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The great fluid debate: methodology, physiology and appendicitis

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In light of the fifth annual International Fluid Academy Days (IFAD) meeting in Antwerp, Belgium, it is time to reflect on the years that have passed since the first IFAD meeting and the publication of the major fluid trials in high profile journals [1–6] . While these produced partly conflicting results, some contained signals of increased mortality and higher incidence of renal replacement therapy associated with the administration of hydroxyethyl starch (HES). This led to warnings by regulatory bodies and virtually imposed a clinical ban on artificial colloids [7]. Incidentally, this also triggered the great fluid debate [8] and arguably fueled the success of IFAD [9].

Many clinicians judged the ban on HES to be premature. It was suggested that the baby would be thrown out with the bathwater, and therefore the studies were extensively and vividly debated on, often becoming a matter of belief vs. evidence [10, 11]. Specific concerns included the amount and type of fluid patients had received before randomization, and the unspecified criteria for starting renal replacement therapy.

While it is not our aim to reiterate these concerns, the review by Dr. Hahn in this issue of Anaesthesiology Intensive Therapy [12] reminds us of the ongoing debate and specifically of the importance of attention to detail. The review discusses the commonly held opinion that hypervolemia should be avoided. This opinion is supported by studies showing the release of atrial natriuretric peptide in response to hypervolemia, which is associated with glycocalyx shedding. The latter could lead to extravasation of proteins and fluids, which seemed to be confirmed by the report that hydroxyethyl starch, only expands the plasma by 40% of the infused volume in conditions of hypervolemia. Dr Hahn challenges these and other studies by critically disputing the validity of the methods used.

Dr. Hahn's meticulous explorations remind us of the importance of a thorough understanding of physiology by both scientists and intensivists. In fact, the practice of intensive care medicine may be viewed as applied physiology at the bedside. Interestingly, a perceived lack of physiologic rationale for fluid therapy was one of the main criticisms of the major fluid trials. As expressed in a commentary [13], "physiology teaches us that it is essential to define a clear hemodynamic endpoint in the individual administration of any solution. Thus, while the trials were impressive, it is unclear if fluids were used correctly".

In general, accepted therapeutic principles must be followed. These include avoidance of fluid overload. At times, no fluid administration will be better than non-indicated administration of whatever type of fluid. Hypervolemia, in the setting of a capillary leak, will lead to extravascular fluid accumulation, possibly causing organ edema, organ failure, and increasing morbidity and mortality. Appropriately defined treatment targets that are continuously being adjusted to the varying phases of critical illness will help one to reduce the risk of such complications.

The importance of attention to detail is exemplified by the fact that commentaries in scientific journals and lectures at scientific meetings dealing with the major fluid trials often cite information only contained in the appendices of the original publications. Given the frequent emotional nature of the

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Table 1. Analysis of the 6S and CHEST trials using the Patient, Intervention, Comparator and Outcome (PICO) method. Bold text indicates information that is only available in the appendix or in the legend of figures (adapted from [1, 2])

Patients	**6S**	**CHEST**
N	804	7000
Setting	ICU, Scandinavia	ICU, Australia and New Zealand
Inclusion criteria	Patients requiring fluid resuscitation in the ICU fulfilling the criteria of severe sepsis during the preceding 24 hours. Severe sepsis (100%). **Definition of severe sepsis: sepsis (focus of infection and at least 2 SIRS criteria) and at least 1 organ failure. Excluded were patients with intracranial hemorrhage or renal replacement therapy were excluded**	Patients requiring fluid resuscitation over and above that required for maintenance. Hypovolemia in medical and surgical ICU patients; Sepsis in 29.2 and 28.4% of patients, respectively. **Excluded were patients after cardiac surgery or with intracranial hemorrhage**
Age and sex	66–67 years; 60–61% male	63 years; 60% male
Illness severity at baseline	Median SAPS II score 50 and 51, respectively; mechanical ventilation in 60 and 61% of patients, respectively; acute kidney injury in 36 and 35% of patients, respectively.	Apache II score 17, respectively; mechanical ventilation in 64.1 and 64.9% of patients, respectively; no patients with impending or current renal failure.
Vital signs at baseline	'Shock' **(mean arterial pressure < 70 mm Hg, need for inopressors, or serum lactate > 4 mmol L^{-1} < 1h before randomization),** in 84% of patients. **CVP 10 mm Hg, respectively; $ScvO_2$ 75 and 73%, respectively; serum lactate 2.0 and 2.1 mmol L^{-1}, respectively; arterial hypertension in 39% of patients, respectively**	Heart rate 89 bpm, respectively; mean arterial pressure 74 mm Hg, respectively; CVP 9.5 and 8.9 mm Hg, respectively; serum lactate 2.1 and 2.0 mmol L^{-1}, respectively
Non-trial fluids before randomization	Median amounts of 3,500 and 3,000 mL in 96 and 97% of patients, respectively	**Not specifically reported; included in 'day 0' = day of randomization.** Excluded were patients having had received > 1,000 mL HES before screening
Blood products before randomization	Median amounts of 838 and 600 mL in 23 and 22% of patients, respectively	**Not specifically reported; included in 'day 0' = day of randomization**
Synthetic colloids before randomization	**Median amounts of 700 and 500 mL in 42% of patients, respectively**	HES in 15% of patients, respectively
Time from admission to randomization	**Medians of 3.7 and 4.0 h, respectively**	Mean 10.9 ± 156.5 and 11.4 ± 165.4 h, respectively
Intervention	**6S**	**CHEST**
Fluid	6% HES with molecular weight of 130 kDa, and substitution ratio of 0.42. **Na^+ 140 mmol L^{-1}, K^+ 4 mmol L^{-1}, Ca^{++} 2.5 mmol L^{-1}, Mg^{++} 1.0 mmol L^{-1}, Cl^- 118 mmol L^{-1}, malate 5 mmol L^{-1}, acetate 24.0 mmol L^{-1}**	6% HES with molecular weight 130 kDa, and substitution ratio of 0.42. Na^+ 154 mmol/L, Cl^- 154 **mmol L^{-1}**
Indication	Hypovolemia as perceived by clinical judgment	Hypovolemia as perceived by clinical judgment + 1 physiological criterion **(i.e., heart rate > 90 bpm, systolic or mean arterial pressure < 100 or < 75 mm Hg, respectively, CVP < 10 mm Hg, PAOP < 12 mm Hg, respiratory pressure variation > 5 mm Hg, capillary refill time > 1s, urine output < 0.5 mL kg^{-1})**
Maximum dose and duration	33 mL $kg^{-1}d^{-1}$ IBW, 90 days	50 mL kg^{-1}, 90 days
Comparator	**6S**	**CHEST**
Fluid	**Na^+ 145 mmol L^{-1}, K^+ 4 mmol L^{-1}, $Ca2^+$ 2.5 mmol L^{-1}, $Mg2^+$ 1.0 mmol L^{-1}, Cl^- 127 mmol L^{-1}, malate 5 mmol L^{-1}, acetate 24 mmol L^{-1}**	Na^+ 154 mmol L^{-1}, Cl^- 154 mmol L^{-1}
Outcomes	**6S**	**CHEST**
Primary outcome	Composite death or dependence on dialysis 90 days after randomization	All-cause mortality 90 day after randomization
Modified intension-to-treat analysis primary outcome	Death at 90 days: HES vs. comparator, RR 1.17 (1.01–1.36), $P = 0.03$. **Survival time censored at 90 days: $P = 0.07$**	Death at 90 days: HES vs. comparator, RR 1.06 (0.96–1.18), $P = 0.26$. Survival time censored at 90 days: $P = 0.27$
Per-protocol analyses primary outcome	**Death at 90 days: Per-protocol analysis 1: HES vs. comparator, RR 1.14 (0.97–1.34), $P = 0.12$. Per-protocol analysis 2: HES vs. comparator, RR 1.16 (0.97–1.37), $P = 0.07$.**	Death at 90 days if sepsis at randomization: RR 1.07 (0.92–1.25), $P = 0.38$. **Death at 90 days, adjusted: RR 1.05 (0.95–1.16), $P = 0.33$**
Patients	**6S**	**CHEST**

