Choosing IV Fluid in Critical Care
Unbalanced vs Balanced

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030719- 10 Oct 24

Zanjan

Resuscitation

- Aim of the fluid treatment is resuscitation and correction of shock with the achievement of an adequate perfusion pressure

Optimization

- Fluids should be administered according to individual needs and reassessed on a regular basis

Stabilization

- Aim to provide water and electrolytes to replace ongoing losses and provide organ support

Evacuation

- Removing excessive fluid which will be frequently achieved by spontaneous diuresis as the patient recovers, although ultrafiltration or diuretics might be necessary


Malbrain et al. Ann. Intensive Care (2020) 10:64
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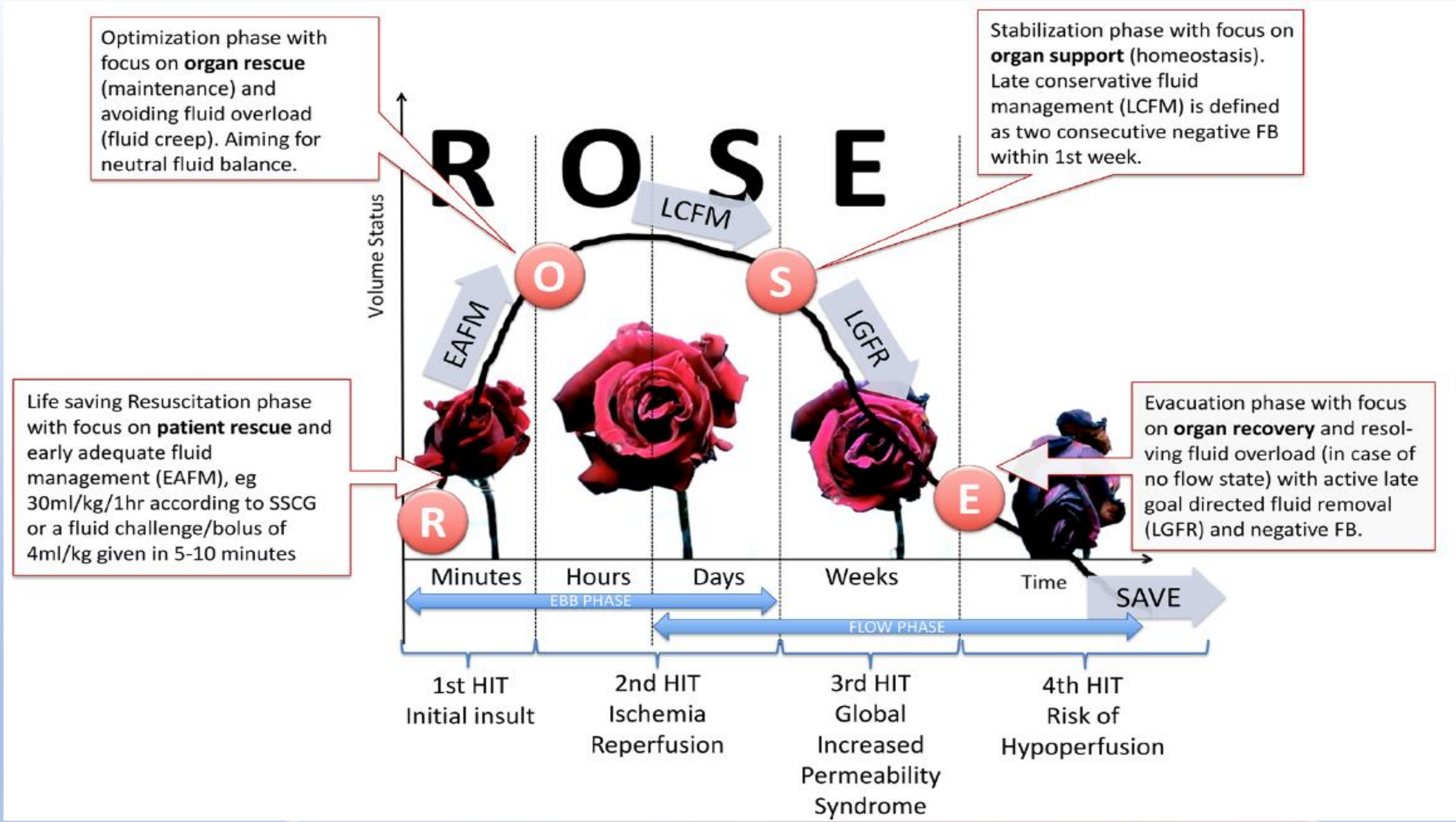
Annals of Intensive Care

