ORIGINAL RESEARCH

Effects of Glucocorticoid-Assisted Continuous Blood Purification on Vital Signs in Patients with Septic Shock

Liyang Lu, MM; Da Liu, MM; Huaigang Xu, MM

ABSTRACT

Background • Septic shock poses a significant threat to life safety, with continuous blood purification as a primary treatment modality. Enhancing the therapeutic efficacy of continuous blood purification holds crucial implications for septic shock management.

Objective • This study aims to observe the therapeutic efficacy of glucocorticoid-assisted continuous blood purification (CBP) in septic shock patients, providing valuable insights for future clinical treatments.

Methods • A total of 200 septic shock patients admitted between October 2020 and January 2023 were selected and categorized into an observation group and a control group. The observation group (n=118) received glucocorticoid-assisted CBP, while the control group (n=82) received standard CBP. Changes in various parameters, including pH, blood urea nitrogen, serum creatinine, bicarbonate, inflammatory cytokines, T lymphocyte subsets, mean arterial pressure, pulmonary vascular permeability index, intrathoracic blood volume index, and cardiac index, were recorded before and after treatment. Complications during treatment were also documented.

Results • Post-treatment bicarbonate and cardiac index showed no significant difference between the two groups ($P > .05$). However, the observation group exhibited higher pH, mean arterial pressure, CD3+, CD4+, and CD8+ levels than the control group, as well as lower blood urea nitrogen, serum creatinine, inflammatory cytokines, and CD4+/CD8+ ratio ($P < .05$). Moreover, no notable difference in complication rates was identified between the groups ($P > .05$).

Conclusions • Glucocorticoids-assisted continuous blood purification therapy effectively improves vital signs and immune function in septic shock patients, offering a more reliable guarantee for patient life safety. (*Altern Ther Health Med.* 2024;30(10):327-331).

Liyang Lu, MM; Da Liu, MM; Huaigang Xu, MM; Department of Intensive Care Medicine, Shuyang County Hospital of Traditional Chinese Medicine, Suqian, Jiangsu, China.

Corresponding author: Huaigang Xu, MM
E-mail: xhuaigang@163.com

INTRODUCTION

Septic shock is characterized by an acute-onset, severe systemic disease that represents a septic syndrome with shock triggered by microorganisms and their products, including toxins.[1] In severe instances, it can lead to multiple organ failure, resulting in high mortality.[2] Research and studies indicate that sepsis occurs in approximately 2.36 per 100 000 people, affecting nearly 2.5 million individuals and imposing a substantial burden on both society and families.[3]

SS advances rapidly, manifesting primarily with a drop in blood pressure, unconsciousness, and cold/clammy skin.[4] Current major clinical treatments include fluid resuscitation, vasoactive drugs, antibacterial and antiviral agents, focal clearance, and organ support therapy.[4-5] Despite prompt intervention, the case fatality rate of SS patients remains as high as 40 to 50 percent.[5] Therefore, optimizing therapeutic schemes and discovering more effective treatments continue to be a prominent research focus in clinical practice.

Continuous blood purification (CBP) therapy is currently a widely utilized clinical treatment for SS. This therapeutic approach involves extracting the patient's blood, utilizing a purification device to eliminate harmful toxins, and supplementing plasma analogs to maintain normal blood flow.[6,7] The primary pathological mechanisms associated with organ failure and poor prognosis in SS patients are reported to involve immune dysfunction and systemic inflammatory response syndrome.[8]

Enhancing immune inflammatory indicators has become a crucial aspect of SS treatment. Clinically, glucocorticoids (GCs) stand out as commonly used anti-inflammatory and anti-shock agents.[9] However, it is noteworthy that in SS, the use of GCs is weakly recommended. In general terms, short-

acting GCs are recommended only for patients whose shock persists despite adequate resuscitation and vasopressor drug administration.[10]

As research progresses, an increasing body of evidence emphasizes that a significant number of deaths in severely infected patients occur after the elimination of pathogenic microorganisms.[11,12] It emphasizes that the key to determining the prognosis of SS patients does not solely rest on the primary infection, thereby necessitating a reevaluation of the role of GC therapy.[13]

Therefore, to understand and affirm the impact of GCs on SS, this study initiated a preliminary observation of the clinical effects of GC-assisted CBP in SS treatment. This study is aimed at providing valuable references and guidance for future clinical interventions.

