Optimizing fluid therapy in the hemodynamically unstable patient

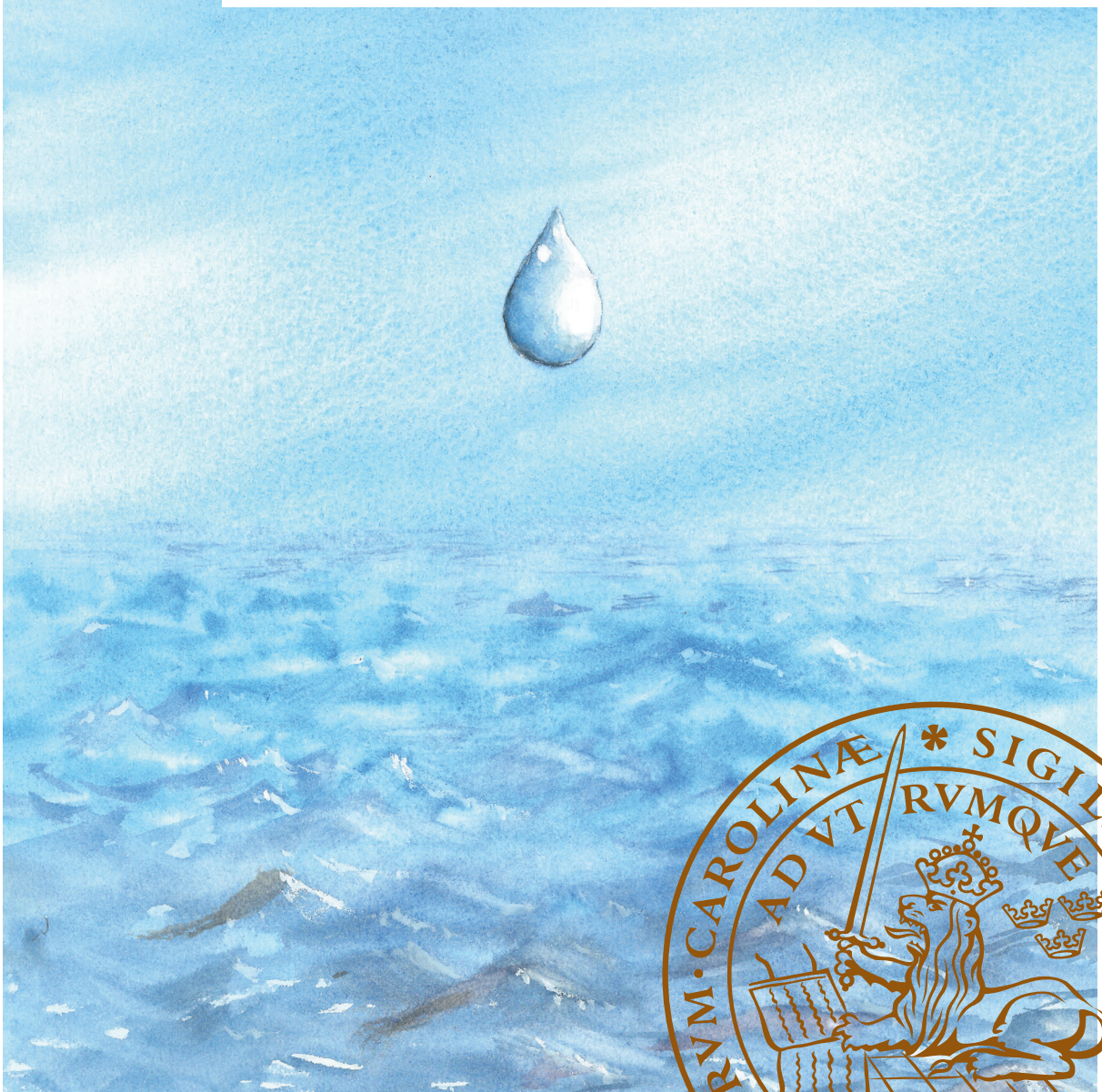
Lindén, Anja

2024

Document Version:
Publisher's PDF, also known as Version of record

Optimizing fluid therapy in the hemodynamically unstable patient

ANJA LINDÉN
DEPARTMENT OF CLINICAL SCIENCES | FACULTY OF MEDICINE | LUND UNIVERSITY



Optimizing fluid therapy in the hemodynamically unstable patient

Optimizing fluid therapy in the hemodynamically unstable patient

Anja Lindén

LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended on April 26th 2024 at 09.00 in Medicinhistoriska museet, Bergaliden 20, 252 23 Helsingborg

Faculty opponent
Professor Markus Skrifvars
Department of Diagnostics and Therapeutics
Helsinki University

Organization: LUND UNIVERSITY

Document name: Doctorial dissertation **Date of issue** 2024-04-26

Author: Anja Lindén

Title and subtitle: Optimizing fluid therapy in the hemodynamically unstable patient

Abstract:

Administration of large fluid volumes is associated with harmful effects in both septic shock and the perioperative setting. In septic shock, many trials have investigated if restrictive administration of resuscitation fluid influences patient-important outcomes but separation in fluid volumes between the intervention and control groups has been small and no treatment effect has been found. Previous research indicates that fluid given for other reasons than to correct hemodynamic disturbances (non-resuscitation fluid) is the major source of fluid administered in septic shock, but the potential for reduction of this fluid is currently unknown.

Preload responsive postoperative patients with signs of inadequate organ perfusion are commonly treated with fluids to increase preload. If fluid is the preferable treatment may however depend on the intravascular volume status of the patient.

The aim of this thesis was to investigate the potential to reduce fluid administration in the hemodynamically unstable patient.

Paper I was a prospective, observational study where fluid administration was quantified and characterized in patients with septic shock during the first five days in the intensive care unit, with special emphasis on non-resuscitation fluids. Potential reduction of non-resuscitation fluids was also assessed. The major part of fluids administered was non-resuscitation fluids where glucose solutions and vehicles for medications were the primary subgroups. When modelling a restrictive protocol of non-resuscitation fluids, a median (interquartile range) potential reduction of 2.8 (1.3-4.9) L was obtained during the first five days in the ICU.

In Paper II and III, a protocol for a randomized clinical trial (RCT) aimed at reducing non-resuscitation fluids in patients with septic shock was designed and the feasibility and efficacy were assessed. Protocolized reduction of non-resuscitation fluids resulted in a median fluid reduction of 3.6 (1.6-5.3) L in the restrictive fluid group versus usual care during the first three days in the ICU. A trial using this design to test if reduced administration of non-resuscitation fluids improves patient-important outcomes is feasible.

Paper IV was a post hoc-analysis of data from an RCT where the blood volume status in preload-responsive postoperative patients was investigated. In 63 patients, two thirds were defined as likely preload responsive. Among these, 44% were hypovolemic, 28% euvolemic and 28% of the patients were hypervolemic. A large fraction of likely preload responsive postoperative patients with signs of hypoperfusion are hypervolemic, a volume status where treatments other than fluid administration may be more rational to prescribe to increase cardiac output.

Key words: Non-resuscitation fluids, septic shock, restrictive fluid administration, postoperative patient, preload responsiveness

Language: English **ISSN and key title**: 1652-8220

Number of pages: 70 **ISBN:** 978-91-8021-537-4

Recipient's notes

Signature Date 2024-03-12

Optimizing fluid therapy in the hemodynamically unstable patient

Anja Lindén

LUND
UNIVERSITY

Faculty of Medicine, Lund University
Department of Clinical Sciences
Anaesthesiology and Intensive Care

ISBN 978-91-8021-537-4
ISSN 1652-8220
Lund University, Faculty of Medicine Doctoral Dissertation Series 2024:44

Printed in Sweden by Media-Tryck, Lund University, Lund 2024

Till mamma och pappa

Table of Contents

List of Papers

Paper I

Lindén-Søndersø A, Jungner M, Spångfors M, Jan M, Oscarson A, Choi S, Kander T, Undén J, Griesdale D, Boyd J, Bentzer P. Survey of non-resuscitation fluids administered during septic shock: a multicenter prospective observational study. *Annals of Intensive Care.* 2019;9:132.70

Paper II

Lindén A, Fischer J, Lilja G, Olsen MH, Sjövall F, Jungner M, Spångfors M, Samuelsson L, Oras J, Linder A, Undén J, Kander T, Lipcsey M, Nielsen N, Jakobsen JC, Bentzer P. Protocolised reduction of non-resuscitation fluids versus usual care in septic shock patients (REDUSE): a protocol for a multicentre feasibility trial. *BMJ Open*. 2023;13:e065392.

Paper III

Lindén A, Spångfors M, Olsen MH, Fisher J, Lilja G, Sjövall F, Jungner M, Lengquist M, Kander T, Samuelsson L, Johansson J, Palmnäs E, Undén J, Oras J, Cronhjort M, Chew M, Linder A, Lipcsey M, Nielsen N, Jakobsen JC, Bentzer P for the REDUSE trial group. Protocolized reduction of non-resuscitation fluid versus usual care in septic shock patients (REDUSE): a multicentre feasibility trial. *Submitted Dec 2023.*

Paper IV

Lindén A, Statkevicius S, Bonnervier J, Bentzer P. Blood volume in patients likely to be preload responsive; a post hoc analysis of a randomized controlled trial. *Intensive Care Medicine Experimental. 2*023;11:14.

Abbreviations

AIR trial	Albumin infusion rate (and plasma volume expansion) trial
AKI	Acute kidney injury
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
CI	Confidence interval
CO	Cardiac output
CRF	Case report form
CVP	Central venous pressure
DAMP	Damage associated molecular pattern
DAP	Diastolic arterial pressure
Hct	Hematocrit
HR	Heart rate
ECF	Extracellular fluid
ED	Emergency department
EGDT	Early goal-directed therapy
EMA	European Medicines Agency
ERAS	Enhanced recovery after surgery
FDA	(American) Food and Drug Agency
HBP	Heparin-binding protein
HES	Hydroxyethyl starch
ICF	Intracellular fluid
ICU	Intensive care unit
ISF	Interstitial fluid
MAP	Mean arterial pressure

NO	Nitric oxide
PAMP	Pathogen associated molecular pattern
PG	Prostaglandin
PLR-test	Passive leg raise test
P_{msf}	Mean systemic filling pressure
PP	Pulse pressure
PRR	Pathogen recognition receptor
PV	Plasma volume
RAP	Right atrial pressure
RCT	Randomized clinical trial
RRT	Renal replacement therapy
SAP	Systolic arterial pressure
SAPS	Simplified acute physiology score
SOFA	Sequential organ failure assessment
SSC	Surviving sepsis campaign
SV	Stroke volume
WHO	World Health Organization

Introduction

"Verily, Sir, this is an astonishing method of medication, and I predict will lead to wonderful changes and improvements in the practice of medicine."

Dr Robert Lewin, on the effect of intravenous fluids in cholera patients,
Letter to *The Lancet*, May 18th,1832

Water is essential for life. It is the main component of the human body and comprises about 60% of the body weight depending on age, sex, and body constitution. Humans can only survive for a few days without it. Water supports cell structure and is the most abundant molecule in the cell. Among its many functions, water keeps the skin and mucus membranes hydrated, thereby maintaining an effective barrier against the surroundings. By way of the blood stream, oxygen, nutrients, and other molecules can be transported to the cells and carbon dioxide and waste products away from the cell, for excretion via the lungs and the kidneys. Water helps us regulate body temperature and is also important for gastrointestinal function (Rhoades et al. 2003).

Intravenous fluid is one of the most common treatments in hospitalized patients (Kaufman et al. 2023). Indications vary from resuscitation purposes for intravascular blood volume expansion, to fluids administered as nutrition or maintenance fluid. Fluid treatment in the critically ill is an area of great interest in the intensive care community. Previous research has studied aspects such as if colloids or crystalloids are the best choice for resuscitation, and if there is such a thing as the optimal crystalloid (Perner et al. 2012; Finfer et al. 2004; Zampieri et al. 2021). In recent years yet another facet of fluid therapy has received increased attention – does *volume* of administered fluid matter in terms of outcome? Critically ill patients often receive large volumes of fluid which increases the risk of potentially detrimental fluid overload. Positive fluid balance in the critically ill has been associated with worse outcome such as increased mortality and acute kidney injury (AKI) (Boyd et al. 2011; Payen et al. 2008). Is there a benefit in reducing fluid administration in the hemodynamically unstable patient? This thesis aims at expanding the existing body of research on how fluid administration can be reduced.

Fluid therapy

The history of intravenous fluids

The start of intravenous fluid therapy dates to the 19th century, when in 1831 a cholera epidemic hit northern England. The main symptoms of the cholera patients were diarrhea and abdominal pains, and the blood of the infected patients was described as "black, thick, cold". The cause of the disease was yet unknown, but a common perception of the cure was to clear the body of this unhealthy blood (Cosnett 1989). With today's perspective, some of the therapies used appear questionable in aiding the recovery of a hypovolemic patient. Common treatments were venesection, emetics and assorted physical assaults (Howard-Jones 1972). To better understand the disease and get closer to an effective treatment, the Royal College of Surgeons of London asked a doctor with an interest in chemistry to study the blood of cholera victims. The name of this doctor was William Brooke O'Shaughnessy (Fig 1). As he studied the contents of blood, he concluded that a large amount of salt, bicarbonate and water had been lost from the body. He suggested in a letter published in *The Lancet* that it was necessary to restore the blood of its natural properties (O'Shaughnessy 1831). The procedure, he explained, could be performed using a tube of gold or ivory inserted into a vein.

Fig 1. Dr. William Brooke O'Shaughnessy.

O'Shaughnessy did not pursue the development of this fluid himself, but his work did inspire the man sometimes referred to as 'the father of intravenous fluid therapy' – Dr Thomas Aitchison Latta (MacGillivray 2009). Just a couple of months after O'Shaughnessy declared his findings, Latta developed an intravenous fluid not all too different from the saline infusions we use today, albeit less concentrated (hypotonic) (Janakan et al. 2013).

As described previously, *adding* fluid to the blood circulation was not a treatment previously recommended or even considered. This novel therapy was initially a last resort-treatment, something to try when all other treatments had failed. After implementing the treatment in six patients, Latta's assistant Dr Robert Lewin described the results in the following words:

> "*injecting a weak saline solution into the veins of the patient… [had]…the most wonderful and satisfactory effect…*"
>
> (Lewin 1832)

A more detailed report written by Latta himself was sent to the Central Board of Health and published in *The Lancet* 1832 (Latta 1832). These illustrative words were written after the administration of intravenous fluid to the very first patient:

> *"Having inserted a tube into the basilic vein, cautiously – anxiously, I watched the effects; ounce after ounce was injected but no visible change was produced. Still persevering, I thought she began to breathe less laboriously, soon the sharpened features, and sunken eye and fallen jaw, pale and cold, bearing the manifest impress of death's signet, began to glow with returning animation; the pulse, which had long ceased, returned to the wrist; at first small and quick, by degrees it became more and more distinct, fuller, slower and firmer and in the short space of half an hour, when six pints had been injected, she expressed in a firm voice that she was free from all uneasiness, actually became jocular, and fancied all she needed was a little sleep; her extremities were warm, and every feature bore the aspect of comfort and health…"*

Latta was of course very satisfied with the result and left the patient in the care of the hospital surgeon to get himself some rest. Unfortunately, the vomiting and purging started again, and this particular patient succumbed five and a half hours later (Cosnett 1989). One might think that a treatment that - at least initially - gave such positive response would have sparked enthusiasm but as it were, it did not on any greater scale. With what we know today, the reasons for an absent public acceptance may have been that 1) the fluid was hypotonic, leading to hemolysis; 2) the fluid was not sterile, leading

to bacteremia; and 3) the fluid was given in too small doses and only to moribund patients, leading to short but non-sustained effects (Cosnett 1989).