REVIEW

Open Access

Intravenous fluid therapy in the perioperative and critical care setting: Executive summary of the International Fluid Academy (IFA)

Manu L. N. G. Malbrain, Thomas Langer, Djillali Annane, Luciano Gattinoni, Paul Elbers,

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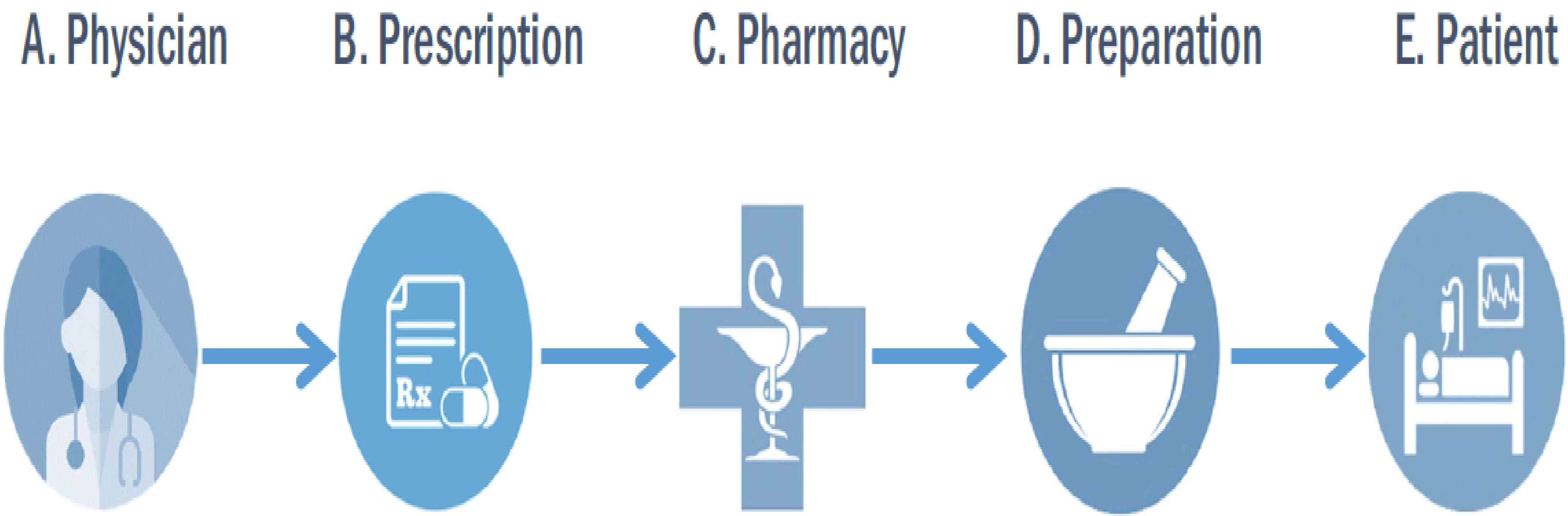

Fig. 3 The 5 Ps of fluid administration. **a** Physician: All starts with the physician's participation in making decisions related to fluid management. **b** Prescription: The physician should engage in writing a prescription that accounts for drug, dose, duration and whenever possible de-escalation. **c** Pharmacy: The prescription is sent to the pharmacy and is checked for inconsistencies by the pharmacist to get a more holistic view. **d** Preparation: The process by which the prescription is prepared and additions (e.g., electrolytes) made. **e** Patient: The filled prescription goes back to the patient and fluid stewards should observe administration, response, and debrief

