Resuscitation fluid therapy- a systematic review of principles and cross-sectional study of clinical practice

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Master thesis in Medicine

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Abstract

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Background: Saline solution has been used in fluid resuscitation since the 19th century. Different colloids have been used the last 60 years. Choice of resuscitation fluid has varied over the years and has been heavily influenced by local traditions and clinicians preference.

Method: This article consists of a systematic review and meta-analysis of current resuscitation fluid research combined with a survey at the Department of Anesthesia and Intensive Care at Sahlgrenska University Hospital backed with data of resuscitation fluid usage at Sahlgrenska University Hospital.

Results: In patients with sepsis albumin has been shown to decrease mortality compared to saline solution and HES increases risk of renal replacement therapy and may increase mortality. In a perioperative setting such risks with HES has not been identified. In both ICU and perioperative environment balanced crystalloid seem superior to saline solution.

Out of 62 respondents in our survey 56% and 69% answered that they used both crystalloids and colloids for perioperative and sepsis resuscitation respectively, and 74% that their first perioperative choice was HES. However, when treating septic shock, 89% answered that their preferred colloid was albumin.

Conclusion: Balanced crystalloids have an important role in fluid resuscitation. Albumin is the preferred colloid in severe sepsis but in other scenarios HES may be considered.

The anesthesiologists at the Department of Anesthesia and Intensive Care had a good adherence to current research although perioperative albumin use ought to be reconsidered due to high cost and lack of evidence.

Introduction

Background

Historical background

Intravenous fluid resuscitation with saline solutions is believed to originate from 1830s England during the time of the Indian Blue Cholera pandemic that struck the country in 1831. The same year O'Shaughnessy was the first to propose "injection of highly oxygenated salts into the venous system" in his paper publicized in Lancet (at age 22!). The theory of oxygenation was soon abandoned to instead focus on water and electrolyte replacement. Early 1832 the first treatments of human subjects were conducted by O'Shaughnessy and later Latta. Of Lattas first four patients only one survived but Latta continued unwavering and modified his solution through several experiments finally arriving at a fairly physiological solution containing 134 mmol/L Sodium, 118 mmol/L Chloride and 16 mmol/L Bicarbonate (See table 1 for human plasma reference). In 1833 came a decline in the development of fluid resuscitation as cholera in England subsided and the two main proponents of saline infusion disappeared from the field (Latta died from pulmonary tuberculosis and O'Shaughnessy, not unlike the youth of today, left for India to study the medical use of cannabis) [1, 2].

Advancement in hemorrhage treatment breathed new life into the field of fluid resuscitation. Several researchers put their names on different solutions. Among these where Sydney Ringer who presented his Ringer's solution in 1883 based on his experiments on frogs where he determined that 0.75% saline "…makes an excellent circulating fluid…". Nasse would later define physiological saline in frogs to be 0.6%. The conclusions drawn from frogs were challenged by HJ Hamburger who in 1896 claimed 0.92% to be the saline concentration of mammalian blood based on his research on cell lysis and the freezing point of blood. 0.9% normal saline, even though not as normal as Hamburger claimed (See table 1),

became the world's most common resuscitation fluid and still is. The simplicity of adding salt to water is a possible explanation [1].

Colloid solutions used for fluid resuscitation is a product of the 20th century. Albumin became available after the invention of blood fractionation and was used as an infusion during world war II in the US [3]. Contemporary to this, Grönwall and Ingelmans research on dextran led to the development of Macrodex [4]. Hydroxyethyl starch is the youngest colloid in the family. In 1959 waxy hydroxyethyl starch polymers first became available and was tested on man by Ballinger et al in 1966 [5].

Physiological background

In medicine, shock is generally defined as circulatory failure resulting in inadequate cellular oxygenation and waste removal. Shock can also be defined as a cause of inadequate cardiac output (CO). Usually CO is decreased during shock but extreme metabolic rate and abnormal tissue perfusion can cause circulatory shock although cardiac output remains normal [6].

A common way to categorize circulatory shock is to divide it into four subtypes based on their pathophysiology; 1) distributive, where vasodilation diminish venous return, 2) hypovolemic, i.e. lack of circulating volume which also diminishes venous return, 3) cardiogenic, diminished pumping ability from e.g. myocardial infarction and finally 4) obstructive, where pumping function is externally hindered e.g. from a cardiac tamponade [6, 7].

Septic shock

Septic shock is the most frequent cause of circulatory shock in ICU patients and also the most common cause of shock-related death in modern hospitals. As such, it deserves special mentioning. Septic shock is caused by an exacerbated bacterial infection that spreads to several tissues through the blood. With a multitude of possible bacterial agents causing septic shock, it displays in many different ways. Typical

though is substantial vasodilation, especially in the infected tissue. About half of the septic shock patients suffer from circulatory shock despite a high cardiac output due to high temperature and high cellular metabolism stimulated by bacterial toxins. Increased amount of carbonic and lactic acid in the tissues makes the blood more acidic and thus prone to local agglutination, a phenomenon called sludging. Micro blood clots may also form as a result. If widespread, this leads to disseminated intravascular coagulation (DIC) where coagulation factors are consumed, causing lethal hemorrhaging. End stage septic shock is very similar to hemorrhagic shock [6, 7].

Hemorrhagic shock

Hemorrhagic shock is more or less synonymous with hypovolemic shock as hemorrhage is the most common cause of hypovolemic shock. Bleeding diminishes filling pressure and reduces venous return which in turn reduces cardiac output (CO). It is possible to lose 10 percent of the total intravascular volume before CO is affected. Decrease of arterial pressure (ABP) usually occurs later than CO and typically not until 20% volume loss. At about 45% blood loss ABP reaches zero, though a person seldom survives more than 30-40% blood loss (without resuscitation). Vasoconstriction due to sympathetic reflexes is the reason why ABP decrease lags behind CO reduction [6].

From level of severity, hemorrhagic shock is divided into two subcategories; Non-progressive and Progressive. Shock is considered non-progressive when the subject is able to compensate and recover without external intervention. If the hemorrhage reaches a critical level though, the shock becomes progressive. When progressive, the shock starts to feed itself through several positive feedback loops. With low enough ABP, cardiac blood flow decreases leading to cardiac depression further hampering CO. By the same principle the vasomotor center becomes suppressed. As in septic shock sludging occurs. Capillary hypoxia also triggers increased permeability, further decreasing circulating volume. Acidosis due lactic acid and carbon dioxide production ads to this vicious circle that will cause the death of the individual if not reversed [6].

Distribution of Fluid

In human adults body fluid constitutes about 50% of the total weight in women and about 60% in men. This fluid is distributed 2/3 intracellular and 1/3 extracellular. The extracellular fluid, 11.7-14L in a 70kg human, consists of 3/4 interstitial fluid and 1/4 Plasma (3-3.5L). Assuming a hematocrit of 0.4, average blood volume is 5-5.8L [6].

Based on the theories of Starling, fluid distribution between interstitium and plasma is governed by hydrostatic and colloid osmotic force while distribution over the cellular membrane depends predominantly on the osmotic effect of sodium, chloride and other smaller solutes. Most resuscitation fluids today strive to be isotonic, similar to extracellular fluid in electrolyte content, aimed at not disturbing the fluid balance between the intra- and extracellular compartments [6, 8]. Colloid osmotic pressure is derived from molecules less able to pass through the semipermeable membranes of vessels, thus exerting osmotic pressure. Different colloid solutions are widely used in fluid resuscitation with the presumption that increased colloid osmotic pressure in the plasma will retain the fluid there while crystalloids (resuscitation fluids lacking colloids) will distribute over the whole extracellular volume. By this concept, a simplified model is that 1000 ml of intravenous crystalloid will add 250 ml to the circulating plasma while 1000 ml of intravenous colloid will add 1000 ml to the circulating [6]. Some guidelines use a 1:3 colloid to crystalloid ratio, roughly based on the same principle [8].

Recent technological leaps in visualization have allowed closer study of the endothelial glycocalyx and its role in fluid exchange and a need to revise our views based on Starling. The endothelial glycocalyx consists of glycoproteins and proteoglycans coating the lumen of blood vessels and varies in thickness from 0.2 to 8 µm (average 2 µm) depending on vessel size. Measurements suggests that its volume might be as high as 1700 ml in the average human, thus, rather than seeing vascular content as plasma and erythrocytes one ought to consider viewing it as plasma, erythrocytes and glycocalyx [9].

The endothelial glycocalyx is semipermeable, stopping larger molecules such as dextran 70 or hydroxyethyl starch. It is suggested that the colloid osmotic pressure gradient is active between plasma and the subglycocalyx spatium rather than between plasma and the interstitium. Inflammatory states (such as sepsis, trauma or surgery) damage the endothelial glycocalyx, underlining the importance of its further study. Even the chronic inflammation of diabetes has shown to damage the glycocalyx, adding the question if this patient group needs special attention in fluid resuscitation. Although endothelial glycocalyx is an exciting new area of research in itself, this article will focus on the resuscitation fluids we are using in today's medicine [9].

Fluid therapy in practical medicine

In the field of Intensive and perioperative medicine, intravenous infusion of fluid is without question one of the most common interventions.

To make a simplified distinction of use, fluid is given as maintenance or fluid resuscitation. The main bulk of fluid therapy is of course given as fluid balance maintenance and will not be covered in this study. Fluid resuscitation on the other hand refers to treatment of an acute ailment, mainly hypovolemia. In the intensive care unit (ICU) common reasons for fluid resuscitation are trauma and severe sepsis/septic shock. Perioperatively, blood loss is the main reason. A distinct difference between these settings is that ICU patients are obviously severely ill with possible multi organ engagement whereas a majority of elective surgery patients presents a limited problem in need of surgical treatment.

Regardless of type of patient and setting, fluid therapy is a treatment involving a large number of different pharmacological products and there is a vast amount of known complications to fluid distribution such as allergic reactions, fluid overload with formation of tissue edema, electrolyte

disturbances and kidney failure. Type of fluid loss and the individual patient's condition is of importance and should also be taken into consideration when choosing and prescribing intravenous fluid treatment.

Choice of resuscitation fluid

A typical way to classify resuscitation fluids is by dividing them into crystalloids and colloids. Choice between and within these two groups is generally based on their physiological qualities but also lean heavily on local tradition and the clinicians own preferences. Below, table 1 shows the composition of some of the more common resuscitation fluids.

