therapy if no clear diagnosis, if still having seizures, if no continuous EEG monitoring available, or if still comatose.

TABLE 2: ZOONOTIC/GEOGRAPHIC EXPOSURE CONSIDERATIONS IN STATUS EPILEPTICUS

Clues	**Etiology**
Ingestion	
Unpasteurized milk	Tick-born virus, Coxiella burnetiid, Brucella
Star fruit	Caramboxin, oxalic acid

Geographical factors (residence, recent travel)	
Africa	West Nile virus
Australia	Murray Valley encephalitis virus, Japanese encephalitis virus, Hendra virus
Central and South America	Eastern Equine Virus, Western Equine Virus, Venezuelian Equine Virus, Saint-Louis Virus, Rickettsia spp.
Europe	West Nile Virus, Tick-Borne Virus, Ehrlichia chaffeensis/Anaplasma phagocytophilum Japanese Virus West Nile Virus Tick-Borne Virus
India, Nepal	Japanese Virus, Tick-Borne Virus, Nipah Virus
Middle East	
Russia	
Southeast Asia, China, Pacific Rim	
Seasonal factors	
Late summer/early fall	Arboviruses, Enteroviruses
Winter	Influenza Virus
Animal exposure	
Cats	Bartonella henselae, Toxoplasma gondii
Horses	Eastern Equine Virus, Western Equine Virus, Venezuelian Equine Virus, Hendra Virus
Raccoons	Baylisascaris procyonis
Rodents	Bartonella quintana, Eastern Equine Virus, Western Equine Virus, Tick-Borne Virus, Powassan Virus, La Crosse Virus, Lymphocytic Choriomeningitis Virus
Sheep and goats	Coxiella burnetii
Swine	Japanese Virus, Nipah Virus
Insect exposure, including travel to infested area	
Mosquitoes	EEE, WEE, Venezuelan Equine Virus, Saint-Louis Virus, Murray Valley Virus, Japanese Virus, West Nile Virus, La Crosse Virus, California Encephalitis Virus, Cache Valley Virus
Ticks	Tick-Borne Virus, Powassan Virus, Rickettsia spp, Ehrlichia chaffeensis/Anaplasma phagocytophilum

TABLE 3: NEUROLOGIC FINDINGS SUGGESTING SPECIFIC DIAGNOSES

Neurologic exam	
Acute lower motor neuron syndrome	Japanese Virus, West Nile Virus, Tick-Borne Virus, Enterovirus (serotype 71, coxsackie)
Acute parkinsonism	Japanese Virus, Saint-Louis Virus, West Nile Virus, Nipah Virus, Toxoplasma gondii
Movement disorder, psychiatric symptoms, ataxia	Anti D2R encephalitis
Neuropsychiatric prodrome, memory impairment, prominent oro-lingual dyskinesias, catatonia, autonomic dysfunction	Anti-NMDA receptor encephalitis
Facio-brachial dystonic seizures, piloerection, paroxysmal dizzy spells and hyponatremia	Anti-VGKC complex (LGI1) encephalitis
Prodromal weight loss and gastrointestinal symptoms, cognitive and behavioral changes, PERM syndrome	Anti DPPX encephalitis
Ataxia	Epstein- Barr Virus, mitochondrial disorder (NARP)
Stiff person syndrome, hyperekplexia, new onset type 1 diabetes	GAD65
Mood changes and movement disorder	mGLU-R1/5
Sensory neuronopathy/autonomic dysfunction, epilepsia partialis continua	ANNA-1/Hu
Stiff person syndrome, progressive encephalopathy with rigidity and myoclonus, transverse myelitis	Amphiphysin antibody
Limbic encephalitis or peripheral nerve hyperexcitability, neuromyotonia, autonomic dysfunction	CASPR2 antibody
NREM, REM sleep disorders, brain stem disorders	IgLON5 antibody

New onset of anosmia and ageusia	COVID-19
EEG findings suggesting specific diagnoses	
Extreme delta brushes Extreme spindles Parieto-occipital epileptiform discharges and seizures	Anti-NMDA receptor encephalitis Mycoplasma pneumoniae Mitochondrial disorder, PRES
MRI	
Prominent mesial temporal lobe involvement	Paraneoplastic and autoimmune limbic encephalitis, anti-VGKC complex encephalitis, herpes family encephalitides
Basal ganglia	Saint-Louis Encephalitis Virus, La Crosse Virus, and Murray Valley Virus Anti CV2(CRMP5), anti D2R
Posterior predominant edema	PRES
Stroke-like findings	POLG1, MELAS
Linear perivascular radial enhancement in periventricular white matter	GFAP alpha encephalitis
Multi focal cortical/subcortical abnormalities	Anti GABA-AR

