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Clinical Case Scenario: New Onset Refractory Status Epilepticus And Their Management.

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Abstract
28 *year old male Bank manager by profession caught with seizure , in-spite of taking multiple medication in different health care the symptom didn't subside. Ultimately he landed to emergency were he started on multiple medication for seizure as the symptom was refractory and later diagnosed with New Onset Refractory Status Epilepticus (NORSE). The causative organism was considered to be Acinetobacter Baumanii on CSF examination.*
On prolonged sedative medication and mechanical ventilation he was diagnosed with Ventilatory associated pneumonia , the causative organism was found to be Klebsiella pneumoniae, Pseudomonas aeruginosa, Providencia infection for which he started on antibiotic therapy. In-spite of all the efforts even due to multiple medication and antibiotic therapy patient landed into septic shock.

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I. Case Scenario

28 year old male , Bank manager by profession, Hindu by religion, Residence of Puducherry, Admitted to Clinic with a chief complaint of Fever 14 days, Seizures 14 days. History of Present illness Patient was apparently normal until 13th july 2024 he appeared for UPSC exams. Later in that evening Patient develop fever that was low grade. Fever not associated with chills and rigors. No history of rash/ Joint pain. No history of nausea vomiting constipation and diarrhea. No history of weakness headache altered mental status. History of mild cough occasionally present. Patient took self medication for fever for two days. He took self medication Tab. Paracetamol, Tab. Azithromycin, Tab-B-Complex, Syrup Asthalin.

During this period patient had one day business trip returned back to home on 17-07-2024.On 18-07-2024 Patient had one episodes of GTCS presenting with Up-rolling of eye, Tongue fits, Drooling of saliva, facial deviation, Lasted 5 minutes involved spontaneous regained of consciousness past seizure activity.

After seizure ended patient has been taken to nearby clinic his vital was checked temperature was found to be 100 degree Fahrenheit, uric acid level was raised. Later referred to Karaikal GH hospital discharge with Tab.Polypod (Cefpodoxime proxetil 200mg), Tab.Emestop (Prochlorperazine 5mg), Tab.Levipill (Levetiracetam 500mg), Tab pcm (Paracetamol 500mg).

On the way to Karaikal hospital patient he got one episodes of seizures, that involved spontaneously. In Hospital 3 GTCS fits lasting for 5 minutes with interictal periods for 1 hours, and there was Complete return of consciousness in between seizures. Referred to Neuro Hospital on July 19th for O_2 supplementation via face mask.

In Neuro Hospital patient has seizure like activity everyday, up rolling of eye, Lip smacking, twitching movement ,the patient GCS was $E_3V_3M_5$,neck stiffness present ,pupil 2mm reactive. On blood examination procalcitonin level above 3.19, White Blood Cell Count 70 (Lymphocyte > Neutrophils). On 25th of July 2024 on MRI Brain ,Flair hyperpigmentation with associated effacement involving sulcal space of Frontal, Parietal, Occipital, Parenchyma.

Treatment given at Neuro Hospital
- Inj.Levipil (Levetiracetam) 1g TDS
- Inj. Lacosamide 100mg TDS
- Inj. Valproate
- Inj. Phenytoin 10mg TDS
- Tab Clobazam 10MG 1-1-2
- Inj Ceftazidime-avibactam 2.5g TDS
- Inj Acyclovir 500mg TDS
- T. Febuxostat 40mg
- T. Fycompa (Perampanel)
- T. Zonisamide

- IV Ig 15 Vials given (10g/ vials)

Past history -No h/o Previous Hospitalization. No h/o drugs/surgery/in the past.
Personal History- No H/o of Habit or Substance Abuse

On examination in Higher Centre Clinic

Parameters	Values	Normal Range
PR	156/Min	60-100/Min
BP	140/90	120/80
GCS	$E_1V_TM_4$	
Only knee reflex	Present	
Plantar reflex	Mute	

After necessary investigation were done and on analyzing the sample it was confirmed a case of NORSE (New Onset Refractory Status Epilepticus). The status was found to be infective, and the causative organisms was Acinetobacter baumanii.
Ophthalmology opinion – send and it found to be negative for Papilledema

ENT Opinion for Pus discharge from the right Nose and on examination Deviated nasal septum DNS to left. MRI Brain Showing-Bilateral floor hypersensitivity involving, maxillary, frontal, ethmoidal sinusitis sign of Pansinusitis. Patient was on long term mechanical ventilation. Advised Tracheostomy for prolonged mechanical ventilation.

Treatment given in Higher center throughout the hospital stay.

Drugs	Dosage	Started On	Ended On	Total duration
Inj. Heparin	5000 unit Q12H	27/07/2024	31/08/2024	4
Inj. Pantoprazole	IV 40mg Q24H	26/07/2024	20/08/2024	25
Inj. valproate	IV 600mg Q6h	26/07/2024	20/08/2024	25
Inj. Phenytoin	Iv 100mg Q8h	26/07/2024	20/08/2024	25
Inj. Levetiracetam	IV 1mg Q8h	26/07/2024	20/08/2024	25
Inj. Lacosamide	IV 200MG Q8h	26/07/2024	20/08/2024	25
Inj. PCM	1g IV stat	26/07/2024	04/08/2024	14
Inj. Meropenem	2g Q8h	26/07/2024	06/08/2024	11
Inj. Dexamethasone	3mg iv Q8h	26/07/2024	20/08/2024	25
Thiopentone sodium	200mg IV BD	26/07/2024	20/08/2024	25
Midazolam	50mg in 50ml saline	26/07/2024	20/08/2024	25
Inj. Meropenem	2g Q8h	16/08/2024	20/08/2024	4
Tab. Lamotrigine	25mg Q12h	26/07/2024	20/08/2024	25
Tab. Zonisamide	PO 100mg Q12h	26/07/2024	20/08/2024	25
Tab. Pyridoxin	PO 50mg Q24h	26/07/2024	20/08/2024	25
Tab. Biotin	PO 20mg Q24h	26/07/2024	20/08/2024	25
Tab. Naproxen	250mg od morning dose	26/07/2024	20/08/2024	25
Tab. Clobazam	10mg (1-1-2)	26/07/2024	20/08/2024	25
Inj. Phenobarbitone	60mg Q12h BD	07/08/2024	08/08/2024	2