Sadly, Latta died only one year later, in 1833 of tuberculosis. His passing, in combination with Dr O'Shaughnessy emigrating from England and the end of the cholera epidemic later that same year, drove the development of intravenous fluids to a halt. Despite further pandemics in 1852 and 1863, the use of these fluids (saline) would not gain acceptance quite yet. The regular use of intravenous fluids for hypovolemic shock was first acknowledged a century later while today it is nearly impossible to be admitted to a hospital without receiving intravenous fluid therapy (Kaufman et al. 2023; Zarychanski et al. 2009).

Fluid indications

The cholera patients treated by Latta experienced fluid loss from the gastrointestinal tract, leading to critical dehydration with circulatory failure. They primarily needed what is now referred to as *resuscitation fluids*, the first major fluid group. Resuscitation fluids are administered to increase preload and cardiac output (Hjortrup et al. 2016). The second major fluid group is perhaps somewhat unusually defined by what it is not, the *non-resuscitation fluids* (van Regenmortel et al. 2018). As the word implies, non-resuscitation fluids are fluids administered for all other reasons than to resuscitate. These indications include nutrition, vehicles for medications, fluids administered to correct electrolyte disturbances and maintenance fluids – fluids administered to cover the requirements for normal hydration.

The different types of fluid

A lot has happened in the development of fluids since the saline solution produced by Latta. Today, there are many types to choose from, and intravenous fluids can be categorized not only by their indication as above, but also by their chemical properties.

Crystalloids

The first group is crystalloids. Crystalloids contain water and electrolytes and can move through a semipermeable membrane (Zampieri et al. 2023). This group can be further subdivided into balanced solutions and normal saline. The balanced solutions refer to the content of electrolytes being similar to the plasma concentration, such as Ringer-

Acetate and Plasmalyte®. In the balanced solutions, the concentration of chloride is close to physiological. The normal saline solution has a higher chloride (and sodium) concentration compared to plasma but is iso-osmotic (see below) when administered intravenously as a small proportion of the preparation remains undissociated in plasma (Malbrain et al. 2024).

Colloids

The second group is colloid solutions. Colloid solutions contain water, electrolytes, and a large compound (Zampieri et al. 2023). These large molecules cannot easily pass through a semipermeable membrane. They can be plasma-derived such as albumin or synthetic colloids, like hydroxyethyl starch (HES), gelatins and dextrans (Malbrain et al. 2024).

Multiple studies have shown HES to be nephrotoxic and to increase the risk of death and renal replacement therapy (RRT) in patients with severe sepsis and septic shock (Perner et al. 2012; Myburgh et al. 2012). Due to the large data on severe side effects and no trial showing benefit of HES compared to crystalloids, the American Food and Drug Administration (FDA) and European Medicines Agency (EMA) have withdrawn HES from the market. The negative effects of gelatins and dextrans are similar to those seen in HES; AKI as well as life-threatening anaphylactic shock and coagulation impairment (Malbrain et al. 2024). No larger trials have compared gelatines or dextrans to other resuscitation fluids in terms of safety or efficacy, but these side-effects limit their use (Malbrain et al. 2024; Moeller et al. 2016). The only colloid not associated with adverse outcomes and therefore, for all practical reasons, the only justifiable colloid to use in the critically ill, is albumin, a plasma-derived colloid (Finfer et al. 2004). In a large multi-center trial, adult patients in the intensive care unit (ICU) were randomized to receive albumin or saline as fluid resuscitation. The 28-day mortality was similar between groups as well as the incidence of AKI and need for RRT. In a subgroup analysis of patients with severe sepsis however, a near-significant benefit of using albumin over saline was described (Finfer et al. 2004). The result was further explored in an Italian multicenter trial (Caironi et al. 2014). Patients with severe sepsis and septic shock were randomized to receive albumin to maintain a certain serum albumin concentration and crystalloid, or crystalloid alone, but no difference in 28-day mortality or RRT was reported. As in the previous trial, the subgroup analysis described an interesting finding, a significant possible mortality benefit in patients with septic shock. If a treatment

benefit of albumin over crystalloids exists in patients with septic shock is currently being investigated in a multicenter trial (NCT03869385) (Sakr et al. 2020).

Other fluids

Glucose solutions are from a chemical point of view also crystalloids but are not considered as such in a practical sense. They consist of water and glucose with or without added electrolytes and are often administered as nutrition. Total parenteral nutrition is a mixture of amino acids, carbohydrates, and lipids, administered intravenously when oral/enteral nutrition is contraindicated or not sufficient to meet caloric needs.

Water balance and fluid compartments

As fluid is ingested or intravenously administered, it distributes into different fluid compartments (Fig 2). Overall, the total body fluid can be divided into the intracellular fluid (ICF) and the extracellular fluid (ECF). The ICF is the fluid within all the many trillion cells in the body and the ECF is the fluid outside of the cell membranes. The intracellular compartment contains ⅔ of the total body water and the extracellular ⅓. The extracellular compartment can be further subdivided into the interstitial fluid (ISF) and lymph, and the plasma volume (PV). ISF and lymph form ¾ of the ECF and PV ¼ of the ECF. The plasma volume therefore makes up 1/12 of the total body water (Rhoades et al. 2003).

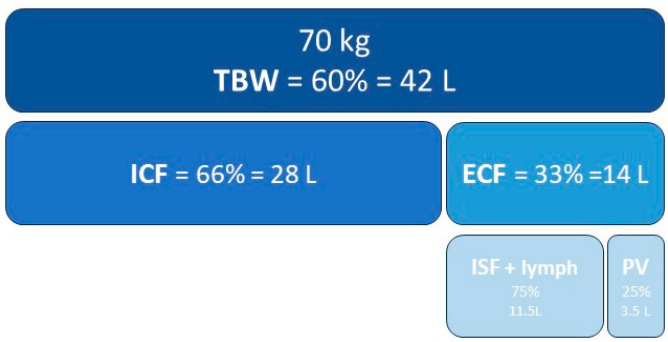


Fig 2. Distribution of water in the different cellular compartments in a 70 kg male. TBW: total body water, ICF: intracellular fluid, ECF: extracellular fluid, ISF: interstitial fluid, PV: plasma volume.

Most cell membranes in the body are semipermeable, allowing water to easily pass from one side of the cell to the other through osmosis - the movement of water from a higher water concentration to a lower water concentration. The distribution of water between the ICF and ECF is determined by the osmolality – the solute concentration. Water will move from the compartment with lower osmolality (high water concentration) towards higher osmolality (low water concentration) until equilibrium between the compartments is reached (iso-osmolality) (Rhoades et al. 2003). Consequently, all body compartments, with one exception – plasma, have the same osmolality and the most important contributors to osmolality are electrolytes (Kaufman et al. 2023). The composition of electrolytes in the various fluid compartments differ, but the total concentration is equilibrated along with electrical neutrality. In plasma, sodium is the primary cation, and its concentration is tightly controlled. Together with its accompanying anions (chloride and bicarbonate), it normally makes up for 95% of the osmolality. As ions cannot be metabolized, the amount of sodium in the body is determined by absorption and excretion. The amount of sodium in the body is therefore the primary determinant of total body water (Rhoades et al. 2003; Kaufman et al. 2023).

While osmolality is determined by the concentration of *all* solutes present, tonicity is determined by solutes present that *do not enter the cell* and is the effective osmotic pressure created by only these particles. Urea is an example of a solute that easily enters the cell, and while it contributes to the total osmolality, it does not contribute to the tonicity. Sodium also enters the cell, but behaves as a nonpenetrating solute, since it is pumped out of the cell by the Na+/K+-ATPase. Sodium is therefore important for the osmolality as well as the tonicity of a fluid (Rhoades et al. 2003; Kaufman et al. 2023).

Fluid distribution

Whatever fluid we choose to administer will, depending on its chemical properties, distribute differently in the fluid compartments of the body.

Isotonic crystalloids added to the plasma volume will stay in the ECF compartment as no change in osmolality has occurred. It will distribute evenly in the ECF sub-compartments. As plasma volume constitutes a quarter of the ECF compartment, only one fourth of the infused volume will stay intravascularly, the rest will distribute to the interstitium. Infusion of hypertonic crystalloids will cause water to move from the ICF compartment and the interstitium towards the intravascular compartment and increase

the plasma volume whereas hypotonic crystalloids cause water to move in the opposite direction (Rhoades et al. 2003; Kaufman et al. 2023).

Infused colloids are too large to easily cross the capillary wall and will therefore initially remain in the plasma compartment. The added colloids from the infusion increase the colloid osmotic pressure, the pressure that keeps water in the intravascular compartment. The plasma expanding effect of colloids depends on the concentration of the solution. The 4-5% solution expands plasma to approximately the same volume that is infused and the 20% solution results in twice the volume expansion of the infused volume (Hedin et al. 2005; Hasselgren et al. 2019).

Glucose solutions are poor plasma expanders, as the glucose molecules will be metabolized and leave only water behind. Water distributes evenly between the ICF and ECF compartments; 2/3 of the infused volume will move intracellularly, 1/12 will stay intravascularly and ¼ into the interstitium. Isotonic glucose solutions (added electrolytes) however, seem to have similar volume distribution as other isotonic crystalloids (Sjöstrand et al. 2001).

In critically ill patients, such as patients with septic shock, the fluid distribution may differ from what is described above. Increased capillary leakage may decrease the effect of volume expansion of both crystalloids and colloids (Fleck et al. 1985; Ernest et al. 2001). In order to restore and maintain intravascular volume and organ perfusion, larger amounts of fluid are often administered. When fluids are administered to increase the circulating blood volume, one may reflect upon what actually determines blood flow and consequently who would benefit from (further) fluid administration. Administration of large fluid volumes of both resuscitation and non-resuscitation fluids may generate a positive fluid balance and deleterious tissue oedema (Malbrain et al. 2024). The next chapter will address these issues further.

Cardiovascular physiology

The basics

The role of the circulatory system is to provide body tissues with oxygen, nutrients, and water, and allow waste products from the metabolism to be removed. The blood volume that circulates the body per unit of time is called cardiac output (CO), the product of stroke volume (SV) and heart rate (HR):

$$CO = SV \times HR$$

SV, in turn, is influenced by preload, contractility and afterload. In resting conditions, normal CO is 5-6 L/min for adults. In states of circulatory failure, fluids are administered primarily to increase preload, with the potential to increase stroke volume and cardiac output (Rhoades et al. 2003).

As the heart ejects blood in each heart stroke, there will be a peak and a nadir in blood pressure in the arteries - the systolic arterial pressure (SAP) and diastolic arterial pressure (DAP, Fig 4). The difference between the two is the pressure created by the pulse, i.e. the pulse pressure (PP). An approximation of the mean arterial pressure (MAP) during the cardiac cycle is the diastolic pressure plus 1/3 of the PP. If SV is increased, the blood volume in the artery will increase SAP while DAP remains unchanged, given that HR and resistance to flow (systemic vascular resistance, SVR) remain constant. The result is an increase in the PP. According to this concept, PP can be used as a surrogate for SV and therefore in consequence CO (Rhoades et al. 2003).

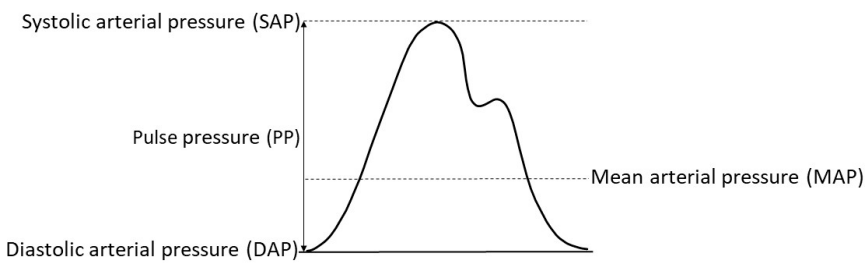


Fig. 4. Arterial pressure wave.

When describing the cardiovascular system, the heart and arterial side often gain most attention. One way of understanding the systemic blood flow, is to consider the left heart as the pump creating the flow of blood from the aorta to the right atrium with primary focus on the determinants of the cardiac function (preload, contractility, and afterload) and arterial properties (compliance and resistance) (Levy 1979). However, the heart has a bigger role to play than just to create blood flow into the arterial system. Moreover, as important as the aforementioned structures and functions are, this perception of the circulatory system is simplified and does not illustrate the importance of a crucial component – the *venous system*.

Venous blood volume and the generation of cardiac output

The venous system contains approximately two-thirds of the total blood volume and acts as a blood reservoir that can be rapidly recruited. The large volume contained in this system implies that variations to the venous volume will have great impact on venous return (Rhoades et al. 2003; Martin et al. 2020).

The venous system can theoretically be divided into two volumes, the *unstressed* and the *stressed volume* as described by Guyton (Guyton 1955). The unstressed volume is the volume that fills the vessels without increasing intravascular pressure and holds approximately 70% of the venous blood volume. Any amount of blood added to the unstressed volume, that stretches the veins and exerts pressure on the vascular walls, is called stressed volume, representing the remaining 30%. These 30% creates the mean systemic filling pressure, P_{msf} (Kaufman et al. 2023; Martin et al. 2020). The difference between P_{msf} and the right atrial pressure (RAP) creates the gradient for venous blood to return to the heart. Here is where the role of the heart can be viewed differently than simply being the pump ejecting blood into the arterial side. As the heart empties the right ventricle in each heart stroke, RAP is lowered, facilitating blood flow towards the right atrium. The P_{msf} and venous return as opposed to arterial pressure, is what actually propels blood flow and generates cardiac output, in this model (Guyton 1955).

Fluid bolus, P_{msf} and CVP

The reason for administering a fluid bolus is to increase the P_{msf}. However, it will only have a positive effect on venous return if RAP, equaling central venous pressure (CVP), is not increased equally or even more by the bolus, as such a condition will decrease the gradient between the two (Guyton 1955). So, who will benefit from a fluid bolus and who will not? It depends on the patient being a preload responder or non-responder.

Preload responders and non-responders

In hemodynamically unstable patients, only 50% of the patients will make use of, or *respond* to, a fluid bolus (Marik et al. 2011). To 'respond' is most often defined as an increase in SV of 10-15% after a bolus of 300-500 ml (Monnet et al. 2023). Such a response is seen in the *preload responders*. The other half, those that do not increase SV by 10-15%, are called *preload non-responders*. It is the degree of actin-myosin filament interaction in the muscle fibers of the ventricle that determines whether the patient is a preload responder or not. As long as the increase in preload keeps stretching the

myofilaments towards their optimum length, the contractility and in consequence, the stroke volume, will increase. The patient is a preload responder as illustrated on the steep part of the Frank-Starling curve (Fig 5). Beyond this point, no further increase in contractility or stroke volume can occur, even if more fluid is presented to the ventricle. The patient has become a preload non-responder, depicted on the flat part of the Frank-Starling curve. In this circumstance, it is not only P_{msf} that increases but also CVP, impeding venous return (Marik et al. 2011; Persichini et al. 2022).

