

Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice

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Abstract

Background: Sepsis is associated with generalised endothelial injury and capillary leak and has traditionally been treated with large volume fluid resuscitation. Some patients with sepsis will accumulate bodily fluids. The aim of this study was to systematically review the association between a positive fluid balance/fluid overload and outcomes in critically ill adults, and to determine whether interventions aimed at reducing fluid balance may be linked with improved outcomes.

Methods: We searched MEDLINE, PubMed, EMBASE, Web of Science, The Cochrane Database, clinical trials registries, and bibliographies of included articles. Two authors independently reviewed citations and selected studies examining the association between fluid balance and outcomes or where the intervention was any strategy or protocol that attempted to obtain a negative or neutral cumulative fluid balance after the third day of intensive care compared to usual care. The primary outcomes of interest were the incidence of IAH and mortality.

Results: Among all identified citations, one individual patient meta-analysis, 11 randomised controlled clinical trials, seven interventional studies, 24 observational studies, and four case series met the inclusion criteria. Altogether, 19,902 critically ill patients were studied. The cumulative fluid balance after one week of ICU stay was 4.4 L more positive in non-survivors compared to survivors. A restrictive fluid management strategy resulted in a less positive cumulative fluid balance of 5.6 L compared to controls after one week of ICU stay. A restrictive fluid management was associated with a lower mortality compared to patients treated with a more liberal fluid management strategy (24.7% vs 33.2%; OR, 0.42; 95% CI 0.32–0.55; $P < 0.0001$). Patients with intra-abdominal hypertension (IAH) had a more positive cumulative fluid balance of 3.4 L after one week of ICU stay. Interventions to decrease fluid balance resulted in a decrease in intra-abdominal pressure (IAP): an average total body fluid removal of 4.9 L resulted in a drop in IAP from 19.3 ± 9.1 mm Hg to 11.5 ± 3.9 mm Hg.

Conclusions: A positive cumulative fluid balance is associated with IAH and worse outcomes. Interventions to limit the development of a positive cumulative fluid balance are associated with improved outcomes. In patients not transgressing spontaneously from the Ebb to Flow phases of shock, late conservative fluid management and late goal directed fluid removal (de-resuscitation) should be considered.

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The administration of intravenous fluids is widely regarded as the first step in the resuscitation of critically ill and injured patients who have evidence of impaired organ perfusion [1–3]. The Surviving Sepsis Campaign recommends “aggressive fluid resuscitation during the first 24 hours of management” [4]. The purpose of fluid resuscitation is to increase venous return and stroke volume [5]. Fluid administration increases the stressed blood volume, increasing the gradient between the mean systemic filling pressure (MSFP) and right atrial pressure (CVP), thereby increasing venous return [6–8]. In patients who are on the ascending limb of the Frank-Starling limb, the increased venous return results in an increase in stroke volume and cardiac index [5].

Despite the above, clinical studies have consistently demonstrated that less than 50% of haemodynamically unstable patients are fluid responders, as defined by an increase in stroke volume of 10–15% following a fluid challenge [5]. Fluid administration serves no useful purpose in those patients whose stroke volume fails to increase following a fluid challenge (non-responders). In these patients, fluid administration may even be harmful. Furthermore, due to the redistribution of fluid, the haemodynamic response in fluid responders is short lived with the stroke volume returning to baseline 30 to 60 minutes following the initial fluid challenge [9]. In healthy individuals, 85% of an infused bolus of crystalloid has been reported to redistribute into the interstitial space after four hours [10]. In critically ill patients with endothelial injury and leaky capillaries, less than 5% of a fluid bolus remains intravascular after 90 minutes [11]. In the Rivers’ Early Goal Directed Therapy (EGDT) study, 4.9 L of crystalloid were given in the first six hours and 13.4 L in the first 72 hours [12]. The Surviving Sepsis Campaign recommends “aggressive fluid resuscitation during the first 24 hours of management” [4].

Large volume fluid resuscitation results in severe tissue oedema and clinical signs of volume overload [13]. Tissue oedema impairs oxygen and metabolite diffusion, distorts tissue architecture, impedes capillary blood flow and lymphatic drainage, and disturbs cell-cell interactions [13]. These effects are pronounced in encapsulated organs, such as the liver and kidneys, which lack the capacity to accommodate additional volume without an increase in interstitial pressure, resulting in compromised organ blood flow [14]. Furthermore, large volume resuscitation increases intra-abdominal pressure (IAP), which further compromises renal and hepatic perfusion. As such, capillary leak significantly contributes to the genesis of intra-abdominal hyper-

tension (IAH) and the abdominal compartment syndrome (ACS) [15–19]. Kelm et al. [20] demonstrated that 67% of patients resuscitated by means of the EGDT protocol had clinical evidence of fluid overload after 24 hours, with 48% of patients having persistent features of fluid overload by the third hospital day.

Multiple studies have demonstrated that a positive fluid balance is independently associated with impaired organ function and an increased risk of death [14, 15, 21–29]. This was recently demonstrated in an elegant study by Murphy et al. [21]. Conversely, achievement of a negative fluid balance is associated with improved organ function and survival [30, 31]. This has been referred to as the Ebb and Flow phases of shock. The Ebb phase was characterised by Cuthbertson in 1932 as: “*Ashen faces, a thready pulse and cold clammy extremities...*”, while during the Flow phase “*the patient warms up, cardiac output increases and the surgical team relaxes...*” [25]. Recent data suggests that many patients do not enter the flow phase spontaneously and in order to avoid a positive cumulative fluid balance with the associated organ oedema and organ dysfunction, they may require therapeutic interventions [32]. However, it remains largely unknown whether strategies that target a neutral or even negative fluid balance after the initial resuscitative phase are associated with improved clinical outcomes in humans.

Goal-directed therapy has become ubiquitous, where the goal of resuscitation is the rapid reversal of shock and hypoperfusion within a few hours. The Surviving Sepsis Campaign Guidelines focus on the initial resuscitation but fail to provide information on the assessment of volume overload or when and how to perform de-resuscitation [4]. Furthermore, the central venous pressure (CVP) provides little useful data as to the patient’s overall volume status and the need for de-resuscitation. The EV1000/VolumeView (Edwards Lifesciences, Irvine, CA, USA) and PiCCO (Pulsion Medical Systems, Munich, Germany) devices allow, besides measurement of cardiac output as well as other parameters such as the global end-diastolic volume index (GEDVI) and extravascular lung water index (EVLWI) which provide useful information on volume status and tissue oedema [33–35]. These devices are helpful when faced with a therapeutic conflict, a situation where each of the possible therapeutic decisions carries some potential harm, with the clinician supporting the organ that carries the highest danger of harming the patient [36, 37]. In high-risk patients, decisions regarding fluid administration should therefore be done within the context of a therapeutic conflict.

The aim of this study was to systematically review the association between a positive fluid balance/fluid overload and outcomes in critically ill adults and to determine whether interventions aimed at reducing fluid balance may be linked with improved outcomes.

In the discussion we will focus on the available literature with regards to fluid overload and a positive cumulative fluid balance in relation to morbidity (e.g. IAH) and mortality and how to deal with it at the bedside. We review de-resuscitation: what, why, when and how?

DEFINITIONS

In this section we will define 'de-resuscitation' and suggest some definitions with regard to fluid management and fluid balance partially based on a conceptual model [38-40].

Resuscitation fluids. Resuscitation fluids are used to correct an intravascular volume deficit or acute hypovolemia. Over the last three decades, there has been much debate over the use of colloids vs crystalloids [41]. However, recent clinical trials suggest that colloids have a limited role in fluid resuscitation [42-44]. More recently the issue has involved the use of normal saline vs balanced salt solutions, with data suggesting improved outcomes with balanced salt solutions [45, 46].

Maintenance fluids. Maintenance solutions are specifically given to provide the patient's daily basal requirements of water and electrolytes.

Replacement fluids. Replacement solutions are prescribed to correct existing or developing deficits that cannot be compensated by oral intake, as seen in situations in which fluids are lost via drains or stomata, fistulas, fever, polyuria and open wounds (including evaporation during surgery or burns) among others.

Global Increased Permeability Syndrome (GIPS). GIPS is characterised by high capillary leak index (CLI, expressed as the ratio of CRP over albumin), excess interstitial fluid and persistent high extravascular lung water index (EVLWI), no late conservative fluid management (LCFM) achievement, and progression to organ failure [32]. GIPS represents a 'third hit' following the acute injury (first hit) with progression to multi-organ dysfunction syndrome-MODS (second hit) [47]. The third hit may develop in patients who do not enter the Flow phase spontaneously. Successful response to acute inflammatory insult tends to be characterised by a crucial turning point on day three. The evolution of cytokines and other pro-inflammatory mediators on the third day after shock initiation allows healing of the microcirculatory disruptions and 'closure' of capillary leakage. This interpretation is supported by observations demonstrating normalisation of microcirculatory blood flow on day three in patients with abdominal sepsis [48]. Further, lower EVLWI and pulmonary vascular permeability indices (PVPI) at day three of shock

have been shown to correlate with better survival [49]. In these patients, excess fluid administration results in oedema formation, progression of organ failure and worse outcome. Therefore, as soon as haemodynamics allow, early transition to conservative fluid management and even fluid removal on the basis of an EVLWI-guided protocol is mandated (late goal directed fluid removal) [21, 32, 47].

Polycompartment syndrome. The recent consensus definitions of the World Society on the Abdominal Compartment Syndrome (WSACS, www.wsacs.org) defined polycompartment as a condition where two or more anatomical compartments have elevated compartmental pressures [50]. As a result of capillary leak and impaired flow phase, overzealous administration of unnecessary fluids in the GIPS phase will lead to gross fluid overload and tissue oedema. Interstitial oedema increases the pressure in all four interconnected major body compartments: head, chest, abdomen, and extremities. As a result, the venous resistance of organs within compartments increases and perfusion pressure decreases contributing to progression of organ failure. As different compartments interact and reciprocally transmit compartment pressures, the concept of polycompartment syndrome was suggested [51-53]. The abdomen plays a central role in GIPS and the polycompartment syndrome, as positive fluid balances are a known risk factor for secondary IAH which in turn is associated with deleterious effects on other compartments and organ functions and may eventually lead to abdominal compartment syndrome (ACS) [15]. With abdominal compliance defined as the measure of the ease of abdominal expansion, which is determined by the elasticity of the abdominal wall and diaphragm, being the determining factor explaining transmission of compartmental pressures from one compartment to another.

