IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 11 Ser.6 (November. 2022), PP 06-11
www.iosrjournals.org

Septic Encephalopathy Treatment in the Intensive Care Unit

Sitti Ziarah[1], Faisal[2]

[1] *Anesthesiology and Intensive Therapy Sub-specialist Physician Education Program, Hasanuddin University, Makassar, Indonesia*

[2] *Intensive Care Unit of Wahidin Sudirohusodo Hospital, Anesthesiology and Intensive Therapy Sub-specialist Physician Education Program, Hasanuddin University, Makassar, Indonesia*

Abstract

Background: *It is a case report of septic encephalopathy in the Intensive Care Unit (ICU) at the Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, Indonesia. Male, 60 years old, admitted to ICU after emergency surgery debridement pedis dextra et causa diabetic ulcer.*

Case Description: *Initial condition Glasgow Coma Scale/GCS 12 (E4M4V4, E = eye, M = motoric, V = verbal), oxygen NRM (non-rebreathing mask) 8 litres/minute, oxygen saturation (SpO_2) 100%, 30 breaths/minute,and hemodynamically stable. Laboratory white blood cell (WBC) 29.300 $10^3/\mu L$, hemoglobin (Hb) 9.4 g/dL, blood glucose (GDS) 78 mg/dL, creatinine (cr) 2.01 mg/dL, urea (ur) 151 mg/dL, albumin 2.3 g/dL, procalcitonin (PCT) 2.82 ng/mL, CRP 44.3 mg/L. Blood gas analysis (AGD) pH 7, 495, $pO_2$151, pCO_2 24.8, $HCO_3$19.3, Pf ratio 290. Radiographsof right thorax pneumonia and right pleural effusion producea sequential organ failure assessment (SOFA) score of 8: and an acute physiology and chronic health evaluation (APACHE II) score of 20.A score of confusion assessment method-intensive care unit (CAM-ICU) was not performed.*

Results: *Treatment for 13 days, mechanical ventilation for 5 days, the condition improved and moved to usual care.*

Conclusion: *Septic encephalopathy treatment can provide the closest guidance to support therapy in providing better outcomes for management in the ICU.*

Key Word: *Septic encephalopathy, emergency surgery, mechanical ventilation*

Date of Submission: 06-11-2022 Date of Acceptance: 20-11-2022

I. Introduction

Sepsis is one of the leading causes of the deadliest disease in the world. Globally, sepsisleads to death is 19.7% annually. In the previous decade, significant changes have been made to improve the management of sepsis. However, in neurology, the function and consequences of sepsis are still elusive. It includes long-term organ dysfunction and neurological damage,which is still debatable.It has a major influence on the sustainability of quality of life.[1]

Sepsis associated with complications is a major problem in health care. Sepsis-associated encephalopathy (SAE = sepsis-associated encephalopathy). Generally, it causes changes in mental status for patients admitted to the Intensive Care Unit (ICU) with severe infection ranging from 8-70% according to diagnostic criteria. Other literature shows the incidence of SAE in the ICU as 9-71%.[2] Septic encephalopathy is associated with the highest mortality rate, although this condition can improve. As for its life expectancy, a long-term cognitive impairment, impaired affective function, verbal learning and memory, life quality, and inability to work were also reported.[1]

II. Case Description

Male patient 60 years old with medical record 5***6, height/weight (TB/BB): 165 cm/65 kg, Body Mass Index (BMI)/Predicted Body Weight (PBW): 23.8 kg/m2 (normof weight)/63 kg. The patient was admitted to ICU (19/05/2022), and he refers from the emergency operating room after conductingdebridement et causa diabetic ulcer dextra. It used MAC anesthesia (monitoring anesthesia care) and local anesthesia during surgery. The operation was conducted for approximately 30 minutes. The initial condition when the patient was admitted to the ICU with the patient breathing spontaneously and adequately, hemodynamically stable, somnolent consciousness with Glasgow Coma Scale/GCS 12 (E4M4V4, E = eye, M = motoric, V = verbal), round pupil size isocor 2.5 mm right and left. Then, there is a light reflex, the temperature is 36.7^oC, with

