Critical Care

BRIEF REPORT

Open Access

Endotoxin hemoadsorption in refractory septic shock with multiorgan dysfunction and extreme endotoxin activity

Juan Carlos Ruiz-Rodríguez[1,2,5], Luis Chiscano-Camón[1,2,5*], Ivan Bajaña[1,2], Adolf Ruiz-Sanmartin[1,2], Juliana Bastidas[1,2], Carolina Maldonado[1,2], Pablo Nicolás-Morales[1,2], Sergi Cantenys-Molina[4], Juan José González[3], Nieves Larrosa[3] and Ricard Ferrer[1,2,5]

Abstract

Endotoxin septic shock is marked by severe organ failure and mortality rate that exceeds fifty percent, underscoring the critical need to tailor management strategies. Monitoring -endotoxin activity can guide the initiation and direction of adjunctive treatment for refractory septic shock through hemoadsorption. Thus, intervening based on the pathophysiological foundation may potentially improve outcomes. This represents a step towards precision medicine in the management of septic shock adjunctive therapies, addressing a knowledge gap in this pathology that remains insufficiently defined. Despite its potential, in the setting of refractory septic shock and multiorgan dysfunction with extreme endotoxin activity (EAA ≥ 0.9), the data about efficacy of endotoxin hemoadsorption is scarce.

Keywords Endotoxin activity, Refractory septic shock, Hemoadsorption, Multiorgan dysfunction

Main text

Endotoxemia and the excessive release of inflammatory substances, manifesting as a cytokine storm, are linked to the severity of sepsis and septic shock and play a crucial role in predicting outcomes [1]. Adamik and colleagues reported a two-fold increase in ICU mortality for patients with septic shock and endotoxemia, and these differences persisted for at least 90 days when mortality was < 50% without endotoxemia and > 70% with endotoxemia. Endotoxic septic shock (ESS) is characterized by high endotoxin activity (EA) (e.g., Endotoxin Activity Assay [EAA] > 0.6) and organ failure and represents a subtype of sepsis affecting approximately 5–7 million individuals globally each year [2]. Patients with ESS may experience severe hyperinflammation, hepatic dysfunction, disseminated intravascular coagulation and septic shock, manifestations that are concordant with the sepsis δ-phenotype [3]. This previous condition confers to ESS a mortality rate exceeding 40%, and effective treatments options are limited. Current research is focused on applying immunomodulatory therapies to ESS and exploring the potential of extracorporeal endotoxin removal and other blood purification methods [4].

Thus, endotoxins have been identified as key targets for the treatment of sepsis and septic shock. Blood purification methods, particularly using hemoadsorption, have been proposed as a mean to eliminate endotoxins [5].

*Correspondence:
Luis Chiscano-Camón
luissilvestre.chiscano@vallhebron.cat
[1] Intensive Care Department, Vall d'Hebron Hospital Campus, Vall d'Hebron University Hospital, Barcelona, Spain
[2] Shock, Organ Dysfunction and Resuscitation Research Group. Vall d'Hebron University Hospital, Vall d'Hebron Hospital Campus., Vall d'Hebron Research Institute (VHIR), Barcelona, Spain
[3] Microbiology Department, Vall d'Hebron Hospital Campus,, Vall d'Hebron University Hospital, Barcelona, Spain
[4] Immunology Department, Vall d'Hebron Hospital Campus, Vall d'Hebron University Hospital, Barcelona, Spain
[5] Departament de Medicina, Universitat Autonoma de Barcelona, Barcelona, Spain

Lately in a multicentred, prospective and observational study, it was concluded that the baseline EA may predict the outcome of critically ill septic patients receiving endotoxin hemoadsorption (ET-HA) [6].