Variable	Human Plasma	Crystalloids					Colloids							
		0.9% Saline	Compounded Sodium Acetate	Compounded Sodium Lactate	Balanced Salt Solution		Albumin 20%	Hydroxyethyl Starch					4% Succinylated Modified Fluid Gelatin	6% Dextran 70
								6% (130/0.4)		6% (130/0.42)				
Trade name		Normal Saline	Ringer's Acetate	Hartmann's or Ringer's Lactate	Plasmalyte		Flexbumin	Voluven	Volulyte	Venofundin	Tetraspan	Gelofusine	Macrodex	
Colloid source							Human Donor	Maize Starch	Maize Starch	Potato Starch	Potato Starch	Bovine Gelatin	Polymerized sucrose	
Osmolarity (mOsm/L)	291	308	277	280,6	295		*	308	286	308	296	274	308	
Sodium (mmol/L)	135-145	154	130	131	140		130-160	154	137	154	140	154	154	
Potassium (mmol/L)	4.5-5		4	5.4	5				4		4			
Calcium (mmol/L)	2.2-2.6		2	2										
Magnesium (mmol/L)	0.8-1.0		1		1.5				1.5		1			
Chloride (mmol/L)	94-111	154	110	111	98		73.5	154	110	154	118	120	154	
Acetate (mmol/L)			30		27				34		24			
Lactate (mmol/L)	1-2			29										
Malate (mmol/L)											5			
Gluconate (mmol/L)					23									
Bicarbonate (mmol/L)	23-27													

Table 1 [8, 10] Composition of solutes in human plasma and a selection of resuscitation fluids

*Baxalta Inc. has been contacted but cannot confirm a figure for the Osmolarity of Flexbumin.

Crystalloids

Internationally, the most commonly used crystalloid is normal saline 0.9% [1]. There are also different balanced solutions where the most common are Ringer's lactate, Ringer's acetate and Plasmalyte. By tradition Ringer's acetate is the most common crystalloid in Nordic countries but seems to see little use elsewhere.

Colloids

Most colloids consist of a saline solution with added macromolecules but some are based on more balanced solutions. There are a number of colloid groups;

Albumin is derived from human donors and heated to prevent spreading of disease. Compared to semisynthetic colloids, it's considerably more expensive. Albumin has a molecular weight averaging 69 000 Da [6, 8].

Hydroxyethyl starch (HES) is derived from either maize or potato starch. HES comes in many different sizes, but modern HES solution molecules weigh 130 000 Da and the ratio of hydroxyethyl groups on the starch molecule is in the range of 0.38-0.42. HES is the most commonly used semisynthetic colloid in Europe [8, 10].

Dextran is a polysaccharide produced by Leuconostoc mesenteroides bacteria in sucrose solution. Molecular weights normally used are 40 000 and 70 000 Da (Rheomacrodex and Macrodex respectively). Anaphylactic reactions are comparatively common and prophylactic Promiten must be given before infusion. Internationally, dextran sees little use in fluid resuscitation [4, 8, 10]. More commonly dextrans are used as perioperative thrombosis prophylaxis [11].

Gelatin solutions are commonly based on bovine gelatin. Molecular weight vary around 30-35 000 Da [10].

Past and present controversies

Throughout history physicians has debated what treatments to use and the field of fluid resuscitation is not spared. At the turn of the century the debate of crystalloids vs colloids for fluid resuscitation was rekindled when new meta-analyses surfaced. Foremost albumin became a subject of controversy [12]. The Cochrane injuries group changed the view on albumin in intensive care more or less over night with a report showing a pooled relative risk of death using albumin vs other fluids of 1.68 (95% CI 1.26-2.23) [13]. At Sahlgrenska University Hospital, spending on albumin dropped by 64% the following year, 1999 [12]. 10 years later, hydroxyethyl starches (HES) came to be questioned as a widely renowned researcher and proponent of HES, professor Joachim Boldt was revealed as a fraud [14, 15]. Several of his articles were withdrawn and the scientific community was left with a knowledge vacuum [14]. With one of the biggest proponents of HES gone and the publication of several large randomized trials on the subject [16-18], the pendulum swung for HES in intensive medicine. In 2013 The U.S Food and Drug Administration (FDA) released an official recommendation against using HES when treating critically ill patients with renal dysfunction and patients undergoing open heart surgery. The recommendations also stated that patients should be informed of the risks involved, and that renal function should be monitored at least 90 days [19]. It was also stated that HES infusion should be discontinued at any sign of coagulopathy. The European Medicines Agency's (EMA) branch Pharmacovigilance Risk Assessment Committee (PRAC) adopted similar restrictions, also in 2013 [20]. The EMA-PRAC statement varied from that of FDA in that EMA-PRAC excludes HES for treating burn victims and do not exclude use in open cardiac surgery. Notably the EMA-PRAC statement gives no references to why burn victims are excluded. If this is the last

word in the colloids debate remains to be seen though. During the last two decades several studies has assessed several different aspects and impacts of fluid resuscitation which will be given an in depth analysis in this article.

Aim

This study aims to systematically review recent international research concerning choice of resuscitation fluid in ICU and perioperative patients and compare this to local praxis in a large university clinic.

Research question

Which type of fluid is recommended internationally in ICU treatment and in perioperative care and how is the Sahlgrenska Anaesthesia and Intensive care clinic's concordance to this? Are crystalloids or colloids preferred, and what type within these groups?

Materials and Methods

Setting

Sahlgrenskas Department of Anesthesia and Intensive Care is the largest unit of its kind in Sweden [21]. This unit employs around 100 anesthesiologists who regularly have to consider fluid resuscitation regime in both an ICU environment and in the operating theatre. Sahlgrenska University Hospital employs about 16 000 people serving some 1950 beds [22].

Study design

This study consists of four parts; a systematic review and a meta-analysis combined with a cross-sectional survey and a retrospective view on resuscitation fluid consumption. To assure the quality of this review, the PRISMA checklist was used [23].

Data collection procedures

Systematic review

To capture the most recent research in the field only studies published 2001-2015 which investigated effectiveness of resuscitation fluids in ICU and perioperative care were considered for inclusion. Articles not written in English or not available in full text through Gothenburg University were excluded. Search for unpublished data was not made. Since cardiac surgery patients usually receive treatment at a separate ICU/operating clinic, articles focusing on cardiac surgery patients were excluded. MeSH terms used where; Double-blind, Fluid Therapy, Fluid Resuscitation, Crystalloid (Solutions), Colloid (Solutions), Isotonic Solutions, Albumin, Hydroxyethyl Starch, Plasmalyte, Ringer's acetate, Ringer's lactate, Sepsis, Critical Illness, Renal Replacement Therapy, Intensive Care Unit and Perioperative (Period). To identify eligible studies, the MEDLINE database and Google Scholar was used. Two reviewers (the authors) independently screened titles and abstracts of the identified studies to filter out those not meeting criteria for inclusion. Eligible studies were read through by the same two reviewers and evaluated using the Jadad scoring method [24]. Those deemed to have the highest scientific value were chosen for inclusion in this article.

Meta-analysis

When performing the meta-analysis, only studies comparing crystalloid vs. colloid treatment were included (See Table 2 and 3 and Figure 1 and 2).

Cross-sectional Survey

An anonymous web based survey was sent out to all anaesthesiologists (n=100) employed at the Department of Anesthesia and Intensive Care at Sahlgrenska University Hospital (SU). The survey consisted of 6 questions (appendix 1) and was sent out by e-mail linked to surveymonkey.com.

Retrospective data on fluid consumption and expense

Statistical information on fluid and blood product consumption and expense in the Department of Anaesthesiology and Intensive Care in SU as well as the whole hospital was collected from the physician responsible of pharmaceuticals in the anaesthesia department and from the Sahlgrenska Immunology & Transfusion medicine clinics research nurse.

Data-analysis

Systematic review

The included studies are summarized in table 2 and 3. Similarities in end points where identified and the results were sorted and analysed according to which substances that were assessed in the studies.

Meta-analysis

For dichotomous data, we calculated the odds ratios (OR) and risk ratios (RR) with 95% confidence intervals using the Mantel–Haenszel random effects model and weighted averages. The significant level of the overall effect was calculated regarding the OR of each outcome. Comprehensive Meta-analysis software version 3 (©2006-2015 Biostat Inc. Englewood, New Jersey, USA) was used for statistical analysis.

Cross-sectional survey

Results of the survey were compiled by Surveymonkey.com and the diagrams created from the data were made in Microsoft Excel®15.0 (©Microsoft corp. 2013). Since the survey was anonymous no individual responders could be identified. Thus no comparative statistical analysis was made.

Retrospective data on fluid consumption and expense

Data was compiled using Microsoft Excel®15.0 (©Microsoft corp. 2013) and spending on blood products were extrapolated using consumer price index and number of operations/patients treated. Statistics are only descriptive since it is not tied to any individuals.

Ethics

The responses to the questionnaire were reported anonymously. Other than that, no ethical considerations were made. Authorization from the ethics committee was deemed unnecessary.

Results

Review of literature

A total of 332 articles were found in the initial database search. After screening, 281 articles were excluded. 51 articles were assessed in their entirety and finally 20 articles were included in this study (Fig 1). 13 of these were included in the meta-analysis. See Figure 1 below.

