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Review

Meeting report of the First International Fluid Academy Day

Part 1: Results of the survey on the knowledge of fluid management

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Abstract ***Background*** Fluid management in the critically ill has been neglected for way too long. Many questions with regard to the type of fluids, the timing and the dosing remain unanswered. Recent data suggest that fluids should be dealt with as any other type of medication. ***Objective*** To assess the awareness and current knowledge on fluid management among critical care physicians. ***Methods*** A 14-item knowledge questionnaire was shown electronically to the participants of the 1st international fluid academy day (iFAD) held in Antwerp (Belgium) on November 19th in 2011. Each question was shown before the lecture covering the topic under study. The same questions were repeated at the end of the iFAD to see whether a learning curve could be observed. Results from the two votings were compared. This paper reports on the results of the first part of the questionnaire including 7 knowledge questions on medical fluids and fluid management. Besides answering the knowledge questions respondents also provided information on their country of residence, basic speciality and years of experience. Participants of the conference voluntarily completed the survey via a voting system and the answers were recorded automatically and exported to an Excel worksheet. Statistical analysis was performed with SPSS software. ***Results*** One hundred fifty nine (80%) of the 200 distributed voting pads among the 274 first iFAD participants were actively used during the conference day. The respondents resided in the following countries: Belgium 43.4%, The Netherlands 20.1%, United Kingdom 9.4%, Germany 5%, France 3.1%, and 18.9% came from other countries. The distribution of the primary speciality was: anaesthesiology 36.5%, intensive care medicine 23.3%, emergency medicine 18.2%, internal medicine 18.2%, surgery 1.3% while 2.5% were not a doctor. With regard to the years of experience in the ICU, 6.3% answered to be in training, 11.9% had 1 to 5 years of experience, 18.9% between 5 and 15 and 44% stated to have more than 15 years experience, finally 18.9% answered not working in an ICU. The average overall score on the 7 knowledge questions on fluids and fluid management after the first vote was 26.6±17.4% *vs* 48.7±21.8% after the second vote ($p<0.0001$). The best score after the first vote was for Belgium with 29.5±18.7% and Germany having the worst (19.3±12.8%). After the second vote this was respectively the Netherlands (51.3±21.7%) and again Germany (40.5±12.1%). Residents in training had the best scores, 36.6±21.4% after the first and 56.8±27% after the second vote ($p<0.0001$). Emergency physicians had the best score after the first vote with 31±14.4% while intensivists performed best after the second vote 54.7±20.8%. ***Conclusions*** There is a general lack of knowledge on fluids and fluid management. Since correct fluid management and early intervention with goal directed therapy but also late conservative fluid management can reduce morbidity and mortality in critically ill patients, further educational efforts should be directed towards improving this knowledge, this can be done by organising state of the art lectures and evaluating acquired knowledge with a voting system.

Key words fluids • fluid management • knowledge • survey • teaching • voting

Introduction

The first International Fluid Academy Day (iFAD) was held on Saturday November 19th in 2011 at the "Elzenveld" Congress and Convention Centre in Antwerp, Belgium. This meeting was attended by 249 doctors, 25 faculty, 104 nurses together with 30 people form the industry totalling 400 medical workers. Fluid management in the critically ill has been neglected for way too long. Many questions with regard to the type of fluids, the timing and the dosing remain unanswered. Recent data suggest that fluids should be dealt with as any other type of medication with indications and contra-indications and possible side effects. The aim of this study was to assess the awareness and current knowledge on fluid management among critical care physicians.

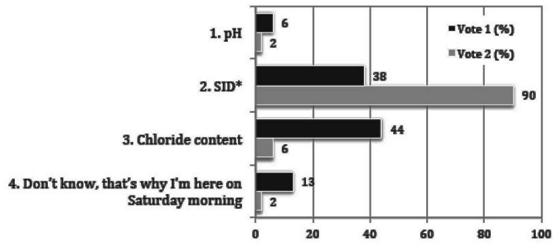

Fig. 1. Knowledge question 1 (KQ1): What is the single most important characteristic of a solution regarding its effect on the patient's acid-base status? Distribution of answers (in percentage) on KQ1, black squares denote first vote and grey squares second vote after the lecture was given. The * denotes the correct answer. SID: strong ion difference