Despite its potential, there is a deficiency of data regarding the application of ET-HA for individuals experiencing refractory septic shock and severe multiorgan dysfunction (MODS) characterized by extreme endotoxin activity (EAA ≥ 0.9). EAA is a rapid diagnostic test using a monoclonal antibody to detect endotoxin, providing results in 15–20 min). It measures LPS activity by assessing the oxidative burst of primed neutrophils, detected via chemiluminescence (S = 85.3%, E = 44% and negative predictive value of 98.6% for excluding Gram-negative infections) [7]. Adsorption capacity of PMX-20R cartridge (Toraymixin ™) is sufficient to remove a clinically significant amount of endotoxin in a majority of endotoxemic septic shock patients; however this may not be the case in patients with a high EAA burden ≥ 0.9 [8]. Therefore, the efficacy of ET-HA in patients with extreme EAA could be controversial [9]. In fact, in the post-hoc analysis of the EUPHRATES trial that shows beneficial results for patients with septic shock and MODS, patients with extreme EA were excluded [10].

Therefore, our objective is to evaluate the efficacy of ET-HA in lowering EA levels in patients affected by with septic shock and MODS who exhibit extreme EAA. While there is disagreement about the efficacy of HA in cases where EAA are ≥ 0.9, we hypothesize that ET-HA can effectively reduce EA in this subgroup of patients.

We performed a retrospective, single-centre observational study from January 2018 to November 2024. The study included patients diagnosed with septic shock according to Sepsis-3 [11] criteria and experiencing MODS with SOFA score > 9 with an EAA of 0.9 or higher, who were treated using ET-HA therapy (whose indication was refractory septic shock [12] and SOFA score > 9 with an EAA > 0.6). EA was assessed using the Endotoxin Activity Assay ™ (EAA, Spectral Medical Inc, Canada) within the first 24 h after the onset of septic shock, before the initiation of ET-HA (EAA preET-HA), and again 18–20 h later (EAA postET-HA) once first ET-HA was finalized and if the patient was still in refractory septic shock. ET-HA (Toraymixin™, Toray Industries, Tokyo, Japan) therapy was administered within the initial 24 h of septic shock development (always as close as possible in time to the determination of the first EAA, while the rest of the septic shock treatment bundles [13] are carried out in parallel) and in parallel to continuous renal replacement therapy with its dose applied to shock clinical scenario (using regional anticoagulation with citrate instead of heparinization of the hemoadsortive circuit; however the adsortive cartridge was primed with 2000UI of unfractioned-heparin as manufacturer recommendations). The ET-HA session last for 2 h, without off-label extension. In some cases, cytokine hemoadsorption was sequentially [14] continued if a septic shock phenotypic profile of hypercytokinemia was identified [15]. If patients had a post-treatment EAA level below 0.6, a second session of ET-HA was not carried out.

During study period, 36 ET-HA were conducted on patients suffering from septic shock, MODS and EAA of at least 0.6. Among these, 12 patients exhibited an EAA of 0.9 or higher (refer to Table 1 for a summary of the characteristics). In this subgroup, the EAA before ET-HA was 1.14 (0.33) and dropped to 0.47 (0.33) [$p = 0.0143$] after the ET-HA therapy (Fig. 1). Consequently, only 4 patients required a subsequent second ET-HA session.

Prior to hemoadsorptive therapy, the patients were receiving norepinephrine at doses exceeding 0.3 µg/kg/min, and vasopressin had been initiated in 10 patients (83%). Even 4 patients (33%) required mechanical support with veno-arterial ECMO during the first hours of shock progression. We did not apply the SOFA score post-ET-HA because up to 5 cases (42%) required ECMO, leading to an artifact in the assessment of oxygenation and hemodynamic dysfunction. However, the reduction in vasoactive drug doses is clinically relevant, as vasopressin was discontinued in all 12 cases (100%), and the norepinephrine dose decreased to < 0.15 µg/kg/min, again, in all cases (Table 2).

We are aware of the extremely high EA levels we have reported and the significant reduction in EA resulting from the use of hemoadsorption compared to other studies [16, 17]. In light of this, a thorough verification has been conducted to ensure that the pre-analytical and analytical processing of the endotoxin sample adhered to established standards [18].

