Critical care ATLAS CLOVERS

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CLOVERS

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The practice of critical care depends not only on the particular patient population served, but also on the context in which critical care is provided, including culture and regional norms and resources. How clinicians interpret and implement new evidence or guideline recommendations is affected by their unique context. In 2023, the Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension (CLOVERS) trial was published. The CLOVERS trial included 1,563 patients and studied early vasopressor initiation vs liberal fluid initiation after an initial fluid bolus for patients with septic shock seeking treatment in the United States. No mortality difference was found between the two treatment arms. In this article, adult and pediatric critical care clinicians from the United States, the United Kingdom, Italy, Rwanda, India, and Brazil describe how CLOVERS has impacted or will impact their practice.

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KEY WORDS: CLOVERS; fluid responsiveness; sepsis; shock; vasopressor

The Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension (CLOVERS) trial in the United States evaluated the effect of liberal fluid resuscitation vs early vasopressor initiation on septic shock mortality.[1] Protocolized sepsis care, recommend by the Surviving Sepsis Campaign (SSC) guidelines, has decreased mortality. Yet, it remains unclear whether the observed improvement in mortality is the result of fluid resuscitation or other sepsis bundle interventions.[2–5] The Protocolized Care for Early Septic Shock (PROCESS), Australasian Resuscitation in Sepsis Evaluation (ARISE), and Protocolised Management in Sepsis (PROMISE) randomized trials demonstrated no superiority in early goal-directed therapy vs current standards of care.[3–5]

Excess fluid resuscitation contributes to volume overload, renal dysfunction, and coagulopathy.[6–10] Conversely, vasopressor use is associated with organ and tissue ischemia and immune system dysregulation.[11,12] Two

ABBREVIATIONS: CLOVERS = Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension; Ea_{dyn} = dynamic arterial elastance; HIC = high-income country; LMIC = low-income and middle-income country; LIC = low-income country; SSC = Surviving Sepsis Campaign

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sepsis trials in Africa, one in children and one in adults, demonstrated worse mortality with either increased initial fluid bolus (the Fluid Expansion as Supportive Therapy [FEAST] trial)[13] or protocolized fluid administration (Simplified Severe Sepsis Protocol [SSSP] trial)[14]. In the Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) (Northern European ICU) trial, patients received an initial 30 mL/kg of fluids followed by restricted or liberal fluid administration. The trial was underpowered for mortality, but renal injury was associated with liberal fluid volumes.[15]

The CLOVERS trial was designed to determine whether resuscitation fluid volume contributes to sepsis mortality. Trial participants received an initial fluid bolus (2 L or approximately what the SSC guidelines call for) followed by 24 h of liberal or restrictive fluid administration (mean difference, 2,134 mL).[1] No difference in 90-day mortality was observed. A trend toward mortality was found in patients with end-stage renal disease receiving liberal fluids. This finding highlights the heterogenous nature of the CLOVERS population, which may have masked personalized medicine resuscitation approaches.

The interpretation of the neutral CLOVERS trial varies based on case mix and resource availability. The following vignettes, from expert adult and pediatric clinicians worldwide (United States, United Kingdom, Italy, Rwanda, India, and Brazil), explore available evidence and local critical care practice patterns in response to the CLOVERS trial.

CONTRIBUTOR(S):	Chandrashish Chakravarty
REGION:	Kolkata, India
SETTING:	Urban
PATIENT POPULATION:	Adult, medical
# OF BEDS IN PRIMARY ICU:	10

In 2017, Andrews et al[14] questioned whether we are giving too much fluid for resuscitation in shock, leading to more death. Most studies that have tried to answer the question of restrictive vs liberal fluids within first 24 h of admission ended in equipoise. However, multiple meta-analyses have correlated mortality to patients with high cumulative fluid balance after 3 to 4 days. The CLOVERS restrictive protocol ended at 24 h, resulting in minimal differences in fluid balance between the two groups after 72 h and no resulting differences in primary or secondary end points. The timeline of the CLOVERS trial raises another question: is the fluid given in first 24 h more important or is it continuation of that liberal strategy for next few days that leads to adverse outcomes?

Comparing the CLOVERS trial with the study by Rivers et al,[16] the average fluid volume used for resuscitation has decreased over the last 2 decades. Has fluid resuscitation in shock become more of a prehospital intervention? Are emergency and critical care physicians monitoring better for fluid responsiveness? Or, is it that we have moved away from large-volume resuscitation? These questions are yet to be answered.

