

Sepsis and Sepsis-Associated Acute Respiratory Distress Syndrome: Current Strategies for Infusion Therapy

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Abstract The aim of the study was to conduct a systematic analysis of current data on the efficiency of various infusion therapy strategies in adult patients with sepsis, septic shock, and sepsis-associated acute respiratory distress syndrome focusing on the role of ultrasound evaluation of fluid status and tolerance to fluid loading. **Background.** Sepsis remains one of the leading causes of mortality in intensive care units and is still associated with a high risk of multiple organ failure and unfavorable outcomes. Acute respiratory distress syndrome plays a significant role among the complications of sepsis; its development is associated with systemic inflammation, endothelial dysfunction, impaired microcirculation, and increased permeability of the alveolar-capillary membrane. **Materials and Methods.** This study was performed in the form of a systematic literature review. A search for publications was conducted in PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and eLibrary for the period from 2015 to 2025, along with the inclusion of selected earlier studies still relevant from a methodological and clinical standpoint. **Results.** The CLASSIC study showed that a restrictive strategy after initial resuscitation did not reduce 90-day mortality compared with the standard approach, but resulted to a reduction of cumulative fluid balance. Similarly, in the CLOVERS study, an early, more restrictive strategy with a faster transition to vasopressor support did not provide any benefits in terms of primary clinical outcomes. Currently, the concept of “fluid tolerance”—a patient’s ability to tolerate an additional fluid load without compromising the function of the lungs, heart, and other organs—is becoming increasingly important. **Conclusion.** Current evidence does not confirm the benefits of a universal fluid resuscitation strategy for sepsis and sepsis-associated acute respiratory distress syndrome. Ultrasound monitoring is particularly important in patients at high risk for pulmonary overload, especially those with acute respiratory distress syndrome.

Keywords Sepsis, Acute respiratory distress syndrome, Infusion therapy, Lung ultrasound, Hemodynamic monitoring

1. Introduction

Sepsis remains one of the leading causes of mortality in intensive care units and is still associated with a high risk of multiple organ failure and unfavorable outcomes [1-7,8-10]. Acute respiratory distress syndrome plays a significant role among the complications of sepsis; its development is associated with systemic inflammation, endothelial dysfunction, impaired microcirculation, and increased permeability of the alveolar-capillary membrane [8,11-12]. Against this backdrop, infusion therapy takes on a dual significance: on the one hand, it is necessary to correct hypovolemia and maintain tissue perfusion; on the other hand, it can increase extravascular fluid accumulation in the lungs and exacerbate respiratory failure [5-6,13-18].

The concept of early aggressive fluid resuscitation long dominated in clinical practice; however, the results of

large-scale studies and updated clinical guidelines led to a reevaluation of this paradigm [1-4,19-21]. Today, the concepts of tolerance to fluid infusion and the need to evaluate not only a patient’s fluid requirements but also the risk of hyperhydration becomes increasingly important [8,22-23].

Ultrasound methods for bedside monitoring are of particular interest in this context, especially the assessment of the inferior vena cava and ultrasound examination of the lungs. Their use allows to assess volume status, the likelihood of a hemodynamic response to infusion, and signs of increasing right-sided congestive heart failure in real time [10-16].

The aim of the study was to conduct a systematic analysis of current data on the efficiency of various infusion therapy strategies in adult patients with sepsis, septic shock, and sepsis-associated acute respiratory distress syndrome focusing on the role of ultrasound evaluation of fluid status and tolerance to fluid loading.

2. Materials and Methods

This study was performed in the form of a systematic literature review. A search for publications was conducted in PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and eLibrary for the period from 2015 to 2025, along with the inclusion of selected earlier studies still relevant from a methodological and clinical standpoint. The search strategy included combinations of the keywords “sepsis,” “septic shock,” “acute respiratory distress syndrome,” “fluid therapy,” “lung ultrasound,” “inferior vena cava,” “FALLS protocol,” and “volume status”.

The review included randomized clinical trials, cohort studies, systematic reviews, meta-analyses, and clinical guidelines focusing on adult patients with sepsis, septic shock, and/or acute respiratory distress syndrome. The data on infusion therapy strategies, monitoring methods, hemodynamic and respiratory parameters, and clinical outcomes were analyzed.

The inclusion criteria were as follows:

- adult patients over 18 years of age;
- sepsis, septic shock, and/or sepsis-associated acute respiratory distress syndrome;
- publications devoted to liberal, restrictive, or individualized infusion therapy;
- studies evaluating ultrasound-based methods for monitoring volume status and infusion tolerance.

The review did not include experimental animal studies, abstracts without full-text versions, isolated clinical observations, publications on pediatric patients, or studies not directly related to the purpose of the review.

3. Results and Discussion

Current concepts of infusion therapy strategy

Infusion therapy remains an essential component of sepsis treatment, especially in the early stages, when hypovolemia and vasodilation lead to a decrease in efficient organ perfusion. However, current literature does not provide evidence supporting the benefits of a fixed, universal fluid volume for all patients [1-4].