Table 1 (cont.). Analysis of the 6S and CHEST trials using the Patient, Intervention, Comparator and Outcome (PICO) method. **Bold** text indicates information that is only available in the appendix or in the legend of figures (adapted from [1, 2])

Secondary outcome	Renal replacement therapy	Renal replacement therapy
Modified intension-to-treat analysis secondary outcome	HES vs. comparator: RR 1.35 (1.01–1.80), $P = 0.04$	HES vs. comparator: RR 1.21 (1.00-1.45), $P = 0.04$ **Adjusted: RR 1.20 (1.00–1.44), $P = 0.05$**
Trial fluid	Day 1: median amounts of 1,500 mL, respectively	**Day 1: mean amount of approx. 480 and 570 mL, respectively.**
	Days 1–3: median amounts of 4,000 mL, respectively	Days 0–3: 2,104 and 2,464 mL, respectively
ICU fluid balance	**Median amounts 5,452 and 4,616 mL, respectively**	**Days 0–3: mean amounts of approx. 3,120 and 3,340, respectively**
Circulatory variables at 24h after randomization	**CVP 11 and 10 mm Hg, respectively; ScvO2 75 and 73%, respectively; serum lactate 2.0 mmol L^{-1}, respectively.**	**Heart rate 87 bpm, respectively; mean arterial pressure 81 mm Hg, respectively; CVP approx. 10.5 and 11.5, respectively; serum lactate approx. 1.5 mmol L^{-1}, respectively**

debate on this subject, this phenomenon might ironically be termed 'appendicitis'. We asked ourselves whether those frequent referrals to the appendices are indeed necessary for accurate interpretation of data. For this purpose, we applied the Patient, Intervention, Comparator and Outcome (PICO) [14] method on the two highly cited 6S [2] and Chest [1] trials on fluid therapy in critically ill patients. Our analysis shows that going over all PICO criteria, the main text of both publications provide insufficient information (Table 1). This may well be clinically relevant.

There is a well-recognized trend in science to present information in an easily comprehensible albeit superficial space after fashion [15]. Busy clinicians, let alone regulatory bodies, are usually not inclined to routinely consult the appendices. If, however, clinically relevant information is contained within them, faulty conclusions and decision making may result. We therefore feel that all clinically relevant information must be contained in the main texts of publications.

The fluid debate provides important lessons in physiology, methodology and appendicitis. Surely, signals of potentially adverse effects of HES generated by the large fluid trials must not be ignored. However, they need to be interpreted in the context of trial-specific patient selection and of the timing and dosing of fluids.

We can possibly learn from other areas of medicine. For example, last year's publication in the New England Journal of Medicine of the MR. CLEAN trial [16] showed the benefit of intra-arterial treatment of stroke despite earlier negative trials. The neurology community succeeded in delineating a group of patients which benefits from a treatment that had previously failed under different circumstances. This re-emphasizes the utmost importance of patient selection, timing of intervention, and dosing of medication (and thus, also fluids) in affecting outcome.

In the context of fluid therapy in critically ill patients, the critical care community is well advised to follow this example. Considering patient safety and the financial implications of therapy with artificial colloids, the burden of proof of possible benefit of such treatment lies with the manufacturers and should only be pursued within the context of controlled clinical trials.

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