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 [38, 54].

Fluid overload. The percentage of fluid accumulation can be defined by dividing the cumulative fluid balance in litre by the patient's baseline body weight and multiplying by 100%. Fluid overload is defined by a cut off value of 10% of fluid accumulation as this is associated with worse outcomes [38, 55].

Fluid bolus. 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 given over 5-10 min with reassessment of haemodynamic status to optimise 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 capillary wedge pres-

Table 1. The 2–5 rule using dynamic changes in CVP (Δ CVP) to guide a fluid challenge

1. Measure baseline CVP (mm Hg):
 - CVP < 8: give 4 mL kg⁻¹ bolus over 10 minutes
 - CVP 8–12: give 2 mL kg⁻¹ bolus over 10 minutes
 - CVP > 12: give 1 mL kg⁻¹ bolus over 10 minutes
2. Re-assess increase in CVP at the end of the bolus (i.e. after 10 minutes from start at point 1)
 - Δ CVP > 5: STOP fluid challenge
 - Δ CVP < 2: restart with point 1
 - Δ CVP 2–5: wait for another 10 minutes and move to point 3
3. Re-assess increase in CVP after another 10 minutes (i.e. after 20 minutes from start at point 1)
 - Δ CVP > 2: STOP fluid challenge
 - Δ CVP < 2: restart with 1
4. Repeat until CVP of 14 mm Hg or rule broken

sure (PCWP) are potentially dangerous and useless to guide a fluid challenge [5, 13, 56, 57]. In the past, dynamic changes in CVP (or PCWP) have been suggested but these may also not be useful [58, 59]. During a fluid challenge, the 2–5 rule is classically followed for CVP and the 3–7 for PCWP. Baseline CVP is measured and re-assessed after each bolus or each ten-minute period (as illustrated in Table 1).

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 of fluids within the first 6–8 hours of resuscitation in a 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 [13, 60].

Late Conservative Fluid Management (LCFM). Recent studies have shown that late conservative fluid management, defined as two consecutive days of negative fluid balance within the first week of ICU stay, is a strong and independent predictor of survival [21]. 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. This is referred to as ‘de-resuscitation’.

Classification of fluid dynamics. Combining early adequate (EA) or early conservative (EC) and late conservative (LC) or late liberal (LL) fluid management, four distinct groups can be identified with regard to the dynamics of fluid management: EALC, EALL, ECLC, and ECLL. These will be discussed further.

METHODS

SEARCH STRATEGY AND CLINICAL QUESTIONS

We searched MEDLINE, PubMed, EMBASE, Web of Science, The Cochrane Database, clinical trials registries and bibliographies of included articles in order to update a previously conducted systematic review and meta-analysis [61]. We sought to identify studies involving critically ill patients that examined the association between a positive fluid balance and outcomes after day 3 of ICU stay. We also sought to update a previously conducted systematic review and meta-analysis the clinical questions of which were formulated according to the PICOD (Patients, Interventions, Comparator, Outcome, Design) format [61]: Our PICOD clinical question was: *Does a management strategy in critically ill patients which attempts to achieve a fluid balance in equilibrium or even negative (conservative fluid strategy) after day 3 (and within the first week) result in a lower IAP and improved patient outcomes compared to a liberal fluid strategy?*

ARTICLE SELECTION AND DATA EXTRACTION

Two authors independently reviewed all titles and abstracts and selected full-text articles for inclusion in the review. These two authors also abstracted the data on study design, methodological quality, patient characteristics, fluid balance and the outcomes of interest. We included studies where: 1) patients were critically ill or injured adults treated in an intensive care unit (some of them also received surgery); 2) The intervention was any strategy or protocol attempting to obtain a neutral or negative cumulative fluid balance after the third day of intensive care; 3) the comparator group received a comparable strategy or protocol not attempting to obtain negative fluid balance or equilibrium after the third day of intensive care allowing for a more liberal fluid management strategy; 4) the primary outcomes were the incidence of IAH and mortality; and 5) the study design was an RCT or observational study. Secondary outcomes included cost, ICU utilisation, length of hospital or ICU stay, incidence of acute renal failure, ACS and requirement for decompressive laparotomy. We also included previously conducted systematic reviews and/or meta-analyses.

RISK OF BIAS ASSESSMENT

We applied the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system to guide assessment of quality of evidence to address the clinical management questions. The best consensus opinion was GRADED from high (A) to very low (D) and to help determine the strength of recommendations from strong *recommendations* indicating that the panel felt the overall desirable effects of the intervention clearly outweighed po-

tential undesirable effects, to weaker *suggestions* indicating that the balance of risks and benefits was less clear for any intervention, to clear uncertainty.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean \pm SD (standard deviation) or as median (with first and third quartile) according to whether they are normally distributed or not. The continuous variables were compared using unpaired Student's *t*-test for normally distributed variables and the Mann-Whitney *U* for non-normally distributed variables. Random effects meta-analysis summary results were calculated giving the average from the distribution (of treatment effects) across studies. A *P*-value below 0.05 was considered as statistically significant. Statistical analysis was done with SAS (version 9.1, SAS Institute, Cary, NC, USA) and SPSS (Windows version 17.0, SPSS, Chicago, IL, USA). The meta-analysis and Forest plots were generated with Review Manager 5 (Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

RESULTS

In total, we included 47 articles (surgical patients were studied in six, burns in three and trauma in one, the other studies included mixed ICU (mainly medical) patients). We also included one individual patient meta-analysis [62], 11 randomised controlled clinical trials (RCTs) (of which four were blinded) [12, 30, 63–71], seven interventional studies [16, 72–77], 24 observational studies [21, 26, 28, 29, 31, 32, 49, 55, 78–93] and four case series [94–97]. Altogether, a total of 19902 critically ill patients were studied and in 20 studies the IAP was measured (Table 2). In updating our previously conducted meta-analysis, we analysed the following specific sub-questions:

Do non-survivors have a more positive fluid balance? A meta-analytic approach was adopted analysing the best available data abstracted from one individual patient meta-analysis [62], nine uncontrolled prospective cohort studies [26, 28, 49, 77, 78, 82, 84, 89, 91], three uncontrolled retrospective cohort studies [21, 31, 32], two retrospective non-randomised controlled cohort studies [72, 79] and a retrospective review [86] of a randomised trial of a separate intervention [68, 86] that considered fluid balance in relation to survival in critical illness. When compiled, the data from a total of 5,445 patients from 17 studies showed that non-survivors ($n=2,609$, 47.9% mortality) had a more positive cumulative fluid balance by day 7 of their ICU stay compared to survivors ($6,982.6 \pm 5,629$ mL vs $2,449.1 \pm 2,965.1$ mL) (Fig. 1). The cumulative fluid balance was on average $4,533.5 \pm 3,626.7$ mL more positive in non-survivors compared to survivors (Figure 2). The collated

findings of these studies are provided in the Forest plot in Figure 3.

Does outcome improve with an intervention to limit fluid intake or lower fluid balance? The compiled data from 15,947 patients enrolled in 28 studies [12, 16, 21, 28–32, 55, 63–68, 71, 72, 79–82, 84–87, 90, 91, 98] involving critically ill and peri-operative patients showed that outcome was significantly improved when associated with a conservative fluid regimen (OR 0.42 [95% CI 0.32 to 0.55]), compared to non-conservative fluid management. This is illustrated in the forest plot in Figure 4. In patients treated with a restrictive fluid regimen, mortality decreased from 33.2% (2,596 deaths in 7,812 patients) to 24.7% (2,007 deaths in 8,135 patients, $P < 0.0001$). Actual data on cumulative fluid balance was available in 8,790 patients from 16 studies [12, 16, 30, 55, 63–72, 90, 98, 99]: overall conservative treatment was associated with a less positive fluid balance compared to a more liberal fluid strategy ($2,131.7 \pm 5,741.8$ mL vs $7,761 \pm 7,391.9$ mL) and the cumulative fluid balance was on average $5,629.3 \pm 3,441.6$ mL less positive after one week of ICU stay (Figs 1, 2). The summary of findings of these studies is given in Figure 5.

Do patients with IAH have a more positive fluid balance? Data was available from 1,517 patients obtained from one individual patient meta-analysis and seven cohort or case-controlled studies [32, 62, 72, 78, 83, 88, 89, 100]. Meta-analysis of the pooled results revealed that the 597 patients with IAH (incidence being 39.4%) had a more positive fluid balance than those without IAH ($7,777.9 \pm 3,803$ mL vs $4,389.3 \pm 1,996.4$ mL) (Fig. 1). The cumulative fluid balance after one week of ICU stay was on average $3,388.6 \pm 2,324.2$ mL more positive (Fig. 2). A summary of the findings of these studies is given in Figure 6.

Does IAP improve with interventions acting on reducing fluid balance? Thirteen studies investigated the effects of fluid removal (use of furosemide or renal replacement therapy with net ultrafiltration) on IAP (Fig. 7). These were case studies or small series [70, 72–75, 77, 90, 92, 94–97]. A total fluid removal of $4,876.3 \pm 4,178.5$ mL resulted in a drop in IAP from 19.3 ± 9.1 to 11.5 ± 3.9 mm Hg (Fig. 8). A dose related effect was observed: the more negative the net fluid balance or fluid removal, the greater the decrease in IAP (Fig. 9).