Ketamine	12mg/hr	26/07/2024	20/08/2024	25
Inj. Propofol	Iv 300mg IV Stat f/b 60mg/hr	28/07/2024	29/07/2024	2
Human Albumin	200g over 4 hr	20/08/2024	20/08/2024	1
Inj. KCl NS	20mg in 1000ml NS	20/08/2024	20/08/2024	1
Inj. $MgSO_4$	1gm in 100ml NS Over 1hr	05/08/2024	20/08/2024	15
Inj. Vancomycin	1gm IV Q 24h	26/07/2024	30/07/2024	4
Inj. Tranexamic acid	1gm iv stat	09/08/2024	09/08/2024	1
Inj. Methyl prednisolone	IV 1g OD	06/08/2024	09/08/2024	4
Tab. Doxycycline	100MG BD	28/07/2024	02/08/2024	5
Inj. Perampanel	2mg HS	28/07/2024	30/07/2024	3
Ryle tube feed	100mL Q4h f/b increasing feed	28/07/2024	16/08/2024	20
Inj. Calcium gluconate	10% 10mL over 10 minutes	30/07/2024	12/08/2024	14
Tab. Domperidone	10 mg BD	03/08/2024	10/08/2024	7
Tab. Minocycline	200mg BD	06/08/2024	12/08/2024	7
IV IG	IV over 2hr	06/08/2024	10/08/2024	4
Inj Ampiciline Sulbactam	9G Q8H	06/08/2024	12/08/2024	7
INJ PIPTAZIDEM	4.5gm, IV Q6H	15/08/2024	15/08/2024	1

On 28/07/2024 – Patient has sent for neurology opinion. EEG examination Frequent rush of b/l ictal rhythm (Frequent multifocal sharp waves) in posterior region of brain sign of Electroencephalographic seizure. Advised for Propofol 5mg/kg loading there by 1 mg/kg/hr infusion , injection Lancosamide 200mg BD, Injection sodium valproate IV 600mg TDS.

On 29/07/2024 EEG was repeated and again multifocal B/l sharp wave discharge was reported. Frequent (around 6 EEG Seizure)ictal rhythm from L>R Posterior region with Spatio-temporal evolution (less frequent than previous EEG), Sign of Non convulsive status epilepticus.

ON 30/07/2024 Patient diagnosed with Refractory Non convulsive status epilepticus. Sign of Feed Intolerance, FT Derangement, AKI, Bladder polyp. Management prescribe was Propofol ,Ketamine dose was tapered, Valproate dose was decreased in view of LFT, Autoimmune panel was sent ($GABA_A$, $GABA_B$,LG-1) for examination . CSF Collected for Anti -TPO, phenobarbital + ketamine added to the treatment.

On 06/08/2024 Super Refractory status epilepticus / Autoimmune/ B/l Limbic encephalits.

On 10/08/2024 Blood culture Acinetobacter baumanii ,injection Ampicillin sulbactam TDS, Minocycline 200mg BD

On 11/08/2024 $E_2V_TM_3$,Complain of 2 episodes of Focal seizure involving Left upper limb lasting 2 minutes, infusion through central line was given.

Parameter	Values	Normal Range
Fever Spikes	101 degree F	97-99 degree F
GCS	$E_3V_TM_4$	
Pupil	3mm, equal not reacting to light	
BP	134/90 mmHg	120/80 mmHg

PR	128/minute	60-100/minute
Respiratory examination	B/l basal crepitation heard	
CNS	Rhythmic movement of mouth /UL/LL	
Abdomen examination	Soft distension	
RT Aspirate	No sign of hematemesis	
Stool passed	Blackish water stool	
Electrolyte	Na^{+}- 155	136-144 mmol/ liter
CSF	ADA-9	0-2.5ul

For Seizure Thiopentone Sodium was started, Ketogenic diet, for Sepsis Antibiotic was continued
On 12/08/2024 ET tube aspiration examination was done and it was found to be positive for Pseudomonas and Providencia.

On 16/08/2024 Urine culture was found to be Positive for Enterobacter-ace.

On 20/08/2024 chest imaging was found to be Positive from right upper lobe Pneumonia.
Blood culture was found to be sterile, Endotracheal tube and urine culture was found to be positive for similar organism. Patient Expired on the same day.

Cause of death- Immediate cause- Septic Shock , Antecedent cause- Ventilatory associated pneumonia/ super refractory status epilepticus/ Bilateral limbic encephalitis.

Management of New onset Refractory Status Epilepticus

Diagnostic evaluation for patients with suspected NORSE (including FIRES)

Screen	Disease/agent tested

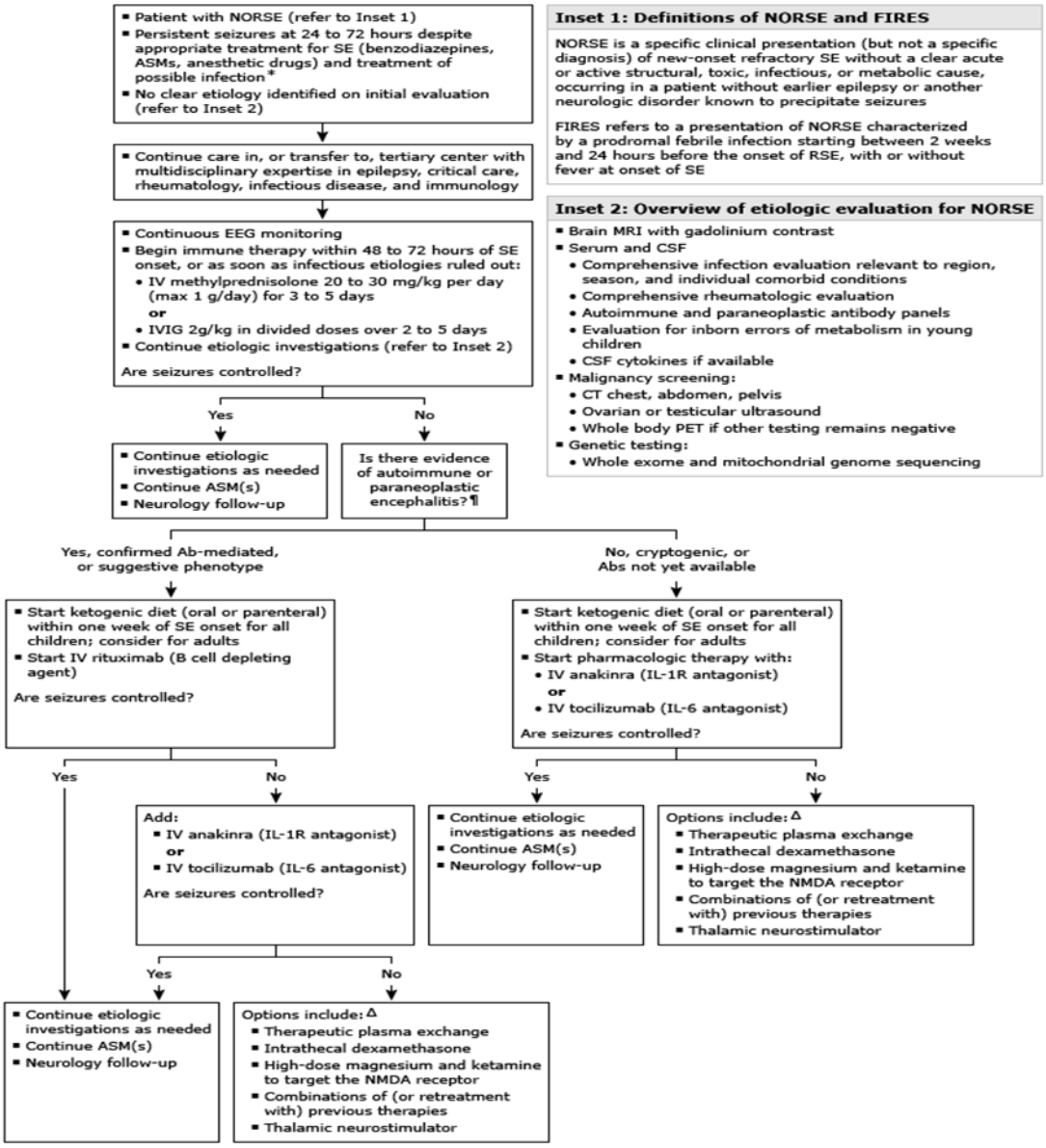
Section.1
Initial workup
	Recommended in most or all patients:
	• **Whole blood/serum:** CBC, bacterial and fungal cultures, RPR-VDRL, HIV-1/2 immunoassay with confirmatory viral load if appropriate.
	• **Serum:** IgG and IgM testing (acute and convalescent) for *Chlamydia pneumoniae*, *Bartonella henselae*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, *Shigella* species and *Chlamydia psittaci*.
	• **Nares or nasopharyngeal swab (the latter preferred):** Respiratory viral DFA panel; SARS-CoV-2 PCR.
	• **CSF:**
	  • Cell counts; protein; and glucose, bacterial, and fungal stains and cultures.
	  • RT-PCR for HIV; PCR for HSV1, HSV2, VZV, EBV, MTb; consider WNV, VDRL, encephalitis panel.
	  • PCR for *C. pneumoniae* and *psittaci*, *B. henselae*, *M. pneumoniae*, *C. burnetti* and *Shigella* species.
	  • Autoimmune epilepsy panel (refer to section 2).
	  • Consider metagenomics for any nonhuman 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:** MTb 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.