TABLE 4: MEDICATIONS, SUBSTANCES AND TOXINS THAT CAN CAUSE OR EXACERBATE SEIZURES

Drugs	
Antibacterial	cephalosporins (especially cefepime), carbapenems(imipenem), quinolones, linezolid, isoniazid (treat with pyridoxine), metronidazole, penicillins,
Antifungal	amphotericin, miconazole
Antiviral	amantadine
Antiparasitic	mefloquine, chloroquine, pyrimethamine,
Antidepressants/antipsychotics	bupropion, tricyclic antidepressants (especially amoxapine) lithium, clozapine, chlorpromazine, high-potency neuroleptics (including haloperidol)
Chemotherapy	platinum-based agents (cisplatin), cytarabine, bleomycin, busulphan, methotrexate, carmustine, chlorambucil, mechlorethamine, vinca alkaloids, gemcitabine irinotecan, ifosfamide interferon-alpha, interleukin-2 humanized monoclonal antibodies (bevacizumab, ipilimumab, rituximab, infliximab) tyrosine kinase inhibitors (imatinib, pazopanib, sorafenib, sunitinib) GMCSF
Immunosuppressive and immunomodulatory drugs	cyclosporine, tacrolimus, sirolimus, azathioprine intravenous immune globulins anti-TNF-alpha (etanercept) anti-lymphocyte globulin high-dose steroids CAR-T cell therapy
Other medications	sympathomimetics (including theophylline, caffeine, amphetamines) anti-histamines (including diphenhydramine) opiates (morphine, tramadol) beta blockers (propranolol) anti-arrhythmic (quinidine, flecainide) anesthetics (enflurane, sevoflurane, etomidate) antiepileptics (phenytoin, carbamazepine) overdose or withdrawal 4-aminopyridine (dalfampridine), baclofen sulfasalazine, flumazenil lindane, permethrin

Abusive drugs	ethanol, ethylene glycol, methanol amphetamines, methamphetamine, cocaine, lysergic acid diethylamide(LSD), phencyclidine(PCP), marijuana
Complementary and alternative medicines	borage oil, neem oil
Environmental toxins	heavy metals including lead, aluminum arsenic, mercury star fruit (oxalic acid, caramboxin) organophosphates, organochlorines and pyrethroids biotoxins (scorpion toxin, anatoxin, ciguatoxin, domoic acid), strychnine cyanide, carbon monoxide, hyperbaric oxygen

Contributors:

Gaspard N, Sculier C, Hirsch LJ, Hocker S, Zubeda Sheikh, Shivani Ghoshal, Yashwanth Pulluru and other members of The NORSE Institute medical advisory board.

References:

1. Gaspard N, Hirsch LJ, Sculier C, Loddenkemper T, van Baalen A, Lancrenon J, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): State of the art and perspectives. Epilepsia. 2018;59(4):745-52.
2. Gofton TE, Gaspard N, Hocker SE, Loddenkemper T, Hirsch LJ. New onset refractory status epilepticus research: What is on the horizon? Neurology. 2019;92(17):802-10.
3. Clarkson BDS, LaFrance-Corey RG, Kahoud RJ, Farias-Moeller R, Payne ET, Howe CL. Functional deficiency in endogenous interleukin-1 receptor antagonist in patients with febrile infection-related epilepsy syndrome. Ann Neurol. 2019;85(4):526-37.
4. Sakuma H, Tanuma N, Kuki I, Takahashi Y, Shiomi M, Hayashi M. Intrathecal overproduction of proinflammatory cytokines and chemokines in febrile infection-related refractory status epilepticus. J Neurol Neurosurg Psychiatry. 2015;86(7):820-2.
5. Jun JS, Lee ST, Kim R, Chu K, Lee SK. Tocilizumab treatment for new onset refractory status epilepticus. Ann Neurol. 2018;84(6):940-5.
6. Hocker SE. Status Epilepticus. Continuum (Minneap Minn) 2015;21(5):1362–1383
7. Kothur, K, Bandodkar, S, Wienholt, L, et al. Etiology is the key determinant of neuroinflammation in epilepsy: Elevation of cerebrospinal fluid cytokines and chemokines in febrile infection-related epilepsy syndrome and febrile status epilepticus. *Epilepsia*. 2019; 60: 1678– 1688.
8. Trinka, E., Cock, H., Hesdorffer, D., Rossetti, A.O., Scheffer, I.E., Shinnar, S., Shorvon, S. and Lowenstein, D.H. (2015), A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia, 56: 1515-1523
9. Zuliani, L.,Nosadini, M., Gastaldi, M. *et al*. Management of antibody-mediated autoimmune encephalitis in adults and children: literature review and consensus-based practical recommendations. *Neurol* Sci 40, 2017-2030 (2019)
10. Annamaria Vezzani, Barbara Viviani, Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability, Neuropharmacology, Volume 96, Part A, Pages 70-82,2015.