SUGGESTIONS FOR CLINICAL PRACTICE

Although the results of this meta-analysis are compelling, they are limited by indirectness and the risk of bias given the inclusion of varying study designs and patient populations and the use of many different interventions. After reviewing much of the above evidence, the World Society of the Abdominal Compartment Syndrome **suggested** us-

Table 2. Summary of findings on studies assessing impact of fluid status on morbidity and mortality

Author	Year	Ref	Nr	Patient Group Characteristics	Design	Blind	Pro/Retro	Intervention	IAP
META-ANALYSIS									
Malbrain	2014	[62]	1,669	Mixed ICU	Observational multicentre	no	Prospective	none	yes
RANDOMISED CONTROLLED TRIALS									
Mitchell	1992	[68]	101	Medical ICU requiring PAC	Single centre RCT	no	Prospective	EVLWI vs WP management	no
Rivers	2001	[12]	263	ER with sepsis or septic shock	Single centre RCT	yes	Prospective	EGDT vs standard (more fluids 0–6 hr; less 7–72 hr)	no
Martin	2002	[66]	37	MV with ALI	Multicentre RCT	yes	Prospective	(albumin with furosemide) vs dual placebo	no
Brandstrup	2003	[64]	141	Post colorectal surgery	Multicentre RCT	observer	Prospective	intra- and postop restrictive FM	no
Finfer	2004	[69, 98]	6,997	Mixed ICU	SAFE: Multicentre RCT	yes	Prospective	albumin 4% vs normal saline	no
Martin	2005	[65]	40	MV with ALI	Multicentre RCT	yes	Prospective	furosemide with (albumin vs placebo)	no
O Mara	2005	[70]	31	Burn patients > 40%TBSA or > 25% with inhalation	Single centre RCT	no	Prospective	crystalloid 20 mL kg ⁻¹ % vs plasma 10 mL kg ⁻¹ %	yes
Wiedemann	2006	[30]	1,000	MV with ALI	FACTT: Multicentre RCT	no	Prospective	more diuretics, less fluids	no
Stewart	2009	[63]	244	Surgical MV with ALI	FACTT: Multicentre RCT	no	Prospective	more diuretics, less fluids	no
McArdle	2009	[67]	20	Surgical ICU (post AAA repair)	Single centre RCT	no	Prospective	restrictive vs standard fluid regimen period	no
Caironi	2014	[71]	1,809	ICU with sepsis or septic shock	ALBIOS: Multicentre RCT	no	Prospective	hypertonic albumin 20% vs crystalloids	no
OTHER INTERVENTIONAL STUDIES									
Balogh	2003	[16]	156	Severe Trauma	Cohort study	no	Retrospective	Supranormal resuscitation	yes
Oda	2005	[76]	17	SAP	Observational	no	Prospective	CVWHDF	yes
Mullens	2008	[73]	40	congestive heart failure	Cohort study	no	Prospective	Medical management (diuretics in > 80%)	yes
Mullens	2008	[74]	4	congestive heart failure	Consecutive	no	Prospective	IHD	yes
Cordemans	2012	[72]	114	Mixed ICU with ALI	Cohort matched control study	no	Retrospective	PAL	yes
De laet	2012	[75]	9	Mixed ICU with ARF (need for RRT)	Observational	no	Retrospective	RRT	yes
Dabrowski	2014	[77]	30	Mixed ICU with septic shock	Observational	no	Prospective	CVWH	yes
OBSERVATIONAL EPIDEMIOLOGIC COHORT STUDIES									
Simmons	1987	[84]	113	Mixed ICU with ALI	Observational	no	Retrospective	none	no
Lowell	1990	[87]	48	Surgical ICU	Observational	no	Prospective	none	no
Schuller	1991	[86]	89	Medical ICU requiring PAC	Observational	no	Prospective	treatment group: PAC guided fluid management	no
Alsous	2000	[31]	36	Medical ICU	Observational	no	Retrospective	none	no
McNelis	2002	[83]	44	Surgical ICU	Observational	no	Prospective	none	yes

cont. →

Table 2 cont. Summary of findings on studies assessing impact of fluid status on morbidity and mortality

Author	Year	Ref	Nr	Patient Group Characteristics	Design	Blind	Pro/Retro	Intervention	IAP
Michael	2004	[81]	26	Paediatric with AKI after stem cell Tx	Observational	no	Retrospective	none	no
Goldstein	2005	[82]	116	PICU with MODS receiving RRT	Observational	no	Prospective	none	no
Sakr	2005	[26]	392	ICU patients; ALI vs no ALI	SOAP: Observational	no	Retrospective	none	no
Malbrain	2005	[89]	265	Mixed ICU	Observational	no	Prospective	none	yes
Kuzkov	2006	[49]	31	Septic shock with ALI	Observational	no	Prospective	none	no
Vidal	2008	[78]	83	Mixed ICU (47% medical)	Observational	no	Prospective	none	yes
Walsch	2008	[85]	106	Surgical ICU	Observational	no	Prospective	none	no
Payen	2008	[29]	1,120	ICU with ARF	SOAP: Observational	no	Retrospective	none	no
Dalfino	2008	[88]	123	General ICU	Observational	no	Prospective	none	yes
Serpytsis	2008	[92]	77	Major abdominal surgery	Observational	no	Prospective	none	yes
Murphy	2009	[21]	212	Septic shock with ALI	Observational	no	Retrospective	none	no
Bouchard	2009	[80]	542	Mixed ICU with AKI	Observational	no	Retrospective	none	no
Rosenberg	2009	[28]	794	ALI from ARDS network	Observational	no	Prospective	treatment group: lower TV (6 mL vs 12 mL)	no
Shum	2011	[79]	639	Mixed ICU with ICU-stay \geq 3 days (51.4% medical)	Observational	no	Prospective	none	no
Cordemans	2012	[32]	123	Mixed ICU with ALI	Observational	no	Retrospective	none	yes
Vaara	2012	[55]	284	Critically ill with RRT	FINNAKI: Observational	no	Prospective	none	no
Pupelis	2012	[90]	130	SAP	Observational	no	Prospective	none	yes
Bellomo	2012	[91]	1,452	Mixed ICU with ARF	RENAL: Observational	no	Prospective	none	no
Micek	2013	[93]	325	Septic shock patients	Observational	no	Retrospective	none	no
CASE SERIES									
Vachharajani	2003	[97]	1	Upper GI bleeding	Case report	no	Prospective	CVVHDF	yes
Kula	2004	[94]	2	ICU patients with severe sepsis	Case report	no	Prospective	CVWH	yes
Bonfim	2007	[96]	5	5 ICU patients, need for RRT	Case series	no	Prospective	IHD	yes
Kula	2008	[95]	2	ICU patients	Case report	no	Prospective	CVWH and albumin	yes

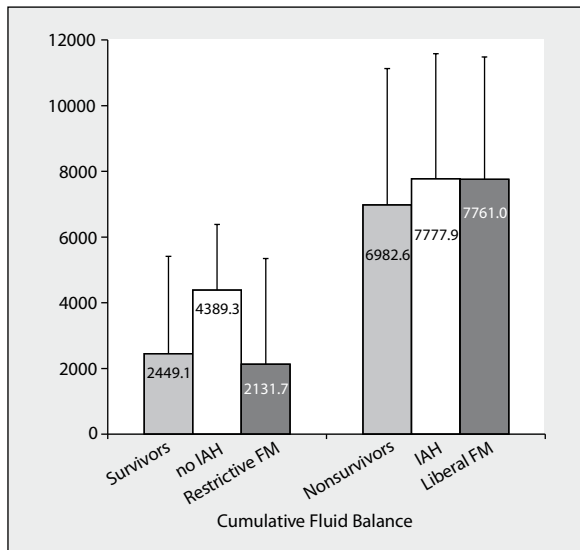


Figure 1. Bar graph showing mean cumulative fluid balance after one week of intensive care unit (ICU) stay. Light grey bars showing cumulative fluid balance in survivors (left) vs nonsurvivors (right), white bars show data in patients without intra-abdominal hypertension, IAH (left) vs IAH (right), and dark grey bars data in patients with restrictive fluid management (left) vs liberal fluid management (right)

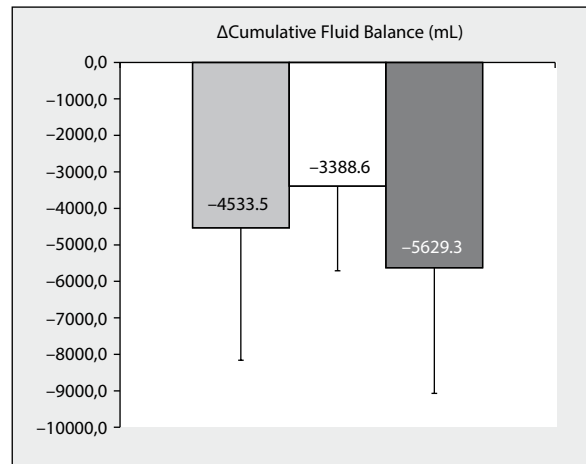


Figure 2. Bar graph showing mean (difference) in cumulative fluid balance (mL) after one week of intensive care unit (ICU) stay being less positive in survivors (light grey), patients without intra-abdominal hypertension, IAH (white) and patients receiving restrictive fluid management (dark grey)

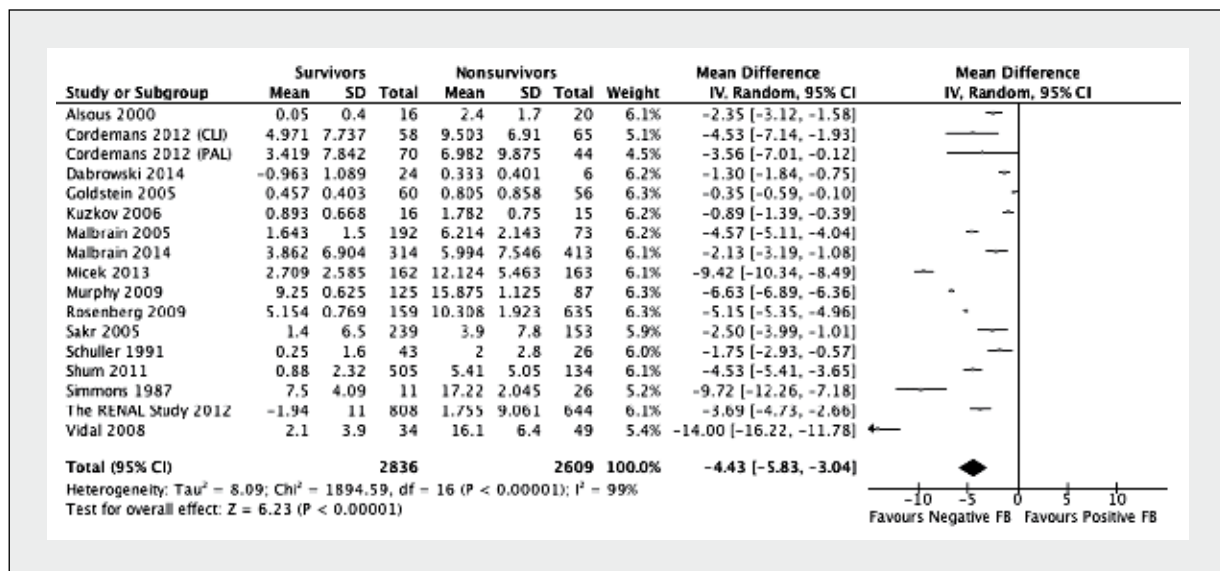


Figure 3. Forest plot looking at cumulative fluid balance after one week* of ICU stay in survivors vs nonsurvivors. Updated and adapted from Malbrain et al. [61]; FB — fluid balance

*In the Sakr study data was only available at 96 hours and not after one week

ing a protocol to avoid a positive cumulative fluid balance in critically ill patients, especially those with, or at risk of, IAH, after the acute resuscitation has been completed and the inciting issues/source control have been addressed (Grade 2C) [50].