Our research suggests that ET-HA in patients with septic shock, MODS and extreme EA is associated with a reduction in EAA levels. Importantly, EAA levels above 0.9 should not deter the initiation of endotoxin hemoadsorption, providing that the core components and protocols of septic shock management are meticulously upheld. Our contribution to the literature in this regard is novel, as patients with extreme high EA are often excluded from studies due to this supposed limited adsorptive cartridge capacity.

In recent years, various initiatives have emerged to improve the diagnosis and treatment of sepsis. Precision

Table 1 Characteristics of the study population

		n = 12
Age (years) m (SD)		57 (12)
Gender (female) n (%)		5 (42)
SOFA m (SD)		13 (3)
Cardiovascular SOFA m (SD)		4(0)
APACHE II m (SD)		25.42 (9.02)
Noradrenaline n (%)		12 (100)
Vasopressin n (%)		10 (83)
Dobutamine n (%)		9 (75)
ECMO veno-arterial n (%)		4(33)
IMV (days) md (IQR)		26 (5.5–29)
RRT n (%)		12 (100)
Infection source n(%)	Respiratory	7 (58)
	Abdominal	5 (42)
Leukocyte count (6 × 10e9/L) md (IQR)		3415 (1315–9080)
Lactate (mmol/L) m (SD)		6.18 (3.76)
CRP (mg/dL) md (IQR)		15.67 (11.75–27.55)
PCT (ng/mL) md (IQR)		52.85 (23.17–108.66)
IL-6 (pg/mL) md (IQR)		163,186 (37,059.5–303,334.5)
EAApreET-HA m (SD)		1.14 (0.33)
EEApostET-HA m (SD)		0.47 (0.33)
ET-HA sessions m (SD)		1.3 (0.47)
Length of hospital stay (days) md (IQR)		20.5 (5–34)
ICU mortality n (%)		7 (58)
In-hospital mortality n (%)		7 (58)

APACHE II, Acute physiology and chronic health evaluation II; CRP, C-reactive protein; EAA, endotoxin activity assay; EAA preET-HA, endotoxin activity pre endotoxin hemoadsorption; EAA postET-HA, endotoxin activity post endotoxin hemoadsorption; ECMO, extracorporeal membrane oxygenation; ET-HA, endotoxin hemoadsorption; HA, Hemoadsorption; ICU, intensive care unit; IL, interleukin; IMV, invasive mechanical ventilation; PCT, procalcitonin; RRT, renal replacement therapy; SOFA, sequential organ failure assessment

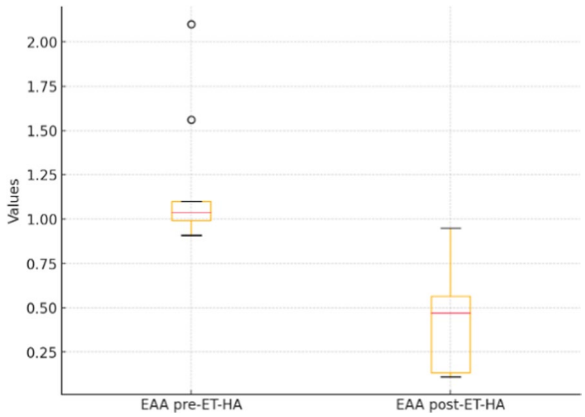

Fig. 1 Flowchart EAA pre and post endotoxin hemoadsorption (ET-HA). the EAA before ET-HA was 1.14 (0.33) and dropped to 0.47 (0.33) [$p = 0.0143$] after the first session of ET-HA. EAA: endotoxin activity assay; EAA preET-HA: endotoxin activity pre endotoxin hemoadsorption; EAA postET-HA: endotoxin activity post endotoxin hemoadsorption; ET-HA: endotoxin hemoadsorption

medicine [19] offers a new paradigm for patient care, allowing for the tailoring of therapeutic strategies to specific subgroups of patients, which may not be effective for the general sepsis or septic shock population. The application of hemoadsorptive therapies, guided by real-time monitoring of EA, can guide the selection of patients candidate to hemoadsorptive therapy. Nonetheless, despite our research and physiopathological understanding, we acknowledge that the SSC guidelines [20] advise against the use of ET-HA due to the overall low quality of supporting evidence. We are fully agree and in line with SSC recommendations, then ET-HA HA should not be routinely indicated for all patients with sepsis and septic shock. However, its use should be personalized, identifying patients whose phenotype and endotype may allow them to benefit from it.