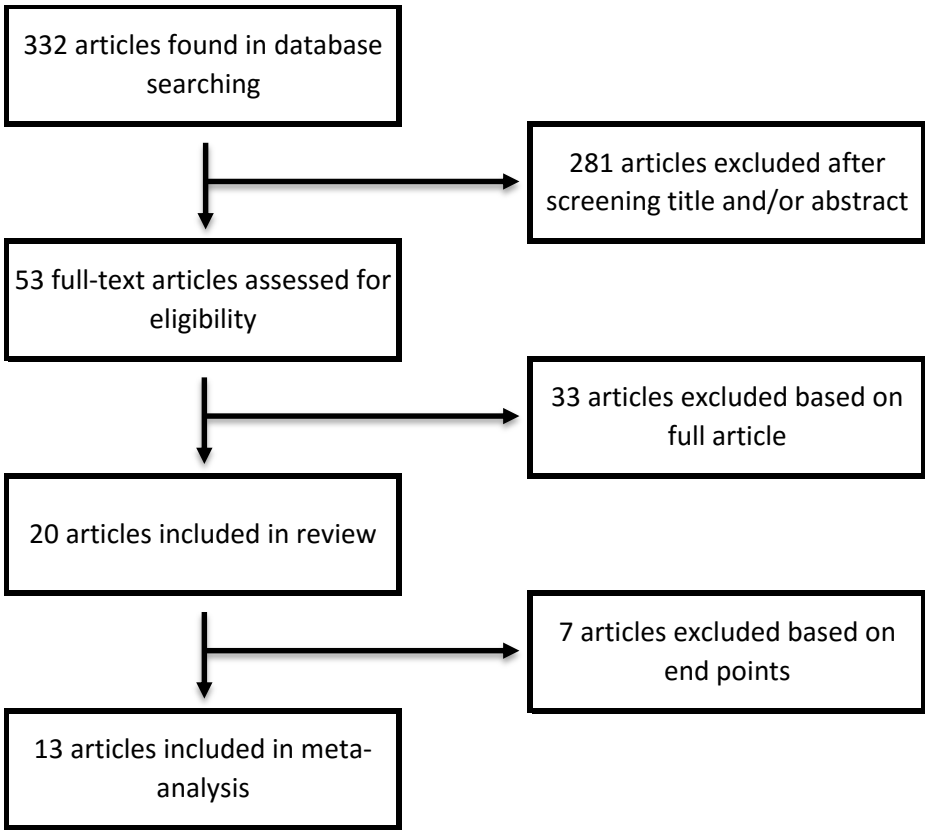


Figure 1 Flow chart of study inclusion process.

The 20 included articles were published between 2004 and 2015 and 15 of them were double blinded studies. The studies included 32015 patients (one article was a long term follow up and one was a subgroup analysis, these patients were not counted twice) and most of these were ICU patients. Table 2 below gives an overview of the included articles.

Article	Type of study	Jadad score	Setting	Fluids compared in study and number of participants	Primary end point	Secondary endpoints of note
Annane et al. 2013*	Randomized, prospective	3	Patients with acute hypovolemia in 57 ICUs (France, Belgium, Algeria, Tunisia and Canada)	Colloids n=1414 (Gelatines, HES, Albumin 4/20%, dextrans) vs Crystalloids n=1443 (iso- & hypertonic saline, lactated Ringer's)	Mortality at 28 days	Mortality at 90 days Renal replacement therapy
Béchir et al. 2013*	Double-blinded randomized prospective	5	Single centre study at a tertiary burn unit in Switzerland.	2:1 ratio Lactated Ringer & 6% HES 130/0.4 n=24 vs Lactated Ringer n=24	Fluid given during the first 72h	Mortality at 28 days Crea/urinary output Post hoc: 90d mort/rrt
Brunkhorst, Engel et al. 2008*	Randomized, prospective	3	Sepsis patients in 18 German ICUs	10% Hemohes 200/0.45-0.55 n=262 vs Sterofundin (lactated Ringer's) n=275	Mortality at 28 days SOFA score	ARF (Crea↑,RRT) Red cell transfusion Time to HDS
Caironi et al. 2014*	Randomized, prospective	3	Sepsis patients in 100 Italian ICUs	20% Albumin+crystalloids n=888 vs Crystalloids N=893	Mortality at 28 days	Mortality at 90 days post hoc septic shock survival
Feldheiser et al. 2013*	Double-blinded randomized prospective	5	Cystoreductive surgery patients in a single centre in Germany	6% HES 130/0.4 (Volulyte) n=24 vs balanced crystalloid (Jonosteril) n=24	Fluid given during surgery	Stroke volume Dose limit reached Plasma given
Finfer et al. 2004*	Double-blinded randomized prospective	5	Patients needing increased intravascular volume in 16 ICUs in Australia and New Zeeland	4% Albumex n=3473 vs Saline solutions n=3460	Mortality at 28 days	Fluid ratio Subgroup: brain injury Subgroup: sepsis
Finfer et al. 2011*	Double-blinded randomized prospective	5	Patients with severe sepsis in 16 ICUs in Australia and New Zeeland	4% Albumex n=603 vs Saline solutions n=615	Mortality at 28 days	Multivariate analysis adjusted for baseline characteristics
Guidet et al. 2012*	Double-blinded randomized prospective	4	Patients with severe sepsis in 24 ICUs in France and Germany	6% HES 130/0.4 (Voluven) n=100 vs Saline solution n=96	Fluid needed to HDS	Time to HDS RRT Mortality at 28/90 days
Hadimioglu et al. 2008	Double-blinded randomized prospective	4	Kidney transplant surgery patients in a single centre in Turkey	Lactated Ringer's n=30 vs Plasmalyte n=30 vs Saline solution n=30	pH BE S-Chloride	Lactate
James et al. 2011*	Double-blinded randomized prospective	5	Trauma patients in a single centre in South Africa	6% HES 130/0.4 penetrating trauma (P) n=36, blunt trauma (B) n=20 vs Saline solution P n=31, B n=22	Fluid during first 24h GI function at day 5	Risk of renal injury Transfusions pH

Abbrevations: ICU=Intensive care unit, HES=hydroxyethyl starch, Crea=Creatinine, SOFA=Sequential organ failure assessment, ARF=Acute renal failure, HDS= hemodynamic stabilization, RRT= renal replacement therapy, BE= base excess, NGAL=neutrophil gelatinase-associated lipocalin, MAP= Mean artherial pressure, DBP= diastolic blood pressure, RIFLE= risk-injury-failure-loss-end stage

Article	Type of study	Jadad score	Setting	Fluids compared in study and number of participants	Primary end point	Secondary endpoints of note
Kancir et al. 2014	Double-blinded randomized prospective	5	Hip arthroplasty patients in a single centre in Denmark	6% HES 130/0.4 (Voluven) n=19 vs Saline solution n=19	u-NGAL (ARF marker), postoperatively	MAP DPB p-NGAL
Kancir et al. 2015	Double-blinded randomized prospective	5	Prostatectomy patients in a single centre in Denmark	6% HES 130/0.4 (Voluven) n=18 vs Saline solution n=18	u-NGAL (ARF marker), postoperatively	Blood loss pAldo,pAlb,pAVP Fluid given
Matiland et al. 2011*	Randomized, prospective	3	Children <12 years with severe febrile illness in 6 non-ICU centres in Kenya, Tanzania and Uganda	5% Albumin bolus 20ml n=1050 ,40ml n=13 vs Saline bolus 20ml n=1047 40ml n=16 vs No bolus n=1044	Mortality at 48h	Mortality at 28 days Neurologic sequele
Mercier et al. 2014	Double-blinded randomized prospective	5	Elective caesarian patients receiving preload before spinal anesthesia in 12 French centres	500ml 6% HES 130/0.4 (Voluven) + 500ml Lactated Ringer's n=82 vs 1000ml Lactated Ringer's n=85	Incidence of maternal hypotension	Coagulopathy Renal function Catecholamines needed
Myburgh et al. 2012*	Double-blinded randomized prospective	5	Patients with hypovolemia in 32 ICUs in Australia and New Zeeland	6% HES 130/0.4 (Voluven) n=3358 vs Saline solution n=3384	Mortality at 90 days	Renal replacement therapy RIFLE-score Organ failure
Perner et al. 2012*	Double-blinded randomized prospective	5	Severe sepsis patients in 26 ICUs in Denmark, Norway, Finland and Iceland	6%HES 130/0.42 (Tetraspan) n=398 vs Ringer's acetate (Sterofundin) n=400	Mortality or dependancy on dialysis at 90 days	Red cell transfusion
Perner et al. 2014	Double-blinded randomized prospective	5	Severe sepsis patients in 26 ICUs in Denmark, Norway, Finland and Iceland	6%HES 130/0.42 (Tetraspan) n=398 vs Ringer's acetate (Sterofundin) n=400	Mortality at 6 months, Mortality at 12 months, Mortality at 13-36 months	(long time follow up of Perner 2012)
Raghunathan et al. 2014	Retrospective cohort	1	Sepsis patients in 360 american ICUs.	Balanced crystalloids (mainly Lactated Ringer's) n=3365 vs unbalanced (mainly Saline) n=3365	In hospital mortality after day 2	ARF
Yates et al. 2014*	Double-blinded randomized prospective	5	High risk colorectal surgery patients in a single centre in Great Britain	6% HES 130/0.4 (Volulyte) n=104 vs lactated Ringer's (Hartmann's solution) n=98	Gastrointestinal morbidity at day 5 after surgery	Post op complications
Yunos et al. 2012	Prospective sequential open label	0	Critically ill patients in an Australian ICU	A chloride liberal (CL) study period (mainly Saline) n=760 vs Chloride restrictive (CR) (mainly Hartmann's solution) n=773	Crea. Increas RIFLE-score	RRT (post hoc)

Abbrevations: ICU=Intensive care unit, HES=hydroxyethyl starch, Crea=Creatinine, SOFA=Sequential organ failure assessment, ARF=Acute renal failure, HDS= hemodynamic stabilization, RRT= renal replacement therapy, BE= base excess, NGAL=neutrophil gelatinase-associated lipocalin, MAP= Mean artherial pressure, DBP= diastolic blood pressure, RIFLE= risk-injury-failure-loss-end stage

Table 2 Characteristics of articles included in this study [16-18, 25-41]

