VIEWPOINT

Septic Shock: First Fill the Pipes Up

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Received on: 13 October 2022; *Accepted on:* 28 March 2023; *Published on:* 03 May 2023

Abstract

The rationale for fluid resuscitation is to increase mean systemic filling pressure (Pmsf), venous return, and cardiac output by increasing circulatory stressed volume. However, several conditions must be fulfilled to achieve desirable outcomes from fluid resuscitation. Vasopressors are also important components of resuscitation in septic shock and can potentially supplement the beneficial effects of fluid. However, the potential benefits of vasopressors must be weighed against several harms associated with vasopressors. Risks associated with vasopressors are more pronounced with underfilling of circulation and in higher doses. Current physiological and clinical evidence supports intravenous fluids as the first-line resuscitation agent in septic shock, with vasopressor infusion as a supplement to the same.

Keywords: Intravenous fluid, Septic shock, Vasopressors.

Journal of Acute Care (2022): 10.5005/jp-journals-10089-0049

Introduction

Septic shock is the leading cause of mortality and morbidity worldwide.[1] Key aspects of the successful management of septic shock are early recognition, administration of adequate antimicrobial(s), source control, organ support, and early aggressive resuscitation. As recommended by international guidelines, resuscitation starts with the rapid intravenous fluid bolus, followed by further fluid administration guided by physiological parameters.[2] Not unexpectedly, the potential consequence of vigorous fluid resuscitation is fluid overload and the development of tissue edema, especially when the resuscitation is not monitored carefully.[3] In response to the risk of fluid overload and with an aim to avoid it altogether, some clinicians have started advocating septic shock resuscitation with only vasopressors or the so-called "squeeze the vein" approach. This approach is perhaps too reactionary and not based on sound physiological rationale or clinical evidence. In subsequent paragraphs, I shall be focusing on why fluids should still be the first-line option in septic shock, possible harms associated with only the "squeeze the vein" approach, and possible ways to limit cumulative fluid balance (and thus avoid potential harm associated with fluid overload) without causing tissue hypoperfusion.

Septic Shock: Pathophysiology

Septic shock is characterized by both macro and microcirculatory dysfunctions. Some of the macrocirculatory changes observed in patients with septic shock are as below:

- Decreased stressed volume—this may be both absolute because of poor intake and/or gastrointestinal loss and relative because of vasodilatation and/or leaky capillaries related to the destruction of the glycocalyx. Reduction in stressed volume leads to a decrease in mean Pmsf, (the upstream pressure for venous return), and venous return.
- Decreased stroke volume—related to the decrease in venous return and/or septic cardiomyopathy.
- Arterial hypotension—vasodilatation leads to arterial hypotension contributing to poor tissue perfusion.
- Tachycardia—increased heart rate maintains the cardiac output but results in poor diastolic filling and loss of ventriculo-aortic coupling.
- Septic cardiomyopathy—poor left ventricular contractility (with normal filling pressure), decreasing cardiac output further. Right ventricular dysfunction, including poor contractility and dilatation.

Resuscitation measures aim at improving macrocirculatory parameters. In the early stages of septic shock, macrocirculatory improvement leads to improvement in microcirculation ("hemodynamic coherence"). However, in the late stages, this coherence between macro and microcirculation is lost, leading to refractory shock.[4]

Rationale: Fluid Resuscitation

Rapid infusion of intravenous fluid can potentially increase Pmsf, provided there is no extreme vasodilatation or the capillary leak is not too much.[5] Increase in Pmsf, if not associated with a simultaneous increase in right atrial pressure, increases venous return. An increase in venous return leads to an increase in stroke volume, provided both right and left ventricles are working in the steep part of the cardiac function curve. Increased stroke volume (and cardiac output) is expected to increase tissue delivery of oxygen (DO_2) and tissue perfusion. An increase in stroke volume may also improve tissue perfusion by increasing mean arterial pressure (MAP), provided ventriculo-aortic coupling is maintained.

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How to cite this article: Ghosh S. Septic Shock: First Fill the Pipes Up. J Acute Care 2022;1(3):143–145.

Source of support: Nil

Conflict of interest: None

Unfortunately, in some patients, the relationship between intravenous fluid bolus and improvement in tissue perfusion is not so straightforward.

- As can be seen from the above discussion, a number of other conditions must be fulfilled for an increase in cardiac output following an intravenous fluid bolus. In fact, after receiving an initial fluid bolus, only half the patients with septic shock remain fluid-responsive.[6] This fact emphasizes the need for checking fluid responsiveness before administering further fluid boluses in the optimization phase of resuscitation.[7]
- An increase in cardiac output and other hemodynamic benefits are seen after a rapid fluid bolus is often only transient.[8]
- Apart from the cardiac output, DO_2 and tissue perfusion are also related to hemoglobin and oxygen saturation.
- Once the coherence between macro and microcirculation is lost, any further fluid boluses can only contribute to fluid overload, not tissue perfusion.