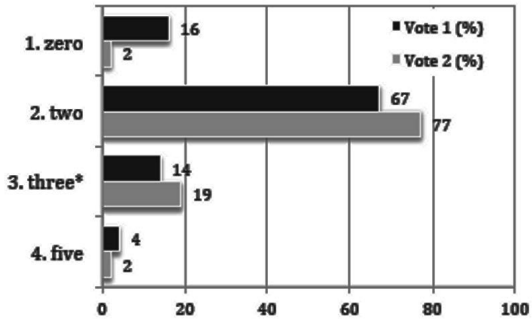

Fig. 2. Knowledge question 2 (KQ2): How many of the following fluids for infusion therapy have a Strong Ion Difference of zero: NaHCO3 8,4%, Glucose 5%, NaCl 0,9%, Lactated Ringer's, HES 6% 130/0.4 (e.g. Voluven®) Distribution of answers (in percentage) on KQ2, black squares denote first vote and grey squares second vote after the lecture was given. The * denotes the correct answer. HES: hydroxy ethyl starch

Methods

During the main medical symposium a voting system was used (n=200). A 14-item knowledge questionnaire was shown electronically to the participants of the 1st international fluid academy day (iFAD) held in Antwerp (Belgium) on November 19th in 2011. Each question was shown before the lecture covering the topic under study. The same questions were repeated at the end of the iFAD to see whether a learning curve could be observed. Results from the two votings were compared. This paper reports on the results of the first part of the questionnaire including 7 knowledge questions (KQ1 to KQ7) on medical fluids and fluid management. Each talk was also preceded with a general question. Participants of the conference voluntarily completed the survey via a voting system and the answers were recorded automatically and exported to an Excel worksheet. Statistical analysis was performed with SPSS software.

Results

Demographics of respondents

The primary discipline of the respondents was anaesthesiology 36.5%, intensive care medicine 23.3%, emergency medicine 18.2%, internal medicine 18.2%, surgery 1.3% while 2.5% were not a doctor. The respondents resided in the following countries: Belgium 43.4%, The Netherlands 20.1%, United Kingdom 9.4%, Germany 5%, France 3.1%, and 18.9% came from other countries. With regard to the years of experience in the ICU, 6.3% answered to be in training, 11.9% had 1 to 5 years of experience, 18.9% between 5 and 15 and 44% stated to have more than 15 years experience, finally 18.9% answered not working in an ICU.

Basic concepts of fluid management

KQ1. What is the single most important characteristic of a solution regarding its effect on the patient's acid-base status? Possible answers were: pH, strong ion difference (SID), chloride content or "I Don't know".

In the *"Back to Basics!"* lecture by Dr Niels Van Regenmortel (Antwerp, Belgium), basic definitions, terminology and concepts were reviewed. During his lecture definitions were given for osmolarity, tonicity and oncoticity, balanced solutions and the Strong Ion Difference (SID). The differences between gelatins, dextrans and starches were illustrated and it was explained how much electrolytes a patient needs. Not only the molecular weight needs to be taken into account but also the charge. During his lecture Dr Van Regenmortel stated that the lower the strong ion difference, the lower the pH will be and the more acidotic the patient will become. In his lecture he tried to state that not all crystalloids are the same. You have to balance them to improve them. Not all colloids are the same and these days we know that the last generation starches are perfectly acceptable and save. So fluid management just make it choice not chance. The correct answer to KQ1 is the SID. Figure 1 shows the distribution of answers (in percentage) on KQ1. The percentage correct answers increased from 38% after the first vote to 90% after second vote at the end of the day when the lecture was given ($p<0.0001$).

Hyperchloremic metabolic acidosis

KQ2. How many of the following fluids for infusion therapy have a Strong Ion Difference of zero? NaHCO3 8,4%, Glucose 5%, NaCl 0,9%, Lactated Ringer's, HES 6% 130/0.4 (e.g. Voluven®). Possible answers were: zero, two, three or five.

