

Review of: "Fluids, Vasopressors and Inotropes to Restore Heart-Vessels Coupling in Sepsis: Treatment Options and Perspectives"

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Innocenti et al. presented an interesting paper on fluids, vasopressors, and inotropes in sepsis. The authors should be commended for raising several issues of debate regarding the management of sepsis.

I would like to outline a few comments that might be useful to the authors:

- Page 2, Introduction:
 - Second paragraph:
 - The authors state that “inflammation represents a stereotyped response of the organism to a variety of stimuli perceived as dangerous...”. The wording “perceived as dangerous” may be misleading. As the authors themselves state further, inflammation is not only the response in terms of defense, but also part of the healing process.
 - A disproportionate inflammatory reaction does not necessarily mean a cytokine storm. Previous studies have shown that the cytokine expression in sepsis is heterogeneous, which may be one of the reasons why anti-cytokine strategies in sepsis have failed.
- Regarding case 1:
 - Taking the history of the patient, did the authors check for fluid responsiveness before the initial fluid bolus of 30 ml/kg within two hours? As the authors themselves discuss later in their paper, there has never been robust evidence to recommend a bolus of 30 ml/kg for every septic patient with hypotension.
 - What does the term “bilateral ubiquitous interstitial syndrome” mean regarding lung ultrasound? Do the authors mean fluid overload of the lungs?
 - Why did the authors infuse fluid at a rate of 1 ml/kg/h if the passive leg raising test was negative?
 - Regarding the conclusion of the authors regarding case 1, I am not sure whether the case illustrates the issue of the correct fluid rate and the total fluid infusion.
 - Table 1: The authors should write out all abbreviations. For example, it is not clear what the abbreviations PA (second row) and PCR (second from last row) mean. Furthermore, they should reconsider reducing the number of items listed in this table because some of the items do not really contribute to the understanding of the case. They

have also listed abbreviations at the foot of the table for several parameters that are not presented in the table.

- Regarding case 2:
 - Looking into the subtitle, did the authors mean “heart” instead of “heat”?
 - Looking into the results of the blood gas analysis in table 2, it is not clear why the authors claim a compensated lactic acidosis. First, the base deficit was mild, just about 3 to 4 mmol/l. Second, blood lactate was only slightly elevated. Therefore, there is no background to diagnose a lactic acidosis.
 - Again, table 2 also requires a critical evaluation regarding the list of variables and the abbreviations thereof.
 - This patient received a fluid bolus of 30 ml/kg within an hour, which is questionable taking the medical history of the patient into consideration. This is even more dramatic taking the fact that the left ventricular ejection fraction was just 20%.
 - It is questionable to state that hemodynamic monitoring was carried out using a central venous pressure measurement, which is not dynamic.
 - At the end, the authors did not discuss the possibly negative effect of the initial fluid bolus in this case.
- Page 7, first paragraph:
 - Regarding the first bolus for early hemodynamic resuscitation, the authors have very well argued that we do not have evidence to support the practice of a fluid bolus of 30 ml/kg. However, they conclude that this could be a reasonable compromise. The effect of fluid resuscitation is to increase cardiac preload, thereby increasing cardiac output. As the authors themselves have discussed in their paper, every sepsis case is in a way unique. While a hypotensive patient with abdominal sepsis (who probably suffers from fluid sequestration in the third space) may benefit from such a fluid bolus, this could be inappropriate for a patient with sepsis of pulmonary origin. A septic hypotensive patient with protracted hyperthermia may benefit from fluid administration, while this may not be the case in an afebrile septic patient. The evidence from the retrospective data analysis by Kuttub et al. is, in my opinion, not sufficient to support the practice of this general fluid bolus. Hemodynamic compromise following sepsis may also be the result of a massive drop in systemic vascular resistance, so that early (probably simultaneous) administration of a vasopressor may be an option. In general, every septic patient should be tested for fluid responsiveness before any fluid is started with the aim of hemodynamic resuscitation. On top of that, regardless of fluid responsiveness, fluid tolerance should also be carefully considered.
 - Actually, the authors have included relevant arguments against the standard practice and guideline recommendations regarding fluid resuscitation in sepsis. However, these are not well organized in their paper.
- Tables 3 and 4: The authors should include the reference numbers in the tables for the studies they have summarized, so that readers can easily find the sources.
- In addition to the issues included regarding the controversies behind the timing of vasopressor treatment, the authors should also consider the relevance of very low diastolic blood pressure as a sign of massive peripheral vasodilatation, which may prompt early vasopressor infusion. In a recent review, Monnet et al. suggested a cutoff for diastolic blood

pressure to consider vasopressor use (Monnet X et al. Crit Care 2023;27:322).

- The authors have very well discussed the drawbacks regarding the role of vasopressors and inotropes in patients with sepsis. Since the inflammation cascade plays a central role, it would also be helpful to discuss hemodynamic modifications during sepsis beyond the mechanistic view.
- Generally, the paper needs English language editing. Here are just very few examples to corroborate this:
 - Page 3: The second paragraph reads as follows: “At the moment of the presentation, early antibiotic therapy aimed at controlling the pathogen widespread and the haemodynamic stabilization are the cornerstone of the treatment in all septic patients, with several points that still represent topics of debate.” This could be rewritten, just as an example, as follows: “Early calculated antibiotic therapy and hemodynamic resuscitation are the cornerstones of the management of sepsis. However, several issues are still a matter of debate.” This is just a suggestion.
 - Better pacemaker electrodes than pacemaker catheters
 - Page 3: Case 1. The second sentence “Referred cough in previous days” is not a complete sentence.
 - Page 5: LV EF instead of LF EF
 - In general, the authors should write out all abbreviations at their first use.