MATERIALS AND METHODS

Study Design

An observational study was conducted, and a total of 200 SS patients admitted between October 2020 and January 2023 were selected and categorized into an observation group (OG) and a control group (CG). The observation group comprised 118 patients receiving GCs-CBP therapy, with an average age of (52.9±4.4) years. In contrast, the control group consisted of 82 patients undergoing CBP treatment, with a mean age of (52.6±4.4) years. The hospital's Medical Ethics Committee thoroughly reviewed and approved the study protocol, ensuring compliance with ethical standards. Additionally, all patients were adequately informed and provided signed informed consent.

Eligibility and Exclusion Criteria

The eligible patients were those diagnosed with SS[14] according to our hospital's criteria and had complete case data. Exclusion criteria encompassed individuals with dysfunction in vital organs such as the heart, kidney, liver, hematopoietic diseases, mental illness, autoimmune diseases, allergies, and/or intolerance to the studied drugs, as well as those with poor compliance. Additionally, patients with a history of glucocorticoid use within the last month were excluded.

Treatment Methods

Upon admission, both groups underwent routine treatment, anti-infective therapy, and mechanical ventilation support to maintain blood oxygen saturation above 95%. Additionally, invasive central venous pressure was monitored, and appropriate interventions, including fluid resuscitation, sedation, and analgesia, were administered. Vital signs were closely monitored throughout the treatment.

Bedside Hemofiltration in the Observation Group (OG). The OG received bedside hemofiltration with a purified replacement fluid flow rate set at 80 mL/(kg·h), and the blood flow was adjusted to 200 mL/min. Heparin served as the anticoagulant, and ultrafiltration volume was tailored to individual patient needs.

Glucocorticoid (GC) Administration in the Observation Group (OG). Simultaneously, GCs, specifically hydrocortisone sodium succinate (Yantai Dongcheng North Pharmaceutical Co., Ltd, H20084319), were administered intravenously twice a day, with a dosage of 100 mg each time, over a 7-day period.

Treatment in the Control Group (CG). Patients in the CG received treatment through bedside hemofiltration, employing the identical method as that utilized for the OG. Notably, no additional administration of GCs was provided in this group.

Specimen Collection and Testing

Arterial and Venous Blood Specimens. Arterial and venous blood specimens (3 mL each) were extracted from patients before and after treatment for comprehensive analysis. Arterial blood was utilized for blood gas analysis, with patient pH meticulously recorded.

Biochemical Analysis. For biochemical analysis, venous blood was processed through centrifugation (10 min after 30 min standing at room temperature, 3000 rpm/min) for the determination of blood urea nitrogen (BUN), serum creatinine (Scr), bicarbonate (HCO3-). Additionally, Enzyme-linked Immunosorbent Assay (ELISA) kits from Beijing Solarbio Biotechnology Co. were employed for the detection of interleukin (IL)-6, interleukin-10, and tumor necrosis factor-α (TNF-α).

Immunological Profiling through Flow Cytometry Analysis. Moreover, peripheral blood CD3+, CD4+, and CD8+ were subject to analysis by flow cytometry using the Partec Flow Cytometer CyFlow from Germany, with the subsequent calculation of the CD4+/CD8+ ratio.

Observation Indexes

Biochemical and Immunological Profiling. Changes in various parameters were systematically recorded to assess treatment efficacy. These included alterations in pH, blood urea nitrogen (BUN), serum creatinine (Scr), bicarbonate (HCO^{3-}), inflammatory cytokines (ICKs), and T lymphocyte subsets before and after treatment in both groups.