There is much ado about hyperchloremic metabolic acidosis caused by fluids. Where does it come from? Is it relevant, is there any animal or human data supporting this statement? How can it be avoided? Is the use of saline still acceptable, because there may be nothing "normal" about "normal saline"? In his lecture entitled "*Stewart Says: Saline Sucks! The Trouble with Hyperchloremic Metabolic Acidosis*", Paul Elbers from Amsterdam (The Netherlands)

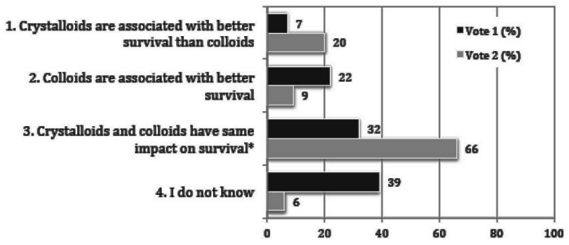

Fig. 3. Knowledge question 3 (KQ3): Fluid therapy and outcome: when I administer fluid in an ICU patients. Distribution of answers (in percentage) on KQ3, black squares denote first vote and grey squares second vote after the lecture was given. The * denotes the correct answer

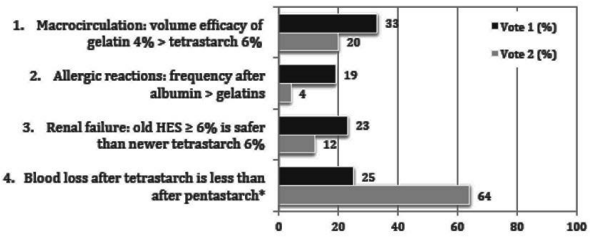

Fig. 4. Knowledge question 4 (KQ4): Exposure to colloids and clinical outcome: which comparison is correct? Distribution of answers (in percentage) on KQ4, black squares denote first vote and grey squares second vote after the lecture was given. The * denotes the correct answer. HES: hydroxy ethyl starch.

talked about saline induced metabolic acidosis. He thinks the Stewart approach really makes it easy to understand why this is a real phenomenon that may cause harm in many patients in whom every detail is critical. He stated "think twice before using saline". The correct answer to KQ2 was three, with glucose 5%, saline and voluven having a SID of zero. Figure 2 shows the distribution of answers (in percentage) on KQ2. The percentage correct answers increased from 67% after the first vote to 77% after second vote at the end of the day when the lecture was given (p=NS).

Crystalloids vs colloids

KQ3. Fluid therapy and outcome: when I administer fluid in an ICU patient… Possible answers were:
1. Crystalloids are associated with better survival than colloids,
2. Colloids are associated with better survival,
3. Crystalloids and colloids have same impact on survival,
4. I do not know.

The never-ending debate: where are we now? Is there merely a difference in cosmetics or also in outcome? What are the flaws of the actual mega-trials and meta-analyses? Are there specific situations or patient groups where colloids behave differently and may have an advantage? Which trials are in the pipeline? In his lecture entitled *"The Clash of the Titans: Crystalloids vs Colloids?"*, Eric Hoste from the Ghent University hospital in Belgium stated that there are some studies that demonstrated that albumin could be better in cirrhosis patients and albumin is also better regarding kidney function. Regarding the question whether colloids or crystalloids are superior for volume replacement in ICU patients one can state that colloids are not superior to crystalloids, they cost more and they have more side effects, so the correct answer was that they have the same impact on survival. However in some subgroups of patients for instance in severe sepsis or in cardiac surgery or in liver cirrhosis, colloids seem to be better when compared to crystalloids, but we need to look into that deeper. Figure 3 shows the distribution of answers (in percentage) on KQ3. The percentage correct answers increased from 32% after the first vote to 66% after second vote at the end of the day when the lecture was given (p<0.0001).

Choice of the colloid

KQ4. Exposure to colloids and clinical outcome: which comparison is correct? Possible answers were:
1. Macrocirculation: volume efficacy of gelatin 4% > tetrastarch 6%,
2. Allergic reactions: frequency after albumin > gelatins,
3. Renal failure: old HES ≥ 6% is safer than newer tetrastarch 6%,
4. Blood loss after tetrastarch is less than after pentastarch.

Many controversies need to be dealt with in relation to gelatins or starches: Are the smaller starches safer? Does the buffer solution in balanced starch solutions (lactate, acetate,…) matter? Is the origin of the starch (maize *vs* potatoes) important? Do we still have to fear for the kidneys and the coagulation with the newest starches? Should we bother about anaphylactic reactions or prior disease when using gelatins?