oxygen therapy using NRM (non-rebreathing face mask) 8 liters/minute. That process obtained 100% oxygen saturation (SpO2) with a respiratory rate of 30 x/minute, vesicular breath sounds, no rhonchi/wheezing, blood pressure (BP) 123/66 mmHg, mean arterial pressure 88 mmHg without support, pulse 77 beats per/minute regular. The patient was diagnosed with septic encephalopathy + diabetic ulcer dextra post-op debridement + anemia + acute kidney injury (AKI) + hypoalbuminemia. Significant laboratory (17/5/2022) white blood cell (WBC) 29.300 103/µL, Hemoglobin (Hb) 9.4 g/dL, blood glucose 78 mg/dL, creatinine (cr) 2.01 mg/dL, urea 151 mg/dL, albumin 2.3 g/dL, procalcitonin (PCT) 2.82 ng/mL, CRP 44.3 mg/L. Arterial Blood Gas (ABG) analysis resulted in pH 7, 495, pO2 151, pCO2 24.8, HCO3 19.3, and Pf ratio 290, with an interpretation of respiratory alkalosis. Chest X-ray (10/05/2022) with the hypothesis of right pneumonia and right pleural effusion. The sequential organ failure assessment (SOFA) score was 8, with a mortality rate of 15-20%,[3]. The acute physiology and chronic health evaluation (APACHE II) score were 20 with a mortality rate of 40%,[3,] and a confusion assessment method-intensive care unit score (CAM- ICU) was not performed.[1,4,5,6]

Initial therapy was given intravenous fluid drug (IVFD) Ringer's lactate (RL) 1000 cc compared to dextrose (Dext) 5% 500 cc per 24 hours, antibiotic meropenem 1 gram (gr) every 8 hours intravenously (iv), metronidazole 500 milligrams (mg) (IV) per 8 hours per iv, tranexamic acid 500 mg per 8 hours per iv, metamizole 500 mg per 8 hours per iv, ranitidine 50 mg per 8 hours per iv, checking gds per 24 hours with a target of 120-180 g/dl and the patient has temporarily fasted. Data on patient care days in the ICU takes place from May 19th, 2022, to May 31st, 2022.

III. Results and Discussion

The main diagnosis used in this case refers to septic encephalopathy. SAE is a severe brain dysfunction with clinical features ranging from altered mental status to coma. The clinical manifestations include changes in mental status, agitation, delirium, and coma. Definitive diagnosis is difficult because there must be specific radiological and biological criteria,not specific clinical manifestations.[1] Clinical support for the patient's mental status is characterized by GCS changes initially admitted with GSC 12. Huang Y et al.,[2] Lower GCS was found in SAE than in those without SAE. One of the main symptoms of SAE is delirium.Although delirium is not only clinical SAE, it is also found in other diseases.[1] Delirium accompanied by changes in behavior and mental status is assessed using the CAM-ICU score. However, evaluation using this score is not sensitive enough to detect the full spectrum of SAE.[1] In this patient, the CAM-ICU delirium score was not performed. In another reference,[2] SAE is defined as an exclusive diagnosis. Before being diagnosed, the effect of the drug must be ruled out. In addition, other potential causes of encephalopathy, such as primary disease of the CNS (central nervous system) and causes of abnormal brain function leading to dysfunction of other organs (such as liver, kidney, lung, and heart), should be ruled out. In clinical practice in the ICU, the GCS scale and delirium score are often used to determine the patient's condition, course of SAE, and prognosis. In this case, a wound was found on the right leg with a suspected diabetic ulcer, and debridement was performed. However, the course of the comorbidities of diabetes mellitus is not found. In references[2] mentioned, a clinical study revealed that insulin therapy as a neuroprotector affects SAE. Hyperglycemia in SAE is thought to be associated with increased oxidative stress and apoptosis. An animal experiment showed that inhibiting nitric oxide (iNOS) synthesis could prevent lipopolysaccharide (LPS) induced neuronal apoptosis. In this case, no insulin was given. Regarding the SOFA score and APACHE II score, in this case, the SOFA score was 8, the mortality rate was 20%, the APACHE II score was 20, and the mortality rate was 40%. Chen et al. 8 suggested the advantage of SOFA and APACHE II scores in assessing the severity and prognosis of critically septic patients concerning encephalopathy. However, there is a mortality rate, while Huang Y et al.,[2] cited higher APACHE II scores in SAE patients. Another study by Xu et al.[9] regarding the performance of SOFA scores in post-cardiac arrest patients in the ICU concluded that SOFA scores >7 are an early warning for poorer outcomes.