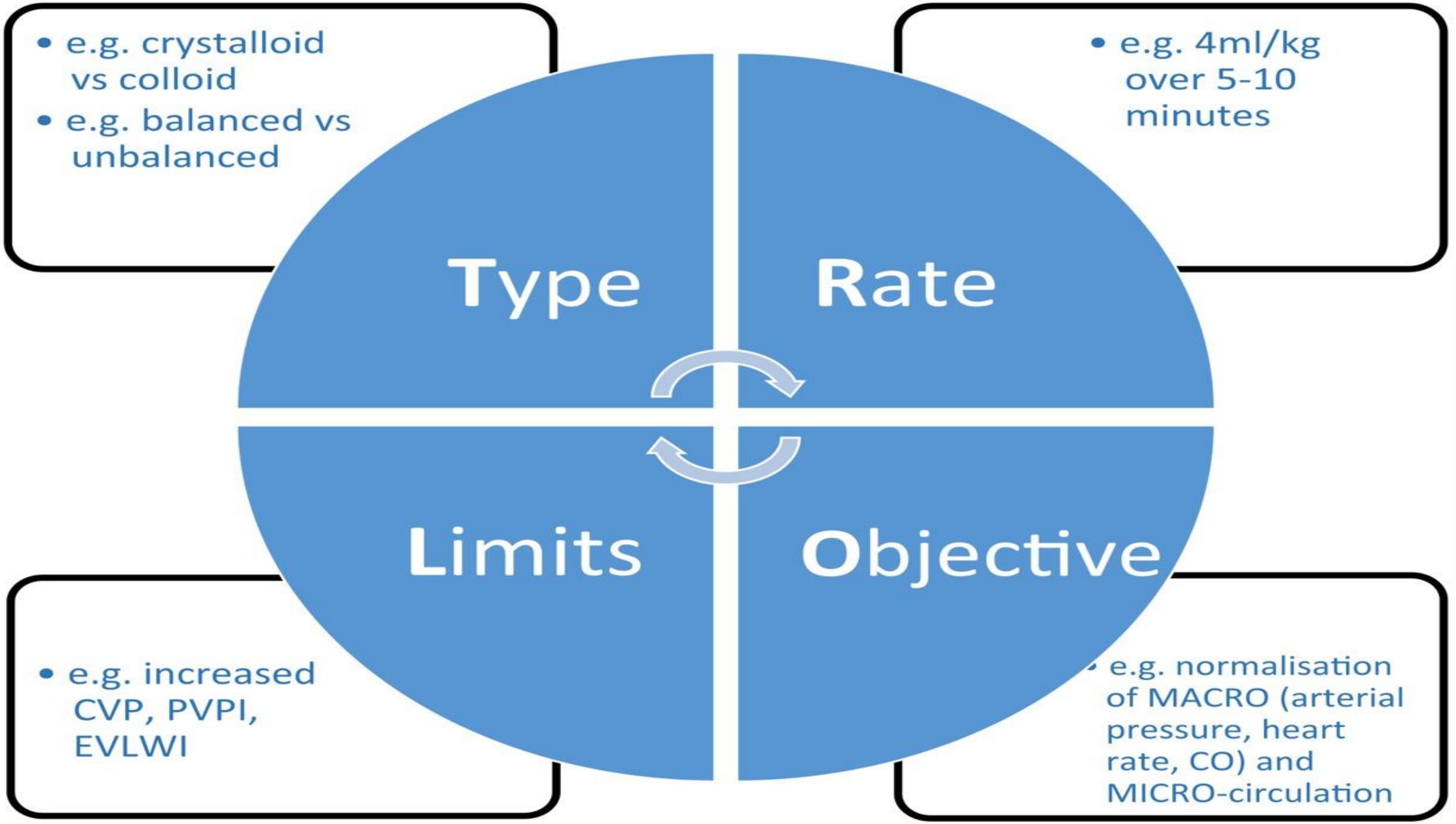

Fig. 2 The TROL mnemonic of fluid challenge: considerations for administration of a fluid bolus in critically ill patients. *CO* cardiac output; *CVP* central venous pressure; *EVLWI* extra vascular lung water index; *PVPI* pulmonary vascular permeability index (Adapted from Vincent and Weil [97])


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*Balanced solutions**

Intravenous "balanced" solutions include crystalloids and colloids,
with minimal effect:
on the homeostasis of the extracellular compartment, and in particular on
acid–base equilibrium and electrolyte concentrations.
fluids with a low chloride content (Cl^-).