I work in a tertiary care hospital in India, where the patient population differs from the CLOVERS trial. Prehospital care is disorganized in most parts of south and southeast Asia, resulting in minimal prehospital fluid administration. In the CLOVERS trial, both groups received 2 L of fluids before randomization. Common conditions include dengue shock, undifferentiated GI sepsis with diarrhea or vomiting, and so on, all of which require increased fluid resuscitation. The CLOVERS trial excluded these patients. Patients seek treatment late with higher lactate levels and Sequential Organ Failure Assessment scores because of poor awareness of sepsis and limited access to tertiary health care centers. The COVERS trial excluded these patients.

This trial demonstrated the safety of norepinephrine through peripheral veins, which decreases the urgency of placing a central line on arrival in the ED. CLOVERS outcomes suggest that patients with end-stage renal disease need cautious fluid.

My practice will not change much in light of the CLOVERS trial. New patients are resuscitated with a 1- to 1.5-L bolus similar to all patients before randomization in the CLOVERS trial. If BP is unrecordable, norepinephrine

is started via peripheral veins as rescue. I assess for poor fluid tolerance (end-stage renal disease with dialysis, severely short of breath with bilateral crackles, and so on). I use early dynamic fluid responsiveness evaluation via point-of-care ultrasound. Unless fluid tolerance is poor, if systolic BP remains < 90 mmHg along with signs of hypoperfusion, I wait to assess whether to administer another fluid bolus before starting vasopressors. My practice differs from the restrictive CLOVERS arm where patients with mean arterial pressure of < 65 mmHg or systolic BP of < 90 mmHg were started on norepinephrine unless the rescue criteria were met. Only around 60% of CLOVERS patients required vasopressors, suggesting a less severely ill patient population. Early vasopressor initiation can increase ICU use. In the CLOVERS trial, certain subgroups who are common in my Indian case mix were excluded (hypovolemic or hypervolemic, late presentation with tropical diseases, and so on). These patients demand more personalized fluid administration using dynamic echocardiographic changes and tissue perfusion makers.

CONTRIBUTOR(S): Theogene Twagirumugabe, Elisabeth Riviello, and Doris Uwamahoro

REGION: Kigali, Rwanda

SETTING: Urban

PATIENT POPULATION: Adult, medical/surgical

 # OF BEDS IN PRIMARY ICU: 2 primary hospitals, 22 and 7 beds

In this unmasked randomized clinical trial, researchers compared two fluid resuscitation approaches on outcomes of patients with sepsis in United States hospitals.[1] Prior studies in high-income countries (HICs) have suggested that liberal fluid strategies are beneficial or neutral.[3–5,17] Studies from low-income countries (LICs) have found a detrimental effect of liberal fluid resuscitation on mortality.[13,14] It is unclear whether these different findings in HIC vs LIC studies are the result of delays in access to hospital admission for patients with sepsis in LICs, differences in case mixes, a relative lack of ventilators to rescue from respiratory failure due to resuscitation-related pulmonary edema in LICs, or something else.

In general, restrictive fluids may be a better choice in our LIC context, given our case mix and resources. The risk of pulmonary edema without availability of mechanical ventilation could be a mechanism by which restrictive fluids perform better in patients with pneumonia, a common cause of sepsis in our hospitals. Delays in presentation may increase the prevalence of sepsis-induced cardiomyopathy and sepsis-induced vasoplegia, both of which benefit from early vasopressor administration. However, intraabdominal sepsis also is very common in our context and often includes prolonged lack of oral intake coupled with vomiting, intestinal obstruction impeding colonic water reabsorption, and third spacing.[16,18] All of these lead to a profoundly hypovolemic state, demonstrated by point-of-care ultrasound findings, dry mucosa, and laboratory hemoconcentration. In this situation, liberal fluid resuscitation is a reasonable approach. In late-presenting intraabdominal sepsis, the risk of intestinal edema modifying peristaltic movement is present, which in turn may predispose patients to higher rates of postoperative pulmonary complications. We emphasize early deresuscitation in these patients. The CLOVERS trial excluded patients with "severe volume depletion from non-sepsis causes," which describes a relatively high proportion of patients with sepsis. Another particular challenge in our setting is patients with underlying severe chronic malnutrition, a group who are not well represented in the CLOVERS cohort.