Section.2 **Autoimmune/ 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 **Toxicologic**	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-1beta, IL-6, IL-10, TNF-alpha, HMGB1, TLR4, IL-1RN, SCN1A, and SCN2A), mitochondrial genome sequencing, and CGH array.
Section.7 **Cytokine assay**	**Serum and CSF:** • Cytokine assay for quantitative measure of IL-1beta, IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-17, granulocyte-macrophage colony stimulating factor, tumor necrosis factor-alpha, 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.

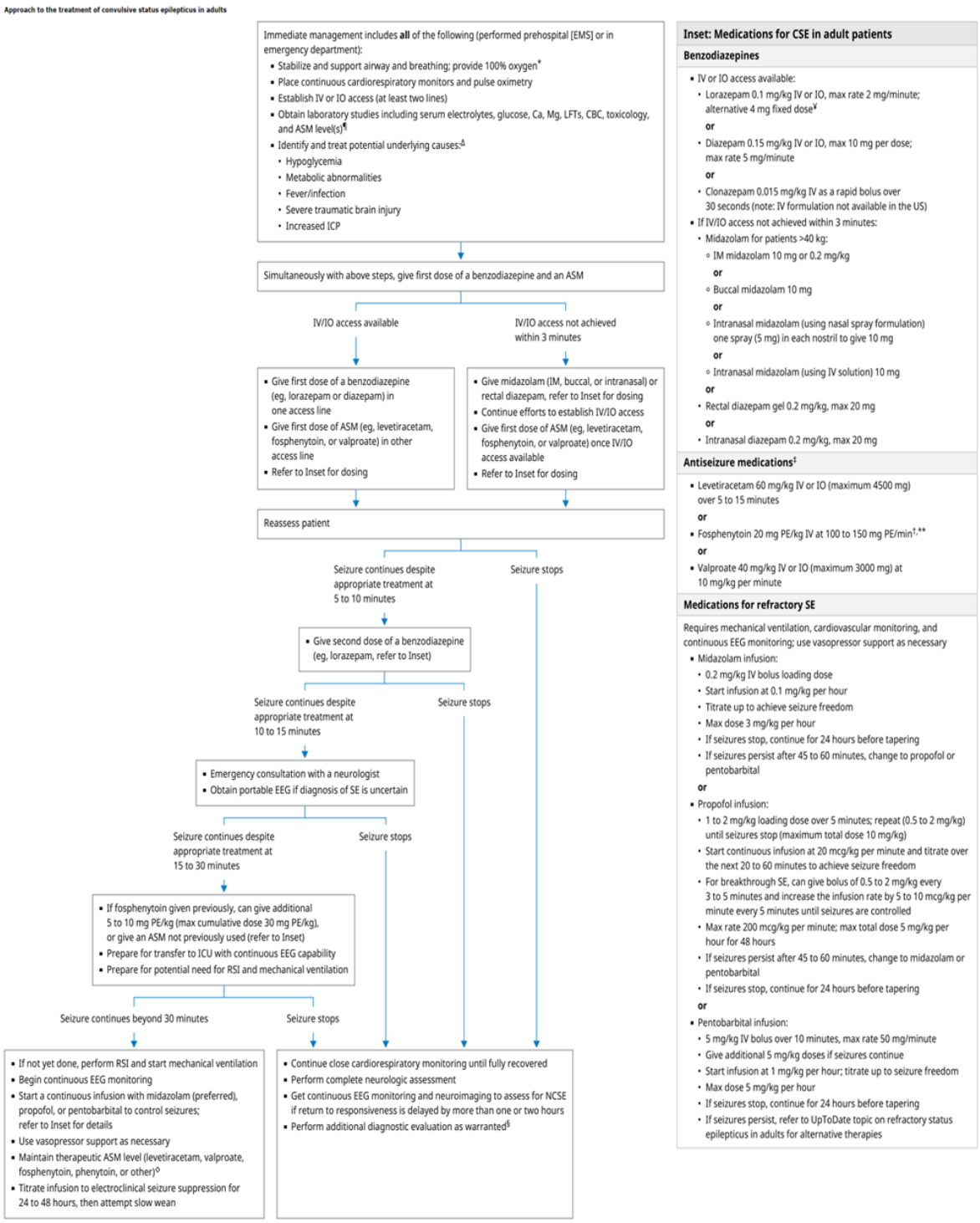
At 72 hours:
- Consider initiation of high-dose parenteral corticosteroids. Transfer to higher level of care for consideration of IVIG, plasmapheresis, or further immunomodulatory therapy if no clear diagnosis, if still having seizures, if no continuous EEG monitoring available, or if still comatose.