*Sydney Ringer and Alexis Hartman developed the physiological salt solution,
which contains less Cl^- and Other electrolytes, now termed as balanced/buffered solution.
Fluid therapy in ICU- A review
2024 Medicover Journal of Medicine
10.4103/MJM.MJM_11_24

there are two main categories of balanced solutions :

(1) fluids causing a minimal effect on acid–base equilibrium, having an electrolyte content with an in vivo strong ion difference (SID), i.e., the SID after metabolism of the organic anion, close to 24–29 mEq/L;

(2) fluids having a normal or sub-normal Cl^- content ($Cl^- \leq 110$ mEq/L).


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The three variables regulating the pH of biologic fluids independently are:

(1)partial pressure of carbon dioxide (PCO2);

(2)the concentration of non-volatile weak acids (A_{TOT});

(3) the strong ion difference (SID) [NaCl (0.9%, 3%, 7.5%) have SID=0] [Balanced solution have positive value of SID, 27 for Ringer's solution, and 50 Acetate Gluconate solution,.

10 Answers to key questions for fluid management in intensive care, Medicina Intensiva, 45 (2021).


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These principles clearly suggest that intravenous fluids may affect pH due to:

(i) the specific electrolyte content characterizing the solution, therefore altering the SID of the extracellular compartment

(ii) the dilution effect due to the volume infused, thus reducing the concentration of A_{TOT}

The ideal balanced solution should:

<u>leave plasma pH unchanged</u> after its administration, at constant PCO2

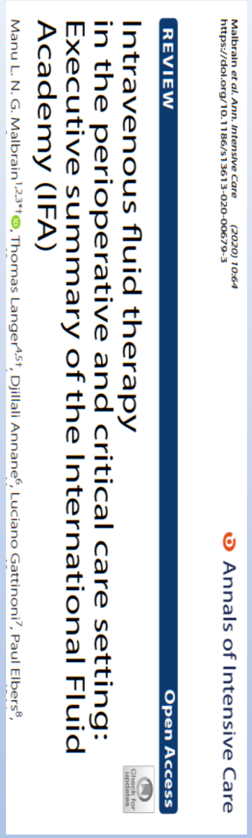
should have an in vivo <u>SID equal to the baseline concentration of HCO3$^-$</u>

SID of the infused fluid > plasma Hco3 → Plasma pH Alkalosis

SID of the infused fluid < plasma Hco3 → plasma pH Acidosis,

NaCl 0.9% unbalanced solution

SID, strong ion difference. the difference between the sum of all strong cations and the sum of all strong anions.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Content of human plasma, 0.9% saline, Lactated Ringer's, and Plasma-Lyte A

			Balanced crystalloids	
	Human plasma	0.9% saline	Lactated Ringer's	Plasma-Lyte A©
Sodium (mEq/L)	135–145	154	130	140
Potassium (mEq/L)	4.5–5.0	0	4	5
Chloride (mEq/L)	94–111	154	109	98
Calcium (mEq/L)	2.2–2.6	0	2.7	0
Magnesium (mEq/L)	0.8–1.0	0	0	3
Bicarbonate (mEq/L)	23–27	0	0	0
Lactate (mEq/L)	1–2	0	28	0
Acetate (mEq/L)	0	0	0	27
Gluconate (mEq/L)	0	0	0	23

Figure 1.

Table 1 from Self WH, Semler MW, Wanderer JP, et al. Saline versus balanced crystalloids for intravenous fluid therapy in the emergency department: study protocol for a cluster-randomized, multipl crossover trial. *Trials*. 2017;18:178. doi:10.1186/s13063-017-1923-6.