Hemodynamic Monitoring. Additionally, the study monitored changes in key hemodynamic indicators, encompassing mean arterial pressure (MAP), pulmonary vascular permeability index (PVPI), intrathoracic blood volume index (ITBVI), and cardiac index (CI).

Complications Surveillance. The study thoroughly documented complications during the treatment period. It encompassed events such as allergies, blood clots, and episodes of low blood pressure.

Statistical Analysis

Data analysis for this study was conducted using SPSS version 23.0 (IBM, Armonk, NY, USA). Differences in categorical variables (% representation) were assessed using chi-square tests (χ^2), while those pertaining to continuous variables (expressed as $\bar{x} \pm s$) were analyzed through independent sample t tests and

Table 1. Clinical Data of Patients

Variables	CG (n = 82)	OG (n = 118)	t/χ^2	*P* value
Gender			0.494	.482
Male	52(63.41)	69(58.47)		
Female	30(36.59)	49(41.53)		
Age	52.6±4.4	52.9±4.4	0.474	.636
BMI (kg/m²)	24.0±2.9	23.3±2.8	1.714	.088
Pathogenic Bacteria			0.167	.683
Gram-Positive	51(62.20)	70(59.32)		
Gram-Negative	31(37.80)	48(40.68)		
Diabetes Mellitus			1.687	.194
Yes	50(60.98)	61(51.69)		
No	32(39.02)	57(48.31)		
Hypertension			2.897	.089
Yes	55(57.89)	65(58.70)		
No	27(42.11)	53(41.30)		
Site of Infection			0.140	.987
Respiratory Tract	15(18.29)	23(19.49)		
Digestive Tract	18(21.95)	26(22.03)		
Blood	14(17.07)	18(15.25)		
Urinary Tract	35(42.68)	51(43.22)		
History of Previous Hospitalization			0.037	.847
Yes	77(93.90)	110(93.22)		
No	5(6.10)	8(6.78)		
APACHE II	15.45±5.63	15.88±5.57	0.532	.595
Body Temperature (°C)	37.24±1.17	37.47±1.27	1.313	.191
Heart Rate (times/min)	124.38±24.59	125.34±24.85	0.270	.787

Abbreviations: CG - Control Group; OG - Observation Group; BMI - Body Mass Index; APACHE II - Acute Physiology and Chronic Health Evaluation II.

paired *t* tests. A significance threshold of $P < .05$ was established for determining statistical significance.

RESULTS

Comparison of Patient Clinical Data

The statistical analysis covered the examination of general patient data, including gender, age, underlying diseases, and pathogens, between the two groups. No statistical differences were identified in these parameters ($P > .05$). Refer to Table 1 for detailed information.

Changes in Pre- and Post-Treatment Vital Signs

After treatment, both the OG and CG exhibited increased pH (Figure 1A), MAP (Figure 1B), and HCO^{3-} levels (Figure 1E). In comparison to CG, OG demonstrated significantly higher pH (Figure 1A) and MAP (Figure 1B) values ($P < .05$), while HCO^{3-} (Figure 1E) levels were comparable between the two groups ($P > .05$). Moreover, a decrease in BUN (Figure 1C) and Scr (Figure 1D) was noted, with OG showing lower levels than CG ($P < .05$).

Changes in Pulmonary Vascular Permeability Index (PVPI) Before and After Treatment

Before treatment, both the OG and CG exhibited a similar PVPI level ($P > .05$). After treatment, a notable reduction in PVPI was observed in both patient cohorts, with OG demonstrating an even lower level ($P < .05$). Concurrently, there was an increase in ITBVI in both cohorts, particularly prominent in OG ($P < .05$). Comparatively, CI was higher in OG than in CG after treatment ($P < .05$). Furthermore, within the Control Group, no significant changes in CI were noted before and after treatment ($P > .05$). Refer to Figure 2.