We **suggest** a goal of a zero to negative fluid balance by day 3 and to keep the cumulative fluid balance on day 7 as low as possible (Grade 2B). A vicious cycle leading to more fluid loading and further IAP increase is illustrated in Fig-

ure 10, and this must be avoided. After reviewing the limited evidence, we can only make **a weak suggestion** regarding the use of diuretics or renal replacement therapy (in combination with albumin) vs no intervention to mobilise fluids in haemodynamically stable patients with IAH and a positive cumulative fluid balance after the acute resuscitation has been completed and the inciting issues/source control have been addressed (Grade 2D). The lack of consensus for this intervention underscores the uncertainty regarding its role

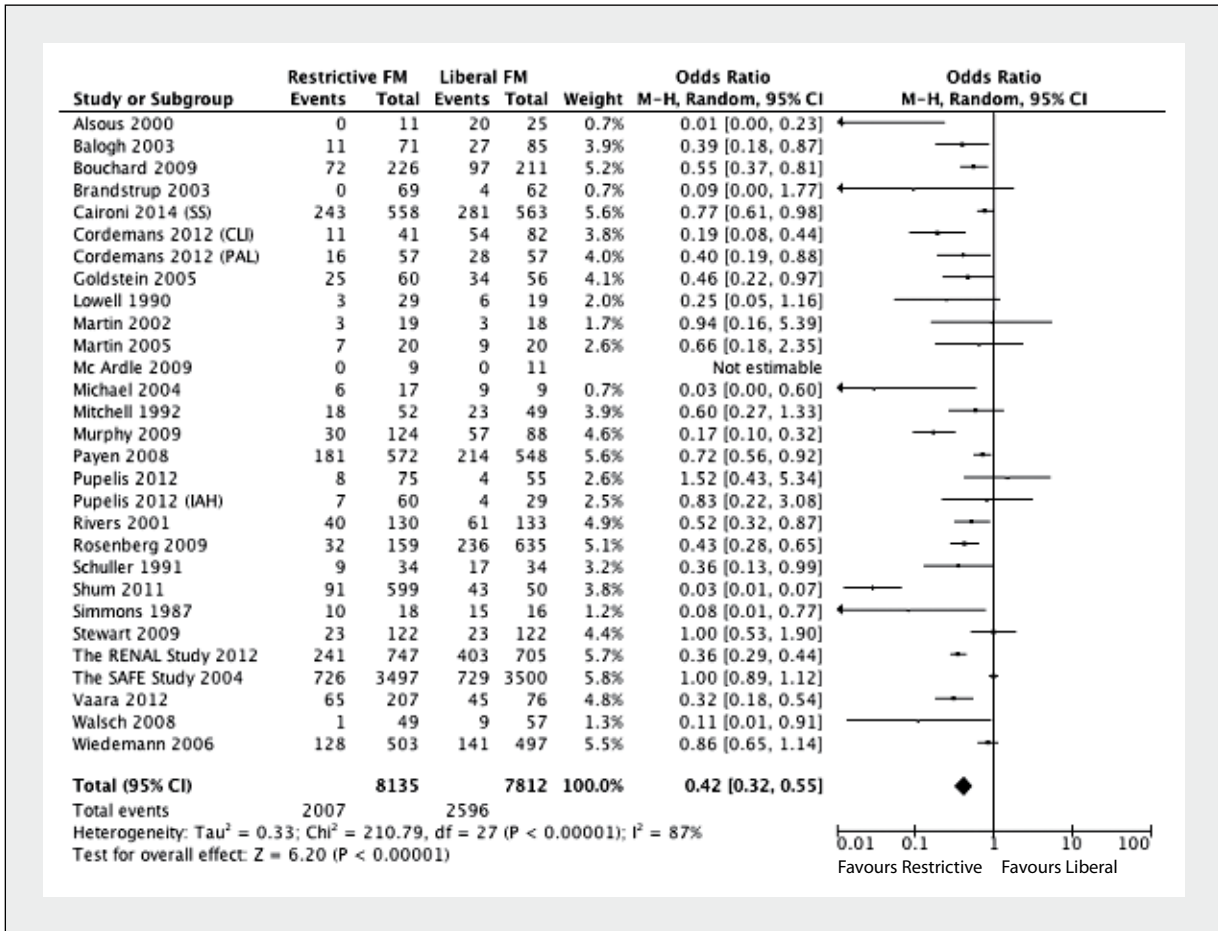


Figure 4. Forest plot looking at the effect of a restrictive compared to a liberal fluid regimen on mortality. Updated and adapted from Malbrain et al. [61]

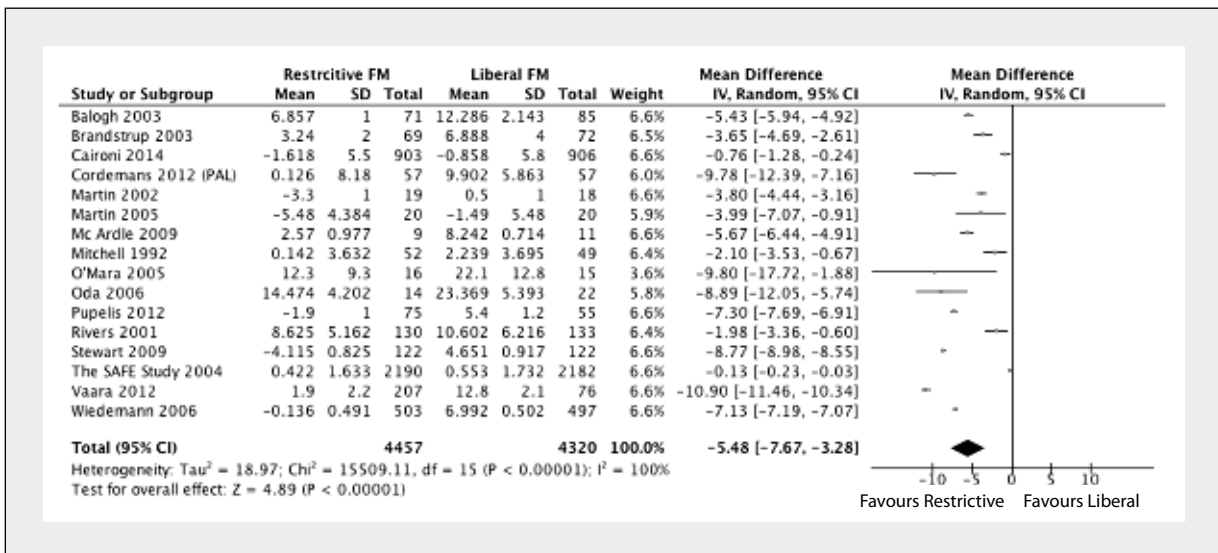


Figure 5. Forest plot looking at cumulative fluid balance after one week* of ICU stay in patients with (restrictive fluid management) and without (liberal fluid management) intervention. Updated and adapted from Malbrain et al. [61]; FM — fluid management; PAL — PEEP, albumin and lasix (furosemide) treatment

*In the Rivers study data was only available at 72 hours and in the Vaara study data was only available at 96 hours and not after one week

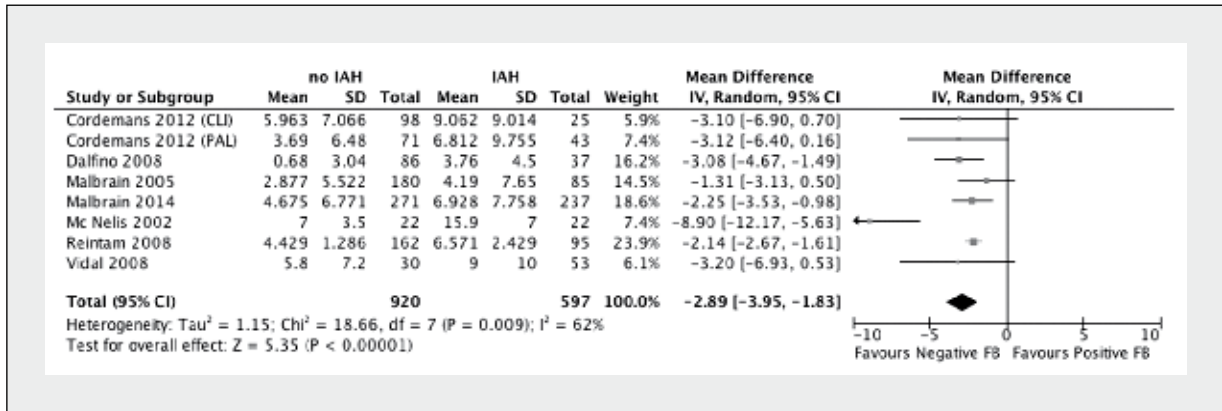


Figure 6. Forest plot looking at cumulative fluid balance after one week of ICU stay in patients with and without intra-abdominal hypertension (IAH). Updated and adapted from Malbrain et al. [61]; IAH — intra-abdominal hypertension; FB — fluid balance