Approach to new-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES)



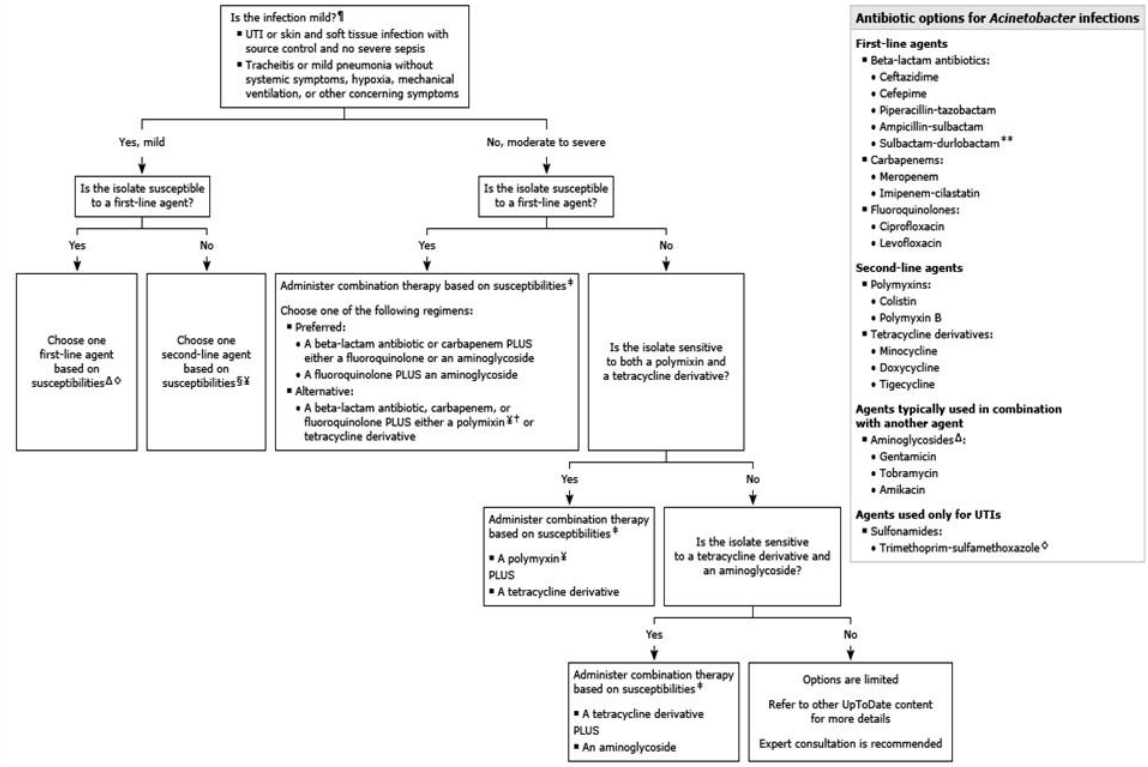
Abs: antibodies; ASM: antiseizure medication; CNS: central nervous system; CSE: convulsive status epilepticus; CSF: cerebrospinal fluid; CT: computed tomography; EEG: electroencephalography; FLAIR: fluid-attenuated inversion recovery; IL: interleukin; IVIG: intravenous immune globulin; IV: intravenous; MRI: magnetic resonance imaging; NCSE: nonconvulsive status epilepticus; NMDA: N-methyl-D-aspartate; PET: positron emission tomography; RSE: refractory status epilepticus; SE: status epilepticus.

Management of Seizures-



Management of Acinetobacter Baumanii

Antibiotic selection for *Acinetobacter* infections, excluding central nervous system infections*



UTI: urinary tract infection.

* Before deciding to treat, it is important to differentiate colonization from infection. Treatment of colonization is not recommended.

¶ Moderate to severe infections either do not meet the criteria for mild infection or have heightened clinical concern.

Δ Aminoglycosides are a first-line agent only for UTIs. For infections outside the urinary tract, they are only used as part of combination therapy.

◇ Trimethoprim-sulfamethoxazole can be used as monotherapy for UTIs. It is not used for other sites of infection or as part of combination therapy.

§ For UTIs, polymyxin B and tetracycline derivatives should not be used as monotherapy. For pneumonia, polymyxin B and colistin should not be used as monotherapy. For bacteremia, tetracycline derivatives should not be used as monotherapy.

¥ Polymyxin B is preferred over colistin, except colistin is preferred for UTIs. In the United States, there are no standards for defining resistance; a minimum inhibitory concentration >2 mcg/L is likely to confer resistance.

‡ For infections other than primary bloodstream infections, severe pneumonia, and severe intra-abdominal infections, we narrow to a single active agent once appropriate clinical response has occurred. First-line agents are preferred over second-line agents, if susceptible.[Δ§¥]

† The combination of a polymyxin and a carbapenem should be avoided (due to studies showing no benefit compared with monotherapy) unless no other combinations of susceptible agents are available.

** We reserve sulbactam-durlobactam for patients with carbapenem-resistant hospital-acquired or ventilator-associated pneumonia or bacteremia whose isolate is resistant to all other first-line agents.

UpToDate®

Dosing of antibiotics for *Acinetobacter* infections in adults with normal renal function