With clinical heterogeneity among patients even within an LIC or HIC cohort, let alone the additional heterogeneity seen in comparison between LIC and HIC settings, it is not surprising to us that neither strategy used in the CLOVERS trial showed show definite harm or benefit over the other. We train our residents to start with the SSC guidelines for initial fluid resuscitation,[17] as was carried out in the CLOVERS trial. However, we use the patient's underlying disease process, volume status on clinical examination, and dynamic assessment measures, particularly with monitoring of fluid

responsiveness with point-of-care ultrasound, to make reasonable decisions that are driven by an individual patient's particular condition. This includes making a choice between vasopressors and fluids depending on the clinical context. Although the CLOVERS trial does not directly confirm or caution against our practice of an individualized decision of escalation with vasopressors vs escalation with fluids, its finding of no difference between the arms is somewhat reassuring that either choice is safe, at least in aggregate. Although to our knowledge no randomized controlled data are available to date that demonstrate improved outcomes with using clinical parameters to guide the choice between emphasizing vasopressors or fluids, we find it reasonable to continue our prior practice of decision-making at the bedside.

CONTRIBUTOR(S): Matteo Di Nardo
REGION: Rome, Italy
SETTING: Urban
PATIENT POPULATION: Pediatric, medical/surgical
 # OF BEDS IN PRIMARY ICU: 6

The CLOVERS trial demonstrated that the use of an early restrictive fluid strategy was not superior to a liberal fluid strategy in reducing mortality in hypotensive patients with sepsis.[1] Trial intervention was limited to the first 24 h, and no data are available on fluid accumulation at the end of the ICU stay. Retrospective pediatric studies have shown poor outcomes associated with fluid overload (eg, higher risk of mortality, greater need for continuous renal replacement therapy, and prolonged mechanical ventilation and ICU length of stay).[19] A meta-analysis including 44 pediatric studies showed a 6% increase in odds of mortality with each 1% increase in fluid overload.[20]

As pediatric intensivist, I consider fluids to be medicine, and thus I try to avoid liberal use during the early phases of septic shock, favoring a tailored and physiologic fluid resuscitation strategy. My personal protocol-guided resuscitation relies on monitoring the parameters of fluid responsiveness at the bedside during mechanical ventilation. Both pulse pressure variation and stroke volume variation are used to evaluate fluid responsiveness at the bedside; however, both are not predictors of BP increase after a fluid challenge test. Furthermore, the accuracy of both pulse pressure variation and stroke volume variation to evaluate fluid responsiveness is low during spontaneous breathing. For all these reasons, I combine these parameters to evaluate dynamic arterial elastance (Ea_{dyn}).[21] This parameter enables understanding whether an increase in cardiac output after an initial fluid challenge may be associated with a change in mean arterial pressure. The Ea_{dyn} is nothing other than a surrogate for arterial load and can be estimated easily at the bedside using hemodynamic monitors able to measure the cardiac output and other dynamic parameters continuously. Ea_{dyn} is calculated as the ratio between pulse pressure variation and stroke volume variation. The normal Ea_{dyn} value is around 1.

In general, in a hypotensive child, if Ea_{dyn} is high ($>$ 1), mean arterial pressure will increase if cardiac output increases after a fluid challenge. However, if Ea_{dyn} is low ($<$ 1), mean arterial pressure will not increase after a fluid challenge, even if cardiac output increases. Based on these physiologic considerations, patients showing a low Ea_{dyn} should not receive high volumes of fluids to increase mean arterial pressure; rather, they should receive vasopressors to correct hypotension. Furthermore, the Ea_{dyn} also may be used to wean patients from vasopressors in those recovering from septic shock.

In conclusion, I believe that the results of the CLOVERS trial should be interpreted with caution. Clinical strategies including the use of both noninvasive hemodynamic devices, ultrasonographic assessments tools, and newer invasive devices to study and interpret the arterial pulse contour may enable clinicians to titrate fluid therapy more physiologically and according to the patient's needs.

Use of fluid during hemodynamic optimization not only is intended to improve mean arterial pressure, but mainly is intended to increase oxygen delivery to the tissues. In this context, Ea_{dyn} could help to determine if a hypotensive patient showing a preload response will require only fluids or fluids and vasopressors.

