

It is time to consider the four D's of fluid management

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We are very excited to present you this special issue of Anaesthesiology and Intensive Therapy (AIT) containing the Proceedings of the Fifth International Fluid Academy Days (iFAD) with some excellent reviews from internationally renowned experts in this fascinating field. This 5th anniversary iFAD will deliver once more a compact two-day program on clinical fluid management and will also emphasize the role of hemodynamic monitoring. The mission statement of the iFA is to foster education, promote research on fluid management and hemodynamic monitoring, and thereby improve survival of the critically ill by bringing together physicians, nurses, and others from throughout the world and from a variety of clinical disciplines. Only recently the medical community has seemed to recognise the importance of looking at fluids beyond their role as replacement or maintenance fluids or for mere hemodynamic stabilization, and to handle them as any other drug we give to our patients [1, 2].

BALANCED VERSUS UNBALANCED SOLUTIONS

The side effects of fluids are without doubt more than relevant. Normal saline, still one of the most employed intravenous crystalloid solutions, presents a *non-physiologically high*, content of Cl⁻ (and Na⁺), and has long been known to induce hyperchloremic metabolic acidosis. Despite the fact that some studies (mainly uncontrolled or retrospective) have shown that unbalanced solutions may not be as innocent as previously thought [3–5], only recently, the SPLIT trial has shed some new light on this issue [6]. This trial (the 0.9% Saline vs. Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy) is the first large randomized controlled trial comparing the clinical effects of two different types of crystalloids [6]. In this double-blind, cluster randomized, double-crossover trial, conducted in 4 ICUs in New Zealand, 2,278 ICU patients in need of crystalloid fluid therapy were enrolled to receive either 0.9% NaCl or Plasma-Lyte 148, as a balanced solution, according to an alternating block of 7-weeks for each specific ICU. The study was designed to evaluate the proportion of patients with acute kidney injury (AKI) during the first 90 days after enrolment as the primary outcome, and to assess sev-

eral clinically relevant endpoints as secondary outcomes. In contrast to the hypothesis, the authors observed an identical proportion of patients developing AKI in the two groups of treatment (9.6% in the balanced solutions group vs. 9.2% in the 0.9% NaCl group), as well as a similar use of renal replacement therapy, and in-hospital mortality.

Although the trial was conducted and analyzed with a rigorous methodology (internal validity) and represents a very important step ahead in the field, it also has some important limitations which leaves some major questions unanswered: Firstly, the study population included was composed, in its vast majority, of post-operative patients, after elective surgery (mainly cardiovascular), with a small incidence of co-morbidities (and relatively low APACHE II score), other sub-groups (like sepsis and trauma) all had small numbers of patients included (less than 5%). Secondly, more than 90% of patients had been exposed to intravenous fluids before enrolment while the majority of pre-enrolment fluid was balanced crystalloid. Since the strong ion difference of Plasma-Lyte is rather high at 50 mEq L⁻¹ (where the strong ion difference of a fluid to avoid acid-base changes lies around 24 mEq L⁻¹), it is possible that the acidifying effect of saline in the trial was annihilated by this fact. Thirdly, only low volumes of NaCl (namely a median of 2 L per entire ICU stay) were used, and, as such, cannot be extrapolated to large-volume resuscitation in patients with e.g. septic shock, burns, hemorrhagic shock, trauma, diabetic ketoacidosis etc. Finally, the effects of both treatments on plasma Cl⁻ concentration have not been measured, making it therefore impossible to assess the potential role in the deterioration of renal function during fluid therapy. As the authors have concluded, these findings, whereas showing a neutral effects of the two strategies in post-operative patients, leave unsolved the potential effects of intravenous balanced solutions in high-risk populations, more exposed to fluid therapy and at risk of AKI. The bottom-line is that the study does provide reassurance that in elective surgery or moderately sick critically ill patients, giving up to a maximum of 2 L 0.9% NaCl (during the entire ICU stay) results in no increased risk of AKI compared with Plasma-Lyte 148.

Although more data and studies are needed to solve this question, in the meantime we want to raise caution in using “normal saline” as resuscitation fluid beyond the 2 L studied in the SPLIT trial.

FLUIDS BEYOND RESUSCITATION

It is imperative to acknowledge that there are three main indications for fluid therapy. The United Kingdom’s National Institute for Health and Care Excellence (NICE) recently provided a complete set of guidelines, algorithms and instructions for intravenous fluid therapy in adult hospitalised patients [7]. The somewhat older GIFTASUP-guidelines [8] summarize evidence specifically for the management of surgical patients. The three indications are as follows:

Resuscitation fluids to correct an intravascular volume deficit or acute hypovolemia. It is this particular indication that has received the most scientific attention by far, especially in light of the recent colloid-crystalloid debate. Therefore, it is sometimes overlooked that a large part of the total infused volume during a patient’s stay in the hospital does not fall into this category.