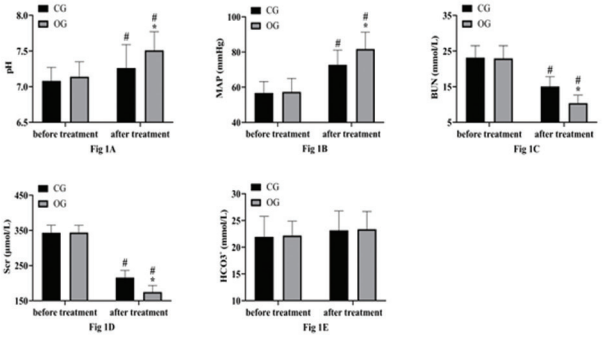
Pre- and Post-Treatment Inflammatory Cytokine (ICK) Levels

Both the OG and CG exhibited no statistically significant differences in ICKs before treatment ($P > .05$). Subsequently, a noticeable reduction in IL-6, IL-10, and TNF-α was observed in both groups after treatment ($P < .05$), with OG demonstrating lower levels compared to CG ($P < .05$). Refer to Figure 3.

Changes in T Lymphocyte Subsets Before and After Treatment

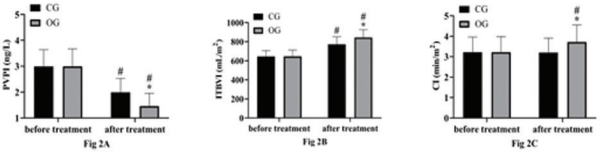
T lymphocyte subsets were assessed in both the OG and CG before and after treatment. Little variation was noted in CD3+, CD4+, CD8+, and CD4+/CD8+ between OG and CG before

Figure 1. Changes in Vital Signs Before and After Treatment in Septic Shock Patients



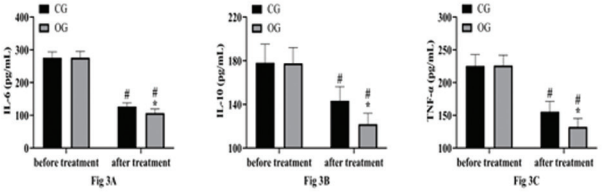
Note: Figure 1 illustrates the alterations in vital signs in septic shock patients. Figure 1A displays changes in pH, figure 1B is mean arterial pressure (MAP), Figure 1C is blood urea nitrogen (BUN), Figure 1D in serum creatinine (Scr), and Figure 1E is bicarbonate (HCO^{3-}) before and after treatment. Significant differences are denoted by #: compared to before treatment, $P < .05$, and *: compared to CG (Control Group), $P < .05$.

Figure 2. Changes in Pulmonary Vascular Permeability Index (PVPI) and Hemodynamic Parameters Before and After Treatment in Septic Shock Patients



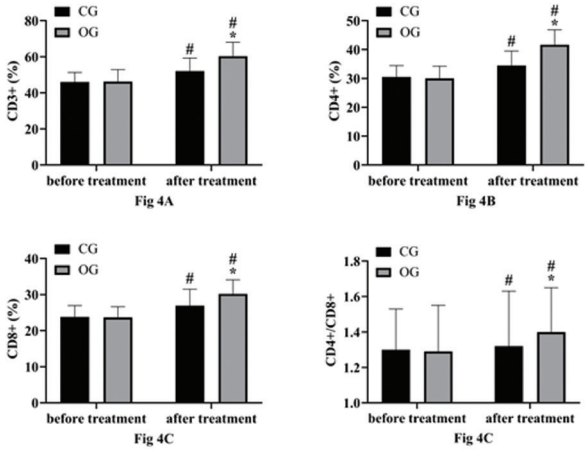
Note: Figure 2 illustrates the variations in PVPI and hemodynamic parameters in septic shock patients. Figure 2A depicts changes in PVPI, Figure 2B is the intrathoracic blood volume index (ITBVI), and Figure 2C is the cardiac index (CI) before and after treatment. Notable differences are denoted by #: compared to before treatment, $P < .05$, and *: compared to CG (Control Group), $P < .05$.