* Included in meta-analysis

Article	Mortality	Renal effects	Volume given	Physiological parameters
Annane et al. 2013*	**Mortality at 28 days; RR of Colloids 0.96 (95%CI 0.88-1.04) p= 0.26 Mortality at 90 days; RR of Colloids 0.92 (95%CI 0.86-0.99) p= 0.03	RRT = RR of Colloids 0.93 (95%CI 0.83-1.03) p=0.19	No direct comparison made.	AUC for blood pressure, mean difference 17.9 (95%CI -1746 to +1782) p=0.85 Weight at 72h, mean difference -0.23 (95%CI -0.61 to +0.15) p=0.23
Béchir et al. 2013*	Mortality at 28 days; RR with HES 0.96 (95%CI 0.27-4.45) p=0.95 In hospital mortality; RR with HES 1.86 (95%CI 0.56-6.19) p=0.31	RRT = RR with HES 0.96 (95%CI 0.35-2.64) p=0.95	**Fluid given during the first 72h; HES vs Ringer's -1213 ml (95%CI -3975 to 1549) p=0.39	S-creatinine at 72h, mean difference 0.4µmol/L (95%CI -18.7 to 19.5) p=0.97 Urinary output at 72h, mean difference -58ml (95%CI -400 to 283) p=0.90
Brunkhorst, Engel et al. 2008*	**Mortality at 28 days; HES 26.7% vs RL 24% p=0.48 Mortality at 90 days; HES 41.0% vs RL 33.9% p= 0.09	ARF= HES 34.9% vs RL 22.8% p=0.002 RRT= HES 31.0% vs RL 18.8% p=0.001	HES vs RL ratio day one 1:1.58 HES vs RL ratio day one to four 1:1.44 HES vs RL ratio entire study 1:1.32	Median CVP; HES 11.8 vs RL 10.7 p<0.001 Median $cvSO_2$; HES 73.6% vs RL 72.4% p=0.04
Caironi et al. 2014*	**Mortality at 28 days; RR of Albumin 1.0 (95%CI 0.87-1.14) p=0.94 Mortality at 90 days; RR of Albumin 0.94 (95%CI 0.85-1.05) p= 0.29	AKI= Alb 21.9% vs Crystalloid 22.7% p=0.71 RRT= Alb 24.6% vs Crystaloid 21.4% p=0.11	Fluid given (all fluids) day one Alb 4300ml vs Crystalloid 4250ml p=0.67 Total fluid given (All fluids) Alb 31867ml vs Crystalloid 31970ml p=0.51	Median CVP day one; Alb 10.5 mmHg vs Crystalloid 10 mmHg, p=0.001
Feldheiser et al. 2013*	Inhospital mortality; HES 1, vs Crystalloid 0, p=1.0 (excluded patients included)	Mean p-Krea no significant difference, p=0.43 Mean p-NGAL no significant difference, p=0.76	**Fluid given during surgery; median/IQR HES 100 (56/100) vs Jonosteril 100 (100/100) p= 0.049	Mean Stroke volume significantly higher in the HES group, p=0.0127 Mean CVP/ABP no significant difference, p=0.24/0.61 respectively
Finfer et al. 2004*	**Mortality at 28 days; RR of Albumin 4% 0.99 (95%CI 0.91-1.09) p= 0.87	Duration of RRT; Alb 4% 0.48 (±2,28) days vs NaCl 0.39 (±2,0) days p=0.41	Alb 4% to NaCl ratio, approximately 1:1.4 Mean study fluid day one; Alb 4% 1184ml vs NaCl 1565ml p<0.001	Median CVP day one; Alb 4% 11.2 mmHg vs Crystalloid 10 mmHg, p<0.001 Median ABP day one; Alb 4% 81.4 mmHg vs Crystalloid 80.9 mmHg, p=0.14
Finfer et al. 2011*	Multivariate logistic regression analysis of severe Sepsis subgroup RR of Albumin 0.71 (95%CI 0.52-0.97) p= 0.03			
Guidet et al. 2012*	Mortality at 28 days; HES 31.0% vs NaCl 25.3% p=0.37 Mortality at 90 days; HES 40% vs NaCl 34% p= 0.33	ARF; HES 24.5% vs NaCl 20%, p=0.454 RIFLE and AKIN scores combarable in the two groups, p=0.81 and 0.59.	**Fluid needed to HDS; HES mean diff. -331 (95%CI -640 to -21) p= 0.0185	
Hadimioglu et al. 2008		24h diuresis, day one NaCl 11.4L vs RL 8.5L vs PL 7.9, NaCl significantly higher. Patients needing dialysis, no significant difference.	Mean fluid given; NaCl 2868ml (1000-3500) vs RL 2770ml (1750-4000) vs Plasmalyte 2756 (1750-3300). Intergroup difference not significant.	pH; Saline-decrease, p<0.05 BE; Saline-decrease, p<0.05 S-Chloride; Saline-increase p<0.05
James et al. 2011*	No significant intergroup difference.	In penetrating trauma; RIFLE R and I HES 3% & 0% vs NaCl 19% & 16% p= 0.043 and 0.018 respectively. Dialysis; no significant difference	**Mean study fluid during first 24h; P-HES 5093ml vs P-NaCl 7473ml p=0.0002. B-HES vs B-NaCl no significant difference.	**GI function at day 5; no significant difference Mean lactate at 24h; P-HES 2.1 vs P-NaCl 3.2 p=0.01. B-HES vs B-NaCl no sign. diff.

Abbrevations: ICU=Intensive care unit, HES=hydroxyethyl starch, Crea=Creatinine, SOFA=Sequential organ failure assessment, ARF=Acute renal failure, HDS= hemodynamic stabilization, RRT= renal replacement therapy, BE= base excess, NGAL=neutrophil gelatinase-associated lipocalin, MAP= Mean artherial pressure, DBP= diastolic blood pressure, RIFLE= risk-injury-failure-loss-end stage, RR=Relative risk, RL= Lactated Ringer´s, AKI=acute renal injury, CVP=central venous pressure, AKIN= acute kidney injury network, GI=gastrointestinal, OR= odds ratio, ICQ=interquartile

Article	Mortality	Renal effects	Volume given	Physiological parameters
Kancir et al. 2014		**Postoperative mean u-NGAL; HES 79.0 ng/ml vs NaCl 80.5 ng/ml p=0.92 Postoperative p-Krea; HES 80 µmol/L vs NaCl 75 µmol/L p=0.53	Mean volume of study fluid; HES 1475 ml vs NaCl 1500 ml p=0.93	Mean MAP during recovery; HES 91 mmHg vs NaCl 83 mmHg p=0.03
Kancir et al. 2015		**Postoperative mean u-NGAL; HES 11 ng/ml vs NaCl 13 ng/ml p=0.363 Postoperative p-Krea; HES 90 µmol/L vs NaCl 88 µmol/L p=0.476	Mean perioperative study fluid; HES 2500ml vs NaCl 2500ml p=0.274	Mean MAP during recovery; HES 88 mmHg vs NaCl 86 mmHg p=0.882
Matiland et al. 2011*	**Mortality at 48h; RR Albumin vs Saline 1.01 (95%CI 0.78-1.29) p=0.96, RR Any vs no bolus 1.45 (95%CI 1.13-1.86) p=0.003 At 28 days bolus vs no bolus RR 1.39		Mean total fluid received at 48h; Albumin bolus 72.6 ml/kg vs Saline bolus 73.9 ml/kg vs no bolus 48.9 ml/kg	
Mercier et al. 2014		Mean creatinine post op; HES 53.1 µmol/L vs RL 52.4 µmol/L p=0.82	After preload of study fluid, all patients received RL 250ml/h.	**Incidence of maternal hypotension; unadjusted OR in HES 0.47 (95%CI 0.25-0.87)
Myburgh et al. 2012*	Mortality at 28 days; RR of HES 1.05 (95%CI 0.93-1.19) p=0.40 **Mortality at 90 days; RR of HES 1.06 (95%CI 0.96-1.18) p=0.26	RIFLE R & I; RR of HES 0.94 & 0.91 respectively p=0.007 & 0.005 respectively RRT; RR of HES 1.21 (95%CI 1.00-1.45) p=0.04	Daily mean study fluid 4 first days; HES 526±425ml vs NaCl 616±488ml p<0.001 D. mean non-study fluid 4 first days; HES 851±675ml vs NaCl 1115±993ml p<0.001	Mean CVP first four days; HES 11.3±4.8 mmHg vs NaCl 10.4±4.4 mmHg p<0.001.
Perner et al. 2012*	Mortality at 28 days; RR of HES 1.08 (95%CI 0.90-1.28) p=0.43 **Mortality at 90 days; RR of HES 1.17 (95%CI 1.01-1.36) p=0.03	RRT; RR of HES 1.35 (95%CI 1.01-1.80) p=0.04 Doubling of p-creatinine level; RR of HES 1.18 (95%CI 0.98-1.43) p=0.08	Median cumultative study fluid received; HES 3000ml (IQR 1570-5100ml) vs RA 3000ml (IQR 2000-5750ml) p=0.20	Median CVP 0-12h; HES 11 mmHg (IQR 7-14) vs RA 10 mmHg (IQR 7-13) p=0.37 Median CVP 0-24h; HES 11 mmHg (IQR 6-14) vs RA 10 mmHg (IQR 6-13) p=0.16
Perner et al. 2014	**Mortality at 6 months, Mortality at 12 months and Mortality at 13-36 months; non-significant			
Raghunathan et al. 2014 (propensity matched)	**In hospital mortality after day 2; RR of balanced crystalloids 0.86 (95%CI 0.78-0.94) p=0.001	ARF without dialysis; RR of balanced crystalloids 0.95 (95%CI 0.78-1.15) p=ns ARF with dialysis; RR of balanced crystalloids 0.95 (95%CI 0.76-1.19) p=ns	Total crystalloids by day 2; balanced fluids 7000ml (IQR 5000-10500) vs no balanced fluids 7000ml (IQR 5000-10000)	
Yates et al. 2014*		Postoperative renal complications; HES n.4 vs Crystalloid n.0 p=?	Total study fluid first 24h; HES 1875ml (ICQ 1500-3000) vs 3175ml *(ICQ 2000-3700) p<0.001	**Gastrointestinal morbidity at day 5 after surgery: OR of HES 0.96 (95%CI 0.52-1.77)
Yunos et al. 2012		Crea. increase; CR 14.8 vs CL 22.6 µmol/L p= 0.03 RIFLE-score; I&F CR 8.4% vs CL 14% p<0.001	Cl^- liberal vs Cl^- restrictive period (L/patient); Saline 3.2 vs 0.6, Gelatin 4% 0.7 vs 0, Hartmann's 0.6 vs 4.1 p<0.001, Plasmalyte 0.08 vs 0.2 p=0.04	

Abbrevations: ICU=Intensive care unit, HES=hydroxyethyl starch, Crea=Creatinine, SOFA=Sequential organ failure assessment, ARF=Acute renal failure, HDS= hemodynamic stabilization, RRT= renal replacement therapy, BE= base excess, NGAL=neutrophil gelatinase-associated lipocalin, MAP= Mean artherial pressure, DBP= diastolic blood pressure, RIFLE= risk-injury-failure-loss-end stage, RR=Relative risk, RL= Lactated Ringer´s, AKI=acute renal injury, CVP=central venous pressure, AKIN= acute kidney injury network, GI=gastrointestinal, OR= odds ratio, ICQ=interquartile ns=non significant

Table 3 Results of articles included.