The CLASSIC study showed that a restrictive strategy after initial resuscitation did not reduce 90-day mortality compared with the standard approach, but resulted to a reduction of cumulative fluid balance [1]. Similarly, in the CLOVERS study, an early, more restrictive strategy with a faster transition to vasopressor support did not provide any benefits in terms of primary clinical outcomes [2]. These data indicate that contrasting liberal and restrictive strategies in isolation from the clinical context is an oversimplification.

Currently, the concept of “fluid tolerance”—a patient’s ability to tolerate an additional fluid load without compromising the function of the lungs, heart, and other organs—is becoming increasingly important [8,22]. In this regard, in cases of sepsis, it is important not only to determine whether the patient is able to increase cardiac

output in response to fluid administration, but also to evaluate whether this infusion will be accompanied by clinically significant fluid overload.

Fluid therapy for sepsis-associated acute respiratory distress syndrome

Infusion therapy requires a particularly cautious approach in patients with acute respiratory distress syndrome. Excessive fluid administration promotes an increase of extracellular fluid in the lungs, impaired oxygenation, decreased lung compliance and prolonged mechanical ventilation [5-7]. A positive cumulative water balance is considered an independent adverse factor in this type of patients [6-7].

The Surviving Sepsis Campaign guidelines continue to emphasize the early administration of crystalloids in septic shock, but stress the need for subsequent reassessment of the response to treatment [4]. More recent guidelines from the European Society of Intensive Care Medicine propose a more flexible approach, emphasizing the need to tailor the volume of infusion to the clinical situation and the patient’s condition [3,22].

Thus, the key challenge in patients with sepsis and acute respiratory distress syndrome is not simply to correct volume depletion, but to maintain a balance between ensuring perfusion and preventing iatrogenic hyperhydration.

Limitations of volemic status traditional indicators

Traditional parameters, such as central venous pressure, blood pressure and diuresis are widely used in intensive care units; however, their abilities to predict the response to infusions are limited [8-10]. Static preload parameters do not accurately reflect actual fluid sensitivity, particularly in patients undergoing mechanical ventilation, as well as in cases of vasoplegia and marked disturbances of vascular tone.

For this reason, modern intensive care focuses on dynamic and multiparametric methods of evaluating the patient’s condition, which allow to interpret infusion therapy not as a standard procedure, but as a personalized intervention [8,22].

Ultrasound evaluation of the inferior vena cava

Ultrasound examination of the inferior vena cava is an accessible and noninvasive method for a preliminary evaluation of venous return and the potential response to an infusion load [10-11]. However, the diagnostic value of this method depends on a number of factors, including spontaneous breathing or mechanical ventilation, intra-abdominal pressure, right ventricular function and the severity of vasoplegia.

According to published data, indices of inferior vena cava collapsibility or distensibility have only moderate prognostic accuracy and should not be used in isolation [10-11]. Their clinical utility increases through integration with the patient’s overall clinical picture and other monitoring methods, particularly ultrasound evaluation of the lungs.

Ultrasound examination of the lungs and evaluation of infusion tolerance

Ultrasound examination of the lungs has become an important part of bedside diagnosis in patients in critical condition in recent years. The method demonstrates high

sensitivity in detecting interstitial syndrome, alveolar edema, and reduced lung aeration, and surpasses standard chest radiography in a number of parameters [12-14].

The Lung Ultrasound Score scale allows to quantitatively evaluate the severity of lung injury and monitor changes during the course of treatment [13-14]. An increase in the number of B-lines and a rise in the total score on the scale are considered signs of impaired lung aeration and an increased risk of fluid overload. It is particularly important that this method allows to evaluate not only the presence of pulmonary involvement, but also the pulmonary circulation's tolerance of infusion therapy.

It should be emphasized that B-lines are not a strictly specific marker of hydrostatic edema. They may be observed in cases of pneumonia, interstitial lung diseases and acute respiratory distress syndrome. Therefore, the results of a lung ultrasound examination should be interpreted in light of the clinical context, the distribution of the findings and data from other diagnostic methods [12,15].

The FALLS protocol as a tool of individualization of infusion therapy

The "Fluid Administration Limited by Lung Sonography" protocol is an ultrasound-guided algorithm that allows to evaluate simultaneously the hemodynamic fluid requirements and the monitoring of the risk of pulmonary fluid overload [15-16]. Its logic is based on the step-by-step elimination of alternative causes of shock and a subsequent evaluation of the feasibility of continuing the infusion until signs of interstitial overload appear.

The practical value of the protocol lies in the fact that it allows to focus not on a fixed volume of fluid, but on the individual tolerance limit for the infusion load. It is particularly relevant in cases of septic shock, when clinicians must constantly balance between correcting hypovolemia and the risk of impaired respiratory function [15].

At the same time, it should be noted that the evidence supporting the use of the FALLS protocol for sepsis and sepsis-associated acute respiratory distress syndrome remains limited. The available data suggest that this approach is promising and clinically reasonable, but its impact on severe outcomes requires further investigation in high-quality prospective studies [16].