Figure 3. Changes in Inflammatory Cytokine Levels (ICK) Before and After Treatment in Septic Shock Patients



Note: Figure 3 illustrates alterations in inflammatory cytokine levels (ICK) in septic shock patients. Figure 3A presents changes in interleukin-6 (IL-6), Figure 3B in interleukin-10 (IL-10), and Figure 3C in tumor necrosis factor-α (TNF-α) before and after treatment. Significant differences are denoted by #: compared to before treatment, $P < .05$, and *: compared to CG (Control Group), $P < .05$.

Figure 4. Changes in T-Lymphocyte Subsets Before and After Treatment in Septic Shock Patients



Note: Figure 4 illustrates modifications in T-lymphocyte subsets in septic shock patients. Figure 4A displays changes in CD3+, Figure 4B is CD4+, Figure 4C is CD8+, and Figure 4D is CD4+/CD8+ before and after treatment. Significant differences are denoted by #: compared to before treatment, $P < .05$, and *: compared to CG (Control Group), $P < .05$.

Table 2. Complications During Treatment

Group	n	Allergies	Blood Clots	Hypotension	Nausea And Vomiting	Total Incidence
CG	82	2(2.44)	2(2.44)	3(3.66)	4(4.88)	11(13.41)
OG	118	3(2.54)	1(0.85)	2(1.69)	3(2.54)	9(7.63)
χ^2						1.801
P value						.180

Abbreviations: CG is the control group; OG is the observation group. All percentages are reported within parentheses.

treatment ($P > .05$). After treatment, CD3+, CD4+, and CD8+ levels notably increased in both OG and CG, while CD4+/CD8+ decreased ($P < .05$). Specifically, OG exhibited even higher levels of CD3+, CD4+, and CD8+, along with a lower CD4+/CD8+ ratio compared to CG ($P < .05$). Refer to Figure 4.

Complications During Treatment

Our findings revealed the absence of serious complications in either the OG or CG during the treatment period. The total complication rate was 7.63% in OG and 13.41% in CG, with no statistically significant difference between the two groups ($P > .05$). Refer to Table 2.

DISCUSSION

SS stands as a leading cause of mortality among patients in the Intensive Care Unit (ICU) at present. Therefore, the intervention and treatment of SS hold paramount significance in ensuring patient safety.[15] CBP emerges as the most direct and effective approach to treating SS, preventing organ failure, and ultimately saving lives. However, the challenge lies in enhancing the safety and therapeutic efficacy of CBP more effectively, a topic that has long been a focal point and a challenging issue in clinical research.

This study explored the realm of improving the safety and therapeutic outcomes of CBP, specifically through GCs-assisted CBP therapy. The findings indicate a significant improvement in the vital signs of SS patients, besides the inhibition of inflammatory reactions. This result suggests that GCs-assisted CBP therapy could serve as a crucial intervention in ensuring the safety of SS patients, holding substantial clinical implications.

Despite the recommendations provided by international guidelines regarding hormone therapy in SS, debates persist regarding application indications, the applicable population, therapeutic dosage, and treatment duration.[16] Furthermore, although clinical observations suggest that GCs can improve toxic manifestations in certain infected patients and potentially reverse systemic inflammatory reactions in severe cases, their role and mechanism in shock have primarily been confirmed through animal experiments. It underscores the need for further validation of their application value in septic shock through clinical trials.[17,18]

In alignment with prior research,[19] this study confirms a notable improvement in patient's vital signs and pulmonary vascular permeability after GCs-assisted CBP therapy when compared to the CG. This finding demonstrates the potential future utility of GCs in the treatment of SS. A study by Li et al.[20] reported that GCs corrected inflammatory responses and bolstered immune function in animals with SS, suggesting that the application of GCs may also serve to mitigate inflammation in SS patients.