* Included in meta-analysis

** Primary endpoint

Albumin

Four [25, 27, 29, 35] articles included in this study investigates albumin vs control. Three of the studies are made in ICUs in industrialized countries. Maitland et al conducted their research in 6 clinical centres in Africa that lacked ICU capability [29]. No articles describing albumin use in a perioperative environment were found.

One of the articles is a subgroup analysis of the same population [27]. None the less, a total of 5411 Patients received albumin in these studies vs a total control population of 6460. Finfer et al.'s study from 2004 (SAFE) carries most of the weight at 6933 of 11871 patients.

The study by Maitland et al. was the only using mortality at 48h as an endpoint, which was very similar when comparing albumin to saline (Relative risk, RR=1.0, p=0.96). The main finding in this study was comparison of any bolus (albumin or saline) vs no bolus. Which showed an increased relative risk of death at 48h of 1.45 (95%CI 1.13-1.86 p=0.003) for the bolus groups [29]. None of the studies found a significant difference in mortality at 28 days in their original analysis. However, the predefined subgroups in the SAFE study found that brain injury patients who received albumin had an increased relative risk of mortality of 1.62 (95%CI 1.12-2.34 p=.009. Trauma patients in the same study showed a trend towards lower survival in the albumin group (p=0.06) whilst sepsis patients showed a trend towards better survival when receiving albumin (p=0.09). The later multivariate analysis of the sepsis subgroup in the SAFE study, adjusting for baseline differences, found that the albumin group had a favourable mortality odds ratio of 0.71 (95%CI 0.52-0.97 p=0.03). The study by Caironi et al. added an analysis of 90 day mortality but found no significant difference between albumin and control. A post hoc subgroup analysis by Caironi et al., singling out patients in septic shock, showed a lowered relative risk of mortality associated with albumin treatment of 0.87 (95%CI 0.77-0.99) [25, 27, 29, 35].

The ratio of fluid administered to patients during the first four days in the SAFE study was approximately 1:1.4 albumin-saline. There was no difference in total fluid administered in the study by Caironi et al. However, during the first seven days the albumin group had a significantly higher mean ABP and a lower cumulative fluid balance [25, 35].

Hydroxyethyl Starch

Twelve articles [16-18, 28, 30, 33, 34, 36-38, 40, 41] in this review examined the effect of HES vs control. Five of these were performed in a perioperative environment. Of the seven studies performed in ICU environment, one is a long term follow up [38]. A total of 8430 patients were included in the ICU studies, Myburgh et al.'s study included 6742 of these, about 80% of the total ICU patients in HES vs control studies.

None of the ICU studies found showed a significant difference in mortality at 28 days. At 90 days, only Perner et al. discovered an inconsistency with an increased relative risk in the HES group of 1.17 (95%CI 1.01-1.36, p=0.03) [18]. Brunkhorst et al. found a non-significant trend towards higher mortality in the HES group (p=0.09) [16]. In the long term follow up by Perner et al., the difference in mortality was no longer significant at 6 or 12 months or at the time point of the longest follow up (13-36 months, median 22 months).

The presence of acute renal failure was also investigated by all the ICU studies. Brunkhorst et al. found that the HES group had a significantly higher rate of acute renal failure (34.9% vs 22.8%, p=0.002) in their study while Bechir et al. and Guidet et al. found no difference between the groups [16, 30, 33]. In the study by article by James et al. patients with penetrating trauma that received HES had significantly better renal outcome, i.e. lower number of patients in RIFLE (R=risk, I=injury, F=failure, L=loss, E=end stage) category R and I (p=0.043 and 0.018 respectively) [28]. A similar find was made by Myburgh et al.

where the saline group had a higher number of RIFLE R and I (p=0.007) [17]. In Perner et al.'s study on the other hand, a trend towards a higher number of RIFLE-I in the HES group was seen (p=0.08) [18].

Three studies identified a significant difference in need of renal replacement therapy (RRT). In Brunkhorst et al.'s study, The HES group received RRT during 18.3% of the total stay in the ICU and the corresponding value in the lactated Ringer's group was 9.2% (p=0.001) [16]. Myburgh et al. showed an increased relative risk for RRT in the HES group of their study of 1.21 (95%CI 1.00-1.45 p=0.04), or 7% of the patients in the HES group vs 5.8% in the saline group [17]. Finally Perner et al. also found an increase in need of RRT in their HES group, 22% of the patients, vs 16% in the Ringer's acetate group, relative risk 1.35 (95%CI 1.01-1.80 p=0.04) [18].

When comparing total volume of fluid administered Bechir et al. and Perner et al. found no significant difference between HES and control [18, 33]. Guidet et al. did not find a difference in total fluid volume either but in their HES group, volume of fluid needed to achieve hemodynamic stabilization (HDS), was -331ml (95%CI -640 - -21, p=0.0185) compared to control [30]. However, there was no significant difference in time to reach HDS between groups. Brunkhorst et al. found that HES normalized CVP faster (p=0.003) but there was no significant difference in MAP and ScvO2 changes between groups [16]. Myburgh et al. also registered a significantly faster CVP increase that remained higher day 0-2. Three studies found a difference in study fluid ratio, where Brunkhorst et al. and James et al. (penetrating trauma only) found that HES vs crystalloid was given at a 1:1.58 and 1:1.47 ratio the first 24h respectively [16, 28]. Study fluid ratio in the whole study of Brunkhorst et al. was 1:1.32 favouring HES [16]. During the first four days of Myburgh et al.'s study, the ratio was 1:1.17, favouring HES. Four studies found that HES patients received significantly more blood products [16-18, 28].

In the five perioperative studies (491 patients) comparing HES and crystalloid, none found a significant difference in renal adverse effects [34, 36, 37, 40, 41]. Four studies reported creatinine values, of which

three studies also used NGAL (Neutrophil gelatinase-associated lipocalin) and urinary output measurements to define renal injury [34, 36, 37, 41]. Feldheiser et al. had the longest follow up, 5 months after surgery, while the studies of Kancir et al. reported follow ups at 10-12 days and 15 days [34, 36, 41]. Yates et al. found no significant difference in overall postoperative complications, but when analysing presence of renal failure, the HES group had 4 cases (of 104 patients) while the crystalloid group (Hartmann's solution) had none [40].

Regarding hemodynamic changes and its relation to total amount of fluid administered, Feldheiser et al. found that the trial fluid dose limit of the study protocol was reached faster ($p=0.006$) and more frequently (91.7% vs 62.5% $p=0.036$) and by using a larger total volume ($p=0.0164$) in the crystalloid group [34]. Yates et al. also found that less trial fluid volume was used in the HES group ($p<0.001$) at a ratio of 1:1.69 during the first 24h [40]. Despite this, Yates et al. found no difference in postoperative gastrointestinal morbidity [40]. Feldheiser et al. identified a higher stroke volume (95 vs 70 ml, $p= 0.008$) and CO (6.7 vs 4.7, $p=0.002$) in the HES group [34]. Likewise, Kancir et al's study from 2014 found a higher postoperative MAP and diastolic blood pressure (DBP) (91vs83 and 72vs63 $p<0.03$) in the HES group. However, in their study from 2015 there was no significant difference in hemodynamic parameters between groups [36, 41]. Mercier et al. presented a lower risk of maternal hypotension during caesarean delivery when adding HES to the fluid preload treatment (odds ratio of 0.47 (95%CI 0.25-0.87)) [37].

Crystalloids

Two studies comparing crystalloids where included in this review [26, 39]. Hadimioglu et al. investigated perioperative use of crystalloids. Their study revealed that patients receiving saline solution had both lower pH ($p<0.05$) and higher s-chloride ($p<0.05$) after surgery, compared to those receiving lactated

Ringer's solution. In addition, patients receiving lactated Ringer's solution had (not surprisingly) a higher s-lactate ($p<0.05$) after surgery while those receiving Plasmalyte had no significant acid-base changes [26]. Consequently, in the retrospective study by Raghunathan et al. in ICU patients with sepsis receiving a balanced crystalloid (97.7% received lactated Ringer's) had a lower 48h mortality, with a relative risk of 0.86 (95%CI 0.78-0.94 p=0.001) when compared to saline solution. They also performed a dose-response analysis and found that mortality was lowered by 3.4% for every 10% increase in proportion of balanced crystalloid. No significant difference in acute renal failure was seen [39].