How about other investigations, such as CT/MRI (computerized tomography/magnetic resonance imaging) and EEG (electroencephalogram)? In this case, not all examinations were performed. Huang et al. summarized a table containing the diagnostic findings in SAE.[2]

Table 1. Diagnostic Findings in SAE[2]

Author and Year	Total Patient	Diagnostic method	Finding
Young et al 1992	62	EEG	SAE severity related to the severity of abnormality on the EEG Delta Wave suppression associated with mortality TWs wave associated with mortality
Sharshar et al. 2007	9	MRI	White matter hyperintensity, ischemic lesion
Suchtya et al. 2010	64	CT/MRI	White matter hyperintensity Brain atrophy Edema hemorrhagic focal

Polito et al., 2013	71	MRI/EEG	White matter hyperintensity Ischemic lesions Chronic malignant EEG waves Acute leukoencephalopathy and brain ischemia
Sutter et al 2013	105	EEG	Theta/delta associated with poor outcome TWs associated with severely altered consciousness and high mortality
Kurtz et al 2014	154	cEEG	PEDpersistent s > 24 hours associated with poor outcome NCSE associated with poor outcome
Orhun et al., 2020	93	MRI	White matter hyperintensity Ischemic lesions Brain atrophy (limbic structures)

Another reference, Heming et al., suggested that MRI may also seem normal in SAE. However, features of focal injury such as white matter hyperintensity and ischemic stroke may also be found.[10] Chung et al., in 52% of cases of SAE with severe symptoms, cerebral imaging that was not found isnot significant, especially in the acute phase. No specific features were found pathologically, occurring in other diseasesnot associated with sepsis.[6] Chung et al. also noted no EEG abnormalities specific to SAE. In theory, they suggest that grey matter or white matter activates microglia, and an increase in microglia has a protective role in the brain and neuronal damage.[6]

What about other medical checkups? Are they available? Giovampaola et al. suggested that several biomarkers related to SAE and neuroinflammation, including NSE (neuron-specific enolation) > 12.5 µg/L, can increase 23-29% risk of 30-day mortality and delirium, *S-100Β-protein*< 4µg/ L. It indicates severe brain ischemia and the presence of hemorrhage. NT-pro CNP can be found with high values in the setting of sepsis, accompanied by high IL-6 (interleukin-6).[1] Chung et al.explained several studies using cerebrospinal fluid biomarkers Specifically associated with the diagnosis and long-term outcome of SAE. The limited protein elevation shows local inflammation or damage to the BBB (blood-brain barrier) without synthesizing specific immunoglobulins. Relate to this case. No examinationwas performed.[6]

Czempik et al., 2020, introduced the term SABD (sepsis-associated brain dysfunction), one of the most common types of encephalopathy in the ICU, which 70% develop into septic encephalopathy. Czempik et al. state that the other examinations that may assist the diagnosis are transcranial Doppler and ONSD (optic nerve sheath diameter) examinations. In this case, there is no such examination performed. Transcranial Doppler to detect changes in cerebral blood flow, with a pulse index >1.3 at 24 hours,indicates brain dysfunction in sepsis. Meanwhile, ONSD can detect increased intracranial pressure in septic patients, but the number of abnormalities is not stated.[11] Suresh said that ONSD measurements correlated with SAE results. Itresults innumbers > 5,5 mm that can detect the SAE.[12]

What is the relationship between clinical and laboratory trends and the incidence of SAE? Here are the trends in the form of table 2 and graph 1, showing changes in GCS, temperature, mechanical ventilation, WBC, PLT, CRP, and PCT during ICU treatment. Laboratory trends and changes in GCS, temperature, the use of mechanical ventilation, WBC, PLT, CRP, and PCT can be seen in table 2 and graph 1 below.