Additionally, the post-treatment levels of ICKs were notably lower in the OG than in the CG, while T lymphocyte subsets exhibited higher levels, thereby further supporting our results. In the analysis of the mechanism of action of GCs, it is observed that the exogenous stimulation of GCs can activate the hypothalamus-pituitary-adrenal axis, leading to increased adrenocorticotropic hormone and cortisol levels. This activation proves conducive to the body's defense against diseases and the maintenance of internal environmental stability.[21,22]

We suggest that this mechanism underlies the impact of GCs on inflammatory responses and immune function in SS patients. Consistent with our results, previous studies have demonstrated that GCs can suppress the expression of pro-inflammatory cytokines such as TNF-α and leukemia inhibitory factors during hypoxic stress. This reduction in pro-inflammatory markers serves to mitigate damage to target organs, thereby playing an anti-inflammatory role. The mechanism involves the inhibition of inflammatory genes and the promotion of anti-inflammatory genes.[23]

Moreover, GCs have been observed to increase the number of CD4+ regulatory T cells in peripheral blood mononuclear cells by down-regulating IL-6 and up-regulating the phosphorylation level of Signal Transducer and Activator of Transcription 5 (STAT5).[24] These findings align with our study's results and collectively validate the efficacy of our approach.

Notably, the absence of statistically significant differences in the complication rate between the OG and CG underscores the high safety profile of GCs-assisted CBP therapy. This finding emphasizes the considerable potential of this combined therapy for patients with SS in critical condition. However, it is

imperative to conduct further analysis to assess the safety of high-dose GCs. Attention should be dedicated to dose control in clinical applications to ensure optimal outcomes.

Study Limitations

This study is constrained by a few limitations stemming from experimental conditions, including a small number of included cases and a relatively short study period. Additionally, the study did not account for the eventual survival of patients, which may limit the representativeness and comprehensiveness of the findings. In future research, we plan to address these limitations by conducting supplementary analyses. This proactive approach aims to enhance the robustness and depth of our research, contributing to a more comprehensive understanding of the subject matter.

CONCLUSION

In conclusion, GCs-assisted CBP therapy emerges as a highly effective intervention in SS patients, presenting notable improvements in vital signs, pulmonary vascular permeability, and immune function while concurrently suppressing inflammatory responses. Importantly, the therapy exhibits a high safety profile. The observed outcomes not only underscore the therapeutic efficacy of GCs-assisted CBP but also suggest its potential to serve as a robust life safety guarantee for SS patients in future clinical applications. This study contributes valuable insights to the optimization of treatment approaches, emphasizing the promising role of GCs in enhancing patient outcomes and ensuring their overall well-being in the challenging context of septic shock.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

FUNDING

None.

