

Fluid therapy in sepsis? Pathogen-specific perspectives

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Dear Editor,

Should intravenous fluid treatment be more restrictive in septic shock? The recently published CLASSIC trial, conducted in five European countries, compared standard treatment with fluid titration based on more stringent criteria for severe hypoperfusion [1]. This resulted in the intervention group receiving approximately 2L less of intravenous fluids. No difference in mortality or other study endpoints between groups was found [1]. While the trial results contribute to further optimising our fluid administration strategy in sepsis, the study is criticised for the small between-group difference in mean volume of fluids administered. This mainly because in clinical

practice, the general fluid management approach in sepsis already appears to have become more restrictive than in the past. The authors of the paper quote the Fluid Expansion Supportive Therapy (FEAST) trial in support of a fluid-restrictive approach [1,2].

We are of the opinion that more cautious framing is warranted when translating results of sepsis trials from one setting to another. The FEAST trial was conducted in East Africa, and a large number of study subjects had complicated malaria, which has a different pathophysiology requiring a more restrictive fluid management approach than bacterial sepsis [2,3]. The problem with recognising this distinction lies further upstream, as sepsis is defined as *a life-threatening organ dysfunction caused by a dysregulated host response to infection*, further characterised by signs of organ dysfunction [4]. In tropical settings, these criteria will not only apply to patients with bacterial sepsis, but also to patients with, for example, severe malaria or severe dengue, both requiring a different approach to fluid management (see Table 1) [3,5]. Therefore, it is clinical reality in tropical regions that patients presenting with a shock-like picture may fit sepsis criteria, but require different fluid resuscitation strategies depending on the causative pathogen. Failure to recognise the issue of applicability of sepsis and septic shock criteria in tropical regions and out-of-context referencing of sepsis trials contribute to malaria patients unrightfully being included in sepsis fluid therapy studies, and harm of undifferentiated fluid resuscitation in sepsis patients in tropical settings [2]. Other factors to take into account in terms of generalisability of sepsis research that greatly differ across world regions include population characteristics such as patient age and co-morbidities; and health-care related factors in resource-limited tropical (often low-income country) settings, such as availability of respiratory support [4,5].

To conclude, most incident cases of sepsis and sepsis-related deaths occur in tropical, resource-limited settings [5]. Yet, there is a lack of primary sepsis research conducted in these settings, resulting in limited applicability of most international sepsis guidelines, as they for example do not include aetiology-specific recommendations [4,5]. Thus, there is a need for consensus on a sepsis and septic shock definition validated in tropical settings, further assessment of the risk and benefit of fluid therapy in bacterial sepsis in low-resource settings, research informing bedside diagnostic and treatment interventions that can be integrated in resuscitation algorithms for low-resource settings, and analyses of the most cost-effective improvements of critical care for sepsis patients

TABLE 1. Examples of pathogens and disease causing a sepsis-like disease presentation requiring a specific fluid therapy approach

Bacterial sepsis	Severe <i>P. falciparum</i> malaria	Severe dengue
Haemodynamic state Intravascular volume is often reduced because of increased capillary permeability, meaning haemodynamic status may in some cases improve with bolus fluid therapy [3].	Haemodynamic state only mildly reduced and peripheral vascular resistance preserved, meaning most malaria patients are not hypotensive and will not benefit from bolus fluid therapy [3].	Haemodynamic state reduced due to increased capillary permeability causing plasma leakage during the critical phase and bleedings may occur, necessitating fluid resuscitation [5].
Fluid therapy recommendation For patients with sepsis induced hypo-perfusion or septic shock, at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 hr of resuscitation [4].	Fluid therapy recommendation When the patient is normotensive, give maintenance fluids only. Consider bolus fluid therapy in case of hypotensive shock only [3,5].	Fluid therapy recommendation Prompt fluid resuscitation is needed in the critical phase, guided by physiological parameters and laboratory values [5].
Issue with evidence As mentioned in the Surviving Sepsis guidelines, based on low quality evidence [4].	Issue with evidence Mainly based on limited observational evidence only [3].	Issue with evidence Limited quality of evidence [5].

worldwide. In order to catalyse this life-saving research, we must frame sepsis fluid therapy studies in their appropriate context.

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