Table 2.

Trends in changes in GCS, temperature, the use of mechanical ventilation, WBC, PLT, CRP, and PCTduring treatment in the ICU

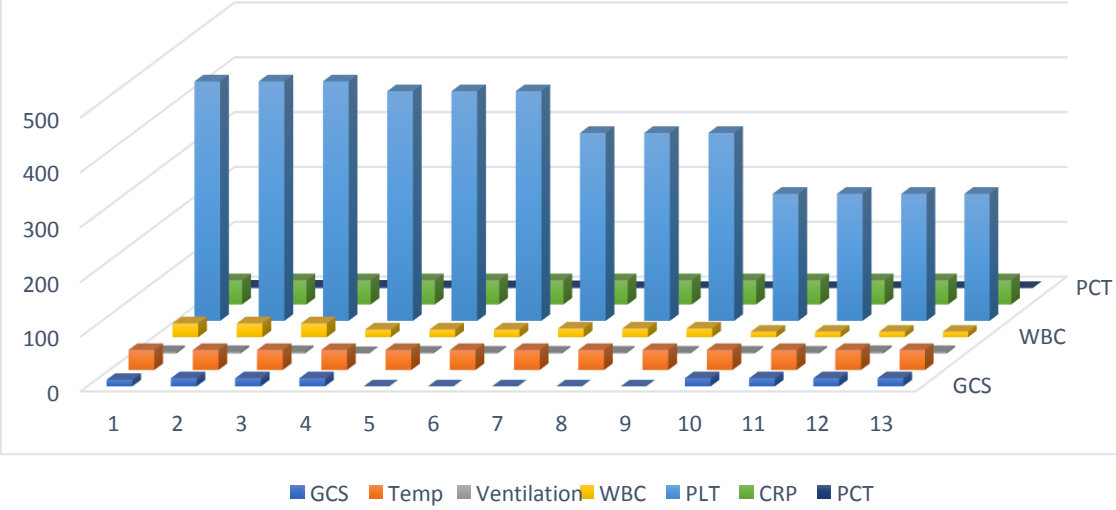
Day Care	GCS	Temperature	Ventilation	WBC	PLT	CRP	PCT
1	12	36.7	3	25.5	437	44.3	2.82
2	15	36.7	3	25.5	437	44.3	2.82
3	15	36.7	3	25.5	437	44.3	2.82
4	15	36.7	1	14.2	419	44.3	1.9
5	0	36.7	2	14.2	419	44.3	1.9
6	0	36.7	2	14.2	419	44.3	1.9
7	0	36.7	2	16.0	343	44.3	0.4
8	0	36.7	2	16.0	343	44.3	0.4
9	0	36.7	2	16.0	343	44.3	0.4

10	15	36.7	2	10.2	232	44.3	0.4
11	15	36.7	2	10.2	232	44.3	0.4
12	15	36.7	3	10.2	232	44.3	0.4
13	15	36.7	3	10.2	232	44.3	0.4

Information:

0: under sedation, 1: using HFNC modality, 2: mechanical ventilation, 3: without mechanical ventilation, WBC and PLT: in units of 10^3

Graph 1. Trends in changes in GCS, temperature, the use of mechanical ventilation, WBC, PLT,



In 13 days of ICU treatment, from the beginning of admission on the first day and on the 13th day, it was planned to move to regular care. On day 4, using HFNC oxygen modality with oxygen saturation was 95%, and for five days, using mechanical ventilation. There was no significant change in temperature, and a decreasing trend of WBC and PCT was found, there was also a change in PLT, and CRP could not be assessed because only one measurement was performed.