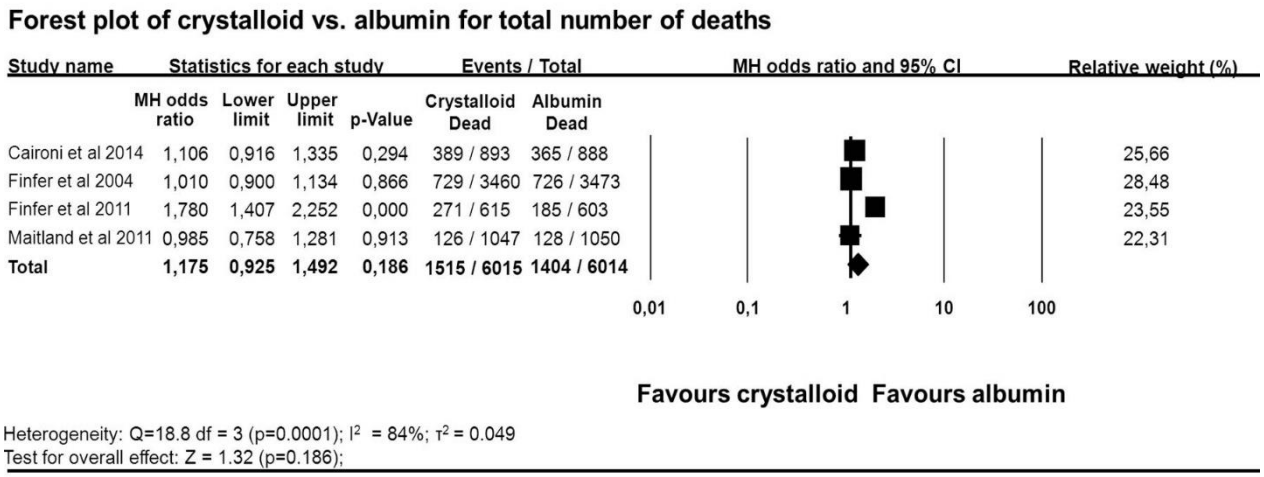
General articles

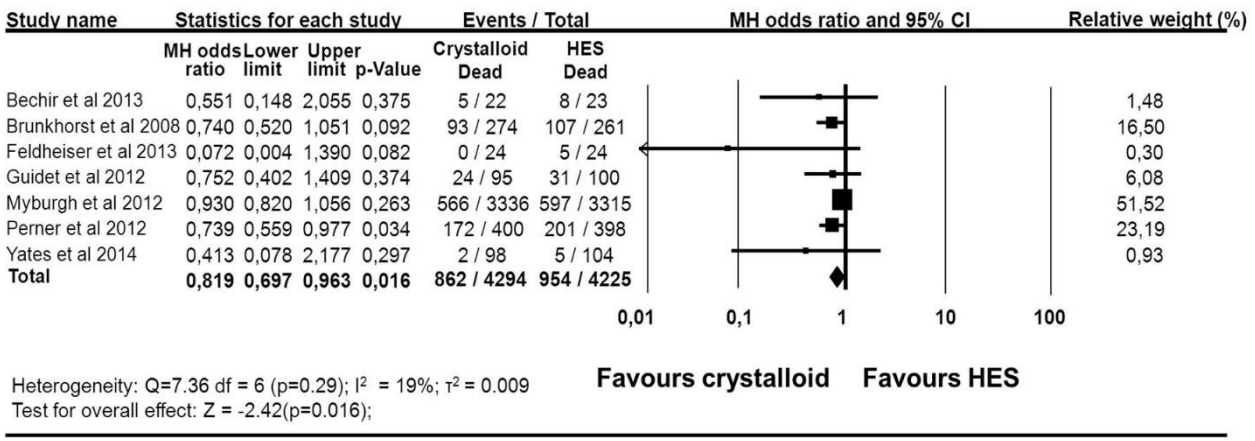
Annane et al. compared all forms of colloid with all forms of crystalloid treatment in ICU patients. In their study no significant difference in mortality was seen at 28 days but at 90 days the colloid group had a beneficial relative risk of mortality at 0.92 (95%CI 0.86-0.99 p=0.03). Subgroup analysis showed that HES gave a survival benefit vs saline solution (RR 0.79 95%CI 0.66-0.95) but not against lactated Ringer's solution. No other colloid showed a significant benefit in this subgroup analysis. When comparing only patients with sepsis, none of the studied fluids produced a significantly lower mortality. Need for renal replacement therapy was similar in the colloid and crystalloid groups [32].

Yunos et al. compared a chloride restrictive (mainly Hartmann´s solution) therapy period vs a chloride liberal (mainly saline solution) period in critically ill patients. No significant difference in mortality was identified when comparing the two periods. There were less patients with more benign RIFLE-scores I & F in the restrictive period, 8.4% vs 14% ($p<0.001$). Less patients receiving the chloride restrictive therapy also required renal replacement therapy, 6.3% vs 10.0% (p=0.005) [31].

Meta-analysis

Thirteen studies comparing crystalloid with colloid treatment were selected for meta-analysis. Only studies that presented the number of deaths and need of renal replacement therapy as endpoints in both groups were included. (Figure 1) The main characteristics of included studies are summarized in Table 2. One study by Annane et al compared all forms of crystalloid treatment to treatment with all forms of colloid solutions, seven studies compared saline to HES, one study by Perner et al. compared Ringers acetate to HES and four studies compared saline to albumin. Study settings and definitions of clinical outcome were found to differ considerably between the studies. Seven studies included only ICU patients, one study included only burn victims, one study included only children with malaria sepsis in a non-ICU setting and one study was performed on perioperative patients. Twelve studies compared total number of deaths and seven studies compared need of renal replacement therapy in both the crystalloid and colloid group. A number of 13 studies were randomized and 9 were blinded. Nine studies scored higher than 3 in the Jadad scale. In sepsis patients use of 4% albumin for resuscitation may decrease mortality compared to saline solution as found by Finfer et al 2011, but when including large randomized studies using 20% albumin in combination with crystalloid as the study by Caironi et al 2014 et al, or studies assessing other critically ill patient groups as Finfer et al 2004 and Matiland et al 2011, this decrease in mortality cannot be confirmed. Albumin 4 % or albumin 20% in combination with crystalloids could be considered safe for critically ill and patients with severe sepsis. (Figure 2) HES may increase mortality and risk of renal replacement therapy in critically ill patients, compared to saline and to Ringer's acetate solution [17, 18, 25, 27, 29, 32, 35].





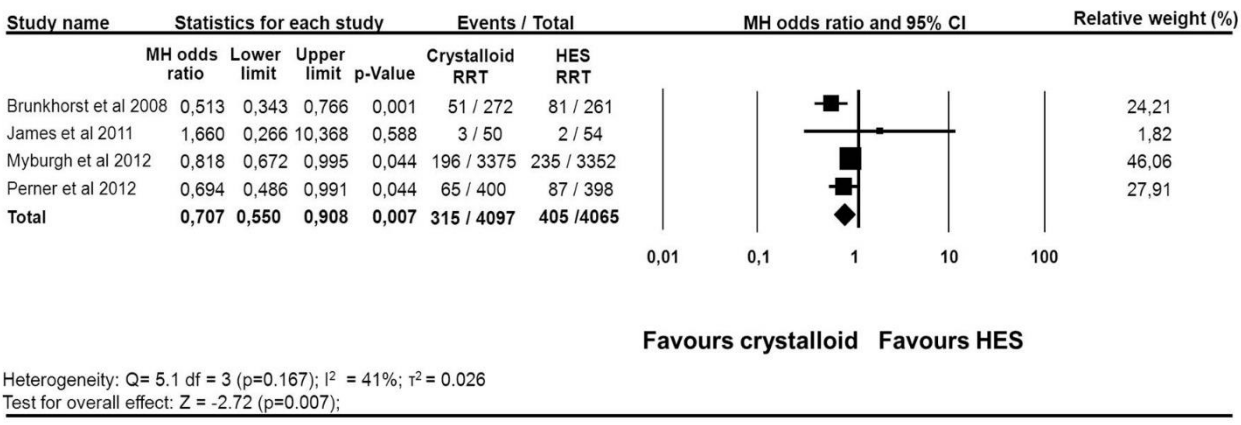


Figure 2 Meta-analysis of studies comparing crystalloid to colloid treatment presenting results from endpoints number of deaths and need for renal replacement therapy (RRT)

Cross-sectional Survey

Of 100 recipients 62 fully answered the survey, giving a 62% answering rate. Out of 62 respondents in our survey 56% and 69% answered that they used both crystalloid and colloid solutions for perioperative and sepsis resuscitation respectively, and 74% that their first hand choice of colloid perioperatively was HES. However, when treating septic shock, 89% answered that their preferred colloid was albumin (See Figure 3).

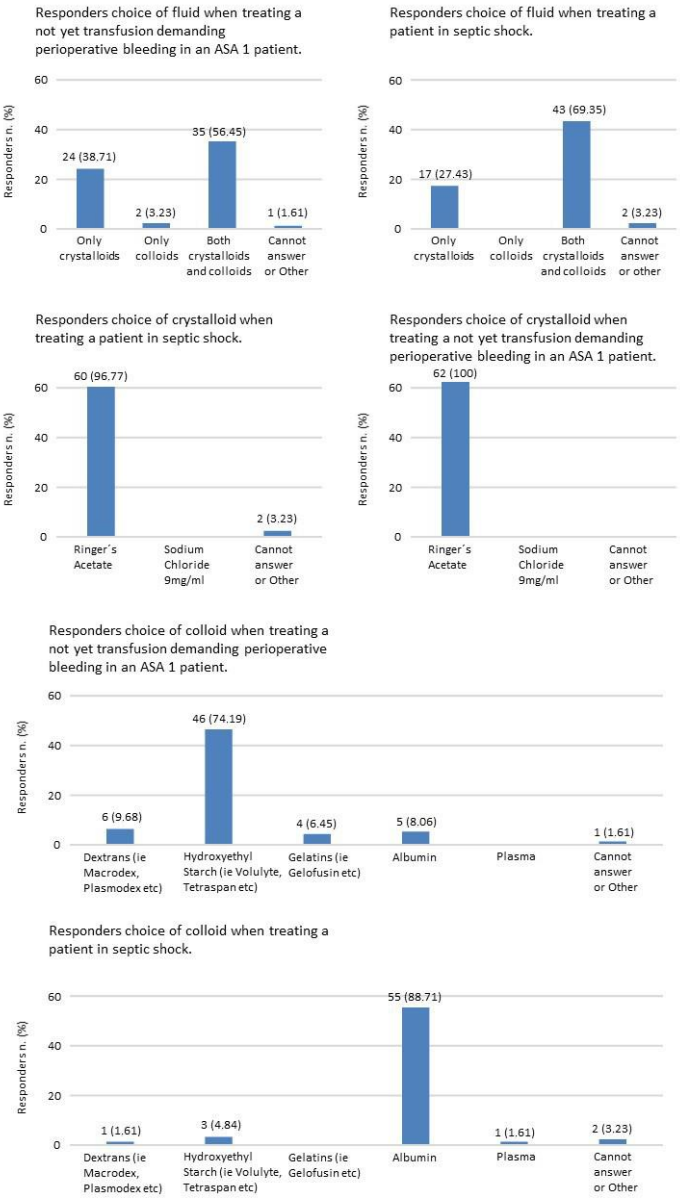


Figure 3 Survey answers and comparative distribution.