Table 2 Electrolyte composition of the main balanced solutions available for intravenous administration. Adapted from Langer et al. [21] with permission

	Crystalloids						Gelatins		Starches	
	Lactated Ringer's	Acetated Ringer's	Hartmann's	PlasmaLyte	Sterofundin ISO[a]	ELO-MEL isoton	Isoplex	Gelaspan	Hextend	Tetraspan
Na^+ [mEq/L]	130	132	131	140	145	140	145	151	143	140
K^+ [mEq/L]	4	4	5	5	4	5	4	4	3	4
Ca^{2+} [mEq/L]	3	3	4	–	5	5	–	2	5	5
Mg^{2+} [mEq/L]	–	–	3	3	2	3	1.8	2	0.9	2
Cl^- [mEq/L]	109	110	111	98	127	108	105	103	124	118
Lactate [mEq/L]	28	–	29	–	–	–	25	–	28	–
Acetate [mEq/L]	–	29	–	27	24	45	–	24	–	24
Malate [mEq/L]	–	–	–	–	5	–	–	–	–	5
Gluconate [mEq/L]	–	–	–	23	–	–	–	–	–	–
Dextrose [g L-1]	–	–	–	–	–	–	–	–	–	–
Gelatin [g/L]	–	–	–	–	–	–	40	40	–	–
HES [g/L]	–	–	–	–	–	–	–	–	60	60
Dextran [g/L]	–	–	–	–	–	–	–	–	–	–
In-vivo SID [mEq/L]	28	29	29	50	29	45	45.8	56	28	29[b]
Osmolarity [mOsm/L]	278	277	279	294	309	302	284	284	307	297

In-vivo SID—all organic molecules contained in balanced solutions are strong anions. The resulting calculated SID (in vitro-SID) is equal to 0 mEq/L, due to electrical neutrality. Once infused, the organic molecules are metabolized to CO_2 and water; the resulting in vivo-SID corresponds to the amount of organic anions metabolized

[a] Sterofundin-ISO or Ringerfundin

[b] In vivo-SID of Tetraspan reported in the Table results from the sum of organic anions; of note, there is a discrepancy as compared to the SID calculated as the difference between inorganic cations and inorganic anions (29 mEq/L vs. 33 mEq/L). No clear explanation has been reported from the seller

If we give one volume of fluid what would be the difference:

Balanced solution	Unbalanced solution
about 10% ↓in plasma volume expansion. So in near-fatal hemorrhagic shock, a lower dose of balanced solution is needed.	NaCl 0.9% causes a higher dose-dependent acidosis and hyperchloremia ☛ contraction of vascular smooth muscle ➤↓ renal pressure. Hyperchloremia cause ↑tubulo-glomerular feedback lead to ↓renal cortical perfusion.
Observational analysis of U.S. insurance data showed that the use of PlasmaLyte versus NaCl 0.9% on the first day of major abdominal surgery led to significantly less renal failure requiring dialysis	NaCl 0.9%, is slightly hypertonic ➤ ↑AVP. These effects causes ↓excretion of NaCl 0.9% as compared to balanced solution. This lead to edema, abdominal discomfort and ↓ gastric perfusion in surgical patients.


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Two important and large randomized controlled trials
comparing the use of balanced solutions and normal saline have been published in the last years.

The Split study:
multi-center double-blind randomized controlled trial performed on 2092 patients, comparing balanced and unbalanced fluids in intensive care units.
It showed no significant difference in the main outcome, i.e., incidence of acute kidney injury. prior administration of PlasmaLyte counterbalanced the effectsof low-dose NaCl 0.9%.