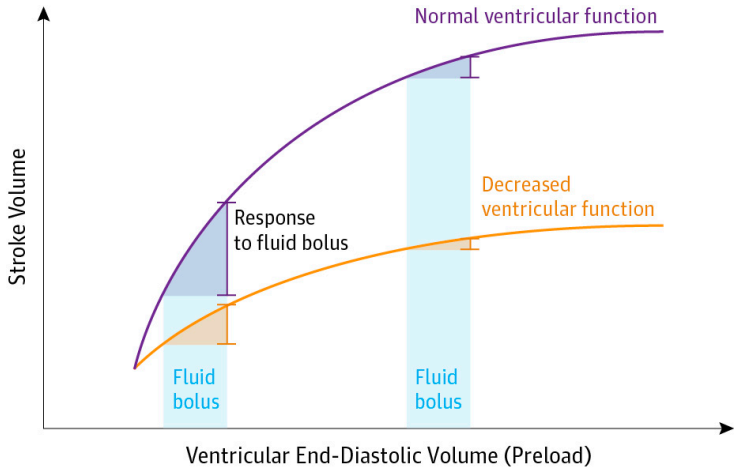


Fig 5. Effect of increase in preload on stroke volume of ventricles with normal and decreased contractility. Frank-Starling curves illustrate that the effect of a given increase in preload on stroke volume is dependent both on ventricular contractility and on baseline preload. From Bentzer et al. 2016 © 2016, American Medical Association. All rights reserved. Reprinted with permission.

The passive leg raising test

Fluids may be beneficial in patients with circulatory impairment, but how can we know if the patient is a preload responder, prior to administering fluids? We can perform what is known as a *passive leg-raising test* (PLR-test, Fig 6) and measure the effect on CO, SV, or a surrogate measure for SV such as change in PP. When performing the test, blood from the lower extremities as well as abdomen moves towards the heart and acts as an endogenous bolus. If the patient proves to be a non-responder, the extremities can be lowered again, and the bolus is "retracted". Meta-analyses have suggested good discrimination between preload responders and non-responders and the test may be used in both spontaneously breathing patients and patients under mechanical ventilation (Bentzer et al. 2016; Monnet et al. 2016; AlvaradoSánchez et al. 2021).

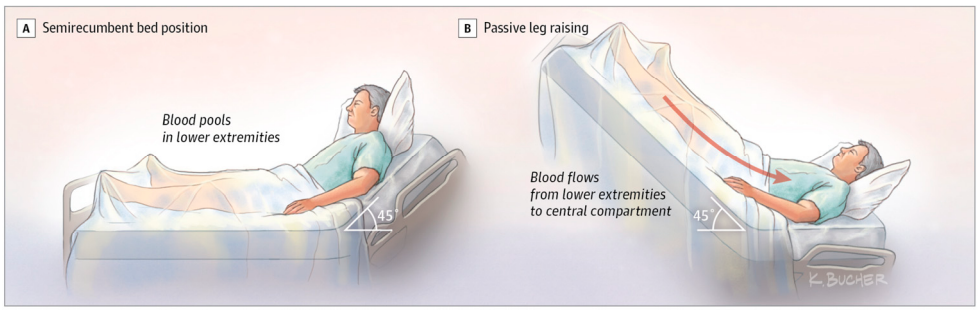


Fig 6. Performance of a passive leg-raising test, from Bentzer et al. 2016. © 2016, American Medical Association. All rights reserved. Reprinted with permission.

Negative effects of fluid overload

Even though we have the methods to evaluate if a patient is a preload responder or not, it is far from always assessed prior to fluid administration (Preau et al. 2016). What harm can come of administering fluids to a preload non-responder? An elevated CVP originated from fruitless fluid administration may not just limit itself to the central circulation. The elevated pressure can be propagated backwards in the circulatory system and diminish the driving pressure for organ perfusion – the difference between MAP and CVP (Martin et al. 2020). This is particularly true in the kidneys, where decreased glomerular filtration can result (Legrand et al. 2013). In the perioperative setting, a certain degree of hypervolemia is often considered necessary, due to anesthesia-induced vasodilation. However, if fluid volumes larger than the compensation for vasodilation are administered, there is a risk of increased filling pressures and myocardial work as well as elevated hydrostatic pressure with increased fluid filtration over the capillary wall (Malbrain et al. 2020).

Not all fluids are administered to increase preload or cardiac output and not all fluid infusions increase CVP. However, all fluids administered add to the fluid balance and the consequence may be deleterious. A common diagnosis in the ICU is septic shock. Increased capillary permeability is part of the pathophysiology in sepsis and allows fluids to pass into the interstitium to a higher degree than in normal conditions. The resulting tissue oedema increases the distance between capillary and target cell, impairs diffusion of oxygen and nutrients and worsens gas exchange, wound healing, and renal function (Malbrain et al. 2020). Both capillary blood flow and lymphatic drainage can be obstructed due to increased interstitial hydrostatic pressure, hindering and/or

reducing venous return. All organs may be affected by these changes (Fig 7), but the lungs and organs enclosed by a capsule, are more vulnerable (Prowle et al. 2014).

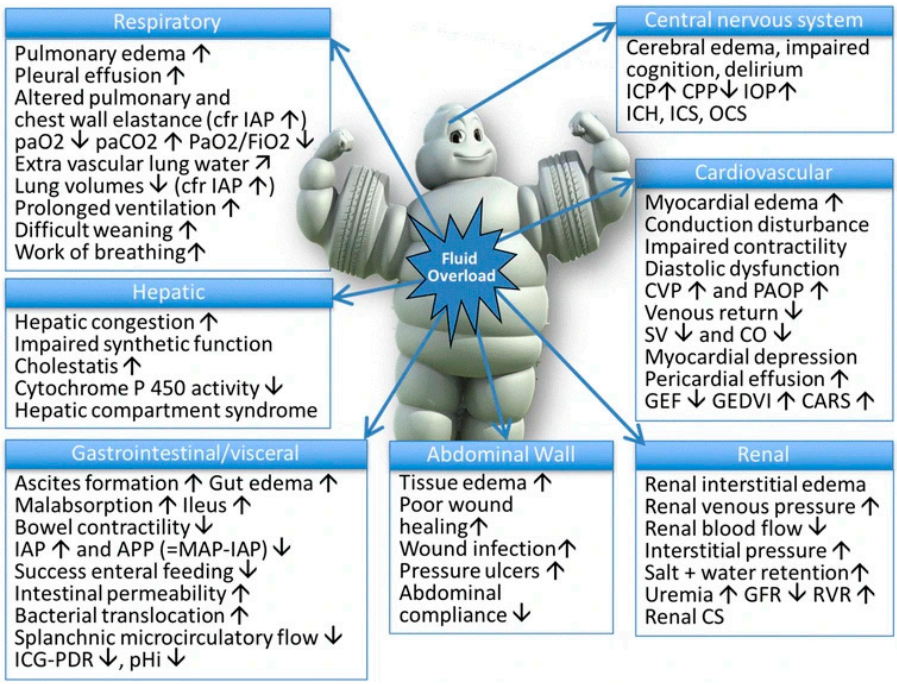


Fig 7. Potential consequences of fluid overload on end-organ function. From Malbrain et al. 2018.
APP: abdominal perfusion pressure, IAP: intra-abdominal pressure, IAH: intra-abdominal hypertension, ACS: abdominal compartment syndrome, CARS: cardio-abdominal-renal syndrome, CO: cardiac output, CPP: cerebral perfusion pressure, CS: compartment syndrome, CVP: central venous pressure, GEDVI: global enddiastolic volume index, GEF: global ejection fraction, GFR; glomerular filtration rate, ICG-PDR: indocyaninegreen plasma disappearance rate, ICH: intracranial hypertension, ICP: intracranial pressure, ICS: intracranial compartment syndrome, IOP: intra-ocular pressure, MAP: mean arterial pressure, OCS: ocular compartment syndrome, PAOP: pulmonary artery occlusion pressure, pHi: gastric tonometry, RVR: renal vascular resistance, SV: stroke volume.

As patients with septic shock in the ICU are at great risk of high fluid administration during their stay, a short description of the condition and pathophysiology will follow.

Sepsis and septic shock

Definition of sepsis

One of the most common diagnoses in the intensive care unit is sepsis and septic shock. The frequency of septic shock at ICU admission is approximately 10% (Vincent et al. 2019).

The word "*sepsis*" comes from the greek word "σηψις" which means "decomposition of animal or vegetable organic matter in the presence of bacteria" (Geroulanos et al. 2006). Most infections that cause sepsis originate from bacteria, but the etiology can also be viral and fungal (Dolin et al. 2019).

The term "sepsis" goes back to Homer and Hippocrates but the first modern definition of sepsis came to light in 1991 (Geroulanos et al. 2006; Bone et al. 1992). Later versions have thereafter been developed, the latest and current definition was published in 2016. It defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection". In other words, sepsis is a life-threatening condition where the body's response to an infection injures its own tissues and organs (Singer et al. 2016).

Diagnostic criteria of sepsis

The current diagnostic criteria for sepsis are described in the Sepsis-3 definitions (Singer et al. 2016). They are:

1. Suspected or confirmed infection, and
2. Organ dysfunction, graded by the Sequential Organ Failure Assessment (SOFA)-score. A score of $\geq$2 points from baseline is needed for the diagnosis.

In the SOFA-score, the degree of organ dysfunction is assessed in six organ systems; the central nervous system, respiration, circulation, coagulation, kidney as well as liver (Vincent et al. 1996).

Diagnostic criteria of septic shock

Sepsis that deteriorates even further can develop into septic shock - a condition where the circulatory and metabolic abnormalities are profoundly affected and consequently leads to a higher mortality than sepsis alone.

The diagnostic criteria for septic shock are:

1. Sepsis, according to the Sepsis-3 definition, and
2. Persisting hypotension requiring vasopressor treatment to keep MAP >65 mmHg and s-lactate >2 mmol/l, despite adequate volume resuscitation (Singer et al. 2016)

Sepsis in numbers

The reporting of sepsis incidence differs depending on the definitions used and the studied population. However, a recent study reported an incidence of 49 million cases worldwide each year, corresponding to 623/100 000 per year (Rudd et al. 2020). Approximately 10% of these patients develop septic shock (Rhee et al. 2017; Ljungström et al. 2019). In 2020, the World Health Organization (WHO) declared sepsis a global health priority (WHO 2020).

The 30-day mortality in patients with sepsis outside of the ICU is reported to be approximately 10% (Shapiro et al. 2009; Glickman et al. 2010; Mellhammar et al. 2023), whereas the 90-day mortality in patients admitted to the ICU is approximately 45% (Payen et al. 2008; Hjortrup et al. 2016). The higher rate in the ICU may be explained by patients in this setting not only having sepsis, but most often septic shock. Important long-term consequences other than high mortality rates are acute kidney injury, cognitive dysfunction and decreased quality of life (Iwashyna et al. 2010). A majority of sepsis survivors are diagnosed with a new medical, psychological or cognitive disorder the first year after hospital discharge (Fleischmann-Struzek et al. 2021).

Pathophysiology in sepsis - a short description

Sepsis and septic shock can affect multiple organs in the body. To understand the basis for organ dysfunction, we will have a short look at the underlying pathophysiology. Many of the mechanisms are common for the major etiological types of sepsis (bacterial, viral, fungal) but as bacterial sepsis is the predominant cause, the following description focuses on this particular pathway.

When bacteria enter the body, certain structures of the bacteria bind to receptors on the surface of the macrophages and dendritic cells. These structures are called pathogen associated molecular patterns (PAMPs, bacterial structure) and pathogen recognition

receptor (PRR, macrophage/dendritic cell receptor). When PAMPs bind to PRR, they are recognized as foreign, activating an intracellular signal via a transcription factor (NFk-beta). This transcription factor activates the production of cytokines which are released extracellularly and upgrades the immune response from a local to a systemic level. The immune response is augmented by cytokine-derived activation of multiple cells – macrophages, monocytes, neutrophil granulocytes, endothelial cells, and lymphocytes. In addition to cellular activation, the cytokines also interact with other cascade systems – the complement, coagulation and fibrinolytic system and further intravascular inflammation and coagulation disturbance develop. Other structures than PAMP can activate the inflammatory system. If the pathogen causes direct cell damage (as with toxins for example), the leakage of intracellular components also activates PRR and cytokine production. These intracellular structures are known as damage associated molecular patterns (DAMPs), such as ATP or DNA (Conway-Morris et al. 2018; Dolin et al. 2019).

In septic shock, the activation of endothelial cells is essential. Granulocytes adhere to the endothelial wall where nitric oxide (NO) and prostaglandins (PG) are released, generating vasodilation, and increased venous capacitance. Also, heparin-binding protein (HBP) is released which increases permeability in the capillaries and causes fluid to exude into the interstitium. These mechanisms - vasodilation, increased permeability and fluid exudation - in combination with ventricular dysfunction, are the causes of hypotension/hypoperfusion characteristic of septic shock (Conway-Morris et al. 2018; Russel et al. 2018; Dolin et al. 2019). The inflammatory response seen in sepsis can affect all organ systems in the body.

In 2002, an initiative called Surviving Sepsis Campaign (SSC) was formed and since 2004 they have issued updated recommendations regarding treatment of patients with sepsis. The last recommendation was published in 2021 with the key elements antimicrobials, oxygen and ventilation support, vasopressor treatment and; *fluids* (Evans et al. 2021).

Fluid perspectives and thesis rationale

Fluid administration during the last 25 years

At the start of the 21st century, the primary treatment for low organ perfusion in severe sepsis/septic shock was fluid therapy. In a landmark single-center randomized trial, patients received large amounts of fluid in pursuit of reaching specific circulatory goals (early goal-directed therapy, EGDT). They reported an administration of 14 L of intravenous fluid in 72 hours and a large decrease in mortality (Rivers et al. 2001). As a consequence, EGDT and the larger fluid volumes attached to it, became the standard of care at the time and was endorsed by international guidelines (Dellinger et al. 2004).

In the following era of administering high fluid volumes, multiple observational studies reported an association between a positive fluid balance in patients with septic shock and worse outcome such as higher mortality and decreased kidney function (Payen et al. 2008; Boyd et al. 2011). Subsequent trials began to question the need for aggressive fluid therapy and EGDT, where three coordinated multicenter trials performed in three different continents found no mortality benefit in the EGDT group compared to the usual care group (Yealy et al. 2014; Peake et al. 2014; Mouncey et al. 2015). In the later recommendations, fluid therapy was no longer recommended to be guided by EGDT but instead to be administered according to the response to dynamic indices (Evans et al. 2021). Reaching specific hemodynamic targets is no longer the main focus but (at least) one important question still remains to be answered: how much fluid should hemodynamically unstable patients receive?