Maintenance solutions are specifically given to cover the patient’s daily basal requirements of water and electrolytes. They are specifically intended to cover daily needs. These basic daily needs are water, in an amount of 25–30 mL kg⁻¹ of body weight, 1 mEq kg⁻¹ sodium and 1 mEq kg⁻¹ potassium per day. It is easily appreciated that with one litre of NaCl 0.9%, with a sodium content of 154 mEq L⁻¹ the daily need for salt is already grossly exceeded [9]. There is an ongoing debate, esp. in paediatric populations, about the tonicity of maintenance infusion. We strongly disagree that in their recent review in the *New England Journal of Medicine* [10], Moritz and Ayus have closed a controversy that is far from settled. Firstly, even in paediatrics it is unfair to measure the quality of maintenance solutions mainly on an outcome parameter that can occur in only one treatment arm and, thus, proving that a solution containing 50 mEq L⁻¹ of sodium entails a higher risk of lowering normal plasma sodium than a solution containing 154 mEq L⁻¹. Secondly, the authors extrapolate their conclusions to adult care based on no more than one small 29-year-old trial in a specific subpopulation [11]. In our opinion the majority of hyponatremia cases can be prevented by careful clinical judgement and follow-up by rigorously identifying (appropriate) ADH-secretion due to poorly corrected hypovolemia. Moreover, it should not be overlooked that hyponatremia often functions as indicator more than a cause of severity of disease (e.g. cirrhosis, heart failure etc. Above all, quality evidence on the deleterious effects of salt overload cannot be ignored [2, 12]. Instead of abandoning common practice and common sense, the authors should realise that their complaint of opinion-based scientific dissent is mutual with our complaint on their pa-

per. Although some specific maintenance solutions are commercially available in certain countries, none of them cover the precise daily needs of the average adult patient (mostly they contain too little potassium in relation to the salt and/or water content). Therefore, in practice it will be necessary to prepare them by adding electrolytes to readily available glucose or dextrose 5 or 10% preparations. Since the amount of fluids or electrolytes already administered by enteral intake, or as part of total parenteral nutrition, are to be subtracted from the maintenance prescription, the main strategies to reduce unnecessary fluid administration are the shortening of preoperative fasting regimens [13, 14] and the promotion of early postoperative feeding, even after abdominal surgery [15–18]. Pursuing this is imperative as a first step in the reduction of fluid-related morbidity.

Replacement solutions are prescribed to correct existing or developing deficits that cannot be compensated by oral intake, as seen in situations where fluids are lost via drains or stomata, fistulas, fever, open wounds (including evaporation during surgery), polyuria (salt-wasting nephropathy or diabetes insipidus) among others. Data on replacement fluids are sparse. Several recent guidelines advise one to match the amount of fluid and electrolytes as closely as possible to the fluid that is being or has been lost [7, 8]. An overview of the composition of the different body fluids can be found in the NICE-guidelines [7]. Most of the time isotonic balanced solutions will be just fine, although some diarrhoea can be hypotonic. An exception is the loss of gastric fluid, which is chloride rich and should be replaced by high chloride solutions, like normal saline. Replacement fluids are frequently overdosed in the perioperative setting due to the misconception that evaporation during surgery is always high. It has been shown that even open abdominal wounds with liberal exposure of organs are associated with a fluid loss of no more than 30 mL per hour [18, 19]. Moreover, the practice of using diuresis as a trigger for fluid administration can easily lead to fluid overload since both anaesthesia and surgery slow down the rate of elimination of crystalloids. Oliguria is poorly correlated with hypovolemia in the perioperative setting and should not trigger fluid administration, although increased diuresis is a good indicator of hypervolemia [20, 21].

THE FOUR D’S OF FLUID THERAPY

Firstly, we will suggest some definitions with regard to fluid management and fluid balance partially based on a conceptual model [2, 22–25].

FLUID BALANCE

Daily fluid balance is the daily sum of all intakes and outputs, and the cumulative fluid balance is the sum total of fluid accumulation over a set period of time [22, 26].

FLUID OVERLOAD

Dividing the cumulative fluid balance in litres by patient's baseline body weight and multiplying it by 100% defines the percentage of fluid accumulation. Fluid overload is defined by a cut-off value of 10% of fluid accumulation, as this is associated with worse outcomes [22, 27].