Retrospective data on fluid consumption and expense

Consumption and cost of blood products from 1998-99 and 2013-14 are presented as well as consumption of resuscitation fluid units and their cost from 2013-14. Swedish consumer's price index for the years 1998, 1999, 2013 and 2014 are 257, 258.1, 314 and 313.5 respectively [42]. The number of ICU patients at Sahlgrenska University Hospital 2013 and 2014 were 5641 and 5705 respectively [43]. The total number of surgical operations (Excluding Queen Silvia's Children's Hospital) for the years 1999, 2013 and 2014 were 46 356, 45 171 and 45 401 respectively. The price per rbc unit was roughly 800 SEK 1998-99 and roughly 1000 SEK 2013-14 while the price per plasma unit was roughly 350 SEK 1998-99 and roughly 500 SEK 2013-14 (adjusted to price level of 2014). The differences are likely due to revaluations after the introduction of leukoreduction. During this time period the consumption of erythrocyte concentrate In Sahlgrenska University Hospital increased by approximately 31 % and the indexed cost increased markedly by approximately 62 %. However, the consumption of plasma units decreased by 23 % resulting in a slight increase in cost by 9 % (Figure 4). From the year 2013 to 2014 the spending on starch colloid dropped by almost 90 % in the ICU department and by 65 % in the Anesthesia department. Correspondingly, the spending on Ringers acetate increased by 19 % and the albumin cost increased by 37 % in the ICU department. Spending on Ringers acetate in the Anesthesia department remained the same while spending on albumin increased by 112%.

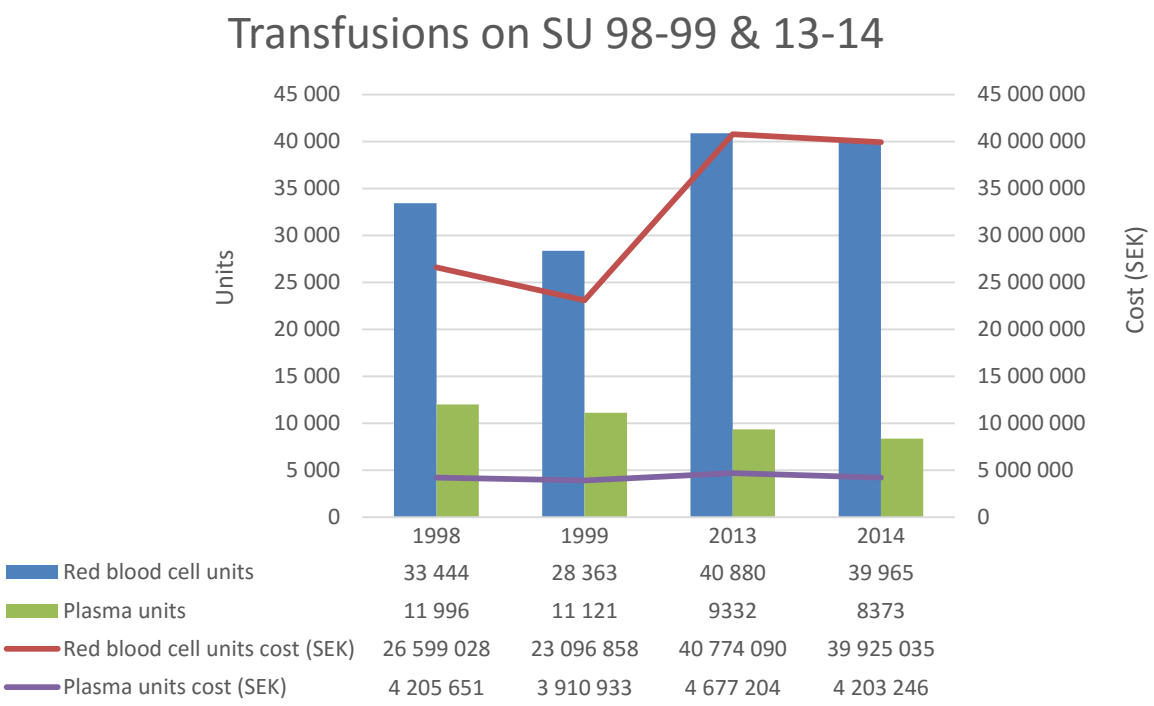


Figure 4 Units used and cost (index corrected to the price level of 2014) for red blood cell transfusions and all types of plasma on Sahlgrenska University Hospital 1998-99 and 2013-14

ICU Units	Cost				Units			
Crystalloids	**2013**	**2014**	**Change**	**Change %**	**2013**	**2014**	**Change**	**Change %**
Ringer´s acetate	39 976	47 722	7746	19.4	4580	5850	1270	27.7
Rehydrex	45 448	33 489	-11 959	-26.3	4820	3450	-1370	-28.4
Colloids	**2013**	**2014**	**Change**	**Change %**	**2013**	**2014**	**Change**	**Change %**
Albumin	2 731 348	3 744 037	1 012 689	37.1	8903	10 174	1271	14.3
Macrodex	6050	1150	-4900	-81	60	12	-48	-80
Rheomacrodex								
Rescueflow	20 832	14 880	-5952	-28.6	42	30	-12	-28.6
Gelofusine	19 040	0	-19 040	-100	340	0	-340	-100
Tetraspan	7700	0	-7700	-100	100	0	-100	-100
Venofundin	54 208	0	-54 208	-100	704	0	-704	-100
Volulyte		7080	7080	x		120	120	x

Operating theaters	Cost				Units			
Crystalloids	**2013**	**2014**	**Change**	**Change %**	**2013**	**2014**	**Change**	**Change %**
Ringer´s acetate	161 569	162 852	1283	0.8	18 266	19 170	904	4.9
Rehydrex	11 432	9154	-2278	-19.9	1410	1060	-350	-24.8
Colloids	**2013**	**2014**	**Change**	**Change %**	**2013**	**2014**	**Change**	**Change %**
Albumin	374494	792982	418488	111.7	1239	2159	920	74.2
Macrodex	68 860	75 958	7098	10.3	684	780	96	14.0
Rheomacrodex	51 300	60 990	9690	18.9	324	312	-12	-3.7
Rescueflow								
Gelofusine	3360	1120	-2240	-66.7	60	20	-40	-66.7
Tetraspan	197 120	26 400	-170 720	-86.6	2560	300	-2260	-88.3
Venofundin	100 100	1540	-98 560	-98.5	1300	20	-1280	-98.5
Volulyte		75 520	75 520	x		1280	1280	x

All of SU Hospital	Cost				Units			
Crystalloids	**2013**	**2014**	**Change**	**Change %**	**2013**	**2014**	**Change**	**Change %**
Ringer´s acetate	2 065 923	2 328 612	262 689	12.7	234 927	272 481	37 554	16.0
Rehydrex	343 985	390 183	46 198	13.4	35 494	32 470	-3 024	-8.5
Colloids	**2013**	**2014**	**Change**	**Change %**	**2013**	**2014**	**Change**	**Change %**
Albumin	8 361 395	10 185 670	1 824 275	21.8	27 210	30 084	2 874	10.6
Macrodex	297 688	326 286	28 598	9.6	2921	3348	427	14.6
Rheomacrodex	62 560	86 347	23 787	38.0	396	444	48	12.1
Rescueflow	32 736	14 880	-17 856	-54.5	66	30	-36	-54.5
Gelofusine	268 800	159 864	-108 936	-40.5	4800	2679	-2 121	-44.2
Tetraspan	361 900	26 400	-335 500	-92.7	4700	300	-4 400	-93.6
Venofundin	805 651	92 517	-713 134	-88.5	5980	1105	-4 875	-81.5
Volulyte	19 844	113 280	93 436	470.9	200	1920	1 720	860.0

Table 3 Resuscitation fluids used at Sahlgrenska University Hospital 2013-14

Discussion

In this review 20 studies were included, data of resuscitation fluid consumption was collected and the anesthesiologists of the department of Anesthesia and Intensive Care at Sahlgrenska University Hospital responded to a survey. A summary of the evidence found in the systematic review was performed and is presented below as well as a comparison with clinical practices based on the cross-sectional and retrospective data.

At the emergency room (or when symptoms present)

Several of the studies investigating critically ill patients randomized their patients up to 24 hours after symptoms had presented [16, 18, 35]. Furthermore, a majority of the studies randomized their patients at admission to the ICU, thus allowing for treatment based on the clinician's judgement before this. Perner et al. reported that 42% and Brunkhorst et al. 58% of the patients in their crystalloid groups received synthetic colloids before randomization [16, 18]. This has been debated before [44-46] and considering the figures above the mortality and ARF/RRT data of these studies cannot rule out HES as a resuscitation fluid in the initial phase.

Considering textbook examples of resuscitation fluid ratio needed, such as a colloid-crystalloid ratio of 1:3, the colloids are put to shame in the studies included in this review where the ratio varied from no difference to 1:1.6. This means that the blinded volume of colloids that was given in relation to crystalloids in the included studies was about twice the volume recommended based on classic fluid distribution theories. Despite this there are some indications of a more effective fluid resuscitation with HES vs crystalloid as both Brunkhorst et al. and Myburgh et al. found it more effective at increasing CVP [16, 17]. The small reduction in total fluid administered when using colloids may seem immaterial but

there are publications pointing out positive fluid balance as a strong prognostic factor of mortality [47, 48].

Maitland et al. also raises the question about the risks involved with a fluid bolus challenge. Without access to an ICU and vasopressor treatment, a fluid bolus carries with it the risk of cardiovascular collapse due to dampened sympathetic stimulation. At least this seems true in children, but if the results can be extrapolated to adults remains to be seen.

In the light of the latest research a balanced crystalloid is a solid first line choice when encountering patients in the early stages of circulatory failure. Modern studies comparing Ringer's acetate vs control are lacking but it is in many ways similar to Plasmalyte. Hydroxyethyl starch may be a feasible second line choice.

In the ICU

Neither Myburgh et al. nor Finfer et al. found any benefit in choosing a colloid for general fluid resuscitation in their huge double blinded trials. The results of Annane et al., which favored colloids, have comparative weaknesses in that it was an open-label (non-blinded) study and recruited trough 9 years. The present evidence favors crystalloids as the choice of resuscitation fluid in critically ill patients. Although randomized trials are needed to confirm the results, the study by Yunos et al. strengthen the view that balanced solutions surpass normal saline.