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REGION:	Belfast, United Kingdom
SETTING:	Urban
PATIENT POPULATION:	Adults, medical/surgical
# OF BEDS IN PRIMARY ICU:	2 units, 12 and 30 beds

The CLOVERS trial found a lack of a difference between liberal and restrictive approaches for fluid administration in a 24-h period in patients with sepsis who already had received initial fluid resuscitation. A delay in commencement of vasopressors to allow for up to 5 L of IV fluid administration and assessment of response, well in excess of the 2-L or 30-mL/kg SSC guidelines, was shown to be both rational and safe. Equally, it must be recognized that further fluid administration after the initial 2 L did not improve clinical outcomes, suggesting that fears of adverse outcomes resulting from excessive vasoconstriction in an underfilled patient likely are misplaced. Our preexisting approach to hypotensive patients with sepsis is to use repeated assessment of response to IV fluid boluses using perfusion-based end points such as capillary refill, with early initiation of vasopressors and discontinuation of fluid administration when fluid responsiveness no longer is present or perfusion is adequate.

Fewer patients in the liberal fluid group required insertion of a central venous catheter and admission to a critical care bed, likely the result of a reduced need for IV vasopressors, which typically would mandate critical care admission. In the United Kingdom health care setting, ICU bed availability is low compared with other HICs (10.5 beds per 100,000 compared with 25.8 beds per 100,000 in the United States). Therefore, from a health system perspective, clinicians practicing in the United Kingdom can continue to prioritize fluid resuscitation over vasopressors during the initial hours of treatment in the expectation that critical care admission may be avoided safely in some patients.

Within both treatment algorithms, clinicians were able to use their judgement to administer fluid and vasopressors as necessary. This is perhaps one reason why the difference in fluid volumes administered was small. Peripheral norepinephrine infusion was found to be safe as an initial approach, which is reassuring and potentially practice changing, because this is not widely used in our setting.

While reassuring that nuances of precisely when to stop administering IV fluids and to start giving vasopressors probably are unimportant, and our current practice is unlikely to change as a result of this trial, unanswered questions remain relating to the periods both before and after the trial intervention. Patients had received 1 to 3 L of IV fluid already before enrollment, and this very early fluid administration may be when harm occurs.[13] Optimal subsequent management of fluid administration and accumulation, which is common in critically ill patients because of a combination of obligate fluid intake (nutrition and drug diluents) and resuscitation fluid, also remains uncertain. Finally, identification of specific sepsis phenotypes might allow further refinement of fluid administration strategies.[22]

Overall, the CLOVERS trial empowers critical care clinicians to exercise reasonable judgment regarding individualized, rather than protocolized, fluid resuscitation in sepsis with relative confidence that we are not walking an imaginary tightrope and should inspire future research into the remaining unanswered questions regarding this almost ubiquitous therapy.

CONTRIBUTOR(S): Daniela Helena Machado Freitas and Juliana Carvalho Ferreira
REGION: São Paulo, Brazil
SETTING: Urban
PATIENT POPULATION: Adults, medical
OF BEDS IN PRIMARY ICU: 10

The burden of sepsis is higher in low-income and middle-income countries (LMICs), where resource scarcity limits access to care and impacts outcomes.[23] Among many challenges to treating sepsis in LMICs is the need for treatment protocols that are applicable in the local context. Adopting treatment protocols developed in HICs can lead to unexpected outcomes, as was the case when using early goal-directed therapy in randomized trials in adults and children in Africa.[13,24]

The CLOVERS trial results offer an interesting opportunity for ICUs in LMICs and other resource-limited settings to develop treatment protocols that are tailored to local infrastructure. Given that previous trials in LMICs found that a liberal resuscitation strategy could be harmful[13,14] and that the CLOVERS trial, performed in high-income settings, showed similar outcomes for liberal and restrictive strategies, implementing a protocolized restrictive fluid strategy adapted to local context and resources is appropriate.

The pragmatic approach of the CLOVERS trial has other implications for limited resource settings. First, the demonstration of safety of administering vasopressors initially through a peripheral IV catheter could reduce the time for shock reversal and impact outcomes in settings where shortages of catheters, number of health care workers per ICU bed, or both can delay the insertion of central venous lines. Second, the resuscitation treatments for both groups used noninvasive and widely available clinical and laboratory parameters such as BP, heart rate, and serum lactate levels, allowing for implementation in a variety of contexts.