The SMART-trial:
A total of 15,802 patients were randomized to receive either NaCl 0.9% or a balanced solution (Plasma-Lyte A or Lactated Ringer’s).
the authors found a small difference in the primary outcome, i.e., the incidence of major adverse kidney events within 30 days (composite of death, new renal replacement therapy or persistent renal dysfunction) in favor of balance solutions.
Looking at the overall outcome, it is important to emphasize that there was no reduction of in-hospital mortality and that neither the incidence of renal replacement therapy (2.5% vs. 2.9%, p = 0.08) nor the incidence of persistent renal dysfunction (6.4% vs. 6.6%, p = 0.60) was statistically significant


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NEJM Evidence

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ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis

Naomi E. Hammond, Ph.D.[1,2], Fernando G. Zampieri, Ph.D.[3,4], Gian Luca Di Tanna, Ph.D.[5], Tessa Garside, Ph.D.[1,2], Derick Adigbli, Ph.D.[1,2], Alexandre B. Cavalcanti, M.D. Ph.D.[3], Flavia R. Machado, M.D., Ph.D.[6], Sharon Micallef, B.N.[1], John Myburgh, Ph.D.[1,7], Mahesh Ramanan, M.Med.[8,9], Todd W. Rice, M.D.[10], Matthew W. Semler, M.D.[10], Paul J. Young, Ph.D.[11,12], Balasubramanian Venkatesh, M.D.[1,13], Simon Finfer, M.D.[1,14], and Anthony Delaney, Ph.D.[1,2]

Drs. Hammond and Zampieri, as well as Drs. Finfer and Delaney, contributed equally to this article.

Abstract

BACKGROUND The comparative efficacy and safety of balanced crystalloid solutions and saline for fluid therapy in critically ill adults remain uncertain.

METHODS We systematically reviewed randomized clinical trials (RCTs) comparing the use of balanced crystalloids with saline in critically ill adults. The primary outcome was 90-day mortality after pooling data from low-risk-of-bias trials using a random-effects model. We also performed a Bayesian meta-analysis to describe the primary treatment effect in probability terms. Secondary outcomes included the incidence of acute kidney injury (AKI), new treatment with renal replacement therapy (RRT), and ventilator-free and vasopressor-free days to day 28.

RESULTS We identified 13 RCTs, comprising 35,884 participants. From six trials (34,450 participants) with a low risk of bias, the risk ratio (RR) for 90-day mortality with balanced crystalloids versus saline was 0.96 (95% confidence interval [CI], 0.91 to 1.01; $I^2 = 12.1\%$); using vague priors, the posterior probability that balanced crystalloids reduce mortality was 89.5%. The RRs of developing AKI and of being treated with RRT with balanced crystalloids versus saline were 0.96 (95% CI, 0.89 to 1.02) and 0.95 (95% CI, 0.81 to 1.11), respectively. Ventilator-free days (mean difference, 0.18 days; 95% CI, −0.45 to 0.81) and vasopressor-free days (mean difference, 0.19 days; 95% CI, −0.14 to 0.51) were similar between groups.

CONCLUSIONS The estimated effect of using balanced crystalloids versus saline in critically ill adults ranges from a 9% relative reduction to a 1% relative increase in the risk of death, with a high probability that the average effect of using balanced crystalloids is to reduce mortality. (PROSPERO number, CRD42021243399.)

The author affiliations are listed at the end of the article. Dr. Finfer can be contacted at sfinfer@georgeinstitute.org.au or at the Critical Care Division, The George Institute for Global Health, University of New South Wales, 1 King St., Newtown, NSW 2042, Australia.

Research

JAMA | Original Investigation

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients
The BaSICS Randomized Clinical Trial

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IMPORTANCE Intravenous fluids are used for almost all intensive care unit (ICU) patients. Clinical and laboratory studies have questioned whether specific fluid types result in improved outcomes, including mortality and acute kidney injury.

OBJECTIVE To determine the effect of a balanced solution vs saline solution (0.9% sodium chloride) on 90-day survival in critically ill patients.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, factorial, randomized clinical trial conducted at 75 ICUs in Brazil. Patients who were admitted to the ICU with at least 1 risk factor for worse outcomes, who required at least 1 fluid expansion, and who were expected to remain in the ICU for more than 24 hours were randomized between May 29, 2017, and March 2, 2020; follow-up concluded on October 29, 2020. Patients were randomized to 2 different fluid types (a balanced solution vs saline solution reported in this article) and 2 different infusion rates (reported separately).