In conclusion, in our series of patients with septic shock, severe MODS and EAA ≥ 0.9, ET-HA was effective in reducing endotoxin levels. The main message is

Table 2 Individual characteristics of the 12 patients with refractory septic shock and EAA ≥ 0.9 included in the study

Patient	APACHEII	PCT	IL6	Outcome	LOS	IMV	CRRT	SOFA (pre ET-HA)	DBT	NOR >0.30µ/kg/min Pre-HA	NOR >0.15 µg/kg/min Post-HA	VP pre-HA	VP post-HA	ECMO	HA technique	EAA pre-ET-HA	EAA post-1st ET-HA	EAA post-2nd ET-HA	ET-HA sessions
1	29	17.08	348,260	Dead	26	20	Yes	12	No	Yes	No	No	No		ET-HA	1.1	NA	0.14	**2**
2	30	62.71	157,913	Alive	14	4	Yes	8	Yes	Yes	No	No	No		S-HA	1	0.11	-	1
3	24	32.43	19,228	Dead	15	15	Yes	15	Yes	Yes	No	Yes	No	VV	S-HA	1.1	0.61	-	1
4	24	114.62	168,459	Alive	30	28	Yes	9	Yes	Yes	No	Yes	No		ET-HA	0.97	0.12	-	1
5	30	29.26	26,191	Dead	8	7	Yes	11	Yes	Yes	No	Yes	No		S-HA	1.05	0.95	-	1
6	28	102.69	229,099	Dead	120	120	Yes	14	Yes	Yes	No	Yes	No	VA	S-HA	2.1	NA	0.49	**2**
7	3	156.28	258,409	Alive	38	28	Yes	17	No	Yes	No	Yes	No		S-HA	1.04	0.98	0.55	**2**
8	23	15.27	133,635	Dead	1	1	Yes	14	Yes	Yes	No	Yes	No		S-HA	0.91	*Dead within 1st day of admission*	-	1
9	13	80	39,666	Alive	42	40	Yes	9	No	Yes	No	Yes	No		S-HA	1.56	NA	-	1
10	32	128.99	34,453	Dead	1	1	Yes	10	Yes	Yes	No	Yes	No	VVA	S-HA	1.01	*Dead within 1st day of admission*	-	1
11	39	43	500,000	Dead	1	1	Yes	16	Yes	Yes	No	Yes	No	VA	S-HA	0.93	*Dead within 1st day of admission*	-	1
12	30	3.72	354,749	Alive	26	26	Yes	16	Yes	Yes	No	Yes	No	VA	S-HA	1.04	1.01	0.45	**2**

Prior to hemoadsorptive therapy, the patients were receiving norepinephrine at doses exceeding 0.3 µg/kg/min and vasopressin had been initiated in 10 patients (83%). Notably except for two cases the rest underwent sequential hemoadsorption (S-HA) due to a hypercytokinemic profile and EAA ≥ 0.9 in the context of refractory septic shock. This means doing firstly an ET-HA 2-h session and afterwards a 20-24h cytokine adsorption session. Three patients (patient 8, 10, 11) did not survive the first day of admission due to shock, so no post-ET-HA EAA sample was obtained. 4 patients (1, 6, 7, 12) required a subsequent second ET-HA session because they were still on refractory septic shock and EAA > 0.6. There are two cases (1, 6) in which a second ET-HA session was performed without determining EAA, as the clinical situation had not changed after the first session (refractory septic shock with a high vasopressor requirement). Additionally, there are two cases (3, 5) in which, despite presenting an EAA > 0.6, the hemodynamic clinical situation had improved sufficiently to no longer warrant rescue through adsorption. We did not apply the SOFA score post-ET-HA because up to 5 cases (42%) required ECMO leading to an artifact in the assessment of oxygenation and hemodynamic dysfunction. However the reduction in vasoactive drug doses is clinically relevant as vasopressin was discontinued in all 12 cases (100%) and the norepinephrine dose decreased to < 0.15 µg/kg/min