The case for restrictive fluid administration

Mortality

In 2011, the FEAST trial was published (Maitland et al. 2011). More than 3100 African children with fever were randomized to receive fluid boluses with normal saline, 5% albumin or no fluid bolus at all. The trial showed significantly higher mortality rates in patients that received fluid boluses compared to patients that did not.

Another trial including adult patients presenting with hypotensive sepsis in the emergency department in Zambia investigated if an early resuscitative fluid protocol during the first 6 hours compared to usual care had an impact on outcome (Andrews

et al. 2017). Over 200 patients participated, and patients receiving more fluid (the interventional group) had an increased mortality compared to usual care.

Mechanical ventilation and AKI

In 2006, a trial by Wiedemann et al. conducted in critically ill patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), compared a conservative fluid approach to a liberal (Wiedemann et al. 2006). The trial included 1000 patients. As a secondary endpoint the restrictive fluid group showed improved lung function and reduced duration of mechanical ventilation compared to the liberal fluid group although no difference in mortality was found between the two.

Performed as a pilot trial and published in 2016, the CLASSIC feasibility trial enrolled 151 patients with septic shock in Scandinavian ICU's (Hjortrup et al. 2016). A liberal versus conservative resuscitation fluid approach was compared and a fluid separation of approximately 0.8 L in five days was presented. Mortality at 90 days was similar between groups but the number of patients with worsening AKI seemed to be lower in the restrictive fluid group with the caveat that this was an exploratory outcome.

A systematic review and meta-analysis comparing conservative fluid management/active fluid removal to usual care/liberal fluid strategy after initial resuscitation in ARDS, sepsis, or SIRS, found no difference in mortality but in secondary outcomes such as increased ventilator-free days (Silversides et al. 2017).

The case for equipoise between restrictive and liberal fluid administration

Mortality

In 2022, simultaneously as we prepared *Paper II and III*, the CLASSIC feasibility trial was followed by the much-awaited large-scale trial, powered to detect a relative risk reduction of 15% (absolute risk reduction 7%) between groups on all-cause mortality at 90 days (Meyhoff et al. 2022). A total of 1554 patients were randomized in 31 ICUs to receive restrictive resuscitation fluid therapy or usual care. A larger separation of fluid administration than in the pilot was achieved, a difference between groups of approximately 1.9 L, but with no apparent effect on mortality. The following year, the results from another large fluid trial was published (Shapiro et al. 2023). Patients with sepsis-induced hypotension in the emergency department (ED) were randomized to conservative fluid therapy (early vasopressor therapy and less fluid) or liberal fluid therapy (prioritizing higher fluid volumes before vasopressor therapy) for 24 hours. A

total of 1564 patients were randomized in 60 North American EDs, and a median of around 2.1 L less fluid was administered in the conservative fluid group in the first 24 hours. At 90 days, there was still no difference in the primary outcome - mortality - between the groups.

An updated systematic review with meta-analysis on fluid restrictive trials in sepsis came in 2023 (Sivapalan et al. 2023). In 13 trials, the total number of patients included was 4006, where the three trials mentioned above contributed with over 80% of the participants (Hjortrup et al. 2016; Meyhoff et al. 2022; Shapiro et al. 2023). The meta-analysis did not show a statistically significant difference in mortality between a conservative and a liberal fluid strategy. Moreover, there was no difference in serious adverse events, use of RRT or vasopressors, or duration of mechanical ventilation.

The case for liberal fluid administration

Cognitive function and AKI

In the previously mentioned trial by Wiedemann et al., the short-term effects on outcomes such as lung function and duration of mechanical ventilation was better in the fluid restrictive group (Wiedemann et al. 2006). However, a sub-study looking at cognitive function showed increased cognitive impairment at 12 months post hospital discharge of survivors in the fluid restrictive group compared to the liberal fluid group. It should however be mentioned that the follow-up rate was poor. Among 406 survivors, only 261 (64%) were approached for the sub-study of which 213 consented. 102 were tested for cognitive function and only 75 of these completed all cognitive tests (Mikkelsen et al. 2012).

Even in the perioperative setting, many trials have investigated what the "right" amount of fluid administration is. In a systematic review with meta-analysis from 2016, a liberal versus a restrictive fluid approach was evaluated in patients going through general elective surgery in 12 RCTs (Schol et al. 2016). The restrictive approach resulted in a lower complication rate in fewer patients, and also a lower rate of infection compared to the liberal approach. A few years later, the largest trial of perioperative fluid management to date was published (Myles et al. 2019). Patients undergoing major abdominal surgery were included, resulting in 3000 randomized patients. During surgery, the restrictive fluid group and the liberal fluid group received a median of 1.7 L and 3 L, respectively. Including all fluids, from surgery up to 24 hours postoperatively, the restrictive fluid group received a median of 3.7 L and the liberal

fluid group received 6.1 L. The trial showed similar mortality rates at one year, but higher rate of AKI in the restrictive fluid group. Rate of renal replacement therapy and surgical-site infection in the restrictive fluid group was initially also higher, but when adjusted for multiple testing the between-group difference was no longer significant. The results contrast with the enhanced recovery after surgery (ERAS) concept which advocates restrictive fluid administration and zero fluid balance (Brindle et al. 2020). An updated meta-analysis came in 2021, in which this large RCT contributed to more patients than all the 17 other trials combined (Messina et al. 2021). No difference in overall postoperative complications between the restrictive and liberal approach was found but there was an association between liberal fluid administration and less renal complications.

Rationale for the thesis

Optimizing fluid administration is desirable in both patients with septic shock and patients in the perioperative setting. The results of previous research when reducing fluid administration in these patient populations are divergent. The external validity of the results from the two African trials is debatable, given the lower rates of malaria and other treatment possibilities such as higher availability of mechanical ventilation in comparable studies performed in other countries (Maitland et al. 2011; Andrews et al. 2017). Furthermore, one might question if a difference between the two treatment groups of 1.9 L after five days in the ICU significantly impacts outcome (Meyhoff et al. 2022). Previous trials have mainly focused fluid restriction on resuscitation fluids. This thesis will explore if a larger fluid reduction can be achieved in shifting the attention to non-resuscitation fluids, in the first three papers.

Postoperative patients that present with signs of hypoperfusion and seem to be preload responsive are often treated with fluid therapy with the aim to increase preload and organ perfusion. However, it is debatable if this is the optimal treatment as it may depend on the blood volume status of the patient. In the last paper of the thesis, blood volume status will be analyzed in postoperative patients after major abdominal surgery to further explore appropriate treatment options.

Aims

The general aim of the thesis was to investigate the potential to reduce fluid administration in the hemodynamically unstable patient.

Paper I

To quantify and characterize fluid administration in patients with septic shock during the first five days in the ICU with special emphasis on non-resuscitation fluids and assess the potential to reduce non-resuscitation fluids.

Paper II

To design a protocol for a randomized clinical trial aimed at reducing administration of non-resuscitation fluids in patients with septic shock.

Paper III

To test the feasibility and efficacy of a protocol aimed at reducing administration of non-resuscitation fluids in patients with septic shock.

Paper IV

To investigate the blood volume status in postoperative patients likely to be preload responsive.

Methods

Paper I

Objective and design

The objective of this study was to quantify and characterize the fluids given to patients with septic shock during the first five days in the ICU. We performed a multicenter prospective observational study in eight intensive care units.

Patients

Six Swedish sites and two Canadian sites participated. The inclusion criteria were septic shock according to the SEPSIS-3 criteria (Singer et al. 2016) within 24 hours of ICU admission in patients ≥18 years old. The only exclusion criterion was prior participation in the study.

Methods

Data on fluid input and output was registered for five days and a designated researcher at each site collected and transferred the data onto the case report form (CRF).

Fluids were classified as *non-resuscitation* fluids or *resuscitation* fluids. Non-resuscitation fluids were glucose solutions, enteral and parenteral nutrition, enteral water, crystalloids administered <5 ml/kg/h and vehicles for medication. Vehicles for medication were further subdivided into type of drug: antibiotics, vasoactive drugs, analgesics, sedatives, potassium, other electrolytes, insulin and "other drugs". Resuscitation fluids included colloids, blood products and crystalloids administered at a rate of ≥5 ml/kg/h.

We calculated the daily balance by subtracting total fluid output except for perspiration, from total fluid input and cumulated fluid balance by adding the daily balances. Along with the fluid data we also collected demographic data and baseline

data such as age, sex, source of sepsis, SOFA- and SAPS-3-score, as well as use of mechanical ventilation and RRT. Patients were followed for a maximum of 30 days. No sample size calculation was performed, and only descriptive statistics were used. Missing data was not imputed.

Model of a restrictive fluid protocol

From the collected data, we simulated how administration of non-resuscitation fluids could be reduced, based on the most restrictive practice already in use at one of the participating sites. This model included: no glucose solutions for nutritional purposes, no maintenance fluids in patients with a positive fluid balance and enteral nutrition administered only at a concentration of 2 kcal/ml in centers that use less concentrated preparations.

Paper II & III

Objective and design

To assess the feasibility and efficacy of a protocol comparing protocolized reduction of non-resuscitation fluids to usual care in patients with septic shock. A multicenter randomized clinical feasibility trial was performed at six Swedish intensive care units. The trial protocol was registered at clinicaltrials.gov (No. NCT05249088) prior to trial initiation.

Patients

Patients were eligible if they fulfilled all of the inclusion criteria and not the exclusion criterion. Inclusion criteria:

- Adult (>18 years)
- Septic shock according to the SEPSIS-3 criteria while in the ICU (Singer et al. 2016)
- Ongoing vasopressor treatment at randomization
- Inclusion within 12 hours of ICU admission

Exclusion criterion was confirmed or suspected pregnancy.

Methods

Eligible patients were randomized using a web-based tool. Patients were allocated to one of the two treatment arms in a 1:1 ratio. Randomization was performed with permuted blocks of varying block size, unknown to the trial investigators and stratified by trial site. Due to the nature of the intervention, the clinical team caring for the patient was not blinded to the allocation, but the study participants, their relatives, outcome assessors and statisticians were. The allocated treatment was started as soon as possible after inclusion, and at the latest within two hours.

Patients allocated to the interventional arm had their maintenance fluid discontinued if positive in their fluid balance and perceived not to be dehydrated. Administration of nutritional glucose solutions was allowed from 72 hours post inclusion if enteral nutrition was not tolerated (earlier if needed in insulin-dependent diabetes) and only at a concentration of 20% or greater. Vehicles for medications were concentrated according to a specific drug protocol, based on the most concentrated drug dilutions described in the literature. Enteral nutrition was administered at a minimum concentration of 2 kcal/ml and parenteral nutrition was administered according to local protocol. Enteral water/intravenous fluids could be given as needed to correct electrolyte imbalances. Patients judged to be negative or neutral in cumulative fluid balance received fluids to ensure that the total dose of fluid covered the daily need of water (1 ml/kg/day) and ongoing losses.

The usual care group received non-resuscitation fluids according to local routines, and prior to trial initiation, each site investigator determined what constituted "usual care" at that specific site. Unless local protocol stated otherwise, maintenance fluids (enteral water/ intravenous glucose solutions/crystalloids) was administered at 1 ml/kg/h, the nutritional glucose solutions were administered at a maximum concentration of 10% and vehicles for medications, enteral nutrition and parenteral nutrition was administered according to local practice. Resuscitation fluids during the salvage and optimization phase were administered according to SSC-guidelines and according to local routines during the stabilization and de-escalation phase (Evans et al. 2021; DeBacker et al. 2023). Patients were invited to a face-to-face follow-up after 6 months where cognitive function and health-related quality of life were assessed (Fig 8).

The following fluids were defined as resuscitation fluids: blood products, colloids, crystalloids administered to correct hemodynamic impairment as noted in patient charts or administered at a rate of ≥5 ml/kg/h if no indication was reported. Non-

resuscitation fluids were enteral nutrition and water, parenteral nutrition, glucose solutions, vehicles for medications and crystalloids <5 ml/kg/h if the indication in the medical charts was unclear.

The primary feasibility outcome was liters of fluids administered within three days (day 0-3) of randomization. The secondary feasibility outcomes were all proportions of participants with clinical outcome data regarding mortality, mechanical ventilation, complications, cognitive function, health-related quality of life, eligibility, and protocol deviations. The primary exploratory clinical outcomes were the actual values/scores of the secondary feasibility outcomes. The secondary exploratory outcomes included cumulative fluid balance on day 3 and 5 from inclusion (see full list of outcomes in the attached original papers).

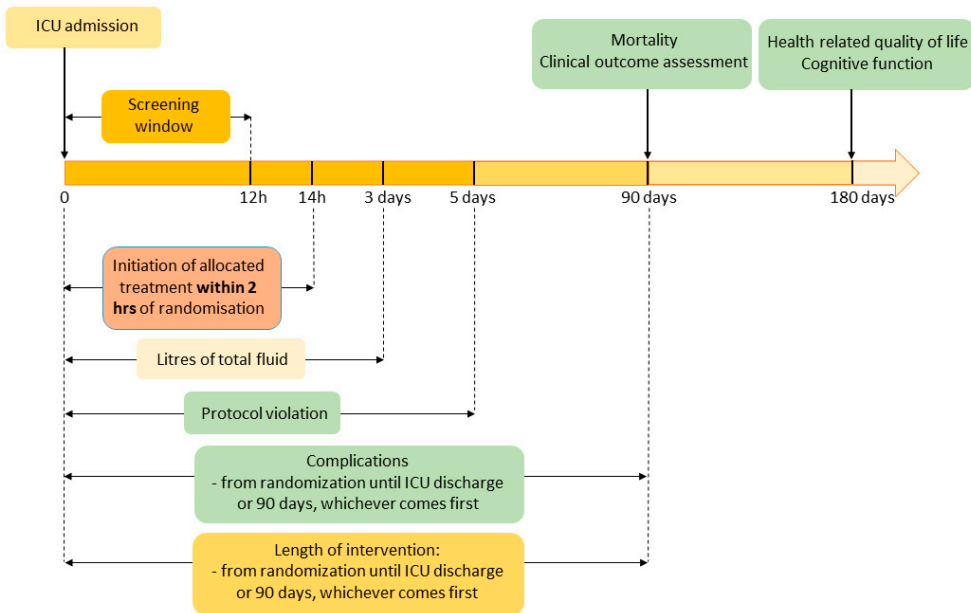


Fig 8. Trial timeline. Vertical arrows indicate specific time points for events or assessments, whereas horizontal arrows describe a certain time period. Complications: cerebral, cardiac, intestinal or limb ischaemia or any acute kidney injury. ICU; intensive care unit.

Statistics

All analyses were performed according to an intention-to-treat principle. All analyses were adjusted for participating site. The primary feasibility outcome was analyzed using the van Elteren test. Median difference and corresponding confidence intervals (CIs)

were estimated using the Hodges-Lehman method. The secondary feasibility outcomes were all proportions and are presented as percentages with CIs calculated using 1-sample proportions test without continuity correction. Exploratory clinical outcomes were analyzed using the van Elteren test with adjustment for site for count outcomes, mixed effect linear regression with site as random intercept for continuous outcomes and mixed effects logistic regression with site as random intercept for dichotomous outcomes. P-values were not adjusted for multiple comparisons due to the exploratory nature of the trial.