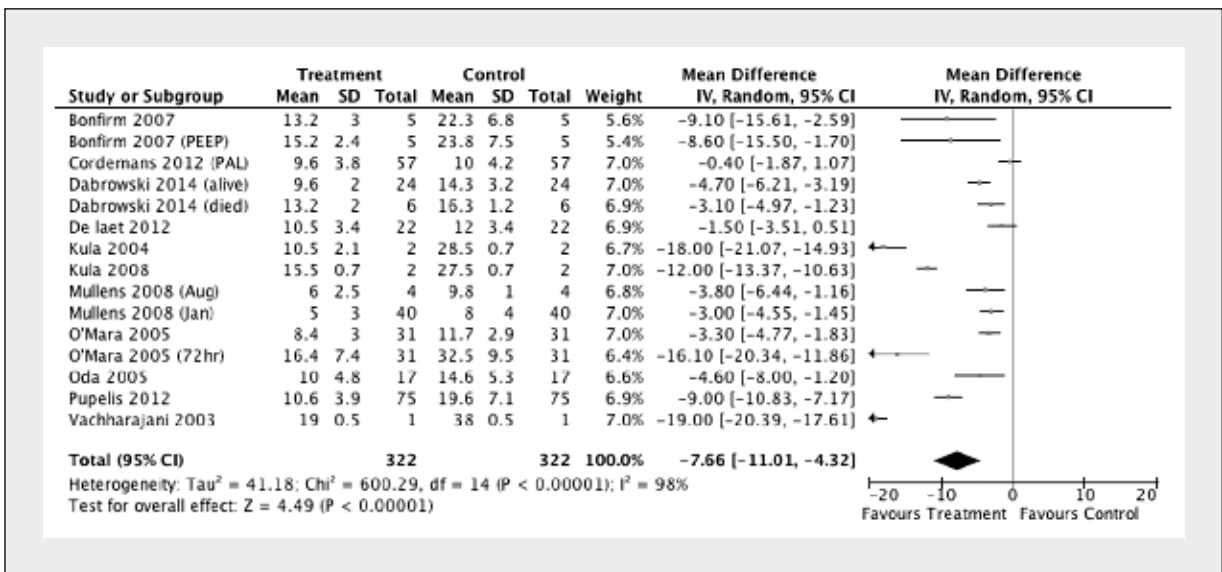


Figure 7. Forest plot looking at the effect of fluid removal on intra-abdominal pressure. Updated and adapted from Malbrain et al. [61]; PEEP — positive end expiratory pressure; PAL — PEEP, albumin and lasix (furosemide) treatment

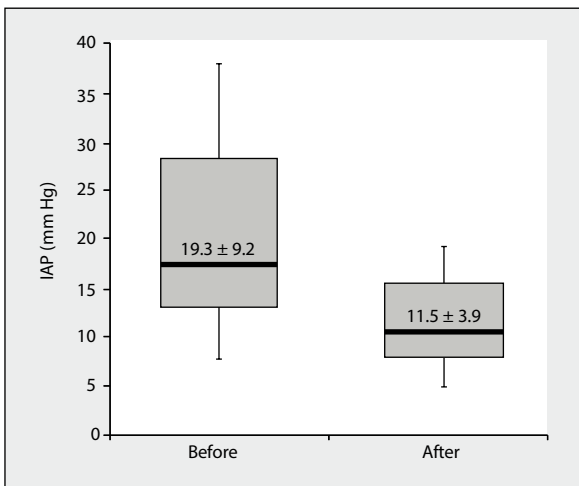


Figure 8. Boxplot showing the effect of fluid removal (after) on intra-abdominal pressure (IAP, mm Hg). Solid line indicates median IAP with interquartile range

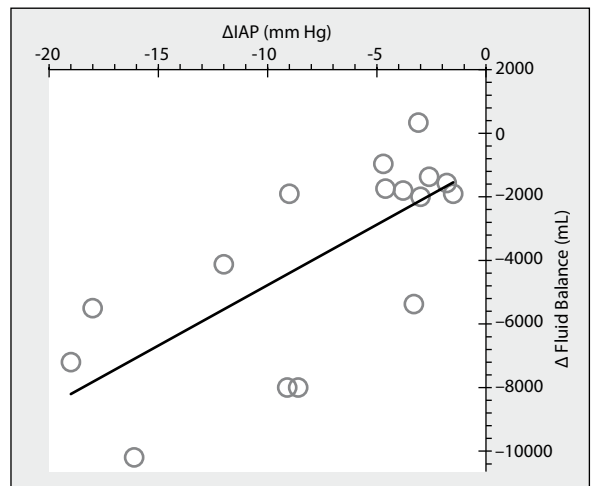


Figure 9. Pearson correlation graph showing the change in intra-abdominal pressure (ΔIAP) in relation to the amount of fluid removed (Δ Fluid Balance)

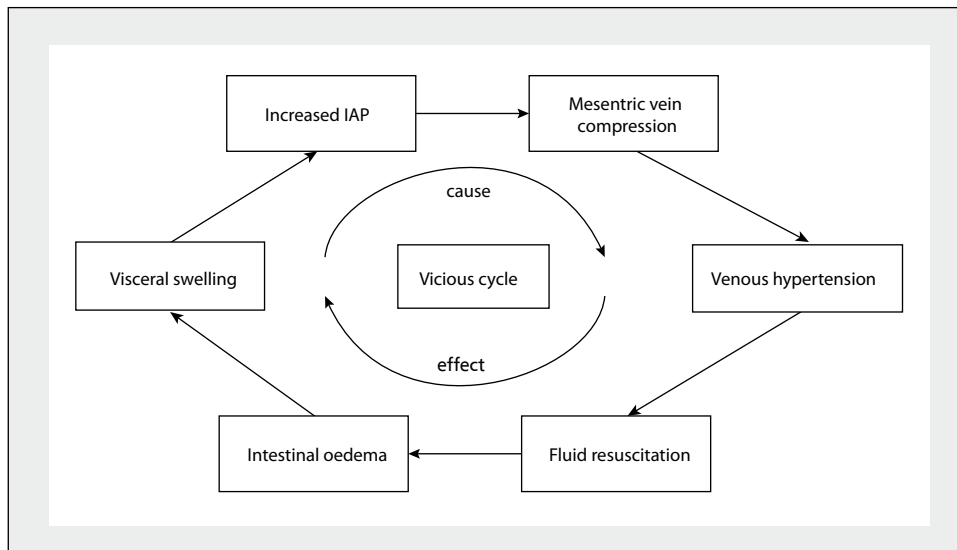


Figure 10. Vicious cycle of futile fluid loading leading to increased IAP and further ongoing fluid administration

in managing the fluid balance and subsequently IAH, and the need for further studies.

In answer to the question ‘Why de-resuscitation?’: ‘Because fluid overload is independently related to morbidity and mortality’.

PATHOPHYSIOLOGY OF FLUID OVERLOAD

This section will address the question: ‘When to de-resuscitate?’ As early as 1942, the concept of a dual metabolic response to bodily injury was introduced. In direct response to initial proinflammatory cytokines and stress hormones, the **Ebb phase** represents a distributive shock characterised by arterial vasodilatation and transcapillary albumin leakage abating plasma oncotic pressure. Arterial underfilling, microcirculatory dysfunction, and secondary interstitial oedema lead to systemic hypoperfusion and regional impaired tissue use of oxygen. In this early stage of shock, adequate fluid therapy comprises adequate goal directed filling to prevent evolution to multiple organ dysfunction syndrome (MODS). As compensatory neuroendocrine reflexes and potential renal dysfunction result in sodium and water retention, positive fluid balances are inherent to the Ebb phase. Patients with higher severity of illness need more fluids to reach cardiovascular optimisation. Therefore, at this point fluid balance may be considered a biomarker of critical illness, as proposed by Bagshaw et al. [101]. Patients overcoming shock attain homeostasis of proinflammatory and anti-inflammatory mediators classically within three days. Subsequent haemodynamic stabilisation and restoration of plasma oncotic pressure set off the **Flow phase** with resumption of diuresis and mobilisation of extravascular fluid resulting in negative fluid balances.

When considering fluid administration, it is important to know when to start giving fluids (what are the benefits of fluid administration), when to stop giving fluids (what are the risks of ongoing fluid administration), when to start removing fluids (what are the benefits of fluid removal), and when to stop fluid removal (what are the risks of removing too much fluid). The literature shows that a negative fluid balance increases survival in patients with septic shock [31]. Patients admitted to the ICU who develop sepsis, respiratory failure, renal failure ARDS, IAH or ACS all have a more positive cumulative fluid balance than those without organ failure [26, 27, 29, 102, 103]. Patients managed with a conservative fluid strategy also seem to have improved lung function, shorter duration of mechanical ventilation and intensive care stay without increasing non-pulmonary organ failure [30]. Monitoring is essential however, as any measurement in the ICU will only be of value as long as it is accurate and reproducible, and no measurement has ever improved survival, only a good protocol can do this. Vice versa a poor treatment algorithm can result in potential harm to the patient [104, 105]. Patients who are in the Ebb or Flow phase of shock have different clinical presentations and therefore different monitoring needs (targets) and different treatment goals [25, 61].

Renal function in particular is strongly affected by fluid overload and IAH, and renal interstitial oedema may impair renal function, even in the absence of IAH [14, 23, 91, 101, 106]. Therefore, fluid overload leading to IAH and associated renal dysfunction may counteract its own resolution [107]. The adverse effects of fluid overload and interstitial oedema are numerous and have an impact on all end organ functions, although some clinicians still

believe that peripheral oedema is only of cosmetic concern [108]. As adverse effects of fluid overload in states of capillary leakage are particularly pronounced in the lungs, monitoring of EVLWI may offer a valuable tool to guide fluid management in the critically ill. A high EVLWI indicates a state of capillary leakage, associated with higher severity of illness and mortality [32, 72, 109, 110]. Previous studies correlated EVLWI with albumin extravasation in patients after multiple trauma [111]. Responders to LCFM overcome the distributive shock and make a transition to the flow phase [32]. On the other hand, nonresponders stay in the grip of the Ebb phase and progress to GIPS, resulting in positive fluid balances, organ failure and death.

In this hypothesis, (change in) EVLWI has a prognostic value as a reflection of the extent of capillary leakage, rather than as a quantification of lung function impairment by lung water [32, 47]. The recent observations may also have direct consequences regarding fluid management in critically ill patients with IAH. Patients at risk for GIPS as assessed by CLI, IAP, changes in EVLWI and fluid balance, require restrictive fluid strategies and even fluid removal guided by extended haemodynamic monitoring including lung water measurements (late goal directed fluid removal) [22, 112]. Previously, the application of EVLWI-guided fluid therapy led to improved outcomes and lower positive fluid balances in states of capillary leakage [68]. To achieve restrictive fluid management may necessitate a greater use of vasopressor therapy, resuscitation with hyperoncotic solutions (e.g. albumin 20%) and early initiation of diuretics and renal replacement therapy, although in the

FACCT trial the conservative arm had a trend towards less requirement for dialysis [30].