Huang Y et al. suggested an association between mechanical ventilation and longer ICU stay in patients with SAE.[2] Zhao L et al., in their cohort study, showed that optimal oxygen therapy of 93%-97% would not increase the incidence of SAE, a saturation of between 92% -96% will not increase SAE mortality in hospitals, and the optimal target saturation for patients with SAE is 93%-96%.[13]

Tong DM et al. suggested that SAE is a brain dysfunction closely related to the inflammatory storm caused by sepsis.[14] In a topic on the cascade mechanism and consequences of inflammatory disorders. Megha KB et al. discussed the clinical aspects of trauma or sepsis. The unregulated synthesis and Interaction of anti-inflammatory mediators can cause multiple organ dysfunction. WBCs are important for the inflammatory response, providing infiltration of the circulatory system, a class of chemotactic constituents such as microbial endotoxin, complement fragment C5a, terminal amino group N-Formyl Methionyl, cytokines, platelet-activating factors, histamine, leukotrienes B1 intensely improve leukocyte infiltration to areas injury. As for cytokines, has the potential to be a regulator of inflammatory pathways that augment the response to infection or inflammation in complex interactions. Therefore, in contrast, uncontrolled cytokine production will lead to tissue damage, change in hematologic parameters, organ dysfunction/failure, and death.[15] Huang Y et al. described the potential pathophysiological mechanisms that follow the occurrence of SAE, played by inflammatory activation, mitochondrial dysfunction, oxidative stress damage to the cerebral microcirculation and BBB, which causes abnormalities in neurotransmitters, cell death program, which in turn leads to brain damage and dysfunction. Regarding inflammatory activity, It is known that tumor necrosis factor-ʃ (TNF-ʃ) and IL-6 have an essential role in the early stages of sepsis, causing microcirculation and BBB disorders which eventually lead to cell

damage and death and neurotransmitter disorders. IL-6 plays an important role in SAE. In glial cells, IL-6 increases the expression of cyclooxygenase 2 (COX 2) and prostaglandin synthesis. It is particularly linked to the hypothalamic-pituitary-adrenal axis and the prostaglandin E2 phase[2]. Molnar R et al. suggested that increased plasma levels of C-reactive protein (CRP) and PCT in septic and non-sepsis patients correlated with the duration of brain dysfunction after ICU treatment.[16] Chen J et al. suggested that patients with sepsis with comorbid hypertension have a more progressive risk of SAE.[8] In this case, there was no comorbid hypertension. A significant decrease in platelet count in SAE was also found in Chen et al.'s study, which showed that platelets participate in immune and inflammatory responses against various pathogens.[8] In this case, the platelet count has decreased since the initial admission to the ICU, but it is still within normal limits.

What about the SAE treatment in the ICU? Huang Y et al. state that there is currently no specific SAE therapy. In the early phase, related to the source of infection, appropriate treatment should be given.[2] Tong DM et al., regarding the use of antibiotics in the first 3 hours after admission to the ICU, can reduce the morbidity and mortality of SAE.[14]Since the first day in the ICU, the patient had received broad-spectrum antibiotics in meropenem 1 gram per 8 hours per iv. Giovampaola et al., clinical management can be in the form of septic restriction.The initial focus is detecting the source of infection, maintaining hemodynamic balance, and preventing metabolic disorders or neurotoxic drugs. SAE treatment becomes difficult because there is no specific therapy for SAE. Early clinical management and control of the source of infection, maintaining hemodynamic stability, optimization of organs, and cerebral perfusion. Supportive treatment includes symptomatic management of delirium and EEG monitoring. Identifying potential factors, such as acute renal failure and metabolic disturbances (hypo/hyperglycemia and hypernatremia), may decrease the development of SAE.[1]The prevention of delirium can be startedby eliminating/using sedation, especially benzodiazepines, reducing the incidence of delirium-associated sepsis, and introducing minimal sedation can become a benefit.[11] In this case, dexmedetomidine sedation was used. Dexmedetomidine, an alpha-2 agonist, has shown neuroprotective effects (inhibition of neuronal apoptosis, reduced septic inflammatory response, and reduced delirium) in septic patients compared to lorazepam, improving encephalopathy, improving ventilation time, and reducing mortality. For delirium control, you may use dexmedetomidine 0.2-0.7 g/kg/day or haloperidol 2-10 mg iv. If the RASS score is> 4, it is necessary to evaluate with the CAM-ICU. The examination can be done twice a day for the CAM-ICU score to assess delirium.[5]