During her lecture *"Some Colloids are More Equal than Others! Does our Choice matter?"* Sibylle Kozek-Langenecker from Vienna (Austria) discussed one of her favourite subjects, namely the potential side effect of colloids and crystalloids on dilution coagulopathy and clinical outcome parameters just as blood loss and transfusion requirement. In her lecture she tried to explain why the choice matters, the choice on the selection of the colloid, on the timing and the dosing and there is a clear superiority in the evidence that we have in hand right now in favour for the use of 6% iso-oncotic tetrastarches *vs* gelatine.

The correct answer to KQ4 is "Blood loss after tetrastarch is less than after pentastarch". Figure 4 shows the distribution of answers (in percentage) on KQ4. The percentage correct answers increased from 25% after the first vote to 64% after second vote at the end of the day when the lecture was given (p<0.0001).

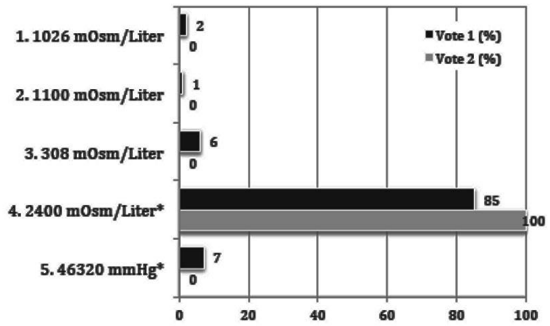

Fig. 5. Knowledge question 5 (KQ5): The osmotic power of 7,5 % saline equals. Distribution of answers (in percentage) on KQ5, black squares denote first vote and grey squares second vote after the lecture was given. The * denotes the correct answer.

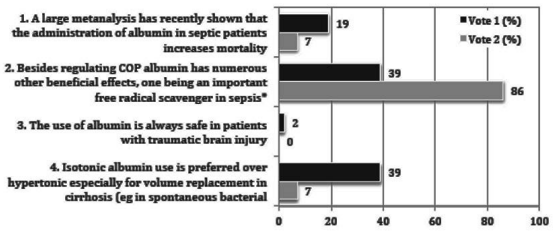

Fig. 6. Knowledge question 6 (KQ6): Which statement is correct regarding albumin? Distribution of answers (in percentage) on KQ6, black squares denote first vote and grey squares second vote after the lecture was given. The * denotes the correct answer. COP: colloid oncotic pressure

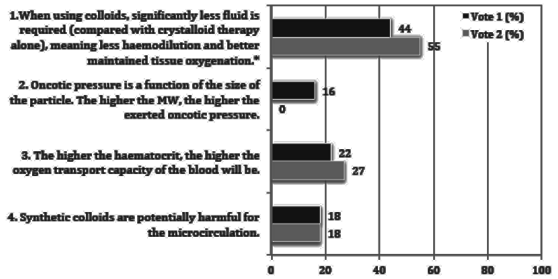

Fig. 7. Knowledge question 7 (KQ7): One of the following statements is true. Which one? Distribution of answers (in percentage) on KQ7, black squares denote first vote and grey squares second vote after the lecture was given. The * denotes the correct answer. MW: molecular weight

Hypertonic solutions

KQ5. The osmotic power of 7.5 % saline equals:
1. 1026 mOsm/Liter,
2. 1100 mOsm/Liter,
3. 308 mOsm/Liter,
4. 2400 mOsm/Liter or
5. 46320 mmHg.

Are hypertonic solutions of any use? What are the possible mechanisms of action? What are the indications? What is the dose? Are there relevant side-effects?

In his talk entitled *"The Hypertonics: Useful or Harmful?"* Dirk Himpe, Cardiac anaesthesiologist at the ZNA Middelheim general hospital (Antwerp, Belgium), stated that sometimes you can use a high concentrated salt solution to attract water from spaces in somebody's body that are on the wrong place and so you can displace water to the right place using hypertonic solutions. Hypertonic solutions being very salty solutions and that was the essence of his talk.

The correct answer to KQ5 was 2400 mOsm/Liter or 46320 mmHg. Figure 5 shows the distribution of answers (in percentage) on KQ5. The percentage correct answers increased from 85% after the first vote to 100% after second vote at the end of the day when the lecture was given (p=0.003).