‘When should de-resuscitation begin?’: De-resuscitation should be considered when fluid overload and fluid accumulation negatively impact end-organ function, so de-resuscitation is mandatory in a case of a positive cumulative fluid balance in combination with poor oxygenation (P/F ratio < 200), increased capillary leak (high PVPI > 2.5 and EVLWI > 12 mL kg⁻¹ PBW), increased IAP (> 15 mm Hg) and low APP (< 50 mm Hg), high CLI, etc.’

PRACTICAL APPROACH

‘How to de-resuscitate?’: Bedside measurement of extravascular lung water (EVLWI) performed by trans-cardiopulmonary thermodilution allows the estimation of the extent of capillary leak and fluid overload. Accordingly, EVLWI correlates well with organ function and survival [49, 102, 109, 113]. Moreover, fluid management aimed at EVLWI reduction results in a more negative fluid balance and improved outcomes [68]. In order to achieve a negative fluid balance, previous prospective trials excluded patients with hypotension and renal failure [30, 65, 68]. Recently in a study of 57 patients who were compared to 57 matched controls, the effects of a restrictive fluid regimen with negative fluid balance using ‘PAL-treatment’ were examined in mechanically ventilated patients with ALI presenting with severe hypoxemia, increased EVLWI and IAP [72]. PAL-treatment combines high levels of positive end-expiratory pressure (PEEP), small volume resuscitation with hyperoncotic albumin and fluid removal with diuretics (Lasix®) or ultrafiltration

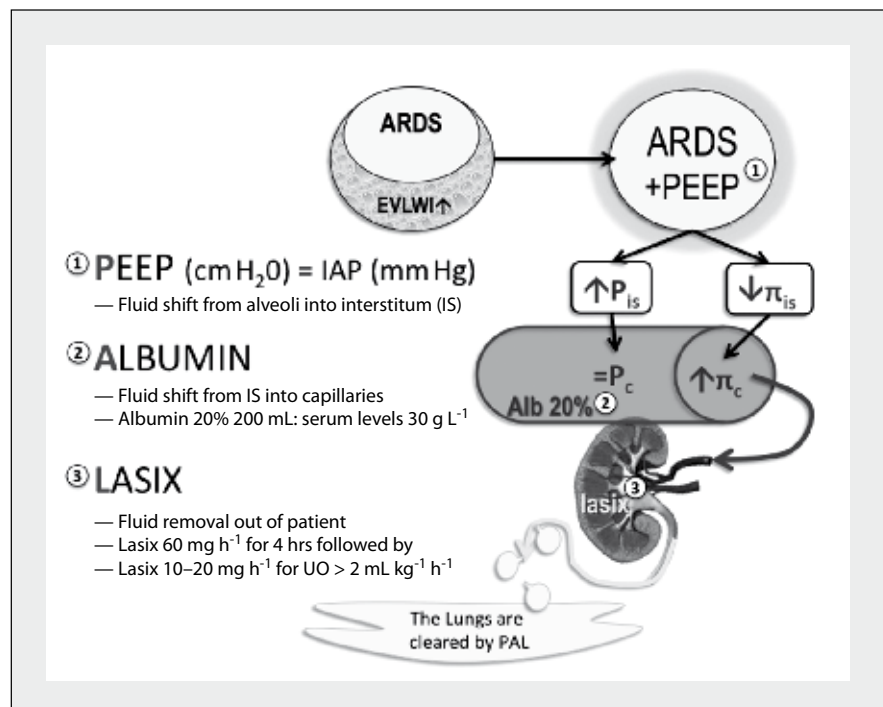


Figure 11. Rationale and working mechanism of PAL treatment. See text for explanation

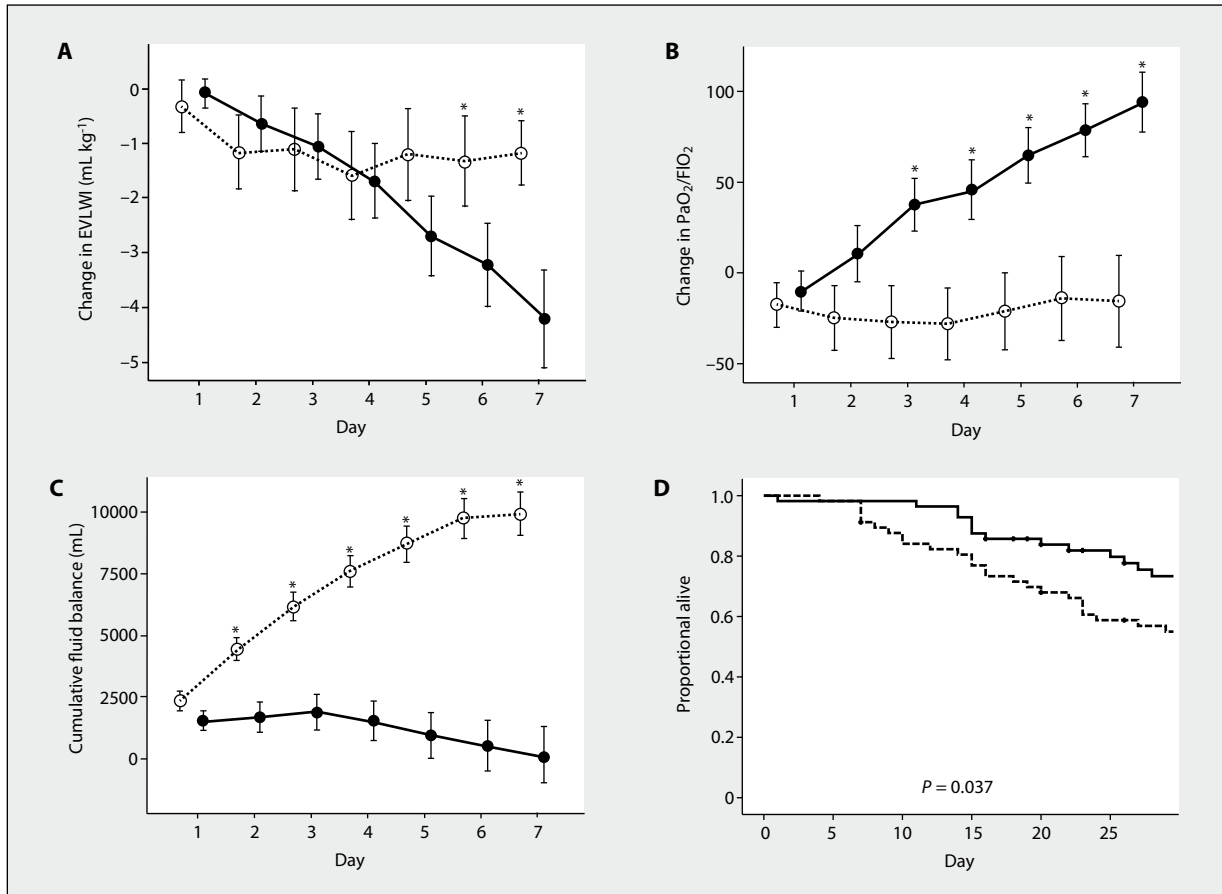


Figure 12. Effects of PAL treatment (adapted from Cordemans et al. [72]). **A** — effect of one week of PAL treatment (closed circles) on extravascular lung water index (EVLWI); **B** — effect of one week of PAL treatment (closed circles) on the PaO₂/FiO₂ ratio; **C** — effect of one week of PAL treatment (closed circles) on cumulative fluid balance (mL). * indicates statistical significance between two groups; **D** — Kaplan-Meier cumulative survival curves in patients receiving PAL treatment (closed line) compared to matched controls (dotted line)

during continuous renal replacement therapy (CRRT). First, a 30-minute application of PEEP is titrated to counterbalance the effects of increased IAP (best PEEP in cm H₂O = IAP in mm Hg). Next, hyperoncotic albumin (20%) solution is administered by 200 mL boluses over 60 minutes twice on the first day and subsequently titrated towards a serum albumin level of 30 g dL⁻¹. Finally, 30 minutes after the first albumin dose a furosemide infusion is initiated with an intravenous loading dose of 60 mg, followed by a continuous infusion at 60 mg per hour for the first four hours and 5–20 mg per hour thereafter, according to haemodynamic tolerance (Fig. 11). In anuric patients, CRRT can be added with an ultrafiltration rate set in order to obtain a neutral to negative daily fluid balance. One week of PAL-treatment had beneficial effects on EVLWI, IAP, organ function and vasopressor therapy, and this resulted in a shorter duration of mechanical ventilation (faster weaning) and improved 28-day mortality (Fig. 12). Combining the results of two recent studies (n = 180), we found that the group of patients treated with conservative initial and late fluid management had the best outcome, followed by those who received initial adequate and late

conservative fluid management [32, 72]. Mortality was significantly increased in those patients who had received late liberal fluid management (Fig. 14). This is in line with previous results by Murphy et al. [21].

DISCUSSION

The results of this meta-analysis and systematic review of the available evidence support the hypothesis that fluid overload is detrimental to patients and is associated with increased morbidity and mortality.

We recently suggested a three-hit model of shock which we would like to extend to a four-hit model in which we can recognise five distinct dynamic phases or stages of fluid administration [32]: Resuscitation, Optimisation, Stabilisation, and Evacuation (ROSE), followed by a potential risk of Hypoperfusion (Table 3, Fig. 15). Logically, these describe the five different clinical phases of fluid therapy, occurring over the time course during which patients experience a different impact on end-organ function (Fig. 15). Similar principles were recently also suggested by others, confirming the need for a multicentre prospective trial with a bimodal approach

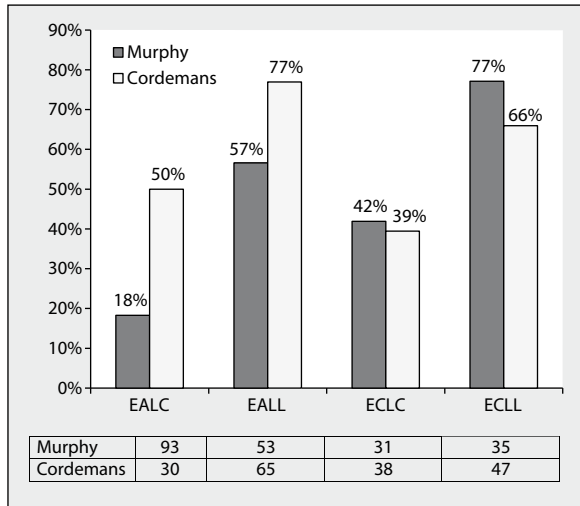


Figure 13. Bar graph showing patient distribution and outcomes in different fluid management categories comparing the data from Murphy (n = 212) [21] and aggregate data from two studies from Cordemans (n = 180) [32, 72]. See text for explanation EA — early adequate fluid management, defined as fluid intake > 50 mL kg⁻¹ first 12–24 hours of ICU stay; EC — early conservative fluid management, defined as fluid intake < 25 mL kg⁻¹ first 12–24 hours of ICU stay; LC — late conservative fluid management, defined as two consecutive zero to negative daily FB within first week of ICU stay; LL — late liberal fluid management, defined as the absence of two consecutive negative daily FB within first week of ICU stay

using late conservative fluid management after the initial early adequate goal-directed treatment in those patients not transgressing spontaneously from the Ebb to the Flow phase [22, 24, 38, 40, 101, 114–116]. We will discuss below the four-hit model of shock, each corresponding to a specific treatment question.