Drug	Dose
First-line agents	
Ceftazidime	2 g intravenously every 8 hours (infuse each dose over 3 to 4 hours)*
Cefepime	2 g intravenously every 8 hours (infuse each dose over 3 to 4 hours)*
Piperacillin-tazobactam	4.5 g intravenously every 8 hours (infuse each dose over 4 hours)*
Ampicillin-sulbactam¶	Mild carbapenem-susceptible infections: 3 g intravenously every 6 hours Mild carbapenem-resistant infections: 3 g intravenously every 4 hours Moderate to severe infections: 9 g intravenously every 8 hours (infuse each dose over 4 hours)*, **or** 27 g intravenously every 24 hours as a continuous infusion*
Sulbactam-durlobactamΔ	Sulbactam 1 g/durlobactam 1g intravenously every 6 hours (infuse each dose over 3 hours) For patients with augmented renal clearance (CrCl ≥130 mL/minute): Sulbactam 1 g/durlobactam 1 g intravenously every 4 hours (infuse each dose over 3 hours)
Meropenem	Cystitis: 1 g intravenously every 8 hours (infuse each dose over 30 minutes) Infections other than cystitis: 2 g intravenously every 8 hours (infuse each dose over 3 hours)*
Imipenem-cilastatin	Cystitis: 500 mg intravenously every 6 hours (infuse each dose over 30 minutes) Infections other than cystitis: 500 mg intravenously every 6 hours, or 1 g intravenously every 6 to 8 hours (infuse each dose over 3 hours)*
Ciprofloxacin◇	400 mg intravenously every 8 hours, or 750 mg orally every 12 hours
Levofloxacin◇	750 mg intravenously or orally once daily
Trimethoprim-sulfamethoxazole§	Cystitis: 1 double-strength tablet (trimethoprim 160 mg and sulfamethoxazole 800 mg) orally twice daily
Second-line agents	
Colistin (colistimethate)¥	**Intravenous dose:** Loading dose of 300 mg CBA (equivalent to approximately 9 million units colistimethate sodium), followed by a daily maintenance dose of 300 to 360 mg CBA (approximately 9 to 11 million units colistimethate sodium) divided into 2 doses infused over 1 hour **Inhaled dose:** 75 to 150 mg CBA (2.25 to 4.5 million units) every 12 hours
Polymyxin B	Loading dose of 2 to 2.5 mg/kg (20,000 to 25,000 units/kg), followed by 1.25 to 1.5 mg/kg (12,500 to 15,000 units/kg) every 12 hours; doses should be based on total body weight
Minocycline‡	200 mg intravenously or orally every 12 hours
Doxycycline‡	100 mg intravenously or orally every 12 hours
Tigecycline‡	Mild infections and carbapenem-susceptible infections: 100 mg loading dose, followed by 50 mg intravenously every 12 hours Moderate to severe carbapenem-resistant infections: 200 mg loading dose, followed by 100 mg intravenously every 12 hours
Cefiderocol	2 g intravenously every 8 hours (infuse each dose over 3 hours); in patients with creatinine clearance ≥120 mL/minute, administer 2 g intravenously every 6 hours (infuse each dose over 3 hours)
Agents typically used in combination with another agent	
Gentamicin◇†	Cystitis: 5 mg/kg/dose intravenously for 1 dose Infections other than cystitis: 7 mg/kg/dose intravenously for first dose with subsequent doses and dosing intervals based on pharmacokinetic evaluation
Tobramycin◇†	Cystitis: 5 mg/kg/dose intravenously for 1 dose Infections other than cystitis: 7 mg/kg/dose intravenously for first dose with subsequent doses and dosing intervals based on pharmacokinetic evaluation
Amikacin◇†	Cystitis: 15 mg/kg/dose intravenously for 1 dose Infections other than cystitis: 20 mg/kg/dose intravenously for first dose with subsequent doses and dosing intervals based on pharmacokinetic evaluation

Recommended dosages of antimicrobial agents administered by the intraventricular route

Antimicrobial agent	Daily intraventricular dose
Amikacin	5 to 50 mg*
Colistin	10 mg colistimethate sodium (CMS), which corresponds to: ▪ 125,000 international units of CMS **or** ▪ 4.2 mg colistin base activity (approximately)¶
Daptomycin	2 to 5 mgΔ
Gentamicin	1 to 2 mg◇ in children 4 to 8 mg◇§ in adults
Polymyxin B	2 mg in children 5 mg in adults
Quinupristin/dalfopristin	2 to 5 mg
Tobramycin	5 to 20 mg
Vancomycin	5 to 20 mg◇§¥

There are no specific data that define the exact dose of intraventricular antimicrobial agents that should be used in cerebrospinal fluid (CSF) shunt and drain infections. Given the smaller CSF volume in infants (approximately 50 mL) compared with adults (approximately 125 to 150 mL), doses in infants should probably be decreased at least 60% or more compared to adults. Antibiotics given through the intrathecal or intraventricular route should be preservative free. *UpToDate Editor's Note:* Pediatric data are limited; consultation with a pediatric infectious diseases specialist is advised.

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* The usual intraventricular dose is 30 mg daily.

¶ The formulation available in the United States is measured as colistin base activity. The total daily dose can be administered as one daily dose or divided into two doses given every 12 hours.

Δ One study used 10 mg every day for 2 days and then 10 mg every 48 hours. Another study used 5 mg or 10 mg every 72 hours. Data are based on isolated case reports.

◇ Recommendations for frequency of administration based on external ventricular drain output over 24 hours as follows:

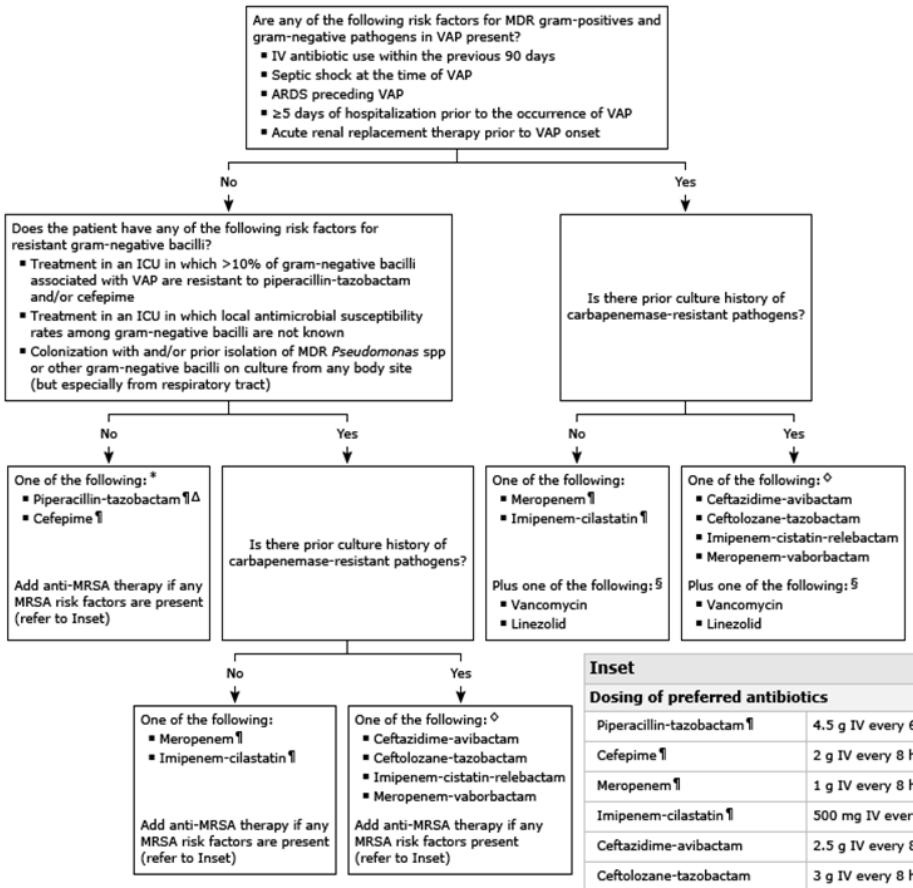
- <50 mL/24 hours: Every third day.
- 50 to 100 mL/24 hours: Every second day.
- 100 to 150 mL/24 hours: Once daily.
- 150 to 200 mL/24 hours: Increase the dosage by 5 mg of vancomycin and 1 mg of gentamicin and give once daily.
- 200 to 250 mL/24 hours: Increase the dosage by 10 mg of vancomycin and 2 mg of gentamicin and give once daily.