Albumin

KQ6. Which statement is correct regarding albumin? Possible answers were:
1. A large meta-analysis has recently shown that the administration of albumin in septic patients increases mortality,
2. Besides regulating colloid oncotic pressure albumin has numerous other beneficial effects, one being an important free radical scavenger in sepsis,
3. The use of albumin is always safe in patients with traumatic brain injury, or
4. Isotonic albumin use is preferred over hypertonic especially for volume replacement in cirrhosis (eg in spontaneous bacterial peritonitis) or after large volume paracenthesis.

It's expensive (at least in Europe), but is it also worth the cash? Is it human or do we just hope it is? Are there still indications for iso- (or even hypo-) oncotic albumin? Is there an advantage of the hyperoncotic formulation to mobilize fluids? Do the kidneys like this strategy? Do we still have to measure plasma levels of albumin and is a correction of a low level necessary? In her talk entitled *"Hero or Has-Been? Is there still a Place for Albumin?"* Julia Wendon from Kings College hospital in London (United Kingdom) discussed the role of albumin. Albumin seems to have a significant benefit in terms of management in patients with liver disease. Essentially there are different roles of albumin. It has a role in liver disease without question particularly in prevention of hepatorenal failure. More interestingly it also has a marked inflammatory and anti-inflammatory capacities. We will see an increasing role for albumin in sepsis where it seems to have a beneficial effect in terms of outcome and mortality in meta-analyses looking at immune function.

The correct answer to KQ6 was "Besides regulating colloid oncotic pressure albumin has numerous other beneficial effects, one being an important free radical scavenger in sepsis". Figure 6 shows the distribution of answers (in percentage) on KQ6. The percentage correct answers increased from 39% after the first vote to 86% after second vote at the end of the day when the lecture was given (p<0.0001).

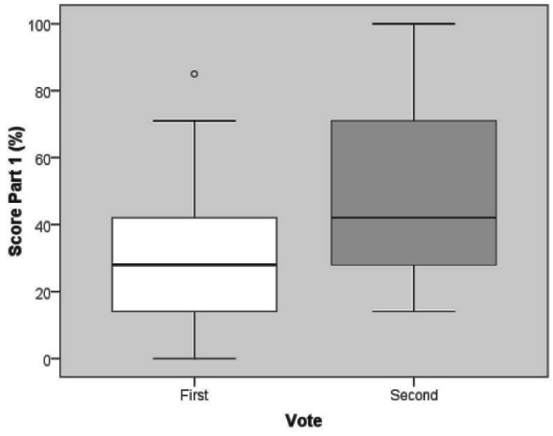

Fig. 8. Boxplots showing final score on knowledge questions 1 to 7 (KQ1 – KQ7) expressed as a percentage before the lecture (white box, first vote) and after the lecture had been given (grey box, second vote)(p<0.0001)

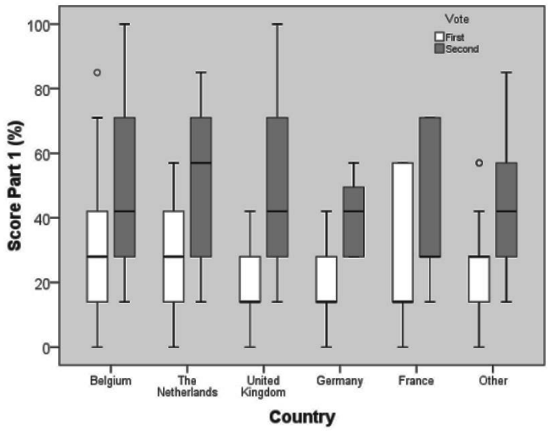

Fig. 9. Boxplots showing final score on knowledge questions 1 to 7 (KQ1 – KQ7) expressed as a percentage before the lecture (white box, first vote) and after the lecture had been given (grey box, second vote) and according to country of origin of participant. P-value <0.0001 for all comparisons between vote 1 and vote 2 except p=0.04 for Germany and p=NS for France.

Microcirculation

KQ7. One of the following statements is true. Which one? Possible answers were:
1. When using colloids, significantly less fluid is required (compared with crystalloid therapy alone), meaning less haemodilution and better maintained tissue oxygenation,
2. Oncotic pressure is a function of the size of the particle. The higher the MW, the higher the exerted oncotic pressure,
3. The higher the haematocrit, the higher the oxygen transport capacity of the blood will be, or
4. Synthetic colloids are potentially harmful for the microcirculation.

