Time to face the book?: “Unfriending” IV fluids. Where are we currently with fluid administration in anaesthesia and critical care?

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"For every complex problem, there is an answer that is clear, simple, and wrong"
- Henry Louis Mencken, (12 Sep 1880 - 29 Jan 1956)

Introduction
The half-life of medical knowledge is known to be short, and yet the recent collapse in many of the basic tenets of fluid administration has come as a surprise to many. It is fairly clear that we need to change our practice with regard to fluid administration. However, a solid and reliable evidence base to inform the exact direction of this change does not exist yet. There are indications of where the underlying problems have been in fluid administration, and some pragmatic recommendations can be made.

The issues with fluids can be broken down into:

Content?
What type of fluid should we give?
This can be subdivided into:
• The crystalloid versus colloid debate
• The fluid composition debate:
  - How much sodium?
  - What osmolality?
  - What alternative negatively charged ions should be included in the solution to avoid exposing the patient to excessive chloride?

When and How?
This can be further subdivided into:
• How do we detect the need for fluid administration?
• How much should we give?
  - What end-points do we target once we decide to give fluids?
• At what rate should fluid be administered?

An overarching feature of both the crystalloid and the colloid debate, and the when and how debate, is the argument over where the administered volume goes. The "third space" concept is dead and buried. However, variable amounts of any administered fluid remain in the intravascular space.

An exciting development over the last few years has been the rediscovery of the glyocalyx. It is now realised that this ubiquitous endothelial layer probably holds the key to the distribution of fluid amongst the body compartments. It is well documented that there is a loss of integrity with regard to the glyocalyx in the clinical scenario physicians' recognise as the "leaky capillary". The glyocalyx is susceptible to damage by many of the agents and/or clinical situations known to lead to profound tissue oedema. Thus the glyocalyx provides both a surrogate end-point for research and a potential therapeutic target.

The following identified causes of disruption to the glyocalyx are known:

Systemic inflammatory states:
• Diabetes
• Hyperglycaemia
• surgery,
• trauma,
• sepsis,
• Inflammatory mediators
  - C-reactive protein,
  - A3 adenosine receptor stimulation,
  - tumour necrosis factor
  - bradykinin,
  - mast cell tryptase
• Acute fluid overload
  - Excess rapid fluid administration
The following therapeutic options for the protection or restoration of the glycolcalyx are known:

- N-acetyl cysteine
- antithrombin III
- hydrocortisone
- sevoflurane anaesthesia
- infusion of GAGs
  - chondroitin sulphate
  - hyaluronic acid

The observed loss of glycolcalyx integrity subsequent to fluid overload and excessively rapid fluid boluses is of great interest. This loss of integrity is seen even when pre-existing fluid depletion is present. This may account for previous observational studies, which have recommended the ongoing administration of large quantities of fluid. In simple terms the more fluid administered, the leakier the endothelial surface becomes. This leads to more of the fluid leaking from the vascular compartment and an apparent need for further large volumes of resuscitation fluid.

The popularity of colloids, particularly starches in the South African market, has been ascribed to many factors, including strong marketing. This marketing was supported with convincing literature. Therefore, it has come as a shock to many South African doctors that the starches were so quickly pulled from the market. It must be remembered that a large body of the literature that backed the use of starches originated from disgraced researcher, Joachim Boldt.

Surprisingly, many reviewers, while diligently removing the effects of the Boldt publications, and trying to compensate for the company-sponsored literature, have continued to mix up the starch molecules, and the carrier solutions of the various starches. It is particularly noteworthy that starches known to have problems have been included in the reviews that condemn the use of modern starches (130 kD).

Examples of this include high molecular weight starches and clotting (450 kD starches) and renal dysfunction and tissue accumulation (200 kD starches).

An additional problem with much of the current evidence condemning starches is that the level and the timing of resuscitation do not reflect real-world scenarios faced by anaesthesiologist. This issue is evident in the "SAFE" (saline versus albumin for fluid resuscitation in the critically ill) trial, where resuscitative fluids were administered over several days to patients who were not shocked by the definitions used for the "on-table" trauma or severe sepsis clinical scenario.

However, some clear signals seem to be emerging in the midst of this confusion. The ratio of colloid to crystalloid requirements is closer to 1:5:1 than the 3:1 up to 4:1 once touted. Anecdotally, many practitioners felt that a startling improvement in patient outcomes was achieved when the starches first became freely available in South Africa. Speculatively, this observation may have arisen due to practitioners reducing the administration of fluid to patients by up to 60%. The observed improved survival with colloid resuscitation may simply have been derived from clinicians avoiding drowning patients!