§ Dosage recommendations in adults based on ventricle size/volume as follows:

- Slit ventricles: 5 mg vancomycin and 2 mg gentamicin.
- Normal size: 10 mg vancomycin and 3 mg gentamicin.
- Enlarged ventricles: 15 to 20 mg vancomycin and 4 to 5 mg gentamicin.

¥ Most studies used a 10 mg or 20 mg dose.

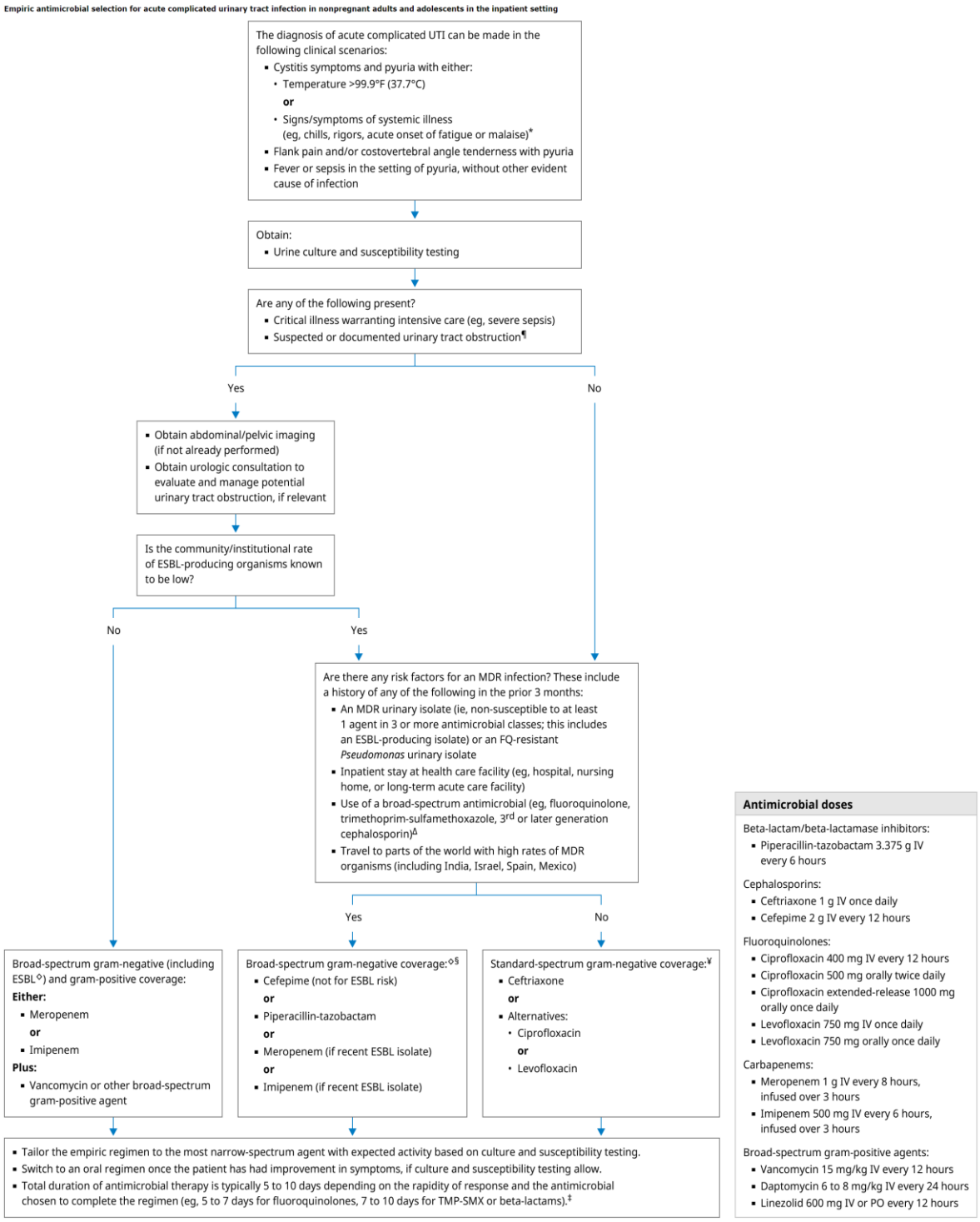
Empiric treatment of ventilator-associated pneumonia (VAP) in adults with normal kidney function



Inset

Dosing of preferred antibiotics	
Piperacillin-tazobactam ¶	4.5 g IV every 6 hours
Cefepime ¶	2 g IV every 8 hours
Meropenem ¶	1 g IV every 8 hours
Imipenem-cilastatin ¶	500 mg IV every 6 hours
Ceftazidime-avibactam	2.5 g IV every 8 hours
Ceftolozane-tazobactam	3 g IV every 8 hours
Imipenem-cilastatin-relebactam	1.25 g IV every 6 hours
Meropenem-vaborbactam	4 g IV every 8 hours
Add anti-MRSA therapy if patient has one of the following risk factors for MRSA: ▪ Treatment in a unit in which >10 to 20% of *S. aureus* isolates associated with VAP are methicillin resistant ▪ Treatment in a unit in which the prevalence of MRSA is not known ▪ Colonization with and/or prior isolation of MRSA on culture from any body site (but especially the respiratory tract)	
Anti-MRSA therapy consists of one of the following: §	
Vancomycin	Generally 15 to 20 mg/kg every 8 to 12 hours for most patients with normal kidney function. Interval adjustments should be based on AUC-guided (preferred) or trough-guided serum concentration monitoring. The vancomycin loading dose is based on actual body weight; the dose is rounded to the nearest 250 mg increment and not exceeding 2000 mg. Within this range, we use a higher dose for critically ill patients.
Linezolid	600 mg IV every 12 hours

Treatment for Urinary Tract Infection



What could be the possible Drug interaction ?