Paper IV

Objective and design

The objective was to investigate the blood volume in postoperative patients likely to be preload responsive. We performed a post hoc analysis of the data from a randomized clinical trial, the albumin infusion rate and plasma volume expansion (AIR) trial (Statkevicius et al. 2019).

Patients

In the AIR trial, adult patients that had gone through major abdominal or gynecological surgery were postoperatively included if the attending physician saw an indication for fluid administration and the patient showed $\geq$1 signs of hypoperfusion (see below). Patients received 5% albumin at different infusion rates to investigate the effect on plasma volume expansion. Prior to albumin administration, baseline plasma volume was measured using radioactively labelled albumin. Exclusion criteria in the AIR trial were hypersensitivity to the drug/tracer, signs of postoperative bleeding, history of heart failure, other fluid protocol prescribed by treating physician, pregnancy, and clinical judgement by treating physician prohibiting participation in the trial.

Methods

In the AIR trial, anesthesia was induced with propofol and maintained using desflurane or sevoflurane. Patients received an arterial line and epidural catheter for intra- and postoperative analgesia unless contraindicated. Intraoperative fluid treatment, both

crystalloids and colloids, were used at the discretion of the attending anesthetist. Postoperatively, the patients were extubated, and epidural analgesia was provided using bupivacaine (2.5 mg/ml) and morphine (0.05 mg/ml) at a rate of 4-6 ml/h.

Inclusion criteria for the *present post hoc analysis* were

- one or more signs of hypoperfusion within 5 hours of admission to the post-anesthesia unit:
    - SAP <90 mmHg or MAP <55 mmHg,
    - s-lactate >2 mmol/l,
    - urine output <0.5 ml/kg/h in the hour prior to inclusion,
    - ScvO2 <70%, and also
- complete data from a PLR-test, as well as
- plasma volume measurement within 30 minutes from the PLR-test.

The PLR-test was considered positive if the pulse pressure increased ≥9%. These patients were considered likely to be preload responders (Preau et al. 2010). Plasma volume was measured using radioactively labelled albumin, ^{125}I human serum albumin (^{125}I-HSA) (SERALB®). A known dose was intravenously injected and 10 minutes later a blood sample was drawn where the plasma concentration was measured using a gamma counter. By dividing the injected dose of ^{125}I-HSA with the measured plasma concentration of ^{125}I-HSA 10 minutes post injection, the plasma volume could be calculated. Hematocrit was measured by colorimetric analysis using a blood gas analyzer (Radiometer 850; Radiometer, Copenhagen, Denmark). Since venous hematocrit (Hct) is higher than the body Hct, the measured Hct-value was corrected by multiplying with 0.9 (Harrison et al. 1982). Blood volume (BV) was calculated from the plasma volume (PV) measurement and hematocrit (Hct):

$$BV = PV/(1 - Hct)$$

The measured blood volume was compared to the predicted blood volume, derived from height and weight of the patient (Brown et al. 1962; Wennesland et al. 1959). A measured blood volume less than 10% of the predicted normal blood volume was considered hypovolemic and blood volume greater than 10% of the predicted normal blood volume was considered hypervolemic (Stéphan et al. 2001). Patients that deviated less than 10% from predicted normal blood volume were defined as

normovolemic. As a sensitivity analysis, we used a deviation of 15% or more from predicted normal value to define hypo- and hypervolemia.

Statistics

No power calculation was carried out; the number of available patients determined sample size. Continuous variables were presented as medians and interquartile range (IQR), and categorical data using proportions with percent. Correlation analysis was performed using Spearman's correlation for non-parametric data.

Ethical considerations

Cognitive impairment is a common feature in septic shock. In such circumstances, it is impossible for the patient to comprehend information about a study/trial and give informed consent. However, fluid administration in the ICU usually starts at admission. As the primary outcome in Paper II/III was to detect a separation in administered volumes between the two treatment groups, the intervention had to start as soon as possible. In the ethics application we therefore sought approval for a deferred consent, allowing patients to consent for continued participation in the trial later in the process, having recovered enough to make an informed decision. Meanwhile, we approached family members/close relatives and informed them about the trial, giving them the opportunity to decline participation on behalf of the patient. We considered this approach to be in line with the Declaration of Helsinki article 30, and the Ethics committee agreed and approved the consent process.

As Paper I was an observational study, there was less emergent need in informing the patient about the study or getting an informed consent. Patients were approached when perceived able to receive the information, commonly at discharge from the ICU or after being transferred to a ward.

Paper IV was a post hoc analysis of an already performed trial, and the ethical approval and informed consent was already in place. In the original paper the patients were informed of the trial in a preoperative meeting (Statkevicius et al. 2019). They were fully awake and able to ask questions to make an informed decision, written informed consent was collected from interested patients. Patients fulfilling inclusion criteria postoperatively were then included.

Ethical review board approval

Paper I: Regional Ethical Review Board, Lund, Sweden, Dnr 2017/565 and Regional Ethical Review Board, Vancouver, Canada, H17-03504.

Paper II and III: Swedish Ethics Review Authority Dnr 2020-06594, Dnr 2021-05363-02 (first amendment) and Dnr 2022-00253-02 (second amendment).

Paper IV: Regional Ethical Review Board, Lund, Sweden, Dnr 2014/15.

Results

The detailed descriptions of all results are presented in the attached original papers.

Paper I

In this descriptive study, 200 patients with septic shock were included. The most common sources of sepsis were abdominal and respiratory infection. The 30-day mortality was 35%. The majority of fluids received during the first five days in the ICU were non-resuscitation fluids. Patients received a median (IQR) of 7870 (4060 to 12340) ml of non-resuscitation fluids and 2820 (1430 to 4580) ml of resuscitation fluids. The distribution of these two different fluids were similar on day 1 but from day 2 and thereafter, non-resuscitation fluids were the major source of fluid administered (Fig 9a). Among the non-resuscitation fluids, vehicles for drugs and glucose solutions were the main contributors (Fig 9a and b and Table 1).

The cumulative fluid balance was positive during the whole five-day observation period (Fig 9c). When designing a model for restrictive administration of non-resuscitation fluids, we found that a theoretical median reduction of 2840 (1270 to 4900) ml per patient was obtainable in the whole cohort during the observation period (Table 2).

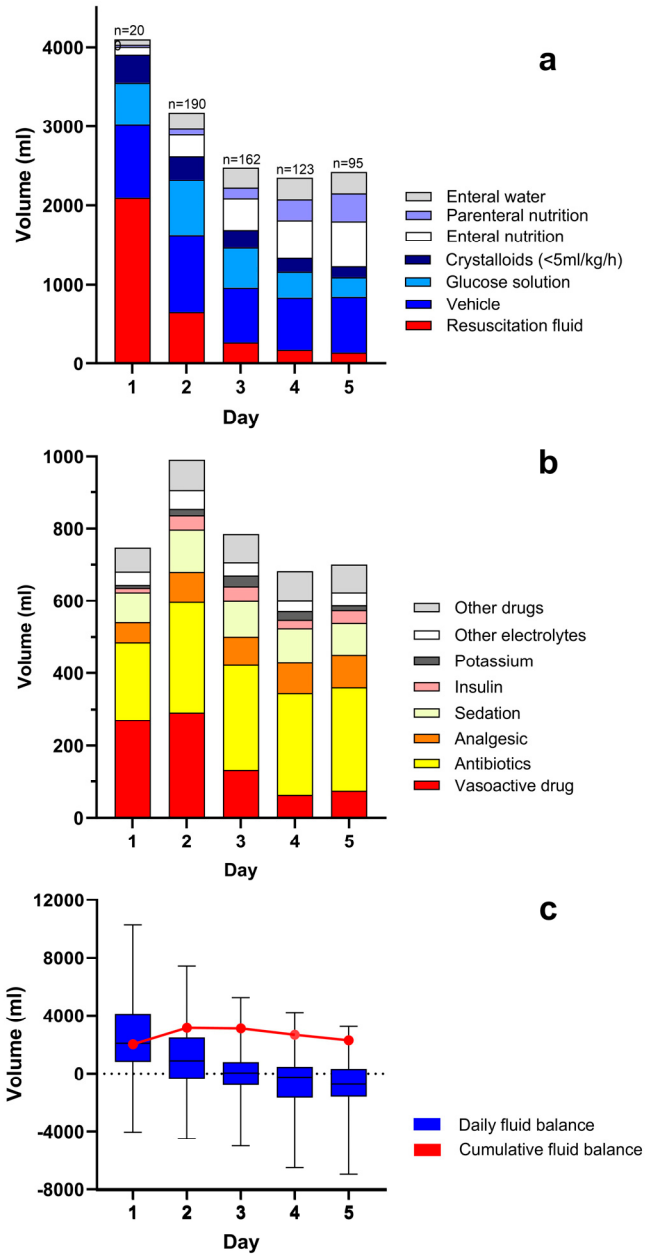


Fig 9. a Median daily volume and type of fluids. Data for type of fluids each day are presented as fraction of total daily volume. Please note that sum of the median daily volume does not equal sums of median non-resuscitation and resuscitation fluids over the whole observation period because of the skewed distribution of the data. N number of patients. **b** Median daily volume and type of vehicle. Data for type of vehicle each day are presented as fraction of total daily volume. N number of patients. **c** Daily and cumulative fluid balance. Daily fluid balance is presented as median, interquartiles and range, and cumulative fluid balance (dots) as median.

Table 1. Daily volume of fluids.

Day	Resuscitation fluid	Vehicle	Parenteral nutrition	Enteral nutrition	Enteral water	Crystalloids < 5ml/kg/h	Glucose	Total non-resuscitation fluid
1	1590 (525-3000)	640 (290-1000)	0 (0-0)	0 (0-0)	0 (0-40)	0 (0-590)	210 (0-860)	1620 (710-2320)
2	400 (0-1260)	820 (390-1240)	0 (0-0)	0 (0-350)	0 (0-190)	0 (0-580)	590 (0-1390)	2580 (1560-3450)
3	60 (0-500)	500 (230-1010)	0 (0-0)	130 (0-620)	110 (0-300)	0 (0-410)	210 (0-890)	2220 (1290-2930)
4	0 (0-270)	490 (200-1010)	0 (0-290)	160 (0-670)	120 (0-350)	0 (0-200)	0 (0-480)	2240 (1390-2930)
5	0 (0-200)	570 (310-970)	0 (0-610)	300 (0-800)	160 (0-350)	0 (0-50)	0 (0-290)	2160 (1700-2840)

Volumes are presented as median (interquartile range). Please note that the sum of the daily medians of the different components of non-resuscitation fluids does not equal the median of the daily total volume of non-resuscitation fluids due to the skewed distribution of the data.

Table 2. Volume and type of fluid during day 1-5 in "standard care" vs "restrictive" protocol

Type of fluid	Standard protocol	Restrictive protocol	Change
Parenteral nutrition	0 (0-0)	0 (0-0)	0 (0-0)
Enteral nutrition	310 (0-1610)	260 (0-1340)	0 (0-220)
Enteral water	280 (0-1000)	280 (0-1000)	0 (0-0)
Crystalloids <5 ml/kg/h	600 (0-1990)	0	600 (0-1990)
Glucose	1490 (0-3130)	0	1490 (0-3130)
Vehicle	2400 (1270-4030)	2400 (1270-4030)	0 (0-0)
Total non-resusc.	**7870 (4060-12340)**	**4200 (2110-7820)**	**2840 (1270-4900)**

Data are presented as median (interquartile range). Please note that the sum of the medians does not equal the median of the total volume of non-resuscitation fluids due to the skewed distribution of the data.

Paper II & III

Between March 7th and September 13th 2020, we included 98 patients in the trial. Three patients were randomized while not fulfilling the inclusion criteria, they did not receive the intervention and had no registered data. Three patients had incomplete fluid charts. Consequently, data on the primary outcome was available in 92 patients.

Patients in the restrictive fluid group received a median (IQR) of 6008 (3960 to 8123) ml fluid and the usual care group 9765 (6804 to 12401) ml. The Hodges-Lehman median difference between groups was -3560 (95%CI -5302 to -1614, p <0.001) ml, see Fig 10.

We also performed a sensitivity analysis of the patients admitted for three days or more. Patients in the restrictive fluid group (n= 24) received a median (IQR) of 7144 (5872 to 8582) ml and patients in the usual care group (n = 28) 12237 (9932 to 14268) ml the first three days, a median difference of -4749 (95%CI -6507 to -2879, p <0.001) ml. Median difference in cumulative fluid balance between the groups was -2109 (-95%CI 3480 to -831, p<0.001) ml after day 3 and -1812 (95%CI -3140 to -502, p=0.002) ml after day 5 for the whole cohort. In patients admitted for five days or longer, the restrictive fluid group (n=17) had a median (IQR) cumulative fluid balance of -500 (-2007 to 1929) ml and the usual care group (n=17) a cumulative fluid balance of 2396 (-1057 to 6641) ml on day 5.

The secondary feasibility and primary exploratory outcomes are shown in Table 3 and 4 below. Hypoglycemia occurred in 10 patients in the restrictive fluid group and in four patients in the usual care group (p<0.08). One episode in the restrictive fluid group was severe (blood glucose ≤ 2.2 mmol/l).

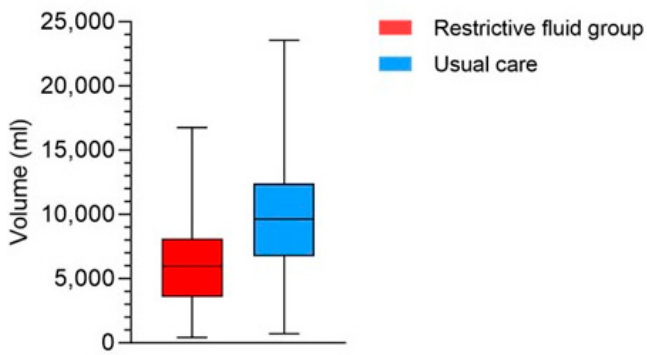


Fig 10. Total volume of fluids administered during the first three days (Day 0-3) in the intensive care unit.

Table 3. Secondary feasibility outcomes

Proportion of eligible patients who were randomized and consented	67 (59-75)
Within 90 days from inclusion	
Proportion of randomized participants experiencing at least one protocol deviation	15 (10-24)
Proportion of participants with clinical data on:	
All-cause mortality	100 (96-100)
Days alive and free of mechanical ventilation	98 (93-99)
Acute kidney injury and ischemic events	98 (93-99)
At 6 months from inclusion	
Proportion of participants with clinical data on:	
MoCA	75 (62-85)
EQ-5D-5L VAS	78 (66-88)

Data presented as percent (95%CI). MoCA: Montreal Cognitive Assessment, EQ-5D-5L: European Quality of life 5-Dimensions 5-Levels visual analogue scale.

Table 4. Primary exploratory clinical outcome

	Restrictive fluid group	Usual care	p-value
At 90 days from inclusion			
All-cause mortality	17/46 (37)	18/49 (37)	0.97
One or more complications (AKI or ischemic event)	39/46 (85)	38/49 (78)	0.37
Days alive and free of mechanical ventilation	86 (3-90)	86 (9.5-90)	0.97
At 6 months from inclusion			
MoCA	19 (16.5-20.5)	19 (18-20)	0.72
EQ-5D-5L VAS	70 (50-80)	70 (58-81)	0.89

Data presented as median (interquartile range) or fraction (%). AKI: Acute Kidney Injury, MoCA: Montreal Cognitive Assessment, EQ-5D-5L VAS: European Quality of life 5-Dimensions 5-Levels visual analogue scale.