**1ST HIT: WHEN DO I START TO GIVE FLUIDS?
ALL ABOUT THE BENEFITS OF FLUIDS**

Resuscitation phase. After the first hit which can be sepsis, burns, pancreatitis, or trauma, the patient will enter the Ebb phase of shock. This phase of severe shock, that can be life-threatening, occurs within minutes and is characterised by low mean arterial pressure, low CO, and microcirculatory impairment. In some patients, fluids are mandatory because oxygen may have convective difficulties to get into the tissues in case of severe hypovolemia [116]. Maintenance fluids should be given at a rate of 1 mL kg⁻¹h⁻¹ in combination with replacement fluids when indicated. Before fluids are administered, correct monitoring of flow (CO) is mandatory and fluid responsiveness should always be assessed with a passive leg raising test or end-expiratory occlusion test before fluid administration. The use of non-invasive or minimally invasive cardiac output monitors are recommended to assess fluid responsiveness.

This phase corresponds of the ‘R’ or *Resuscitation* within the ROSE concept. During the initial stages of the resuscita-

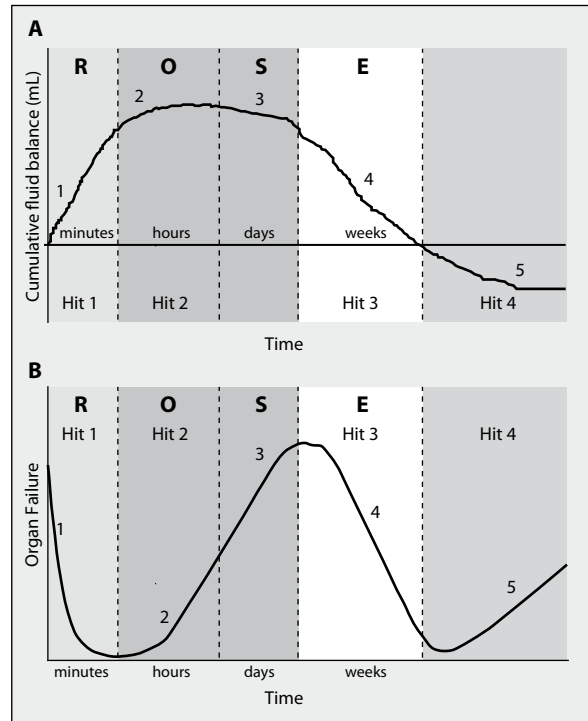


Figure 14. The five fluid phases of shock. **A** — graph showing the four-hit model of shock with evolution of patients’ cumulative fluid volume status over time during the five distinct phases of resuscitation: **R**esuscitation (1), **O**ptimisation (2), **S**tabilisation (3), and **E**vacuation (4) (ROSE), followed by a possible risk of **H**ypoperfusion (5) in a case of too aggressive deresuscitation. See text for explanation; **B** — graph illustrating the four-hit model of shock corresponding to the impact on end-organ function in relation to the fluid status. On admission patients are hypovolemic (1), followed by normovolemia (2) after fluid resuscitation, and fluid overload (3), again followed by a phase going to normovolemia with deresuscitation (4) and hypovolemia with risk of hypoperfusion (5). In a case of hypovolemia (phases 1 and 5) O₂ cannot get into the tissues because of convective problems; in a case of hypervolemia (phase 3) O₂ cannot get into the tissues because of diffuse problems related to interstitial and pulmonary oedema, gut oedema (ileus and abdominal hypertension). See text for explanation

tion phase, fluids should be administered quickly as a bolus (4 mL kg⁻¹ over 10 to 15 minutes) and they can be life-saving, therefore treatment during this phase is referred to as salvage or rescue treatment. The goal is early adequate goal directed fluid management (EAFM), fluid balance must be positive and the resuscitation targets are: MAP > 65 mm Hg, CI > 2.5 L min⁻¹m⁻², PPV < 12%, LVEDAI > 8 cm m⁻².

**2ND HIT: WHEN DO I STOP TO GIVE FLUIDS?
ALL ABOUT THE RISKS OF FLUID OVERLOAD**

Optimisation phase. The second hit occurs within hours and refers to ischaemia and reperfusion. Fluid accumulation should be seen as a biomarker for the severity of illness [24]. The greater the fluid requirement, the sicker the patient. The use of transpulmonary thermodilution techniques (PiCCO, Pulsion Medical Systems, Munich,

Table 3. Characteristics of the different dynamic phases of fluid resuscitation

	Resuscitation (R)	Optimisation (O)	Stabilisation (S)	Evacuation (E)	
HIT	First	Second	Second	Third	Fourth
Cause	Inflammatory insult (sepsis, SAP, burns, trauma, etc.)	Ischaemia and reperfusion	Ischaemia and reperfusion	GIPS	Hypoperfusion
Phase	Ebb	Flow	Flow/ No Flow	No Flow	No Flow
Type	Severe shock	Unstable	Stable	Recovering	Unstable
Example	Septic shock, major trauma, haemorrhagic shock, ruptured AAA, SAP, Severe burns (> 25% TBSA)	Intra- and perioperative GDT, less severe burns (< 25% TBSA), DKA, severe GI losses (vomiting, gastroenteritis)	Postoperative patient (NPO or combination of TEN/TPN), abdominal VAC, replacement of losses in less severe pancreatitis	Patient on full enteral feed in recovery phase of critical illness, polyuric phase after recovering from ATN	Patient with cirrhosis and anasarca oedema (GIPS) and no Flow state, hepatosplanchnic hypoperfusion
Question	When to start fluids?	When to stop fluids?	When to stop fluids?	When to start unloading?	When to stop unloading?
Subquestion	Benefits of fluids?	Risks of fluids?	Risks of fluids?	Benefits of unloading?	Risks of unloading?
O ₂ transport	Convective problems	Euvolemia, normal diffusion	Diffusion problems	Euvolemia, normal diffusion	Convective problems
Fluids	Mandatory	Biomarker of critical illness	Biomarker of critical illness	Toxic	
Fluid therapy	Rapid bolus (4 mL kg ⁻¹ 10–15 min)	Titrate maintenance fluids, conservative use of fluid bolus	Minimal maintenance if oral intake inadequate, provide replacement fluids	Oral intake if possible Avoid unnecessary IV fluids	Avoid hypoperfusion
Fluid Balance	Positive	Neutral	Neutral/Negative	Negative	Neutral
Result	Life Saving (Rescue, salvage)	Organ Rescue (Maintenance)	Organ Support (Homeostasis)	Organ Recovery (Removal)	Organ Support
Targets	Macrohaemodynamics (MAP, CO); lactate; volumetric preload (LVEDAI); functional haemodynamics; fluid responsiveness (PLR, EEO)	Organ macroperfusion (MAP, APP, CO, S _{cv} O ₂); volumetric preload (GEDVI, RVEDVI); GEF correction; R/L shunt; think of PolyCS, CARS	Organ function (EVLWI, PVPI, IAP, APP); biomarkers (NGAL, cystatin-C, citrullin); capillary leak markers (COP, OSM, CLI, RLI); daily and cumulative FB, body weight	Organ function evolution (P/F ratio, EVLWI, IAP, APP, PVPI) Body composition (ECW, ICW, TBW, VE)	Organ microperfusion (pH _i , S _{cv} O ₂ , lactate, ICG-PDR); Biomarkers; Negative cumulative FB
Monitoring tools	A-line, CV-line, PPV or SVV (manual or via monitor), uncalibrated CO, TTE, TEE	Calibrated CO (TPTD, PAC)	Calibrated CO (TPTD); Balance; BIA	Calibrated CO (TPTD); Balance; BIA; DE-escalation	LiMON, Gastric tonometry, Micro-dialysis
Goals	Correct shock (EAFM)	Maintain tissue perfusion	Aim for zero or negative FB (LCFM)	Mobilise fluid accumulation (LGFR) = emptying or DE-resuscitation	Maintain tissue perfusion
Timeframe	Minutes	Hours	Days	Days to weeks	Weeks

Germany or VolumeView/EV1000, Edwards Lifesciences, Irvine, CA, USA) that allow volumetric preload monitoring with GEDVI and measurement of EVLWI is suggested during this phase [34, 117]. The clinician should be cognisant of the polycompartment syndrome and the possibility of CARS [51, 118]. In the setting of increased IAP other thresholds may apply and the clinician must be aware that the PLR test may be false negative [119, 120].