Lessons learned from the CLOVERS trial and other recent studies[13,14] provide the basis for the implementation of evidence-based treatment protocols that can be feasible in ICUs with limited resources, promoting optimization of treatment. For ICUs in middle income-countries, like our ICU in Brazil, where both vasopressors and fluids are available, but the ratio of ICU nurses to beds is reduced, a restrictive fluid strategy can be advantageous. Our treatment protocol, which was based on vasopressor infusion exclusively through central venous lines and unstructured fluid strategy that favored a restrictive approach, but lacked standardization, is being adapted to favor a protocolized fluid restrictive strategy allowing peripheral vasopressor infusion. After the initial fluid resuscitation, if adequate levels of BP and clinical parameters of tissue perfusion are not met, a vasopressor will be started through a peripheral line unless a central venous a catheter is already inserted to avoid delays in initiating treatment. Patient response, need for rescue fluid therapy, and fluid tolerance will be monitored to avoid complications. If the patient continues to need vasopressors for more than 4 to 6 h or needs increasing doses of vasopressors or other forms of advanced life support, a central venous line should be inserted. Other ICUs in resource-limited settings may prefer to implement a liberal fluid strategy, depending on what best fits the local context. In either case, monitoring ICU indicators and conducting implementation research will be essential to confirm that the local treatment protocol effectively contributes to reversing septic shock, optimizing interprofessional care, and impacting patient-centered outcomes, while also contributing to rational and equitable resource allocation.

CONTRIBUTOR(S):	Michael Root and Mark E. Mikkelsen
REGION:	Denver, Colorado
SETTING:	Urban
PATIENT POPULATION:	Adults, medical
# OF BEDS IN PRIMARY ICU:	24

Sepsis is a common condition encountered in EDs, hospital wards, and ICUs across the globe. A threat to public health, principles of sepsis management have been infused into guidelines, protocol campaigns, and performance measures. Sepsis-induced hypotension is a recognized prelude to multisystem organ failure and death; yet, whether clinicians should embrace a restrictive or liberal fluid strategy when encountered remains controversial.

The CLOVERS trial randomized patients with sepsis-induced hypotension to a restrictive (less fluid, earlier vasopressors) or liberal resuscitation strategy. When considering how to implement CLOVERS practices, given that no difference in mortality between the groups was found, it is useful to divide the study into two distinct phases—before and after randomization—with several questions in mind. First, how much fluid should be administered? Second, when and how should vasopressors be initiated?

Before randomization, the median volume of fluid administered was 2,050 mL, consistent with guideline recommendations to administer at least 30 mL/kg of IV fluid within 3 h to patients with sepsis-induced hypoperfusion or septic shock. After randomization, fluid administration differed substantially. By 6 h, the restrictive group had received a median of 500 mL compared with 2,300 mL for the liberal group, corresponding to an additional 7 mL/kg or 33 mL/kg for a 70-kg patient, respectively. By 24 h, the gap widened to more than 2 L. These differences were realized through differential use of vasopressors, which were initiated earlier (1.8 h after randomization vs 3.2 h after randomization), more often (59% vs 37%), and for longer (9.6 h vs 5.4 h) among the restrictive group. Peripheral vasopressor administration was common, yet safety events were rare: only 3 of 500 patients experienced extravasation, none of whom needed intervention.

The CLOVERS trial affirms several practices implemented within our health system. First, we use a system-wide low-dose peripheral pressor protocol with specification for a 20-gauge or larger IV line limited to the upper extremity. The protocol facilitates earlier vasopressor initiation, fewer fluids, and avoidance of central line complications. To promote adherence to the Centers for Medicare and Medicaid Services sepsis performance measure bundle (SEP-1), we use electronic health record-integrated pathways, order sets, and documentation tools in the ED and acute care setting. Our fluid orders recommend balanced crystalloid fluids and support more rapid boluses, coupled with reassessment prompts, when deemed appropriate. Our health system recognizes the balance between compliance with quality measures and providing individualized care to patients. Although our tools nudge providers to administer 30 mL/kg of IV fluid, we acknowledge situations where less fluid and earlier vasopressors may be preferred and prompt the clinician to justify their clinical decision-making to ensure SEP-1 compliance.

The CLOVERS trial supports earlier use of vasopressors (centrally or peripherally) with smaller volumes of crystalloid in early resuscitation as a strategy to decrease the risk of volume overload. Because the heterogeneity of sepsis warrants individualized care, our philosophy is that institutional protocols and electronic health record-integrated tools can bring evidence-based care to the bedside and simultaneously can support the clinician to deliver individualized care.

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