All things considered, a balanced crystalloid remains the first choice resuscitation fluid in the ICU. Lack of evidence for using either HES or Albumin and in the case of HES, risk of acute renal failure, makes the colloids an inferior choice to be considered in specific patient groups.

Patients with severe sepsis

The studies by Perner et al. and Brunkhorst et al. advocate balanced crystalloids over HES in severe sepsis. While Perner et al. compares a balanced HES vs a balanced crystalloid, Brunkhorst et al. makes an unblinded comparison of an outdated 10% 200/0.45-0.55 HES solution to lactated Ringer's. This leaves the study by Perner et al. as the main speaker against HES in severe sepsis, still of course backed by Myburgh et al mentioned above. The results of Guidet et al. were somewhat positive to HES. Their only favorable find was a not very impressive but significant ratio of fluid needed of 1:1.24 favoring HES [30]. Additionally, the study by Guidet et al. has been accused of reporting bias as they overestimated the treatment efficiency and underestimated the safety risks according to Hartog and Reinhart [49]. In the choice of what crystalloid to give to sepsis patients, the study by Raghunathan et al. concludes that lactated Ringer's solution is superior to saline solution [39].

Considering this, severe sepsis patients seem to be a patient group where albumin has a role in treatment. Both Finfer et al. and Caironi et al. found indications that albumin is superior to crystalloids in fluid resuscitation of severe sepsis patients, although both are cautious in the interpretation of their results [27, 35]. Adding to the doubt, Caironi et al. had several protocol violations only mentioned in the supplementary appendix. Roughly 23% of the patients in both groups received a synthetic colloid at least once. Furthermore, since Finfer et al. compared albumin to saline, how well does it stand against a balanced crystalloid?

In conclusion, when choosing resuscitation fluid in severe sepsis, both albumin and balanced crystalloids seems to be valid alternatives but they need to be compared in future studies.

Non-sepsis ICU patients

In burn victims, the Study of Bechir et al. found similar outcomes using a combination of HES and lactated Ringer's compared to lactated Ringer's only. Although not a revolutionary find, it raises the question why EMA-PRAC advises against HES in burn victims.

James et al. found HES superior in patients with penetrating trauma and explains the lack of such findings in blunt trauma with large difference in damage severity in those groups.

Again, a balanced crystalloid is an adequate first choice but HES might very well still have a future in trauma fluid resuscitation. Albumin on the other hand should be considered contraindicated in trauma with suspected brain injury according to the predefined subgroup analysis in Finfer et al.'s study [25].

In the surgical theatre

Although there were fewer patients in the included studies examining perioperative fluid resuscitation HES solutions seems promising in both fluid resuscitation and as spinal anesthesia preload. There is not much evidence that should raise concern for increased risk of renal injury, though studies with long term follow up are necessary. Hadimioglu et al. found that Plasmalyte may have benefits over lactated Ringer's but of its superior to Ringer's acetate remain to be seen in future randomized trials.

Considering current knowledge, a combination of balanced crystalloids and HES can be regarded as a valid choice in perioperative fluid resuscitation.

Adaption to current research in the Department of Anesthesiology and Intensive Care

In the surgical theatre

Regarding fluid resuscitation in the surgical theatre, the responders´ answers were mainly consistent with the findings in our reviewed articles. All responders used balanced crystalloids as opposed to saline solution which hardly comes as a surprise in Sweden, but is unusual from an international point of view. Choice of colloid had wider diversity. HES solutions were the most common choice followed by Dextrans, Albumin and Gelatins (46, 6, 5 and 4 answers of 62 respectively). Since Macrodex is a Swedish invention a stronger tradition in our department is to be expected but it is sparsely used internationally. Comparing the answers with fluid consumption 2014, reported gelatin use can be considered negligible. However, reported albumin use stands out as 8% of the responders answered that they prefer albumin as their first choice in perioperative fluid resuscitation. Currently Finfer et al.´s SAFE study backed by Caironi et al.´s ALBIOS study are the only evidence for albumin use and do not cover perioperative use. Spending on Albumin in perioperative use increased by 111.7% between 2013 and 2014 alone, with a total cost more than 10 times that of Volulyte (Table 3).

Patients with severe sepsis

The second part of the survey covered treatment of septic shock. Again the responders were on par with contemporary research. Excluding the resident anesthesiologists who had yet to have their ICU training, all responders chose Ringer's acetate and/or albumin as resuscitation fluids in septic shock. It seems as pharmaceutical companies are well aware of the change in practice as the ICU unit price of albumin went from 309.6 SEK to 364.9 SEK between 2013 and 2014 and that of Volulyte from 99.2 SEK to 59 SEK. In 2014 the Sahlgrenska University Hospital ICUs spent roughly three point seven million SEK on albumin, 97.5% of the total resuscitation fluid spending of 2014 (of the fluids presented in this material).

Considering that the main evidence for albumin use in sepsis (the SAFE study by Finfer et al.) compares with 0.9% Sodium Chloride, studies comparing albumin to balanced crystalloids are sorely needed. Further, cost-effectiveness analyses are necessary.

Retrospective data on blood-product consumption and expense

Regarding transfusions in Sahlgrenska University Hospital (SU), red blood cell transfusions have increased about 30% during the last 15 years, although the number of surgical procedures is roughly the same. There are many possible explanations for this, especially since the numbers reflect the whole of Sahlgrenska University Hospital. During this time period a large reorganization of the public health service has led to an increased concentration of high-risk surgery to the SU. Further studies would be necessary to establish any connection to HES which was associated with increased transfusion need in several of the articles reviewed [16-18, 28]. In the same time period plasma transfusions went down by roughly 23%, which probably is a result of a conscious introduction of a more restrictive policy regarding plasma transfusions in the perioperative and intensive care units in SU.

Conclusions and Implications

Balanced crystalloids have an important role in fluid resuscitation but further research comparing balanced crystalloids is needed. Albumin is the preferred colloid in severe sepsis but declaring it contraindicated as resuscitation fluid in brain injury ought to be considered. In other scenarios than sepsis HES may be considered.

The anesthesiologists at the Department of Anesthesiology and Intensive Care had a good adherence to current research although perioperative albumin use ought to be reconsidered due to high cost and lack of evidence.

Populärvetenskaplig sammanfattning (svenska)

Vätsketerapi – en litteraturöversikt och enkätundersökning

Sedan 1800-talets kolera epidemi i England har vätskeersättningsdropp med koksaltlösning varit en del av vården som erbjuds svårt sjuka med lågt blodtryck. Idag används många sorters vätskor för detta. Några vanliga exempel förutom koksaltlösning är balanserad saltlösning (med en mer naturlig saltbalans än koksaltlösning), donerat mänskligt albumin samt stärkelselösningar (HES).

1998 släpptes en omfattande forskningsrapport som visade att albumin som behandling mot lågt blodtryck ledde till ökad dödlighet. Därefter slutade man nästan helt att använda albumin i detta syfte. HES blev istället populärt vid behandling av lågt blodtryck. På senare år har pendeln svängt tillbaka igen efter forskningsrapporter som förespråkar albumin och andra som belyser riskerna med HES.

Med denna artikel har vi gjort en litteraturöversikt av det nuvarande forskningsläget angående vätskedropp till svårt sjuka samt även gjort en enkätanalys och granskat statistiska data för att ta reda på hur detta efterföljs på AnOpIVA-kliniken på Sahlgrenska Universitetssjukhuset.

I vår litteraturöversikt har vi tittat på stora studier gjorda under de senaste 15 åren. De visar att Albumin bör användas vid behandling av svår blodförgiftning (sepsis) men att det bör undvikas hos patienter med misstänkt hjärnskada. HES däremot bör undvikas vid sepsisbehandling då det i detta sammanhang kan orsaka njurskada och ökat behovet av dialys. Möjligen kan det även leda till ökad dödlighet. I övriga sammanhang där lågt blodtryck behöver behandlas med vätska rekommenderas dock balanserade

saltlösningar. HES kan vara ett bra komplement till behandlingen av lågt blodtryck pga. blödning men fler studier behövs för att säkerställa detta.

Vår enkät där 62% svarade visar att en klar majoritet av läkarna på AnOpIVA-kliniken verkar hålla med om vår tolkning av den senaste forskningen. Dock ser vi både i enkäten och i vårt statistikunderlag att allt mer albumin används under operationer vilket det inte finns något stöd för i forskningen. Under operationer bör HES kunna ta en större roll vilket skulle kunna leda till att 100 000-tals kronor årligen i besparingar.

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Appendices

Appendix 1:

Survey sent to An/Op/IVA anaesthesiologists

1	**When treating a not yet transfusion demanding perioperative bleeding I use (ASA 1 patient):**
*	Only crystalloid fluid infusion
*	Only colloid fluid infusion
*	Both crystalloid and colloid fluid infusion
*	Cannot answer/Other
*	Comments

2	**My first choice of crystalloid fluid when treating a not yet transfusion demanding perioperative bleeding is (ASA 1 patient):**
*	Ringer´s Acetate
*	Sodium Chloride 9 mg/ml
*	Cannot answer/Other
*	Comments

3	**My first choice of colloid when treating a not yet transfusion demanding perioperative bleeding is (ASA 1 patient):**
*	Dextran based colloid (ie Macrodex, Plasmodex)
*	Starch based colloid (ie Venofundin, Volulyte, Tetraspan)
*	Gelatin based colloid (ie Gelofusin)
*	Albumin
*	Plasma
*	Cannot answer/Other
*	Comments

4	**When treating septic shock I use:**
*	Only crystalloid fluid infusion
*	Only colloid fluid infusion
*	Both crystalloid and colloid fluid infusion
*	Cannot answer/Other
*	Comments

5	**My first choice of crystalloid fluid when treating septic shock is:**
*	Ringer´s Acetate
*	Sodium Chloride 9 mg/ml
*	Cannot answer/Other
*	Comments

6	**My first choice of colloid fluid when treating septic shock is:**
*	Dextran based colloid (ie Macrodex, Plasmodex)
*	Starch based colloid (ie Venofundin, Volulyte, Tetraspan)
*	Gelatin based colloid (ie Gelofusin)
*	Albumin
*	Plasma
*	Cannot answer/Other
*	Comments