FLUID BOLUS

A fluid bolus is a rapid fluid infusion given as a bolus to correct hypotensive and hypovolemic (septic or haemorrhagic) shock. It typically includes the infusion of at least 4 mL kg⁻¹ given over a maximum of 10 to 15 minutes.

FLUID CHALLENGE

A bolus of 100–200 mL is given over 5–10 min, with a reassessment of hemodynamic status to optimize tissue perfusion. This allows the construction of a so-called Frank-Starling curve in order to assess the type of the curve and the position where the patient is located on the curve. The CVP and pulmonary artery occlusion pressure (PAOP) are potentially dangerous and useless in order to guide a fluid challenge [28–30].

EARLY ADEQUATE GOAL DIRECTED FLUID MANAGEMENT (EAFM)

Most studies looking at goal directed treatment define achieving the early goal as giving 25 to 50 mL kg⁻¹ (o, average 30 mL kg⁻¹) of fluids within the first 6 to 8 hours of resuscitation in case of septic or hypovolemic shock. However, others have argued that such large volumes of fluid lead to "iatrogenic salt water drowning" and have proposed a more conservative strategy [28].

LATE CONSERVATIVE FLUID MANAGEMENT (LCFM)

Recent studies showed that late conservative fluid management defined as 2 consecutive days of negative fluid balance within the first week of ICU stay is a strong and independent predictor of survival [31]. In contrast, patients with persistent systemic inflammation maintain transcapillary albumin leakage and do not reach the flow phase mounting up positive fluid balances.

LATE GOAL DIRECTED FLUID REMOVAL (LGFR)

In some patients, more aggressive and active fluid removal by means of diuretics and renal replacement therapy with net ultrafiltration is needed [32]. This is referred to as de-resuscitation.

CLASSIFICATION OF FLUID DYNAMICS

In combining early adequate (EA) or early conservative (EC) and late conservative (LC) or late liberal (LL) fluid management, four distinct groups can be considered with

regard to the dynamics of fluid management: EALC, EALL, ECLC, ECLL. The EALC and ECLC groups carry the best prognosis [25].

Now we have listed some basic definitions on fluids we will elaborate further on fluids as drugs.

Fluid resuscitation with colloid or crystalloid solutions is a ubiquitous intervention in acute medicine [23]. Although the selection of resuscitation fluids is mostly based on physiological principles, clinical practice is determined largely by clinician preference, with marked regional variations. There is emerging evidence that considering resuscitation fluids as drugs may affect patient-centred outcomes. Analogous to antibiotic therapy, we must take into account the 4 D's of fluid therapy: drug, dosing, duration and de-escalation. This is summarized in Table 1.

DRUG

All resuscitation fluids can contribute to the formation of interstitial edema, particularly under inflammatory conditions in which resuscitation fluids are used excessively [23]. Critical care physicians should consider fluids as drugs, each coming with indications and contraindications and potential side effects (hyperchloremic metabolic acidosis). As such, the best fluid is probably that which has not been given to the patient (especially if it was unnecessary). Different indications need different types of fluids. Replacement fluids must mimic the fluid that has been lost; maintenance fluids must deliver basic glucose metabolic needs while resuscitation fluids should focus on rapid restoration of circulating volume. The osmolality, tonicity, chloride and potassium levels etc. must all be taken into account, as well as patient factors (underlying conditions, kidney or liver failure, presence of capillary leak, albumin levels, fluid balance etc. when choosing the right fluid for the right patient at the right time. One must remember that from 1 L of glucose 5% given, only 10% will remain intravascular after one hour, vs. 25% for crystalloids and 100% for colloids.

DOSING

As Paracelsus nicely stated, it is the dose that makes the poison, and this is no less true when it comes to fluid management in the critically ill: although it is all about the dose, the timing and the speed of administration are also important. The requirements for fluid resuscitation and the response to fluid resuscitation vary greatly during the course of any critical illness. No single physiological or biochemical measurement adequately reflects the complexity of fluid depletion or the response to fluid resuscitation in acute illness [23]. Fluid boluses of 4 mL kg⁻¹ given over 15 minutes, or 200 mL of colloid vs 1000 mL of crystalloid given over 20 to 30 minutes, have been described. The bottom line