APACHE II, Acute physiology and chronic health evaluation II; CRP, C-reactive protein; DBT, dobutamine; EAA, endotoxin activity assay; EAA preET-HA, endotoxin activity pre endotoxin hemoadsorption; EAA postET-HA: endotoxin activity post endotoxin hemoadsorption; ECMO, extracorporeal membrane oxygenation (VV, veno-venous. VA, veno-arterial. VVA, veno-venousarterial); ET-HA, endotoxin hemoadsorption; HA, Hemoadsorption; ICU, intensive care unit; IL, interleukin (pg/ml); IMV, invasive mechanical ventilation (days); LOS, length of stay (hospital) (days); NA, not available; NOR, norepinephrine PCT, procalcitonin (ng/ml); RRT, renal replacement therapy; S-HA, sequential hemoadsorption; SOFA, sequential organ failure assessment; VP, vasopressin

that in this subgroup of patients, EAA levels greater than 0.9 should not exclude the indication of ET-HA.

Abbreviations

aHUS	Atypical hemolytic-uremic syndrome
APACHE II	Acute physiology and chronic health evaluation II
CRP	C-reactive protein
EA	Endotoxin activity
EAA	Endotoxin activity assay
EAA preET-HA	Endotoxin activity assay pre endotoxin hemoadsorption
EAA postET-HA	Endotoxin activity assay post endotoxin hemoadsorption
ECMO	Extracorporeal membrane oxygenation
ESS	Endotoxic septic shock
ET-HA	Endotoxin hemoadsorption
HA	Hemoadsorption
ICU	Intensive care unit
IL	Interleukin
IMV	Invasive mechanical ventilation
MAS	Macrophage activation syndrome
MODS	Multiorgan dysfunction syndrome
PCT	Procalcitonin
RRT	Renal replacement therapy
SOFA	Sequential organ failure assessment
PMX-HA	Polymixin hemoadsorption

Acknowledgements
No contributions from individuals or organizations.

Author contributions
We were all involved in providing care for the patient. We were all involved in writing and reviewing the manuscript. The authors read and approved the final manuscript.

Funding
No funding.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
We complied with the guidelines for human studies and our research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Information revealing the subject's identity is to be avoided. The study was approved by the local Clinical Research Ethics Committee [PR(AG)229/2024] with exemption from informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 14 December 2024 Accepted: 14 March 2025
Published online: 20 May 2025