- Medication given on **26/07/2024**, including **Pantoprazole, Valproate, Lacosamide, Levetiracetam, Paracetamol, Thiopentone Sodium, Midazolam, Acyclovir, Meropenem, Dexamethasone, Lamotrigine, Zonisamide, Pyridoxine, Biotin, Naproxen, Clobazam, Ketamine, and Vancomycin**, the following are the key **drug-drug interactions** that may occur:

1. **Valproate and Meropenem**:

Meropenem can significantly reduce **Valproate** levels, potentially leading to loss of seizure control. **Valproate** efficacy is diminished due to faster elimination caused by Meropenem.

2. **Valproate and Lamotrigine**:

Valproate increases **Lamotrigine** levels, raising the risk of **Lamotrigine** toxicity (e.g., rash or severe skin reactions like Stevens-Johnson syndrome). Dose adjustment or close monitoring of **Lamotrigine** is necessary.

3. **Lacosamide and Clobazam**:

Combining **Lacosamide** with **Clobazam** can increase CNS depressant effects, leading to enhanced sedation and dizziness. Monitoring for excessive sedation is important.

4. **Midazolam and Thiopentone Sodium**:

Both drugs are CNS depressants, and using them together increases the risk of respiratory depression, excessive sedation, and hypotension. Continuous monitoring of respiratory and cardiovascular function is essential.

5. **Acyclovir and Vancomycin**:

Both drugs have nephrotoxic potential, especially when used together in high doses or in patients with pre-existing kidney dysfunction. Monitoring kidney function is important to avoid renal toxicity.

6. **Lamotrigine and Levetiracetam**:

Although no direct pharmacokinetic interactions are documented, the combined use of **Lamotrigine** and **Levetiracetam** can increase the likelihood of CNS side effects, such as dizziness, drowsiness, and fatigue.

7. **Paracetamol and Naproxen**:

While both drugs are commonly used together for pain relief, long-term or high-dose use increases the risk of liver and gastrointestinal toxicity. **Pantoprazole** is being used here to mitigate GI risks, but monitoring liver function and limiting prolonged use is important.

8. **Clobazam and Ketamine**:

Both drugs can increase CNS depression, which may result in excessive sedation, confusion, or even respiratory depression when used together. Careful titration and monitoring of the doses are necessary.

9. **Dexamethasone and Naproxen**:

Both drugs increase the risk of gastrointestinal bleeding or ulceration, even with **Pantoprazole** providing protection. Close monitoring for signs of GI bleeding is recommended.

10. **Acyclovir and Valproate**:

Acyclovir may increase the risk of **Valproate**-induced neurotoxicity, particularly in high doses or with pre-existing renal impairment. Monitoring for symptoms such as confusion or agitation is advised.

11. **Thiopentone Sodium and Midazolam**:

Both are sedatives that depress the central nervous system (CNS), which may lead to excessive sedation or respiratory depression if used concomitantly. This combination requires continuous respiratory and cardiac monitoring.

12. **Levetiracetam and Clobazam**:

While **Levetiracetam** and **Clobazam** don't have a direct interaction, their combined CNS effects can heighten drowsiness, dizziness, and coordination problems, requiring close observation for sedation.

13. **Valproate and Clobazam**:

Valproate can increase the plasma concentration of **Clobazam**, leading to enhanced sedative effects. Close monitoring for increased drowsiness or respiratory depression is necessary.

- Medication regimen on **27/07/2024**, Injection Heparin added to the treatment,

Heparin and Dexamethasone/Naproxen:

Heparin (an anticoagulant) combined with **Dexamethasone** or **Naproxen** (both increase bleeding risk) heightens the risk of **gastrointestinal bleeding** or other haemorrhagic events. Regular monitoring of clotting factors (e.g., aPTT for heparin) is necessary to prevent adverse bleeding events.

Heparin and Ketamine:

There is a theoretical risk of increased bleeding with **Heparin** in patients receiving **Ketamine**, particularly during invasive procedures, due to its anticoagulant properties.

Heparin and Meropenem:

Although no direct interaction is known, caution is advised when **Heparin** is administered with antibiotics like **Meropenem** due to potential bleeding risks.

- On **28/07/2024 to 29/07/2024**, consisting of **Doxycylcine, Perampanel, and Propofol**, added here are the important **drug-drug interactions** to be aware of:

Doxycycline and Calcium/Magnesium

Mechanism: Calcium and Magnesium can decrease Doxycycline absorption when taken concurrently.
Clinical Impact: Separate administration times or monitor Doxycycline efficacy for infections.

Propofol and Midazolam:

Both **Propofol** and **Midazolam** are sedatives that act on the CNS, and their combined use can cause **profound sedation**, respiratory depression, and hypotension. This requires close monitoring of respiratory and cardiovascular status during use.

Perampanel and Clobazam:

Perampanel, a glutamate receptor antagonist, when combined with **Clobazam** (a benzodiazepine), can lead to increased CNS depression and sedation. Monitoring for excessive sedation or dizziness is crucial.

Valproate and Perampanel:

Valproate may increase the concentration of **Perampanel**, enhancing the risk of side effects such as dizziness, fatigue, and aggression. Careful monitoring for CNS effects is important, and dose adjustments may be necessary.

Heparin and Propofol:

No direct interaction is noted, but caution is advised due to **Heparin's** anticoagulant properties, especially if **Propofol** causes prolonged sedation or impairs patient movement, increasing the risk of clotting or bleeding complications.

Propofol and Ketamine:

Both agents affect CNS sedation and anaesthesia. **Ketamine** has dissociative properties, while **Propofol** is a sedative-hypnotic. When combined, they can cause enhanced CNS effects, including deep sedation, requiring careful titration and monitoring of cardiovascular function.

- Treatment given on **30/07/2024** Propofol stopped and Calcium Gluconate .
- For the **31/07/2024** Perampanel and clobazam stopped.
- For the **01/08/2024-02/08/2024** drug regimen Acyclovir and Heparin stopped.
- On the treatment of **03/08/2024-05/08/2024** Doxycyclin stopped.
- The combination of drugs administered on **06/08/2024**, Paracetamol stopped, Phenobarbitone, Magnesium sulphate, Methyl prednisolone, Domeperidone , Minocycline , IV IG ,Ampicillin sulbactam added to treatment here are key drug-drug interactions and their potential effects:

Domperidone and Ketamine

- **Mechanism**: Concurrent use may increase QT prolongation risk.
- **Clinical Impact**: Consider alternative antiemetics or monitor ECG if both are necessary.