4. Conclusions

Current data do not provide evidence of the benefits of a universal fluid resuscitation strategy for sepsis and sepsis-associated acute respiratory distress syndrome. Neither a liberal nor a strictly restrictive approach can be considered optimal outside of a clinical context. A personalized approach, based on a dynamic evaluation of the hemodynamic response and tolerance to the infusion load, appears to be the most reasonable strategy.

Ultrasound monitoring is particularly important in patients at high risk of pulmonary overloading, especially those with

acute respiratory distress syndrome. Evaluation of the inferior vena cava may be useful for a preliminary assessment of the response to infusion therapy, whereas lung ultrasound allows to detect signs of interstitial syndrome timely and to monitor the safety of the therapy.

The FALLS protocol should be viewed as a promising practical tool of personalized infusion therapy. Its use may facilitate more balanced clinical decision-making; however, further research is needed to definitively evaluate its impact on outcomes.

Conflict of Interests' Statement

The authors declare no conflict of interest.

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The article is published for the first time and is part of a scientific work.

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REFERENCES

- [1] Meyhoff TS, Hjortrup PB, Wetterslev J, et al. Restriction of intravenous fluid in ICU patients with septic shock. *N Engl J Med.* 2022; 386(26): 2459-2470.
- [2] Shapiro NI, Douglas IS, Brower RG, et al. Early restrictive or liberal fluid management for sepsis-induced hypotension. *N Engl J Med.* 2023; 388(6): 499-510.
- [3] Mekontso Dessap A, AlShamsi F, Belletti A, et al. European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients: part 2 - the volume of resuscitation fluids. *Intensive Care Med.* 2025; 51(3): 461-477.
- [4] Rosstalnaya AL, Maxsudov DR. Acute Respiratory Distress Syndrome: Ways to Optimize Respiratory Support depending on Breathing Pattern and Mechanics (*Literature Review*) *Shoshilinch tibbiyot axborotnomasi*, 2023, 16-tom, #4: 104-112.
- [5] Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med.* 2021; 47(11): 1181-1247.
- [6] Bos LD, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes. *Lancet.* 2022; 400(10358): 1145-1156.
- [7] Van Mourik N, Metske HA, Hofstra JJ, et al. Cumulative fluid balance predicts mortality and increases time on mechanical ventilation in ARDS patients. *PLoS One.* 2019; 14(10): e0224563.

- [8] Messmer AS, Zingg C, Muller M, et al. Fluid overload and mortality in adult critical care patients - a systematic review and meta-analysis. *Crit Care Med.* 2020; 48(12): 1862-1870.
- [9] Teboul JL, Liu J, Hamzaoui O. Initial fluid resuscitation in septic shock: reassessing the 30 mL/kg paradigm. *J Intensive Med.* 2025; 5(4): 298-300.
- [10] Bentzer P, Griesdale DE, Boyd J, et al. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA.* 2016; 316(12): 1298-1309.
- [11] Long E, Oakley E, Duke T, Babl FE. Does respiratory variation in inferior vena cava diameter predict fluid responsiveness: a systematic review and meta-analysis. *Shock.* 2017; 47(5): 550-559.
- [12] Orso D, Paoli I, Piani T, et al. Accuracy of ultrasonographic measurements of inferior vena cava to determine fluid responsiveness: a systematic review and meta-analysis. *J Intensive Care Med.* 2020; 35(4): 354-363.
- [13] Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med.* 2012; 38(4): 577-591.
- [14] Mongodi S, Bouhemad B, Orlando A, et al. Modified lung ultrasound score for evaluating and monitoring pulmonary aeration. *Ultraschall Med.* 2017; 38(5): 530-537.
- [15] Smit MR, Pisani L, Winterton D, et al. Lung ultrasound score to monitor disease progression and predict clinical outcomes in acute respiratory distress syndrome. *Ann Intensive Care.* 2021; 11(1): 129.
- [16] Lichtenstein DA. The FALLS-protocol: lung ultrasound in hemodynamic assessment of shock. *Heart Lung Vessels.* 2013; 5(3): 142-147.
- [17] Li Y, Du H, Guo C, et al. Ultrasound-guided fluid management using the FALLS concept in septic shock: a comparative clinical approach.
- [18] Meyer NJ, Prescott HC. Sepsis and septic shock. *N Engl J Med.* 2024; 391(22): 2133-2146.
- [19] Corl KA, Levy MM, Holder AL, et al. Moderate intravenous fluid resuscitation is associated with decreased mortality in sepsis. *Crit Care Med.* 2024; 52(4): e557-e567.
- [20] Matthay MA, Arabi YM, Arroliga AC, et al. A new global definition of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2024; 209(1): 37-47.
- [21] Sun B, Lei M, Zhang J, et al. Acute lung injury caused by sepsis: how does it happen? *Front Med.* 2023; 10: 1289194.
- [22] Iba T, Maier CL, Helms J, et al. Managing sepsis and septic shock in an endothelial glycocalyx-friendly way. *Ann Intensive Care.* 2024; 14(1): 64.
- [23] Ostermann M, Al Shamsi F, Artigas A, et al. ESICM clinical practice guideline on fluid therapy in adult critically ill patients. Part 3: fluid removal at the de-escalation phase. *Intensive Care Med.* 2025; 51: 1749-1763.