References

1. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39:517–28.
2. Adamik B, Smiechowicz J, Jakubczyk D, Kübler A. Elevated serum PCT in septic shock with endotoxemia is associated with a higher mortality rate. Medicine (Baltimore). 2015;94(27):e1085. https://doi.org/10.1097/MD.0000000000001085.
3. Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, Berry S, Clermont G, Cooper G, Gomez H, Huang DT, Kellum JA, Mi Q, Opal SM, Talisa V, van der Poll T, Visweswaran S, Vodovotz Y, Weiss JC, Yealy DM, Yende S, Angus DC. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA. 2019;321(20):2003–17. https://doi.org/10.1001/jama.2019.5791.
4. Kellum JA, Ronco C. The role of endotoxin in septic shock. Crit Care. 2023;27(1):400. https://doi.org/10.1186/s13054-023-04690-5.
5. Ruiz-Rodríguez JC, Plata-Menchaca EP, Chiscano-Camón L, Ruiz-Sanmartin A, Ferrer R. Blood purification in sepsis and COVID-19: what´s new in cytokine and endotoxin hemoadsorption. J Anesth Analg Crit Care. 2022;2(1):15. https://doi.org/10.1186/s44158-022-00043-w.
6. Cutuli SL, De Rosa S, Ferrer R, Ruiz-Rodriguez JC, Forfori F, Ronco C, et al. Endotoxin activity trend and multi-organ dysfunction in critically ill patients with septic shock, who received Polymyxin-B hemadsorption: a multicenter, prospective, observational study. Artif Organs. 2023;00:1–10.
7. Marshall JC, Walker PM, Foster DM, Harris D, Ribeiro M, Paice J, Romaschin AD, Derzko AN. Measurement of endotoxin activity in critically ill patients using whole blood neutrophil dependent chemiluminescence. Crit Care. 2002;6(4):342–8. https://doi.org/10.1186/cc1522.
8. Romaschin AD, Obiezu-Forster CV, Shoji H, Klein DJ. Novel Insights into the direct removal of endotoxin by Polymyxin B Hemoperfusion. Blood Purif. 2017;44(3):193–7. https://doi.org/10.1159/000475982.
9. Honore PM, De Bels D, Barreto Gutierrez L, Redant S, Gallerani A, Boer W. Endotoxin removal by polymyxin B: is it a question of dose or duration or both? Crit Care. 2019;23(1):297. https://doi.org/10.1186/s13054-019-2584-5.
10. Klein DJ, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med. 2018;44(12):2205–12. https://doi.org/10.1007/s00134-018-5463-7.
11. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10. https://doi.org/10.1001/jama.2016.0287.
12. Antonucci E, Polo T, Giovini M, Girardis M, Martin-Loeches I, Nielsen ND, Lozsán FJC, Ferrer R, Lakbar I, Leone M. Refractory septic shock and alternative wordings: a systematic review of literature. J Crit Care. 2023;75:154258. https://doi.org/10.1016/j.jcrc.2023.154258.
13. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med. 2018;44(6):925–8. https://doi.org/10.1007/s00134-018-5085-0.
14. Ruiz-Rodríguez JC, Chiscano-Camón L, Palmada C, Ruiz-Sanmartin A, Pérez-Carrasco M, Larrosa N, González JJ, Hernández-González M, Ferrer R. Endotoxin and cytokine sequential hemoadsorption in septic shock and multi-organ failure. Blood Purif. 2022;51(7):630–3. https://doi.org/10.1159/000518229.
15. Chiscano-Camón L, Ruiz-Sanmartin A, Bajaña I, Bastidas J, Lopez-Martinez R, Franco-Jarava C, Gonzalez JJ, Larrosa N, Riera J, Nuvials-Casals X, Ruiz-Rodríguez JC, Ferrer R. Current perspectives in the management of sepsis and septic shock. Front Med (Lausanne). 2024;15(11):1431791. https://doi.org/10.3389/fmed.2024.1431791.
16. Cutuli SL, Artigas A, Fumagalli R, Monti G, Ranieri VM, Ronco C, Antonelli M. EUPHAS 2 collaborative group. Polymyxin-B hemoperfusion in septic patients analysis of a multicenter registry. Ann Intensive Care. 2016;6(1):77. https://doi.org/10.1186/s13613-016-0178-9.
17. Forin E, Lorenzoni G, Ferrer R, De Cal M, Zanella M, Marchionna N, Gregori D, Forfori F, Lorenzin A, Danzi V, Ronco C, De Rosa S. Endotoxin removal therapy with Polymyxin B immobilized fiber column: a single center experience from EUPHAS2 registry. Sci Rep. 2023;13(1):17600. https://doi.org/10.1038/s41598-023-44850-9.
18. Romaschin AD, Harris DM, Ribeiro MB, Paice J, Foster DM, Walker PM, Marshall JC. A rapid assay of endotoxin in whole blood using autologous neutrophil dependent chemiluminescence. J Immunol Methods. 1998;212(2):169–85. https://doi.org/10.1016/s0022-1759(98)00003-9.
19. Ruiz-Rodriguez JC, Plata-Menchaca EP, Chiscano-Camón L, et al. Precision medicine in sepsis and septic shock: from omics to clinical tools. World J Crit Care Med. 2022;11:1–21.

20. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Møller MH, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181–247. https://doi.org/10.1007/s00134-021-06506-y.

Publisher's Note