INTERVENTIONS Patients were randomly assigned 1:1 to receive either a balanced solution (n = 5522) or 0.9% saline solution (n = 5530) for all intravenous fluids.

MAIN OUTCOMES AND MEASURES The primary outcome was 90-day survival.

RESULTS Among 11 052 patients who were randomized, 10 520 (95.2%) were available for the analysis (mean age, 61.1 [SD, 17] years; 44.2% were women). There was no significant interaction between the 2 interventions (fluid type and infusion speed; $P = .98$). Planned surgical admissions represented 48.4% of all patients. Of all the patients, 60.6% had hypotension or vasopressor use and 44.3% required mechanical ventilation at enrollment. Patients in both groups received a median of 1.5 L of fluid during the first day after enrollment. By day 90, 1381 of 5230 patients (26.4%) assigned to a balanced solution died vs 1439 of 5290 patients (27.2%) assigned to saline solution (adjusted hazard ratio, 0.97 [95% CI, 0.90-1.05]; $P = .47$). There were no unexpected treatment-related severe adverse events in either group.

CONCLUSION AND RELEVANCE Among critically ill patients requiring fluid challenges, use of a balanced solution compared with 0.9% saline solution did not significantly reduce 90-day mortality. The findings do not support the use of this balanced solution.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02875873

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Intensive Care Medicine Experimental

REVIEWS **Open Access**

Pathophysiology of fluid administration in critically ill patients

Antonio Messina[1,2*], Jan Bakker[3,4], Michelle Chew[5], Daniel De Backer[6], Olfa Hamzaoui[7], Glenn Hernandez, Sheila Nainan Myatra[9], Xavier Monnet[10], Marlies Ostermann[11], Michael Pinsky[12], Jean-Louis Teboul[10] and Maurizio Cecconi[1,2]

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Abstract

Fluid administration is a cornerstone of treatment of critically ill patients. The aim of this review is to reappraise the pathophysiology of fluid therapy, considering the mechanisms related to the interplay of flow and pressure variables, the systemic response to the shock syndrome, the effects of different types of fluids administered and the concept of preload dependency responsiveness. In this context, the relationship between preload, stroke volume (SV) and fluid administration is that the volume infused has to be large enough to increase the driving pressure for venous return, and that the resulting increase in end-diastolic volume produces an increase in SV only if both ventricles are operating on the steep part of the curve. As a consequence, fluids should be given as drugs and, accordingly, the dose and the rate of administration impact on the final outcome. Titrating fluid therapy in terms of overall volume infused but also considering the type of fluid used is a key component of fluid resuscitation. A single, reliable, and feasible physiological or biochemical parameter to define the balance between the changes in SV and oxygen delivery (i.e., coupling "macro" and "micro" circulation) is still not available, making the diagnosis of acute circulatory dysfunction primarily clinical.

Take-home messages

– Fluids are drugs used in patients with shock to increase the cardiac output with the aim to improve oxygen delivery to the cells. The response to fluid administration is determined by the physiological interaction of cardiac function and venous return. In septic shock, the beneficial clinical response of fluid administration is rapidly reduced after few hours and fluid titration is crucial to avoid detrimental fluid overload. The fluid challenge is a fluid bolus given at a defined quantity and rate to assess fluid responsiveness.
– The ideal fluid for critically ill patients does not exist; however, crystalloids should be used as first choice. Balanced crystalloid solutions may be associated with better outcomes but the evidence is still low. Albumin infusion may have a role in already fluid resuscitated patients at risk of fluid overload.