Paper IV

A total of 63 out of the 70 patients from the AIR trial were included, seven patients were excluded due to unsuccessful baseline blood volume measurement n=1, no hypoperfusion criteria n=4 and missing PLR data n=2. Baseline characteristics and characteristics of the perioperative management can be seen in Table 5. The most common hypoperfusion inclusion criterion was lactate >2mmol/l (67%), followed by diuresis < 0.5 ml/kg/h (45%), hypotension (32%) and $ScvO_2$ <70% (30%). We found

43 out of 63 patients (68%) likely to be preload responders while 20 patients (32%) were not. Among the likely preload responders, 19/43 patients (44%) were hypovolemic, 12/43 patients (28%) were euvolemic and 12/43 patients (28%) were hypervolemic (Fig 11). In patients unlikely to be preload responsive (n=20) we found 5/20 (25%) to be hypovolemic, 11/20 (55%) to be euvolemic and 4/20 (20%) to be hypervolemic.

In the sensitivity analysis, a deviation of 15% or more from predicted normal value was used to define hypo- and hypervolemia. Adopting these criteria in patients likely to be preload responsive, 10/43 (23%) were hypovolemic, 25/43 (58%) were euvolemic and 8/43 (19%) were hypervolemic. In patients unlikely to be preload responders 1/20 (5%) were hypovolemic, 16/20 (80%) were euvolemic and 3/20 (15%) were hypervolemic.

We found no correlation between change in pulse pressure and blood volume (r=-0.146, 95% CI [-0.386 to 0.113], p=0.254) (Fig 12).

Table 5. Baseline characteristics and perioperative management

No of patients	63
Age, yrs	68 (58-74)
Sex - Female, % (no.) - Male, % (no.)	 60 (38) 40 (25)
Weight, kg	73 (62-86)
Height, cm	169 (164-176)
POSSUM physiology score	15 (13-17)
ASA	2 (2-3)
Type of surgery, % (no.) - Whipple - Gynecological	 54 (34) 46 (29)
Peroperative bleeding, ml	600 (300-1000)
Peroperative diuresis, ml/kg/h	0.7 (0.4-1.1)
Peroperative crystalloids, ml	4400 (4000-5250)
Peroperative colloid, ml	600 (425-1000)
Length of surgery, min	404 (329-497)
Length of anesthesia, min	503 (448-585)
Epidural anesthesia, % (no.)	92 (58)
Perioperative use of vasopressor, % (no.)	84 (53/63)
Perioperative use of inotropy, % (no.)	14 (9/63)

ASA – American Society of Anesthesiologists physical status, POSSUM – Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. Data presented as median (interquartile range) or percentage (no.).

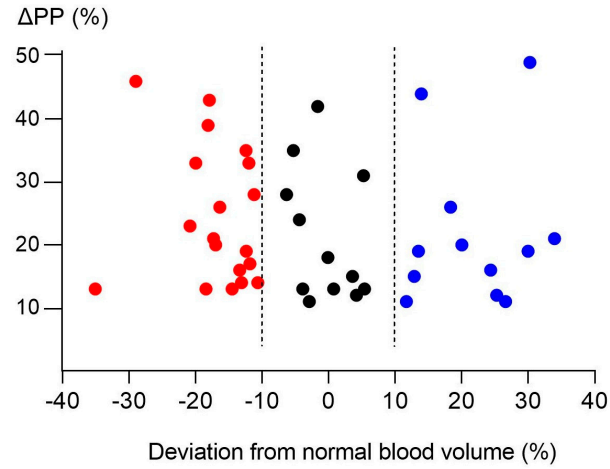


Fig 11. Change in pulse pressure (ΔPP) following a passive leg raising test and deviation of blood volume from normal blood volume. Dotted lines illustrate limits of euvolemia

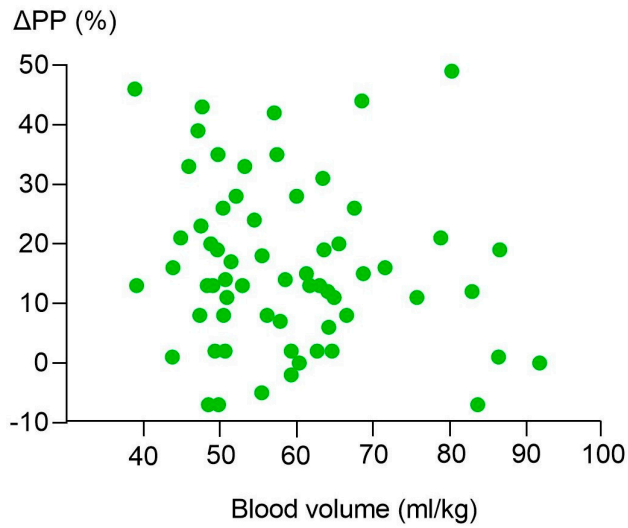


Fig 12. Change in pulse pressure (ΔPP) following a passive leg raising test in relation to blood volume.

Discussion

Paper I, II & III

As the intensive care community began to question the large fluid volumes administered in patients with septic shock, multiple trials were designed to investigate a possible reduction in resuscitation fluid volumes. In these trials it became evident that resuscitation fluids were not the only type of fluid prescribed to the patients. Patients received fluids for other indications as well – the non-resuscitation fluids. As the trials rarely focused on this group of fluid, the details regarding its usage were scarce. If fluid restriction in critically ill patients was to be investigated, knowledge about this fluid group appeared essential.

In line with previous trials, *Paper I* demonstrated that the largest fluid volumes administered to patients with septic shock early in the ICU stay are non-resuscitation fluids (Chen et al. 2015; Hjortrup et al. 2016). We found differences between sites in the use of non-resuscitation fluids and that local routines rather than evidence guide the administration, as has been reported by others (Silversides et al. 2018). The novelty of *Paper I* was the prospective design, detailed description of the indication, type, and amount of fluids that patients with septic shock receive during their first five days in the ICU. The meticulous fluid data allowed us to develop a model for volume reduction based on the most restrictive local routine already in use at any of the participating sites. A reduction of nearly three liters of non-resuscitation fluids could theoretically be achieved by restricting only three subgroups of non-resuscitation fluids.

Based on the results of *Paper I*, the protocol designed in *Paper II* and tested in *Paper III* clearly demonstrated that protocolized fluid restriction focusing on non-resuscitation fluids can result in a large decrease in fluid administration.

The fluid reduction was mainly achieved by reducing the administration of glucose solution as nutrition, a result worthy of discussion. Glucose solutions are primarily administered to avoid starvation ketosis and to maintain hydration, however not all

countries utilize these fluids. Different traditions rather than evidence seem to mandate daily practice. Most Scandinavian countries as well as Belgium and the United Kingdom advocate the use, whereas Canada, Australia and New Zeeland do not (Balloni et al. 2016; Bihari et al. 2016; NICE-guidelines 2017; Silversides et al. 2018; van Regenmortel et al. 2018; DASAIM 2019). The European and North American nutritional guidelines do not mention glucose solutions, but rather recommend starting enteral nutrition as soon as possible (Singer et al. 2016; McClave 2018). The use of glucose solutions is debatable, on the one hand glucose used as maintenance fluid in the critically ill may diminish total sodium load as compared to using normal saline or balanced crystalloids (van Regenmortel et al. 2021). On the other hand, administration of glucose solutions generally elevates plasma glucose levels possibly entailing prescription of insulin, a treatment associated with hypoglycemia and death when targeting tight glucose control (Finfer et al. 2009). Furthermore, carbon dioxide production increases after glucose administration, as well as lipogenesis (Tappy et al. 1998). In patients with an already decreased pulmonary capacity, increased carbon dioxide may be disadvantageous. Additionally, high plasma glucose may increase the risk of infection (Butler et al. 2005). Our main concern when omitting glucose solutions in the restrictive fluid group was hypoglycemia, the incidence was therefore registered. Hypoglycemia (blood glucose level $\leq$3.9 mmol/l) developed in 14 patients – ten in the fluid restrictive group and four in the usual care group. One of the patients in the restrictive fluid group had severe hypoglycemia (blood glucose level $\leq$2.2 mmol/l). There was no statistical difference between the groups, but the finding is something to be observant of. An adequately powered trial is needed to explore if an increased risk of hypoglycemia is present in the intervention group.

Fluid restrictive trials have so far not resulted in a treatment effect compared to usual care (Sivapalan et al. 2023). Possible explanations might be, there is no treatment effect to be found in fluid restriction, or the lack of effect in these trials may be linked to the *type* of fluid being restricted – resuscitation fluids rather than non-resuscitation fluids. If reduction of resuscitation fluids has a different profile in terms of benefit and harm in comparison to non-resuscitation fluids is still unknown. Another explanation for an absent effect may be that fluid separation between groups has been too small, even if the recent CLASSIC trial achieved a larger fluid separation than previous trials (Meyhoff et al. 2022; Sivapalan et al. 2023). Moreover, cumulative fluid balance may be more important than administered fluid. In a retrospective study of an RCT, a large cumulative fluid balance at day 4 was associated with higher mortality, the median

cumulative fluid balance in the cohort was 11 L (Boyd et al. 2011). The difference in cumulative fluid balance in previous fluid restrictive trials has been limited, to at most one liter (Chen et al. 2015; Hjortrup et al. 2016; Meyhoff et al. 2022). Maybe the lack of effect of a restrictive fluid approach is not due to the small difference in fluid volume administration between groups but due to an even smaller difference in cumulative fluid balance. In *Paper III* we did not see a cumulative fluid balance as large as reported in the retrospective study but found a median difference twice as large as other trials have reported (Chen et al. 2015; Hjortrup et al. 2016; Meyhoff et al. 2022). Looking only at the patients still admitted on the fifth day in the ICU, the difference was three times greater (Meyhoff et al. 2022). It may be that the volume of fluid administration is of minor importance as long as the fluid balance is not positive.

Most fluid restrictive trials have focused on reducing the administered fluid, but an alternative approach to affect fluid balance is to actively remove already accumulated fluid, a concept known as de-resuscitation. In a pilot trial, 180 ICU patients on mechanical ventilation were randomized between 24 and 48 hours from ICU admission to *a)* a combination of conservative fluid administration and de-resuscitation or *b)* usual care, with fluid balance 24 hours after randomization as primary outcome (Silversides et al. 2022). In the de-resuscitation group, fluid balance was minimized by both administering less fluid but also by decreasing an existing positive fluid balance (RRT or diuretics). At day 3, 24 hours after randomization, the de-resuscitation group and usual care group had a fluid balance difference of one liter but no effect on 28-day mortality in the whole cohort. Interestingly, in a subgroup analysis of septic patients, an increased mortality was seen in the de-resuscitation group compared to usual care but no difference in other patient-important outcomes was observed. The increased mortality in the sepsis subgroup contrasts to results in the other fluid restrictive sepsis trials (Sivapalan et al. 2023). However, the trial randomization process was not stratified for diagnosis and the authors reported baseline imbalances between the groups. The small sample size may also have introduced a type I error. More data on the benefits and harms of de-resuscitation will be available as the results of the ongoing GODIF trial are published (Wichmann et al. 2022). In this multicenter RCT, 1000 ICU patients with fluid overload are randomized to fluid removal with furosemide or placebo. The primary outcome is days alive and out of hospital 90 days after randomization.

Limitations

Even though every effort was made to register all administered fluids in *Paper I* and *III*, we cannot rule out that small amounts of fluid may have been administered without being reported.

In *Paper II and III*, usual care was not strictly protocolized and may therefore have varied from site to site. This pragmatic approach was decided upon as there are no guidelines to define "usual care" and to gain results based on current care practice.

The external validity of the trial results may on a global scale be limited to some extent. The major component resulting in fluid reduction was decreased administration of glucose solutions. As many counties outside of Europe do not administer these fluids for nutritional/maintenance purposes, the total fluid reduction in these areas may be less than what we report in our trial. In *Paper I* we did however discover that the concentration of vasopressors was up to 20 times more diluted in the Canadian sites compared to the lowest concentration later incorporated in the restrictive protocol for medications. Moreover, the Canadian sites also administered crystalloids/enteral water as maintenance fluids in patients with a positive fluid balance, in line with the rest of the study sites. Hence, local routines may differ but still enable a reduction of total fluid administration in the restrictive fluid group.

Paper IV

In this post hoc analysis, a large fraction of postoperative patients likely to be preload responsive were hyp*er*volemic. We found no association between change in pulse pressure response to PLR and blood volume.

Recommendations of fluid therapy in patients undergoing surgery states that fluids should be cautiously administered to avoid large positive fluid balances (Martin et al. 2020). Decreased blood pressure, low diuresis, increased lactate and low $ScvO_2$ are often interpreted as signs of hypoperfusion and trigger administration of fluid boluses (Cecconi et al. 2015). The intention is to increase organ perfusion by incrementing preload and thereby cardiac output.

Theoretically, knowing the blood volume status may support the choice of the optimal treatment. A hypovolemic patient may best be treated with fluids, whereas eu- or hypervolemic patients may benefit from treatments other than fluid therapy. Preload is

not only dependent on vascular volume but also the degree of venous vascular tone, moreover, cardiac output can be increased by other measures than adjusting preload.

In Paper IV, we calculated blood volume from plasma volume measurements gained by the administration of radioactively labelled albumin and a gamma counter. However, this is not standard equipment available in the post-anesthesia- or intensive care unit. Novel methods available at the bedside, developed for use in everyday clinical practice could possibly help identify patients with normal blood volume where cardiac output may be increased by treatments other than fluids.

Limitations

The most obvious limitation in our study is the lack of a cardiac output monitor to assess preload responsiveness. Such a monitor was not required to test the primary hypothesis in the AIR trial and was therefore not part of the AIR protocol.

Another potential limitation is that we calculated the blood volume in each patient as opposed to measure it. In the AIR trial, plasma volume measurement was preferred over blood volume measurement. To convert the plasma volume to blood volume we had to use hematocrit, adjusted for body hematocrit in relation to large vessel hematocrit, potentially introducing errors compared to measuring blood volume directly.

There was no sample size calculation done prior to the analysis, as the included cohort was determined by the sample size from the AIR trial. Regarding the non-existing association between blood volume and pulse-pressure response, the low sample size may have introduced a type II error.

Conclusions

- Volumes of non-resuscitation fluids and resuscitation fluids are similar on the first day in the ICU in patients with septic shock, thereafter non-resuscitation fluids surpass.
- Non-resuscitation fluids represent the largest volume of fluid administered during the first five days in the ICU.
- Vehicles for medication and glucose solutions represent the largest subgroups among the non-resuscitation fluids.
- It is feasible to design a restrictive fluid protocol targeting non-resuscitation fluids that efficiently reduces total volume of administration the first three days in the ICU compared to usual care.
- To use the protocol for reduction of non-resuscitation fluids in a trial to test if fluid restriction of non-resuscitation fluids improves outcome seems feasible.
- Postoperative patients likely to be preload responsive are often hypervolemic in their blood volume status. In these patients, therapies other than fluid administration may be a more rational approach to increase cardiac output.