Rationale: Vasopressor

The goal of vasopressor infusion is to quickly restore MAP and improve tissue perfusion (MAP being the upstream pressure for organ perfusion). Studies have shown prolonged hypotension to be associated with increased mortality.[9] Moreover, norepinephrine can also increase Pmsf through its venoconstriction effect and potentially improve venous return and cardiac output.[10] Early initiation of norepinephrine infusion has also been shown to reverse the shock state earlier.[11]

Unfortunately, these potential benefits of vasopressor infusion come at a high cost.

- Norepinephrine infusion may actually decrease cardiac output by increasing resistance to venous return.[5] This becomes particularly prominent in the presence of hypovolemia (both relative and absolute).
- Vasopressors can potentially increase organ ischemia by vasospasm. In the multicenter SEPSISPAM study, incidences of acute myocardial infarction, mesenteric ischemia, and digital ischemia were 1.8, 2.3, and 2.6%, respectively, in the "high MAP" target group.[12]
- All vasopressors are associated with the risk of potentially life-threatening cardiac arrhythmias. In the SOAP II study, overall incidences of arrhythmias were 24.1% in "the dopamine arm" and 12.4% in "the norepinephrine arm." [13]
- Other metabolic disturbances like hyperlactatemia are also known with a certain vasopressor infusion. In the multicenter CAT study, 12.9% of patients included in the "epinephrine group" withdrew because of transient but significant metabolic side effects, especially hyperlactatemia.[14]

Fluid and Vasopressor Interaction: Clinical Evidence

In a retrospective analysis of data from 2,849 patients with septic shock, admitted in one of the 24 hospitals across three countries and survived for at least 24 hours, authors found a strong interacting association between fluid and vasopressors and mortality.[15] Mortality was lowest when vasopressors were begun 1–6 hours after hypotension onset and after >1 L of fluids. The authors concluded that in the 1st hour of septic shock resuscitation focus should be on aggressive fluid administration.

In another multicenter observational study, 616 patients admitted with septic shock and who required at least one vasopressor within 24 hours of shock onset were evaluated to determine whether the intensity of vasopressor dosing is associated with mortality and whether the same is modified by concomitant fluid administration.[16] In the first 6 hours after shock onset, increasing vasopressor dosing intensity was associated with mortality, and the strength of association was dependent on the amount of fluid administered prior to starting the vasopressor infusion. Mortality did not increase significantly with an increasing dose of vasopressor if the pressor was initiated after at least 2 L of fluids.

Limiting Cumulative Fluid Balance

As seen in the evidence discussed so far, not administering fluid cannot be the solution to prevent fluid overload, and only the "squeeze the vein" approach is actually going to harm the patient. Rather, a comprehensive strategy should be in place to limit cumulative fluid balance.

- Large fluid boluses of 30 mL/kg over 3 hours, as suggested by surviving sepsis guidelines, are not based on robust clinical evidence and may possibly be harmful.[2] It is reasonable to follow the resuscitation strategy originally described by Latta "... having no precedence to guide me, I injected ounce after ounce of fluid closely observing the patient''.[17] Minimum fluid volume to be administered at a time should be at least 4 mL/kg of bodyweight.[18] While deciding the volume of fluid to be administered, clinical must consider patient phenotype; for example, evidence of obvious dehydration or history of fluid loss and any risk associated with fluid bolus ("fluid tolerance").
- Before administering further fluid boluses, the clinician should be reasonably certain about their positive impact on cardiac output, and appropriate tests for fluid responsiveness can help in this regard.[19]
- Vasopressor should be initiated early. In the REFRESH study, a strategy of initiating norepinephrine infusion after 1 L of fluid had shown to reduce the cumulative fluid balance.[20] However, further fluid administration should not be limited after starting norepinephrine infusion. In certain patients, the vasopressor infusion should be started along with fluid boluses, especially if the initial diastolic blood pressure is <50 mm Hg[21] or the diastolic shock index is >2.3.[22]
- In selected patients, resuscitation with hyperoncotic albumin (20 or 25%) may limit cumulative fluid balance. However, we need further data to widely use this strategy.[23]
- Most importantly, there is a need to limit maintenance fluid and "fluid creep" as they contribute to almost two-thirds of fluid intake in an ICU patient.[24] If the clinician feels the need for maintenance fluid after careful consideration, moderately hypotonic maintenance fluid is compared to an isotonic fluid to avoid sodium overload and cumulative fluid balance.[25]

Conclusion

Septic shock resuscitation must follow a personalized approach instead of a protocolized one. Fluid boluses remain the first-line approach to resuscitation in septic shock, either alone (in most patients) or along with vasopressors (in certain patients). Well thought out, multimodal monitoring is helpful in deciding the need for further fluid boluses, the timing of vasopressor initiation, need for inotropic support or blood transfusion. An approach of only "squeezing the vein" does not have any physiological rationale or clinical data supporting it and must be avoided to achieve a desirable outcome.

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