Referring to the study proposed by Tong DM et al., the definition of SAE/SAE criteria included in their study sample was when they met at least 2 of the following 4 criteria: (1) patients with GCS scores < 15 or found diffuse abnormal EEG/brain topography, (2) presence of inflammatory clinical manifestations or inflammatory features with one or more organ dysfunction, (3) if brain dysfunction with extracranial organ failed (especially multiple organs), (4) if pure brain dysfunction (without extracranial organ failure), Cerebrospinal analysis fluid should be performed to exclude meningitis or direct encephalitis. The clinical manifestations used are SIRS (systemic inflammatory response syndrome) 2 criteria, which include: (1) temperature> 38^{o}C or <36^{o}C, (2) pulse > 90 per minute, (3) tachypnea > 20 per minute or PCO2 < 32 mmHg, (4) WBC > 12.0 x 109/L or < 4.0 x 109/L. The SOFA score was also calculated to indicate acute organ dysfunction with a value of 2.[14.] The data found in this case supported Tong DM et al.[14]. It includes GCS 12 (score < 15). These clinical manifestations met SIRS criteria≥ 2 (tachypnea 30 x/min, PCO2 24,8 mmHg, WBC 29.300 10^{3}/µl), SOFA score 8, and the chest radiograph showed right pneumonia. Other laboratory results found at the beginning of this case were ur value 151 mg/dL, cr 2.01 mg/dL, with urine production of 45 cc/hour (BB: 65 kg, production > 0.5 cc/hour), and albumin. 2.3 g/dL. The next therapy given is the diuretic furosemide / iv. Zhao et al. state that critically ill patients often use diuretics. Furosemide may support the restoration of kidney function. Theoretically, furosemide prevents AKI by decreasing glomerular filtration rate (GFR) and tubular action and reducing renal medullary oxygenation. In addition, it can also act as a renal vasodilator.[17]Then, for albumin, Bounden et al.state that albumin production is inhibited by pro-inflammatory mediators such as IL-6, IL-1, and tumor necrosis factor. Hypoalbumin can occur because of (rarely) decreased albumin production, increased albumin loss (lots of albumins lost) in the kidneys, gastrointestinal tract, skin, or extravascular space, or increased albumin catabolism or a combination of these mechanisms. In the case of sepsis, there is an increase in vascular permeability and capillary leakage resulting in loss of albumin from the intravascular compartment. In addition, there is a reduction in albumin synthesis and an increase in albumin catabolism. The use of albumin infusion in critically ill patients is still controversial regarding whether it will have the benefit or not.[18] Soeters PB et al., low serum albumin is an indicator of the severity of inflammation. Therefore, the focus of treatment is directed at the cause of the inflammation.[19]

In addition, there is little review of the term encephalopathy, i.e., sepsis-associated brain dysfunction unrelated to bacterial infection. Therefore, it is common to use the term "encephalopathy" rather than encephalitis. As for the current issue regarding this term, is "sepsis-associated encephalopathy" replaced with "sepsis-associated encephalitis"? (sepsis-associated encephalitis).[20] In addition, the term "sepsis-associated brain dysfunction" is also known, which is the most common type of encephalopathy in critically ill patients.

However, it is still relevant to use the term "sepsis-associated encephalopathy/SAE" 11. This term is also used in this case report.

IV. Conclusion

Although it is still difficult to diagnose Sepsis Encephalopathy in the Intensive Care Unit, with various approaches, it is expected that it can provide the closest guidance to support therapy in providing better outcomes for management in the Intensive Care Unit.

References

[1]. Giovampaola MD, CavalliI, MasciaL. Neuropsychological Outcome of Critically Patients with Severe Infection. Biomedicines 2022, 10, https://doi.org/10.3390/Biomedicines10030526.

[2]. Huang Y, Chen R, Jiang L, Lis, Xue Y. Basic Research and clinical Progress of sepsis- associated encephalopathy. Journal of Intensive Medicine 1 (2021) 90-95. https://doi.10.1016/j.jointm.2021.08.002.