Ampicillin-Sulbactam and Calcium Gluconate

- **Mechanism**: These drugs can form insoluble complexes when co-administered intravenously.
- **Clinical Impact**: Avoid mixing in the same IV line; flush lines thoroughly to prevent crystallization.
- On **07/08/24-08/08/24**, Meropenem stopped and phenobarbitone started. Analysis on key interactions:

Phenytoin and Phenobarbitone: Both can lower Valproate levels by enzyme induction, reducing its effectiveness in seizure control. Valproate, in turn, can increase free Phenytoin levels, raising toxicity risks.

Ampicillin-Sulbactam with Calcium Gluconate

Mechanism: Risk of precipitation if administered through the same IV line.
Clinical Advice: Use separate lines or thoroughly flush between administrations to prevent line clogging.

- On **09/08/24**, Tranexamic Acid here are significant drug-drug interactions, along with their mechanisms and potential clinical implications:

Tranexamic Acid with Antiepileptic Drugs (Phenytoin, Valproate)
Mechanism: Tranexamic Acid can lower the seizure threshold, potentially counteracting the anticonvulsant effects of medications like Phenytoin and Valproate.
Clinical Impact: Use cautiously, and consider seizure monitoring if clinically indicated.

Intravenous Immunoglobulin (IV IG)
Mechanism: IV IG can interact with various medications, influencing immune response and drug metabolism, but specific direct interactions may be limited.

Biotin and Antiepileptics (Valproate, Phenytoin)
Mechanism: Long-term use of antiepileptic drugs can reduce biotin levels, potentially requiring supplementation for deficiency prevention.

- On-**10/08/24**, Tranexamic acid , methyl prednisolone stopped, Domperidone and minocycline last dose.
- On- **11/08/24- 12/08/24**, calcium gluconate , Ampicillin-sulbactam, minocycline last dose
- Combination on **13/08/24–14/08/24**, No new drug added.
- On **15/08/24**, Pipatazedime 1 dose given. What could be the possible interaction?

Doxycycline with Magnesium, Naproxen, and piptazidime (Pip-Taz)
Magnesium: Can reduce Doxycycline absorption. Administer Doxycycline separately by two hours if possible.
Naproxen: Increased GI irritation risk with Naproxen, which Pantoprazole may help mitigate.
PipraTazidime: While there is no direct severe interaction, the combination with Doxycycline might require dosing adjustments to avoid competitive binding in infections.

- On **16/08/24-19/08/24** Meropenem added to the treatment again .What could be the possible interaction?

Meropenem with Valproate
Mechanism: Meropenem can decrease Valproate's serum levels significantly, potentially lowering its anticonvulsant efficacy and leading to seizure breakthrough.
For the listed medications from **20/08/2024**, Potassium chloride, Human albumin possible drug interaction.

Potassium Chloride and CNS Depressants
Mechanism: Caution is necessary as both magnesium sulfate and potassium chloride influence electrolyte balance, which, combined with CNS depressants, may complicate neuromuscular function.

Human Albumin and Potential Electrolyte Shifts
Mechanism: Albumin can alter drug binding in plasma, potentially impacting free levels of drugs like valproate, phenytoin, and lamotrigine.

New Onset Refractory Status Epilepticus (NORSE) and Super-Refractory Status Epilepticus (SRSE):

NORSE is a condition that occurs suddenly without any known prior neurological condition, it has leads to **super-refractory status epilepticus (SRSE)**, where seizures persist despite aggressive treatment, including multiple anticonvulsants, anaesthetics, and immunotherapy. As we have seen in case scenario that progression of seizures continued even after administering high doses of **levetiracetam**, **valproate**, **phenobarbital**, and other sedative agents like **propofol** and **ketamine**.

The use of **immunotherapy (IVIG)** and autoimmune panels suggests disease might be an autoimmune origin for NORSE, which is common in such cases. Autoimmune encephalitis and antibodies like **anti-GABA** are often involved in NORSE, but it found to be negative and despite with treatment, the condition can remain unresponsive.

2. Complications of Sepsis and Multi-Organ Involvement:

Sepsis played a significant role in deteriorating health while Prolonged mechanical ventilation, combined with **pneumonia**, and infections from organisms like **Acinetobacter baumannii**, **Pseudomonas**, and **Providencia**, worsened his prognosis, Sepsis had caused systemic inflammation, leading to **septic shock**, a critical condition that involves widespread tissue damage and organ failure. This lead to immediate cause of death.

Ventilator-associated pneumonia (VAP) is a common complication in patients due to long-term mechanical ventilation. In the case scenario, pneumonia, detected in his right upper lobe, contributed to worsening

his respiratory status and sepsis. VAP increases mortality risks significantly, especially in patients already weakened by underlying conditions like SRSE.

3. Complex Pharmacological Management and Drug Interactions:

Managing SRSE requires the use of multiple drugs with potential for interactions. In this case, the concurrent use of **valproate** with **meropenem** is known to reduce valproate levels, which may have impacted seizure control. Similarly, prolonged use of **propofol**, **ketamine**, and **thiopentone sodium** introduces risks of hypotension, metabolic acidosis, and long-term sedation-related complications.

The LFT AND KFT derangement may also have challenges in balancing anticonvulsant efficacy with the management of this infections. The use of broad spectrum antibiotics (including **meropenem**, **vancomycin**, and **ampicillin-sulbactam**) aimed at targeting multi-drug resistant organisms also increased the risk of **nephrotoxicity** and **electrolyte imbalances**, as evidenced by his high **sodium levels**.

4. Infective and Autoimmune Contributions:

NORSE usually has an unclear etiology, with infections or autoimmune triggers being common culprits. In this case, **Acinetobacter baumannii**, a multi-drug resistant organism, was identified in blood cultures. However, given the bilateral limbic encephalitis findings and the use of autoimmune panels (GABA-A, GABA-B, LG-1), proves the diseases likely considered an autoimmune contribution as well.

5. Prognosis in Refractory Epileptic Syndromes:

The prognosis of NORSE, especially when it turns into SRSE, is extremely poor. **Mortality rates** can reach up to 30%, with survivors often experiencing long-term neurological sequelae. The aggressive treatment protocols involving **deep sedation**, **antiepileptic polytherapy**, and immunotherapy reflect the desperate attempts to control the condition, but the complications of infections, multi-organ failure, and drug toxicity often tip the balance toward a poor outcome.

II. Conclusion:

This case of NORSE evolving into SRSE underscores the challenges of managing refractory epileptic syndromes, especially when complicated by sepsis and multi-drug resistant infections. Due to Prolonged treatment with multiple medication the Patient health first improved but than started deteriorating as he was not able to maintained oral feed . Multiple medication with their interaction may had decreased the effectiveness of individual drugs, and patient also acquired infection during the course of treatment which had further regress his health progress, leading to ventilatory associated pneumonia causing death due to Septic Shock .

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References

[1] Treatment Flowchart Uptodate