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Table 1 Recent randomized controlled trials comparing saline 0.9% versus balanced crystalloids

Study	SPLIT [77]	SMART [78]	BaSICS [62]	PLUS [79]
Setting	4 ICUs in New Zealand	5 ICUs in single center in USA	75 ICUs in Brazil	53 ICUs in Australia and New Zealand
Study design	Double-blind, cluster-randomized, double-crossover trial	Open-label, cluster-crossover trial	Double-blind, factorial, randomized clinical trial	Double-blind randomized controlled trial
Number of participants	2,278	15,802	11,052	5,037
Population	Critically ill adults (mainly surgical)	Critically ill adults	Critically ill adults (~50% elective surgery)	Critically ill adult patients (expected to stay in the ICU for at least 72 h)
Intervention	Plasmalyte	RLS/Plasmalyte	Plasmalyte	Balanced multielectrolyte solution
Control	0.9% NaCl	0.9% NaCl	0.9% NaCl	0.9% NaCl
Primary outcome (intervention vs control)	AKI (9.6% vs 9.2%; $p=0.77$)	MAKE30 (14.3% vs 15.4%; $p=0.04$)	90-day mortality (26.4% vs 27.2%; $p=0.47$)	90-day mortality (21.8% vs 22%; $p=0.90$)
Secondary outcomes (intervention vs control)	In-hospital mortality (7.6% vs 8.6%) RRT (3.3% vs 3.4%)	In-hospital mortality (25.2% vs 29.4%) RRT (2.5% vs 2.9%)	AKI with RRT (0.88% vs 0.93%) NeuroSOFA > 2 (32.1% vs 26%)	New RRT (12.7% vs 12.9%) No significant difference in maximum increase in serum creatinine

ICU intensive care unit, *RLS* ringer-lactate solution, *AKI* acute kidney injury, MAKE30 clinical outcome consisting of death from any cause, new renal replacement therapy or persistent renal dysfunction within 30 days, *NaCl* saline solution, *RRT* renal replace therapy, *SOFA* sequential organ failure assessment score

In summary, we can **avoid** fluid-induced metabolic acidosis and excessive chloride loading simply using balanced solutions.

Therefore, the use of balanced solutions, particularly in patients that potentially need a significant amount of intravenous fluids, seems to be a reasonable pragmatic choice.

On the contrary, ***saline*** may be an intuitive **choice** for patients with hypovolemic hyponatremia or hypochloremic metabolic alkalosis and cerebral edema(traumatic brain injury, CVA, DKA).
In any other settings, the most important reason to choose NaCl 0.9% over balanced solutions is likely economic in nature.

Therefore, the patient's serum chloremia is an important factor to determine the appropriate type of fluids.


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SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS FOR BALANCED CRYSTALLOIDS VS. ISOTONIC SALINE

Q7 **Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients in general?**

R We suggest using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients in general.[a] — LOW CERTAINTY OF EVIDENCE

Remark: In settings with a limited supply of balanced crystalloids, it is advised to prioritize using balanced crystalloids rather than isotonic saline in patients who require large volumes of resuscitation fluids and those with hyperchloremia or acidosis.

Remark: In settings where balanced fluids are unavailable, isotonic saline is an acceptable alternative.

Remark: Conversely, isotonic saline should be considered in patients with hypochloremia or metabolic alkalosis.

Q8 **Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients with sepsis?**

R We suggest using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with sepsis. — LOW CERTAINTY OF EVIDENCE

Q9 **Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients with traumatic brain injury?**

R We suggest using isotonic saline rather than balanced crystalloids for volume expansion in adult critically ill patients with traumatic brain injury. — VERY LOW CERTAINTY OF EVIDENCE

Remark: Most of the evidence is based on data from randomised controlled trials that used balanced fluids with near-normal osmolarity.

Remark: More hypotonic balanced fluids, such as Ringer's lactate (or acetate), probably should be avoided in patients with traumatic brain injury.

Q10 **Should balanced crystalloids or isotonic saline be used for volume expansion in adult critically ill patients with kidney injury?**

R We suggest using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with kidney injury. — VERY LOW CERTAINTY OF EVIDENCE

CERTAINTY OF EVIDENCE:
NO EVIDENCE / VERY LOW / LOW / MODERATE / HIGH

Q QUESTION — R RECOMMENDATION — REMARK

NO RECOMMENDATION — CONDITIONAL RECOMMENDATION — STRONG RECOMMENDATION

CONDITIONAL RECOMMENDATION AGAINST — STRONG RECOMMENDATION AGAINST

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GUIDELINES

European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1: the choice of resuscitation fluids

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