Future perspectives

Multiple previous trials have demonstrated that non-resuscitation fluid is the greatest source of fluid administration, contributing to a positive fluid balance in patients with septic shock. This thesis has demonstrated that a protocolized reduction of non-resuscitation fluids is possible. What we do not yet know is whether such a reduction makes a difference in the real world – in the life of the patient. Does it affect mortality? Are there complications associated with such a reduction?

The next natural step is to perform a large-scale randomized clinical trial, where non-resuscitation fluids as opposed to resuscitation fluids are reduced. With adequate power, such a trial will contribute to clarifying whether fluid restriction has possible beneficial effects, compared to usual care. On November 27th 2023, a trial fitting this description started - The REDUSE trial. A multicenter randomized superiority trial (NCT06140147), based on the restrictive protocol designed and tested in paper II and III. With 1850 patients to come, the trial is adequately powered to investigate all-cause mortality at 90 days as the primary outcome. Patient enrolment is expected to continue through 2027 and the last patient follow-up will be performed in 2028.

It is a well-known fact that climate change impacts human health. At the same time, the health care sector also contributes to climate change. The greenhouse gas (GHG) emission from the healthcare sector varies between countries, but studies estimate the emissions to be approximately 5% of the national GHG footprint (Pichler et al. 2019). As an addition to the primary and secondary outcomes in the REDUSE trial, the intervention will also be examined in a climate and environmental footprint analysis. Waste prevention (avoid, reduce, reuse, recycle, reprocess) can reduce the environmental impact of healthcare (McCain et al. 2020). The results from the REDUSE trial will show if avoidance and reduction of fluids in the intervention group can have a positive effect on climate change. This analysis will be of particular importance if the clinical effect of the two treatment arms is similar.

Sammanfattning på svenska

Vatten utgör den allra största beståndsdelen i våra kroppar. Drygt hälften av vår kroppsvikt kan tillskrivas vatten, men påverkas av kroppstyp, ålder och kön. Vattnet har många funktioner i kroppen. Det bygger upp våra celler och därmed våra organ. Vattnet håller huden och slemhinnorna fuktiga och bidrar till att skapa en skyddsbarriär mot omgivningen. Via blodet kan vi transportera olika ämnen till och från cellerna, såsom syre och näringsämnen liksom koldioxid och slaggprodukter från metabolismen. Vattnet hjälper oss också att reglera kroppstemperaturen, påverkar tarmfunktionen och hjälper oss bli av med avfallsämnen via urinen.

Olika typer av vätska

Vanligtvis får vi i oss tillräckligt med vatten via dryck och matintag, men vid sjukdom kan vätska behöva ges via en infart i ett blodkärl eller via en näringssond som placeras i matsäcken via näsa/mun. Vätska kan ges av många olika anledningar, dessa kan grovt sammanfattas i två grupper: *1) resusciteringsvätska* - den ges för att kunna förbättra cirkulationen och underlätta transporten av syrgas ut till cellerna, *2) icke-resusciteringsvätska* – vätska som ges av alla andra anledningar än det ovan beskrivna, såsom vätska i form av näring, vätska som läkemedel blandas i och vätska som ges för att tillgodose det dagliga vätskebehovet (underhållsvätska).

En av de vanligaste diagnoserna på en intensivvårdsavdelning (IVA) är *septisk chock*, ett allvarligt tillstånd som påverkar cirkulationen, orsakat av en infektion. Patienter med septisk chock behöver resusciteringsvätska för att återfå/upprätthålla en acceptabel blodvolym men också annan vätska - *icke-resusciteringsvätska* - såsom vätska som läkemedel blandas i, till exempel antibiotika eller blodtryckshöjande läkemedel och näring. Under den första tiden på IVA ges totalt sett mycket vätska. Även om vätska i många situationer är bra att få, så tyder vissa studier på att det går sämre för de patienter som får mest vätska, och att det går bättre för patienter som får mindre vätska. Mycket vätska kan leda till svullnad av organ och att syrgasleveransen till cellerna försvåras.

En annan grupp patienter som ofta får mycket vätska är patienter som genomgått stor kirurgi och befinner sig på uppvakningsavdelningen. Efter operationen uppvisas ofta indirekta tecken på att blodgenomströmningen till organen är minskad. Exempel på detta kan vara minskad urinproduktion eller nedsatt blodtryck. Dessa tecken betyder inte nödvändigtvis att organen faktiskt *har* nedsatt blodgenomströmning men används ofta som startskott för att ge vätska, den s k *resusciteringsvätskan*. Syftet med denna vätska är att öka blodvolymen och därmed förbättra cirkulationen, men även hos denna patientgrupp rekommenderas försiktighet då man sett att stor vätskeadministrering kan ge svullnad av vävnader, försämrad läkning och att njursvikt kan utvecklas.

Varför denna avhandling?

Eftersom det finns forskning som tyder på att det går sämre för patienter med septisk chock som fått mycket vätska under sin tid på IVA, så har man i flertalet studier försökt minska den givna vätskan genom att fokusera på resusciteringsvätskan. Vätskebesparingen som åstadkommits i dessa studier har varit liten och en effekt på utfall som dödlighet och njursvikt har inte kunnat påvisas. I dessa studier har det framkommit att icke-resusciteringsvätskan verkar vara den vätska det ges mest av. Man skulle därför kunna föreställa sig att det vore klokt att minska denna typ av vätska i stället, eftersom besparingen potentiellt skulle kunna bli större.

För att kunna minska icke-resusciteringsvätskorna ville vi i avhandlingens delarbete I, II och III ta reda på vilka vätskor och hur stora vätskevolymer patienter med septisk chock får den första tiden på IVA. Hur mycket utgörs av resusciterings- respektive icke-resusciteringsvätska? Vilka vätskor kan minskas? Hur mycket kan dessa vätskor minskas? Om ovan nämnda vätskor minskas, kommer patienterna då få mindre vätska totalt sett under IVA-tiden eller kommer minskningen kompenseras genom att andra vätskor ges mer av?

De postoperativa patienternas nytta av vätska kan tänkas bero på vilken blodvolym de har. Om blodvolymen är låg så kan vätska vara en bra behandling, men om blodvolymen är hög så kanske annan behandling är mer fördelaktig för att öka cirkulationen. I delarbete IV ville vi undersöka: vilken blodvolym har egentligen patienter som uppvisar tecken på nedsatt organgenomblödning?

Vad visade avhandlingen?

Delarbete I visade att den absolut största delen vätska som patienter med septisk chock fick de första fem dagarna på IVA var icke- resusciteringsvätskor. Patienterna fick i

genomsnitt 2,8 liter resusciteringsvätskor jämfört med 7,8 liter icke-resusciteringsvätskor. Sockerlösningar och vätska som läkemedel blandas i gavs det mest av. Genom att minska vissa icke-resusciteringsvätskor de första fem dagarna skulle en potentiell minskning av den totala vätskan på 2,8 liter kunna åstadkommas.

I **Delarbete II** gjorde vi ett förslag på hur icke-resusciteringsvätskorna skulle kunna minskas, ett protokoll, till en kommande studie. För att få en skillnad på minst 2 liter mellan gruppen som skulle få ”mindre mängd” vätska och gruppen som skulle få ”vanlig mängd” vätska räknade vi ut att det behövdes 98 patienter i studien.

Delarbete III var utformat som en pilotstudie, där vi testade vårt protokoll från delarbete II. I studien inkluderades 98 patienter och protokollet fungerade väl. Genom att endast protokollisera en minskning av icke-resusciteringsvätskan blev skillnaden i total vätskevolym mellan grupperna betydligt större än förväntat, 3,6 liter. Det skulle alltså vara möjligt att använda detta protokoll i en storskalig studie för att se om minskningen av vätska gör någon *riktig* skillnad för patienten, till exempel om behandlingen kan sänka dödligheten hos patienter med septisk chock.

I **Delarbete IV** använde vi oss av insamlad data från en tidigare utförd randomiserad klinisk studie. Vi inkluderade 63 patienter i vår analys och visade att en stor del av patienterna faktiskt har en blodvolym som är större än förväntat utifrån patientens längd/vikt/kön. Om man vill förbättra cirkulationen hos denna patientgrupp kan det vara mer rationellt att ge annan behandling än vätska.

Obesvarade frågor och framtida forskning

I avhandlingen har vi hittat ett effektivt sätt att minska vätskan som patienterna med septisk chock får. Det vi fortfarande dock inte vet är om en sådan minskning gör någon skillnad för patientens liv och välmående. Nästa steg är således att testa detta i en större studie, en studie som är stor nog att kunna påvisa en verklig effekt av vätskeminskningen om en sådan finns. I slutet av 2023 startade vi en sådan studie och den kommer fortsätta till 2028. Studien kan förhoppningsvis bidra med en viktig pusselbit i vad som är den mest optimala behandlingen för patienter med septisk chock.

Acknowledgements

Peter Bentzer: My main supervisor that patiently has guided a novice like myself into the world of research. You have such a clear vision and great knowledge, and it's obvious to us all that performing research is embedded in your DNA. Thank you for putting up with me for all these years, and for always being only a phone call away.

Adam Linder: My co-supervisor, thank you for your expertise and for your availability when needed.

Svajunas Statkevicius and Johan Bonnevier: Thank you for all your effort involved in the AIR-trial, for gathering and generously sharing the data that was the foundation for Paper IV.

Jean-Louis Vincent: Thank you for being the colorful person that you are. I greatly appreciate diversity, also in the intensive care community. Thank you for reviewing Paper II and for delivering this unforgettable comment:

> *"Hopefully, if the patients are adequately monitored, one can anticipate the investigators will give more resuscitation fluids in the patients who receive less 'non-resuscitation' fluids, so that there will be no difference in fluid balance.* ***It will be a useless study****."*

…which is now framed and decorates the office wall. You have perfectly illustrated the necessity of clinical trials – even the most experienced, well-renowned professor does not possess the gift of foresight.

The SURF- and REDUSE-team: This thesis only exists because of your hard work at each of the participating sites. Thank you for sharing your thoughts and competence, for your flexibility and your time. A special thanks to **Mårten Jungner** and **Martin Spångfors** for our collaboration in SURF, you were a huge help and a great support. **Jane Fisher** - I am very grateful that you are a part of the REDUSE-team. Always attentive, competent, and eager to help.

Forskarskolan Helsingborg: Being a rookie with all of you was the most wonderful and joyous experience! I will always remember and appreciate all of you. Thank you **Niklas Nielsen** and **Ulla-Britt Karlsson** for creating an atmosphere that allowed us to learn, grow and laugh together.

Tomaz Tekavec: Colleague and Head of the *Department of Clinical Physiology* in Helsingborg. Discussing physiology with you for several hours was such a beautiful moment, your knowledge and kindness will always be remembered and treasured. I'll be back. If you let me.

All clinical colleagues at the *Department of Anesthesiology and Intensive Care* in Helsingborg: My family away from home. I greatly appreciate each and every one of you and love that our morning meetings are filled not only with important case-discussions but also with laughter and warmth.

All nurses and assistant nurses in the ICU, Helsingborg: thank you for the receptive atmosphere in the ICU and for the great teamwork – bedside as well as in the SURF study and REDUSE trials.

All clinical colleagues at the *Department of Cardiothoracic Surgery, Anesthesia and Intensive Care* in Lund: My other family away from home. I was welcomed with open arms and received nothing but enthusiasm and kindness. The beautiful porcelain heart (which I still love) is a daily reminder. Our paths will cross again, I'm sure.

Martin Annborn: Competent, kind, attentive and supporting. Also, the first one to encourage me to enter the world of research. You are the definition of a great boss - and you are MY boss! Lucky me!

Florian Ebner: I was once afraid of you, but who can stay afraid after bonding outside of a bondage-store in Brussels? Thank you for sharing your great knowledge and inspiring the rest of us to stay up-to-date and perform our best.

Maria Adrian: Angel from Lund with the most amazing voice! It started with a song and has continued ever since. Thank you for always having my back and for sharing both happy and hard times with me.

Jenny Engdahl: The fastest, happiest, most energetic friend I have! It was love at first sight 9 years ago and I love you even more today! Let's talk about love.

Björn Bark: An unexpected friendship that has been life-saving at times. Thank you for always giving me good advice, for making me laugh and for never growing tired of me.

Johannes Quiding Lood: Music, meditation, life. We share many things, all originating from the heart.  .

Jan Winther: My dear creative uncle, thank you for devoting your time and artistry when painting the beautiful cover aquarelle.

Stig Søndersø: I am so grateful for our deep and genuine friendship, and for you being the best co-parent one could ask for.

Mom and dad: For giving me an Astrid Lindgren-upbringing – freedom, green grass, clean air and the possibility to run around barefoot. Thank you for giving me nothing but love and for always being proud of me, just for being me.

Anders, Annika and Anton: My awesome siblings, always supportive and warmhearted. Anders: Thank you for all the late evening discussions eating *knäckebröd* in the kitchen. Annika: thank you for always looking out for me – as kids, when you packed the extra everything for our short picnic next-door, and still today. Anton: you are still five years old (not 34) in my dreams. Thank you for sharing *All for love* with the world (the family) with such passion (and thank you mom for filming it).

Isla och Nevi: kloka, varma, roliga. Att få vara er mamma är det finaste i världen. Det jag är allra mest stolt över är att ni redan som barn vet vad som är viktigast. Kärlek, kärlek, kärlek.

Till **dig** jag älskar lika högt som livet. Tack för innerligheten, närheten, friheten. För skratten, för det ärliga och öppna. För att du känner mig bättre än någon annan. Tack för att du är du, det enda jag någonsin vill att du ska vara. 3.27.

References

AlvaradoSánchez JI, CaicedoRuiz JD, DiaztagleFernández JJ, et al. Predictors of fluid responsiveness in critically ill patients mechanically ventilated at low tidal volumes: systematic review and meta-analysis. Ann Intensive Care 2021;11(1):28

Andrews B, Semler MW, Muchemwa L, et al. Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension: The Simplified Severe Sepsis Protocol 2 Trial. JAMA 2017;318(13):1233-1240.

Balloni A, Lari F, Giostra F. Evaluation and treatment of hyperglycemia in critically ill patients. Acta Biomed. 2016;87(3):329-333.

Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? JAMA 2016;316(12):1298–1309.

Bihari S, Watts NR, Seppelt I, et al. Maintenance fluid practices in intensive care units in Australia and New Zealand. Crit Care Resusc 2016;18:89–94

Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101(6):1644-1655.

Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med. 2011;39(2):259-265.

Brindle M, Nelson G, Lobo DN, Ljungqvist O, Gustafsson UO. Recommendations from the ERAS® Society for standards for the development of enhanced recovery after surgery guidelines, BJS Open, 2020;4(1):157–163.

Brown E, Hopper J Jr, Hodges JL Jr, Bradley B, Wennesland R, Yamauchi H. Red cell, plasma, and blood volume in the healthy women measured by radiochromium cell-labeling and hematocrit. J Clin Invest 1962;41:2182–2190

Butler S, Btaiche I, Alaniz C. Relationship between hyperglycemia and infection in critically ill patients. Pharmacotherapy 2005;25(7):963–976.

Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med*. 2014;370(15):1412-1421. doi:10.1056/NEJMoa1305727

Cecconi M, Hofer C, Teboul JL, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. Intensive Care Med 2015;41(9):1529–1537

Chen C, Kollef MH. Targeted fluid minimization following initial resuscitation in septic shock. Chest. 2015;148(6):1462-1469.

Conway-Morris A, Wilson J, Shankar-Hari M. Immune Activation in Sepsis. Crit Care Clin. 2018;34(1):29-42.

Cosnett JE. The origins of intravenous fluid therapy. Lancet 1989;1:768-71.

Danish Society of Anaesthesiology and Intensive care medicine. Nutrition for the critically ill (in danish). https://dasaim.dk/guides/pdf-nbv-ernaering-til-kritisk-syge-2019/ Accessed January 9th 2024.

De Backer D, Cecconi M, Chew MS, et al. A plea for personalization of the hemodynamic management of septic shock. Crit Care 2022;26:372.

Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock [published correction appears in Crit Care Med. 2004 Jun;32(6):1448. Dosage error in article text] [published correction appears in Crit Care Med. 2004;32(10):2169-70]. Crit Care Med. 2004;32(3):858-873.

Dolin HH, Papadimos TJ, Chen X, Pan ZK. Characterization of Pathogenic Sepsis Etiologies and Patient Profiles: A Novel Approach to Triage and Treatment. Microbiol Insights. 2019;12:1178636118825081.

Ernest D, Belzberg AS, Dodek PM. Distribution of normal saline and 5% albumin infusions in cardiac surgical patients. Crit Care Med. 2001;29(12):2299–302.

Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181–1247.

Finfer S, Bellomo R, Boyce N, et al. SAFE study. N Engl J Med 2004; 350:2247-2256.

Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-1297.

Finfer S, Micallef S, Hammond N, et al. Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults. N Engl J Med. 2022;386(9):815-826.

Fleck A, Raines G, Hawker F, Trotter J, Wallace PI, Ledingham IM, Calman KC. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet 1985;325:781–4.

Fleischmann-Struzek C, Rose N, Freytag A, et al. Epidemiology and Costs of Postsepsis Morbidity, Nursing Care Dependency, and Mortality in Germany, 2013 to 2017. *JAMA Netw Open*. 2021;4(11):e2134290.

Geroulanos S, Douka ET. Historical perspective of the word "sepsis" Intensive Care Med. 2006;32:2077.

Glickman SW, Cairns CB, Otero RM, et al. Disease progression in hemodynamically stable patients presenting to the emergency department with sepsis. Acad Emerg Med. 2010;17(4):383-390.

Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 1955;35:123–129.

Harrison MH, Graveney MJ, Cochrane LA. Some sources of error in the calculation of relative change in plasma volume. Eur J Appl Physiol Occup Physiol 1982;50(1):13–21

Hasselgren E, Zdolsek M, Zdolsek JH, Björne H, Krizhanovskii C, Ntika S, Hahn RG. Long intravascular persistence of 20% albumin in postoperative patients. Anesth Analg. 2019;129(5)1232–1239.

Hedin A, Hahn RG. Volume expansion and plasma protein clearance during intravenous infusion of 5% albumin and autologous plasma. Clin Sci. 2005;106:217–24.

Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42(11):1695-1705.

Howard-Jones, Norman. Cholera therapy in the nineteenth century. Journal of the History of medicine and allied sciences. 1972;27:4:373.

Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis. JAMA. 2010;304(16):1787–1794.

Janakan G and Ellis H. Dr Thomas Aitchison Latta (cl796-1833): pioneer of intravenous fluid replacement in the treatment of cholera. Journal of Medical Biography 2013;21(2):70-74.

Kaufman, DA, Lopes M, MaviyaN, Magder, SA. The Ins and Outs of IV Fluids in Hemodynamic Resuscitation. Critical Care Medicine 2023;51(10):p 1397-1406.

Latta T. Malignant cholera. Documents communicated by the Central Board of Health, London, relative to the treatment of cholera by the copious injection of aqueous and saline fluids into the veins, Lancet, 1832;18:274-80.

Legrand M, Dupuis C, Simon C, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit Care. 2013;17(6):R278. Published 2013 Nov 29. doi:10.1186/cc13133

Levy MN. The cardiac and vascular factors that determine systemic blood flow. Circ. Res 1979;44:739-47.

Lewin, Robert. Injection of Saline Solutions into the Veins — Injection of Saline Solutions into the Veins, Adopted with Success in Malignant Cholera. Boston Med Surg J 1832;6:373-375 .

Lindén A, Fisher J, Lilja G, et al. Protocolised reduction of non-resuscitation fluids versus usual care in patients with septic shock (REDUSE): a protocol for a multicentre feasibility trial BMJ Open 2023;**13:**e065392.

Lindén A, Statkevicius S, Bonnervier J, Bentzer P. Blood volume in patients likely to be preload responsive; a post hoc analysis of a randomized controlled trial. Intensive Care Medicine Experimental. 2023;11:14.

Lindén-Søndersø A, Jungner M, Spångfors M, Jan M, Oscarson A, Choi S, Kander T, Undén J, Griesdale D, Boyd J, Bentzer P. Survey of non-resuscitation fluids administered during septic shock: a multicenter prospective observational study. Annals of Intensive Care. 2019;9:132.70

Ljungström L, Andersson R, Jacobsson G. Incidences of community onset severe sepsis, Sepsis-3 sepsis, and bacteremia in–Sweden–- A prospective population-based study. pLoS One. 2019;14(12):e0225700.

MacGillivray N. Dr Thomas Latta: the father of intravenous infusion therapy. Journal of Infection Prevention. 2009;10(1_suppl):S3-S6.

Mailtland et al. FEAST: Mortality after Fluid Bolus in African Children with Severe Infection. FEAST Trial Group, 2011, NEJM;364(26)2483-95.

Malbrain MLNG, Langer T, Annane D, Gattinoni L, Elbers P, Hahn RG, De Laet I, Minini A, Wong A, Ince C, Muckart D, Mythen M, Caironi P, Van Regenmortel N. Intravenous fluid therapy in the perioperative and critical care setting: Executive summary of the International Fluid Academy (IFA). Ann Intensive Care 2020;10(1):64.

Malbrain, M.L.N.G., Van Regenmortel, N., Saugel, B. et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann. Intensive Care 2018;8:66.

Malbrain MLNG, Wong A, Nasa P, Ghosh S. Rational use of intravenous fluids in critically ill patients. Springer International Publishing 2024.

Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. Ann Crit Care 2011;1(1):1.

Martin GS, Kaufman DA, Marik PE, et al. Perioperative Quality Initiative (POQI) consensus statement on fundamental concepts in perioperative fluid management: fluid responsiveness and venous capacitance. Perioper Med 2020;9:12–12.

McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N.). Crit Care Med. 2016;44:390–438.

McGain F, Muret J, Lawson C, ShermanJD. Environmental sustainability in anaesthesia and critical care. BJA 2020;125(5):680-692.

Mellhammar L, Wollter E, Dahlberg J, et al. Estimating Sepsis Incidence Using Administrative Data and Clinical Medical Record Review. *JAMA Netw Open*. 2023;6(8):e2331168.

Messina A, Robba C, Calabrò L, et al. Perioperative liberal versus restrictive fluid strategies and postoperative outcomes: a systematic review and metanalysis on randomised-controlled trials in major abdominal elective surgery. Crit Care. 2021;25(1):205.

Meyhoff TS, Hjortrup PB, Wetterslev J, et al. Restriction of intravenous fluid in ICU patients with septic shock. N Engl J Med 2022;386:2459–70.

Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, Localio AR, Demissie E, Hopkins RO, Angus DC. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012 Jun 15;185(12):1307-15.

Moeller C, Fleischmann C, Thomas-Rueddel D, Vlasakov V, Rochwerg B, Theurer P, et al. How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. J Crit Care. 2016;35:75–83.

Monnet X, Malbrain MLNG, Pinsky MR. The prediction of fluid responsiveness. *Intensive Care Med*. 2023;49(1):83-86. doi:10.1007/s00134-022-06900-0

Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Med 2016;42(12):1935–1947.

Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301-1311.

Myburgh J, Finfer S, Bellomo R, Billot L, et al. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. N Engl J Med 2012; 367:1901-1911.
O'Shaughnessy WB. Proposal of a new method of treating the blue epidemic cholera by the injection of highly-oxygenized salts in to the venous system. Lancet 1831–2;1:366 – 71.

Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. N Engl J Med. 2018;378(24):2263-2274.

NICE-guidelines: Intravenous fluid therapy in adults in hospital. Clinical Guideline 174. Published Dec 10 th 2013, updated May 5 th 2017.

Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12:R74.

Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496-1506.

Perner A, Haase N, Guttormsen A, Tenhunen J, et al. Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. N Engl J Med 2012; 367:124-134.

Persichini, R., Lai, C., Teboul, JL. et al. Venous return and mean systemic filling pressure: physiology and clinical applications. Crit Care 2022;26(1):150.

Pichler, Peter-Paul & Jaccard, Ingram & Weisz, Ulli & Weisz, Helga. International comparison of health care carbon footprints. Environ Res Lett. 2019;14:064004

Preau S, Dewavrin F, Demaeght V, et al. The use of static and dynamic haemodynamic parameters before volume expansion: A prospective observational study in six French intensive care units. Anaesth Crit Care Pain Med 2016;35(2):93-102.

Preau S, Saulnier F, Dewavrin F, Duroche A, Chagnon JL. Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. Crit Care Med 2010;38(3):819–825.

ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683-1693.

Prowle JR, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. Nat Rev Nephrol 2014;10:37–47

Rhee C, Dantes R, Epstein L, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. JAMA 2017;318(13):1241-1249.

Rhoades RA, Tanner GA. Medical physiology. Second edition. Philadelphia: Lipincott Williams & Wilkins. 2003.

Rivers E, Nguyen B, Havstad S, Ressler J, et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. N Engl J Med 2001;345:1368-1377.

Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200-211.

Russell JA, Rush B, Boyd J. Pathophysiology of Septic Shock. Crit Care Clin. 2018;34(1):43-61.

Sakr Y, Bauer M, Nierhaus A, et al. Randomized controlled multicentre study of albumin replacement therapy in septic shock (ARISS): protocol for a randomized controlled trial. *Trials*. 2020;21(1):1002. Published 2020 Dec 7. doi:10.1186/s13063-020-04921-y

Schol PBB, Terink IM, Lancé MD, Scheepers HCJ. Liberal or restrictive fluid management during elective surgery: a systematic review and meta-analysis. J Clin Anesthesia 3, 25-39 (2016).

Shapiro NI, Douglas IS, Brower RG, et al. Early restrictive or liberal fluid management for sepsis-induced hypotension. N Engl J Med 2023;388:499–510.

Shapiro NI, Trzeciak S, Hollander JE, et al. A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. Crit Care Med. 2009;37(1):96-104.

Silversides JA, Fitzgerald E, Manickavasagam US, Lapinsky SE, Nisenbaum R, Hemmings N, et al. Deresuscitation of patients with iatrogenic fluid overload is associated with reduced mortality in critical illness. Crit Care Med. 2018;46:1600–7

Silversides JA, Major E, Ferguson AJ, et al.Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Med 2017;43(2):155-170.

Silversides JA, McMullan R, Emerson LM, et al. Feasibility of conservative fluid administration and deresuscitation compared with usual care in critical illness: the Role of Active Deresuscitation After Resuscitation-2 (RADAR-2) randomised clinical trial [published correction appears in Intensive Care Med. 2023;49(11):1440]. Intensive Care Med. 2022;48(2):190-200.

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801–10.

Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutrit. 2018;38:48–79.

Sivapalan P, Ellekjaer KL, Jessen MK, et al. Lower vs Higher Fluid Volumes in Adult Patients With Sepsis: An Updated Systematic Review With Meta-Analysis and Trial Sequential Analysis. Chest. 2023;164(4):892-912.

Sjöstrand F, Edsberg L, Hahn RG. Volume kinetics of glucose solutions given by intravenous infusion [published correction appears in Br J Anaesth 2002 May;88(5):753]. Br J Anaesth. 2001;87(6):834-843.

Statkevicius S, Bonnevier J, Fisher J et al. Albumin infusion rate and plasma volume expansion: a randomized clinical trial in postoperative patients after major surgery. Crit Care 2019;23(1):191.

Stephan F, Flahault A, Dieudonne N, Hollande J, Paillard F, Bonnet F. Clinical evaluation of circulating blood volume in critically ill patients—contribution of a clinical scoring system. Br J Anaesth 2001;86(6):754–762

Tappy L, Schwarz JM, Schneiter P, Cayeux C, Revelly JP, Fagerquist CK et al. Effects of isoenergetic glucose-based or lipid-based parenteral nutrition on glucose metabolism, de novo lipogenesis, and respiratory gas exchanges in critically ill patients. Crit Care Med. 1998;26(5):860-7.

Van Regenmortel N, Moers L, Langer T et al. Fluid-induced harm in the hospital: look beyond volume and start considering sodium. From physiology towards recommendations for daily practice in hospitalized adults. Ann. Intensive Care 2021;11:79.

Van Regenmortel N, Verbrugghe W, Roelant E, Van den Wyngaert T, Jorens PG. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. Intensive Care Med. 2018;44:409–17.

Vincent JL, Jones G, David S et al. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Crit Care 2019;23:196.

Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22:707–10.

Wennesland R, Brown E, Hopper J, et al. Red cell, plasma and blood volume in healthy men measured by radiochromium (Cr51) cell tagging and hematocrit: influence of age, somatotype and habits of physical activity on the variance after regression of volumes to height and weight combined. J Clin Invest 1959;38(7):1065–1077

WHO. Global Report on the Epidemiology and Burden of Sepsis: Current Evidence, Identifying Gaps and Future Directions; World Health Organization: Geneva, Switzerland, 2020.

Wichmann S, Itenov TS, Berthelsen RE, Lange T, Perner A, Gluud C, et al. Goal directed fluid removal with furosemide versus placebo in intensive care patients with fluid overload: A trial protocol for a randomised, blinded trial (GODIF trial). Acta Anaesthesiol Scand. 2022;66(9):1138-1145

Wiedemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564-2575.

Zampieri FG, Bagshaw SM, Semler MW. Fluid Therapy for Critically Ill Adults With Sepsis: A Review. JAMA. 2023;329(22):1967-1980.

Zampieri FG, Machado FR, Biondi RS, et al. 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. JAMA. 2021;326(9):1-12.

Zarychanski R, Ariano RE, Paunovic B, Bell DD. Historical perspectives in critical care medicine: blood transfusion, intravenous fluids, inotropes/vasopressors, and antibiotics. *Crit Care Clin*. 2009;25(1):201-x. doi:10.1016/j.ccc.2008.10.003

ANJA LINDÉN is a specialist in anesthesiology and intensive care at Helsingborg Hospital, Helsingborg, Sweden. Her thesis focuses on the potential to reduce fluid administration in hemodynamically unstable patients.

Printed by Media-Tryck, Lund 2024 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Anaesthesiology and Intensive Care
Department of Clinical Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2024:44
ISBN 978-91-8021-537-4
ISSN 1652-8220