The signal that renal damage is an issue with starches appears to be strong, particularly in the patient with sepsis. However much of this work comes from severe sepsis and ongoing critical care. It is probably reasonable to continue to administer colloids in acute hypovolaemia. Clinicians should probably avoid pure colloid resuscitation. (This action lessens the risk of colloid nephropathy; a particular subtype of colloid fluid damage). Clinicians should also observe the recommended dose limit for colloids. Starches should probably be restricted to the acute resuscitation phase on the first day of illness.

Further to this, a significant separate signal of harm in sepsis from starches appears to be emerging. Presently, practitioners should avoid the use of starches in overtly septic patients until the exact issues here have been delineated.

Turning to the When and How, even as simple a concept as the bolus administration of fluid to help a shocked child is now under review. In a major surprise, the Fluid Expansion as Supportive Therapy (FEAST) trial demonstrated that harm would come to shocked children who were administered a fluid bolus. This was irrespective of whether the bolus was saline or albumin. It was particularly noteworthy that even shocked patients who initially showed a good clinical response to a fluid bolus subsequently experienced increased mortality. The full meaning and impact of this trial is still being dissected, but the presence of the signal of increased mortality from fluid administration raises questions about the fundamental objectives of fluid administration and of the end-points that we use as clinicians.

Uncertainty over the implications of FEAST leads to the issue of how fluids should be administered and in what volume. Researchers have had difficulties for many years with defining appropriate end-points for resuscitation. Shoemaker made the still valid observation that survivors of sepsis attained a higher cardiac output than non-survivors. The problem arose with trying to convert this simple observation (well patients do better than sick patients) into a set of end-points that could be used to try and convert sick patients into well patients. This methodological error has been repeated frequently with other end-points.

We are all familiar with the difficulties that one particular end-point is currently facing: central venous pressure (CVP) measurement. Many noted intensivists have removed this measurement from their practice, together with the pulmonary artery catheter. The issue with the CVP measurement essentially arises from the fact that it is a pressure measurement that is being used to inform on a volume requirement in the complete absence of any compliance data. However, no truly reliable replacement for CVP measurement has come forward for this end-point.

This has resulted in the inclusion of the following statement in the 2012 surviving sepsis guideline:
"A. Initial Resuscitation

- Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L).
- Goals during the first 6 hrs of resuscitation:
  - Central venous pressure 8–12 mm Hg
  - Mean arterial pressure (MAP) ≥ 65 mm Hg
  - Urine output ≥ 0.5 mL/kg/hr
  - Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C)."

The pragmatic inclusion of a CVP target in these guidelines is an acknowledgement that there is no universally acceptable alternative. Pulse pressure variation, systolic pressure variation and pulse oximeter plethysmographic assessments are only validated and/or possible in ventilated patients. In addition, they are associated with just as many sources of error as the CVP. Blindly following these numbers would lead to the same difficulties as blindly administering fluid to a particular CVP value.

In summary, there are issues and problems in all aspects of fluid administration which have only been touched on briefly in these notes. The practitioner is encouraged to have an open mind, and to realise that a major paradigm shift in fluid administration is occurring. This will lead to better patient care in the future.

**Conclusion**

A refresher course lecture should end with practical advice that can be applied to delegates’ practice from the moment that they return to work. This cannot be given at this time with regards to fluid administration.

Indeed, this lecture ends with some guiding principles:

- We are all probably giving too much fluid.
- Excess fluid is harmful to the majority of our patients. However, unmet fluid needs in patients still have great potential to cause harm.
- Uncontrolled unmonitored fluid administration at any time is harmful.
- All of the components of the fluid bag that is being administered should be regarded as drugs, with indications and contraindications. Each component of the administered fluid should be provided in its indicated amount.
- No single assessment can assure that fluid is the correct therapy for a patient. It is important to understand the physiological basis of each assessment method, the limitations behind each method of measurement, and to seek multiple clues, form a hypothesis, act on the hypothesis, and reassess.
- The majority of patients can probably be resuscitated with crystalloids. Chloride administration is an issue so balanced salt solutions should be utilised.
- Albumin is a good colloid, but the issue of cost remains.
- When stances return, it is important to stay inside the dose limits. They should not be administered in sepsis.

As Henry Mencken so elegantly stated, there have been many solutions to the complex problem of resuscitation. Several of them have been shown to be wrong. We look forward to better answers in the future.

**Conflict of interest**

Dr Farina has served on the advisory board and/or received sponsorships and/or received lecturer fees from B Braun Melsungen and Fresenius Kabi who distribute intravenous fluids in the South African market. This work is entirely that of Dr Farina, and has not been reviewed or altered by any other author.

The following articles and the PowerPoint slides associated with this talk can be obtained from the author.

**Bibliography**