REFERENCES

1. De Backer D, Ricottilli F, Ospina-Tascón GA. Septic shock: a microcirculation disease. *Curr Opin Anaesthesiol*. 2021;34(2):85-91. doi:10.1097/ACO.0000000000000957
2. Patel JJ, Shukla A, Heyland DK. Enteral nutrition in septic shock: A pathophysiologic conundrum. *JPEN J Parenter Enteral Nutr*. 2021;45(S2):74-78. doi:10.1002/jpen.2246
3. Thompson K, Venkatesh B, Finfer S. Sepsis and septic shock: current approaches to management. *Intern Med J*. 2019;49(2):160-170. doi:10.1111/imj.14199
4. Hellman T, Uusalo P, Järvisalo MJ. Renal Replacement Techniques in Septic Shock. *Int J Mol Sci*. 2021;22(19):10238. doi:10.3390/ijms221910238
5. De Backer D, Cecconi M, Lipman J, et al. Challenges in the management of septic shock: a narrative review. *Intensive Care Med*. 2019;45(4):420-433. doi:10.1007/s00134-019-05544-x
6. Zuccari S, Damiani E, Domizi R, et al. Changes in Cytokines, Haemodynamics and Microcirculation in Patients with Sepsis/Septic Shock Undergoing Continuous Renal Replacement Therapy and Blood Purification with CytoSorb. *Blood Purif*. 2020;49(1-2):107-113. doi:10.1159/000502540
7. Guan M, Wang H, Tang X, et al. Continuous Renal Replacement Therapy With Adsorbing Filter oXiris in Acute Kidney Injury With Septic Shock: A Retrospective Observational Study. *Front Med (Lausanne)*. 2022;9:789623. doi:10.3389/fmed.2022.789623
8. Norse AB, Guirgis F, Black LP, DeVos EL. Updates and controversies in the early management of sepsis and septic shock. *Emerg Med Pract*. 2021;23(Suppl 4-2):1-24.
9. Venkatesh B, Finfer S, Cohen J, et al; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med*. 2018;378(9):797-808. doi:10.1056/NEJMoa1705835
10. Nedel W, Lisboa T, Salluh JIF. What Is the Role of Steroids for Septic Shock in 2021? *Semin Respir Crit Care Med*. 2021;42(5):726-734. doi:10.1055/s-0041-1733900
11. Tabah A, Buetti N, Barbier F, Timsit JF. Current opinion in management of septic shock due to Gram-negative bacteria. *Curr Opin Infect Dis*. 2021;34(6):718-727. doi:10.1097/QCO.0000000000000767
12. Kethireddy S, Light RB, Mirzanejad Y, et al; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Group. Mycobacterium tuberculosis septic shock. *Chest*. 2013;144(2):474-482. doi:10.1378/chest.12-1286
13. Genga KR, Shimada T, Boyd JH, Walley KR, Russell JA. The Understanding and Management of Organism Toxicity in Septic Shock. *J Innate Immun*. 2018;10(5-6):502-514. doi:10.1159/000487818
14. Font MD, Thyagarajan B, Khanna AK. Sepsis and Septic Shock - Basics of diagnosis, pathophysiology and clinical decision making. *Med Clin North Am*. 2020;104(4):573-585. doi:10.1016/j.mcna.2020.02.011
15. Sweeney DA, Wiley BM. Integrated Multiorgan Bedside Ultrasound for the Diagnosis and Management of Sepsis and Septic Shock. *Semin Respir Crit Care Med*. 2021;42(5):641-649. doi:10.1055/s-0041-1733896
16. Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis. *Intensive Care Med*. 2022;48(1):16-24. doi:10.1007/s00134-021-06558-0
17. Vandewalle J, Libert C. Glucocorticoids in Sepsis: To Be or Not to Be. *Front Immunol*. 2020;11:1318. doi:10.3389/fimmu.2020.01318
18. Rygård SL, Butler E, Granholm A, et al. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2018;44(7):1003-1016. doi:10.1007/s00134-018-5197-6
19. Alder MN, Opoka AM, Wong HR. The glucocorticoid receptor and cortisol levels in pediatric septic shock. *Crit Care*. 2018;22(1):244. doi:10.1186/s13054-018-2177-8
20. Li X, Li M, Liu L, Tian X, Liang Y. Protective effects of glucocorticoid on liver injury in a rat sepsis model. *Exp Ther Med*. 2019;18(4):3153-3160. doi:10.3892/etm.2019.7899
21. Cvijanovich NZ, Anas N, Allen GL, et al. Glucocorticoid Receptor Polymorphisms and Outcomes in Pediatric Septic Shock. *Pediatr Crit Care Med*. 2017;18(4):299-303. doi:10.1097/PCC.0000000000001058
22. Lemieux SM, Levine AR. Low-dose corticosteroids in septic shock: has the pendulum shifted? *Am J Health Syst Pharm*. 2019;76(8):493-500. doi:10.1093/ajhp/zxz017
23. Cohen J, Pretorius CJ, Ungerer JP, et al. Glucocorticoid Sensitivity Is Highly Variable in Critically Ill Patients With Septic Shock and Is Associated With Disease Severity. *Crit Care Med*. 2016;44(6):1034-1041. doi:10.1097/CCM.0000000000001633
24. Bergquist M, Lindholm C, Strinnholm M, Hedenstierna G, Rylander C. Impairment of neutrophilic glucocorticoid receptor function in patients treated with steroids for septic shock. *Intensive Care Med Exp*. 2015;3(1):59. doi:10.1186/s40635-015-0059-9