[3]. Sean P, Kane B. 2018. Sequential Organ Failure Assessment (SOFA) Calculator-ClinCalc.com [online]. Retrieved: Juni 5, 2019, form:https://clincalc.com/icuMortality/SOFA.aspx

[4]. Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, et al. The CAM-ICU-7 DeliriumSeverity Scale: A Novel Delirium Severity Instrument for Use in the Intensive Care Unit. CritCareMed.2017May;45(5):851-857

[5]. Seo Y, Lee HJ, HaEJ, HaTS. 2021 KSCCM clinical practice guide line for pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit. Acute and Critical Care 2022February37(1):1-25.https://doi.org/10.4266/acc.2022.00094.

[6]. Chung HY, Wickel J, Brunk horst FM, Geis C. Sepsis-Associated Encephalopathy: From Delirium to Dementia? J. Clin.Med.2020, 9,703;doi:10.3390/jcm9030703.

[7]. Nair AS, Naik VM, Rayani BK. FAST HUGSBID: Modified Mnemonic for Surgical Patient. Indian J Crit Care Med 2017; 21:713-4

[8]. Chen J, Shi X, Diao M, Jin G, Zhu Y, Hu W dkk. A. retrospective study of sepsis-associated encephalopathy: epidemiology, clinical features, and adverse outcomes. BMC Emergency Medicine (2020)20:77. https://doi.org/10.1186/s12873-020-003743

[9]. Xu F, LiW, Zhang C, Cao R. Performance of Sequential Organ Failure Assessment and Simplified Acute Physiology Score II for Post-Cardiac Surgery Patients in Intensive Care Unit. Front. Cardiovasc. Med. (2021) 8:774935.doi:10.3389/fcvm.2021.774935.

[10]. Heming N, Mazeraud A, Verdonk F, Bozza FA, Chretien F, Sharshar T. Neuro anatomy of sepsis-associated encephalopathy. Critical care (2017) 21:65.DOI10.1186/s13054-017-1643-z

[11]. Czempik PF, Pluta MP, Krzych LJ. Sepsis-Associated Brain Dysfunction: A Review of Current Literature. Int. J. Environ Res. Public Health 2020, 17,5852;doi:10.3390/ijerph17165852

[12]. Suresh V. Optic nerves heath diameter guided detection of sepsis-associated encephalopathy. Critical care (2020)24:520.https://doi.org/10.1186/s13054-020-03232-7

[13]. Zhao L, Wang Y, Ge Z, Zhu H, Li Y. Optimal Oxygen Saturation Targets in Patients with Sepsis-Associated Encephalopathy: A Cohort Study from the MIMIC-IV Database. Research square. May7th, 2021. https://doi.org/10.21203/rs.3.rs-478223/v1.

[14]. Tong DM, Wang SD, Wang YW, Wang Y, Gu YY, Zhao YJ. Sepsis-associated Encephalopathy in ICU Admissions: Prevalence, Early risk of death, and its Early Prevent and Control. Research Square. August20th, 2020. https://doi.org/10.21203/rs.3rs58687/v1

[15]. Megha KB, Joseph X, Akhil P, Mohanan PV. Cascade of immune mechanism and consequences of inflammatory disorders. Phytomedicine 91 (2021)153712. https://doi.org/10.1016/j.phymed.2021.153712

[16]. Molnar R, Falesdi B, Nemeth N, Molnar C. Sepsis-associated encephalopathy: A literature review. Neurol India 2018; 66:352-61

[17]. Zhao G, Xu C, Ying J, Lu W, Hong G, Li Metal.Association between furosemide administration and outcomes in critically ill patients with acute kidney injury. Critical care (2020) 24:75. http://doi.org/10.1186/s13054-020-2798-6

[18]. Bounden V, Vaskisht R, Jialal. Hypo albuminemia. National library of medicine. 2022. June 19th

[19]. Soeters PB, Wolfe RR, Shankin A. Hypoalbuminemia: pathogenesis and clinical significance. JPEENJ Parenter Enteral Nutr. 2019; 43:184-193.

[20]. Mazeraud A, Bozza FA, Sharshar T. Sepsis-associated Encephalopathy is Septic. American Journal of Respiratory and Critical Care Medicine. 2018 March 15th. 197(6): 698-99.

Sitti Ziarah, et. al. "Septic Encephalopathy Treatment in the Intensive Care Unit." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(11), 2022, pp. 06-11.