Table 1. Analogy between the 4 D's of antibiotic and fluid therapy

| | Description | Antibiotics | Fluids |
|---------------|-----------------------|---|--|
| Drug | Inappropriate therapy | More organ failure, longer ICU LOS, longer hospital LOS, longer MV | Hyperchloremic metabolic acidosis, more AKI, more RRT, increased mortality |
| | Appropriate therapy | Key factor in empiric AB selection is consideration of patient risk factors (prior AB, duration MV, corticosteroids, recent hospitalisation, residence in nursing home etc. | Key factor in empiric fluid therapy is consideration of patient risk factors (fluid balance, fluid overload, capillary leak, source control, kidney function, organ function). Do not use glucose as resuscitation fluid |
| | Combination therapy | Possible benefits: broader spectrum, synergy, avoidance of emergency of resistance, less toxicity etc. | Possible benefits: specific fluids for different indications (replacement vs. maintenance vs. resuscitation), less toxicity |
| | Appropriate timing | Survival decreases with 7% per hour delay. Needs discipline and practical organisation | In refractory shock EGDT has proven beneficial. The longer the delay the more microcirculatory hypoperfusion |
| Dosing | Pharmacokinetics | Depends on distribution volume, clearance (kidney and liver function), albumin level, tissue penetration | Depends on type of fluid: glucose 10% IV, crystalloids 25%, vs. colloids 100% IV after 1 hour, distribution volume, osmolality, oncoticity, kidney function |
| | Pharmacodynamics | Reflected by the minimal inhibitory concentration. Reflected by "kill" characteristics, time (T > MIC) vs. concentration (Cmax/MIC) dependent | Depends on type of fluid and where you want it to go: IV (resuscitation), IS vs. IC (cellular dehydration) |
| | Toxicity | Some ABs are toxic for kidneys, advice on dose adjustment needed. However, not getting infection under control does not help the kidneys | Some fluids (HES) are toxic for the kidneys. However, not getting shock under control does not help the kidneys either |
| Duration | Appropriate duration | No strong evidence, but trend towards shorter duration. Do not use AB to treat fever, CRP, infiltrates etc. but use AB to treat infections | No strong evidence but trend towards shorter duration. Do not use fluids to treat low CVP, MAP, UO etc. but use fluids to treat shock |
| | Treat until response | Stop AB when signs and symptoms of active infection resolve. Future role for biomarkers (PCT) | Fluids can be stopped when shock is resolved (normal lactate). Future role for biomarkers (NGAL, cystatin C, citrullin, L-FABP) |
| De-escalation | Monitoring | Take cultures first and have the courage to change a winning team | After stabilisation with EAFM (normal PPV, normal CO, normal lactate) stop ongoing resuscitation and move to CLFM and LGFR (=de-resuscitation) |

AB — antibiotic; AKI — acute kidney injury; Cmax — maximal peak concentration; CO — cardiac output; CRP — C reactive protein; CVP — central venous pressure; EAFM — early adequate fluid management; EGDT — early goal directed therapy; IC — intracellular; ICU — intensive care unit; IS — interstitial; IV — intravenous; LCFM: late conservative fluid — management; L-FABP — L-type fatty acid binding protein; LGFR — late goal directed fluid removal; LOS — length of stay; MAP — mean arterial pressure; MIC — mean inhibitory concentration; MV — mechanical ventilation; NGAL — neutrophil gelatinase-associated lipocalin; PCT — procalcitonin; PPV — pulse pressure variation; RRT — renal replacement therapy; UO — urine output

is that fluids in cases of shock should be given early and in a speedy manner. Surrogate parameters are often used to titrate fluid therapy, such as central venous pressure, mean arterial pressure, urine output, volumetric preload or functional hemodynamic parameters (such as pulse pressure variation or stroke volume variation). Dynamic tests such as passive leg raising or the end-expiratory occlusion test can help to predict who will respond to fluid therapy.

DURATION

The duration of fluid therapy is equally important while the volume must be tapered when shock is resolved. However, although many clinicians use certain triggers to start, they are not aware of the triggers to stop fluid resuscitation,

hence carrying the potential of fluid overload with deleterious effects on patient morbidity and mortality [25].

DE-ESCALATION

The final step in fluid therapy is to consider withholding or withdrawing resuscitation fluids when they are no longer required. Basic needs with regard to maintenance and replacement fluids need to be covered at all times, however.

Although the use of resuscitation fluids is one of the most common interventions in medicine, the ideal fluid does not exist [23]. In light of recent evidence, a reappraisal of how resuscitation fluids are used in acutely ill patients seems warranted. As summarized in Table 1, the selection,

duration, timing and dosing of intravenous fluids should be evaluated as carefully as they are in the case of any other intravenous drug (e.g. antibiotics), with the aim of maximizing efficacy and minimizing iatrogenic toxicity.

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