During the *Optimisation* phase the situation is still unstable but the patient is no longer in immediate life-threatening danger but rather in a stage of compen-

sated shock (still at high risk of decompensation) and any additional fluid therapy should be given more cautiously, and titrated with the aim of optimising cardiac function to improve tissue perfusion with the ultimate goal of avoiding end-organ dysfunction or failure (organ rescue) [38]. Hence, the goal is to maintain tissue perfusion, and fluids should be seen as maintenance but can be organ-saving, fluid balance should go from positive to neutral and the resuscitation targets are: MAP > 65 mm Hg, CI > 2.5 L min⁻¹m⁻², PPV < 14%, LVEDAI 8–12 cm⁻¹m⁻². In this phase IAP (< 15 mm Hg) is monitored and APP (> 55 mm Hg)

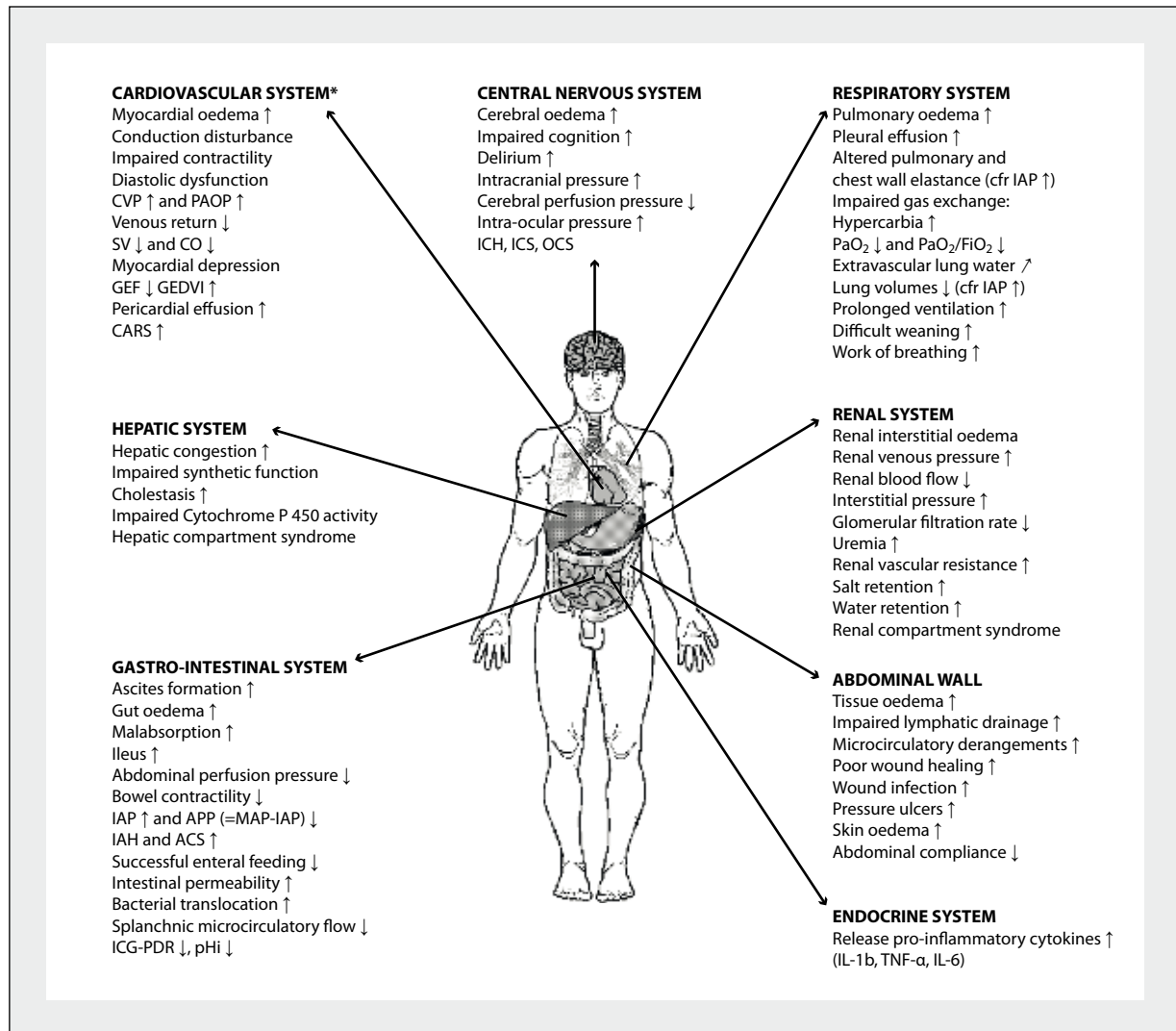


Figure 15. Pathophysiologic effects of fluid overload on end-organ function. See text for explanation
IAP — intra-abdominal pressure; IAH — intra-abdominal hypertension; ACS — abdominal compartment syndrome; ICH — intracranial hypertension; ICS — intracranial compartment syndrome; OCS — ocular compartment syndrome; CARS — cardio abdominal renal syndrome

is calculated. Preload should be optimised with GEDVI 640–800 mL m⁻² and in a case of high values via the use of a GEF correction formula [33].

Stabilisation phase. After the Optimisation phase follows the Stabilisation phase evolving over the next days. This homeostasis phase focuses on organ support and reflects the point at which a patient is in a stable steady state so that fluid therapy is now only used for ongoing maintenance and replacement either in the setting of normal fluid losses (i.e. renal, gastrointestinal, insensible), but this could also be fluid infusion (including rehydration) if the patient was experiencing ongoing losses because of unresolved pathologic conditions. However, this stage is distinguished from the previous two by the absence of shock (compensated or uncompensated) or the imminent threat of shock. Ideally body weight should be measured daily and cumulative

fluid balance should be calculated to assess the risk for fluid overload. Bio-electrical impedance analysis (BIA) with calculation of extra- and intracellular water (ECW, ICW), total body water (TBW) and volume excess (VE) can provide additional information. Monitoring with calibrated TPTD is continued and the goal during this phase is late conservative fluid management (LCFM), aiming for a zero or negative fluid balance, and fluids should be seen as maintenance and replacement and to support organ function, and the resuscitation targets are shifting towards organ function: EVLWI < 10–12 mL kg⁻¹ PBW, PVPI < 2.5, IAP < 15 mm Hg, APP > 55 mm Hg, COP > 16–18 mm Hg, and CLI < 60. During this phase biomarkers (NGAL, cystatin-C, citrullin, etc.) may be helpful to assess organ function in the setting of accumulated fluid overload as oxygen diffusion to the tissues may be impaired.

3RD HIT: WHEN DO I START UNLOADING FLUIDS?**ALL ABOUT THE BENEFITS OF FLUID REMOVAL**

Evacuation phase. After the second hit, two things can happen: either the patient further recovers and enters the Flow phase spontaneously with evacuation of the excess fluids that have been given previously. However many ICU patients remain in a 'no Flow' state followed by a third hit usually resulting from a global increased permeability syndrome (GIPS) with ongoing fluid accumulation due to capillary leak [47]. Further fluid administration at this stage becomes harmful for the patient. Peripheral and anasarca oedema is not only of cosmetic concern, as believed by some [108], but harmful to the patient as it results in organ dysfunction. Figure 15 illustrates the negative effects of fluid overload on end-organ function. While in the first three stages ('ROS'), fluids are usually administered (initially as rescue, followed by maintenance and finally as replacement), in the last stage, the evacuation phase (corresponding to the 'E' within the ROSE concept), fluids will need to be actively removed from the patient during the following days to weeks in order to support organ recovery. The goal here will be to promote a negative fluid balance by mobilising accumulated fluids with late goal directed fluid removal (LGFR) strategy, also referred to as **de-resuscitation**. Monitoring during this phase should focus on assessment of fluid overload and its impact on end-organ function with TPTD and BIA: P/F ratio, EVLWI, PVPI, IAP, APP, ECW, ICW, TBW, and VE. The motto here is 'dry lungs are happy lungs'.

4TH HIT: WHEN DO I STOP UNLOADING FLUIDS?**ALL ABOUT THE RISKS OF FLUID REMOVAL**

The last hit needs to be avoided as it is often iatrogenous after overly enthusiastic fluid removal during the previous stage. A negative cumulative fluid balance and resulting hypovolemia may give rise again to convective problems causing hypoperfusion and tissue hypoxia. During the recovery weeks, tissue perfusion must be maintained and monitoring with LiMON (Pulsion Medical Systems, Feldkirchen, Germany), gastric tonometry (Datex Ohmeda, Helsinki, Finland), microdialysis, etc. should focus on hepatosplanchnic and microperfusion with monitoring of $S_{cv}O_2$, ICG-PDR, pH, and biomarkers. The motto here is 'a dry liver may result in a dead patient'.

CONCLUSIONS

Capillary leak is an inflammatory condition with diverse triggers that results from a common pathway that includes ischaemia-reperfusion, toxic oxygen metabolite generation, cell wall and enzyme injury leading to a loss of capillary endothelial barrier function.

In such a state, plasma volume expansion to correct hypoperfusion predictably results in extravascular move-

ment of water, electrolytes and proteins. Peripheral tissue oedema, visceral oedema and ascites may be anticipated in proportion to the volume of prescribed resuscitation fluid. A variety of strategies are available to the clinician to reduce the volume of crystalloid resuscitation used while restoring macro- and microcirculatory flow. Regardless of the resuscitation strategy, the clinician must maintain a heightened awareness of the dynamic relationship between capillary leak, fluid loading, peripheral oedema, intra-abdominal hypertension and the abdominal compartment syndrome.

Late conservative fluid management and de-resuscitation may in the long run be more important than the initial resuscitation efforts during the Ebb phase in patients with shock. EVLWI can be used at the bedside as a safety guide to initiate late conservative fluid management strategy or late goal directed fluid removal in those patients who do not transgress spontaneously from the Ebb to the Flow phase of shock. However, we must remember that no single parameter can change outcome, this can only be achieved by a good protocol. PAL-treatment seems a good example of such a protocol, but further prospective studies are needed.

It is important for the bedside clinician to know and to understand:

When to start giving fluids (low MAP, low CO, increased lactate, low LVEDAI, low GEF/GEDVI, high PPV and positive PLR or EEO)

When to stop giving fluids (high GEF/GEDVI, low PPV, negative PLR, positive daily fluid balance, weight gain)

When to start removing fluids (low P/F ratio, high EVLWI, high PVPI, raised IAP, low APP defined as MAP minus IAP, positive cumulative fluid balance, increased BIA parameters (ECW, TBW, VE), high CLI, or high RLI, renal leak index (urine albumin over creatinine ratio)

When to stop fluid removal (low ICG-PDR, low APP, low $S_{cv}O_2$, neutral or negative cumulative fluid balance)

However one must realise that the above-mentioned thresholds are moving targets but also with moving goals (from early adequate goal directed therapy, over late conservative fluid management towards late goal directed fluid removal). And above all, one must always bear in mind that unnecessary fluid loading may be harmful.

If the patient does not need fluids, don't give them, and remember that the best fluid may be the one that has not been given to the patient!

It is essential to give the right fluid at the right time in the right fashion, and to use the correct monitor correctly.

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AWK is a member of the Executive Committee and President Elect of the World Society on the Abdominal Compartment Syndrome.

NVR is a member of the Executive Committee of the International Fluid Academy.

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