The fluid therapy of the future! Do the newer fluids have additional properties beyond correcting volume deficits? Can they avoid or even treat capillary leak with a so-called sealing effect? Are there relevant anti-inflammatory effects? Do we have to shift our attention from the macro- to the microcirculation? Maybe it is time to resuscitate the microcirculation: open the microcirculation and keep it open! Can Ince, physiologist at the academic medical center and Erasmus medical center in Rotterdam (The Netherlands) gave a lecture entitled *"Pushing the Boundaries! What's beyond the Final Frontier?"*. His interest in fluids emanates from its impacts on the tissues next to the organs. And what was recently found is that fluids are very poor oxygen carriers and not very effective in transporting oxygen, they also cause inflammation and oxidative stress. For this reason a new generation of fluids will need to be developed which take into consideration oxidative stress, inflammation and promote oxygen transport to the tissues of the organs.

The correct answer to KQ7 was "When using colloids, significantly less fluid is required (compared with crystalloid therapy alone), meaning less haemodilution and better maintained tissue oxygenation". Figure 7 shows the distribution of answers (in percentage) on KQ7. The percentage correct answers increased from 44% after the first vote to 55% after second vote at the end of the day when the lecture was given (p=NS).

Final knowledge score on fluid management

The total final score obtained by adding the individual results for KQ1 to KQ7 is shown in Figure 8. A significant increase was observed in the total final score from 26 .6±17.4 % to 48.7±21.8% after the second vote (p<0.0001). The best score after the first vote was for Belgium with 29.5±18.7% and Germany having the worst (19.3±12.8%). After the second vote this was respectively the Netherlands (51.3±21.7%) and again Germany (40.5±12.1%). Residents in training had the best score 36.6±21.4% after the first and also after the second vote with 56.8±27% (p<0.0001). Emergency physicians had the best score after the first vote with 31±14.4% while intensivists performed best after the second vote with 54.7±20.8%.

Figure 9 shows the evolution of the final score for each country (a significant increase was observed in all countries except France) and Figure 10 shows the final score according to primary speciality (a significant increase was observed for all specialities except surgery).

Discussion

The results of this survey of 7 knowledge questions on fluid management show that the use of a voting system before and after state of the art lectures can be a useful tool to demonstrate a learning curve. The bottom line however is that there is still a lack of general knowledge on fluids and fluid management. It is time that fluids are no longer seen as a mere method for hemodynamic stabilisation of patients in the emergency room, the operating room or the ICU but as a real drug with potential benefits but also side effects.

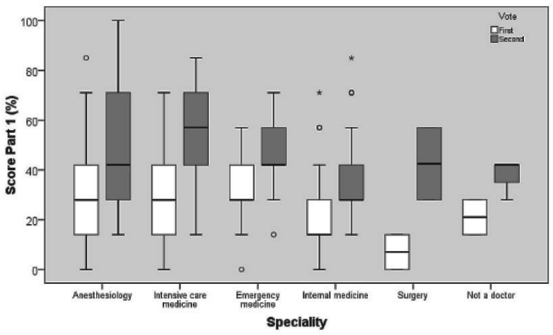

Fig. 10. Boxplots showing final score on knowledge questions 1 to 7 (KQ1 – KQ7) expressed as a percentage before the lecture (white box, first vote) and after the lecture had been given (grey box, second vote) and according to primary speciality of participant. P-value <0.0001 for all comparisons, except p=0.003 for Internal medicine, p=0.017 for not a doctor and p=NS for surgery.

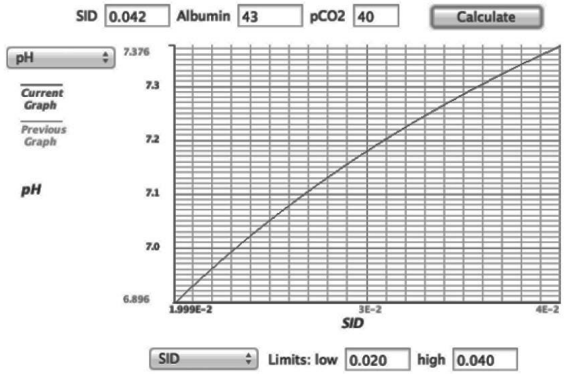

Fig. 11. Computer simulation from www.anesthetist.com Panel A. Effect of change in SID whilst keeping other parameters the same. Increasing SID from 20 to 40 mMol increases the pH from 6.9 to 7.38.

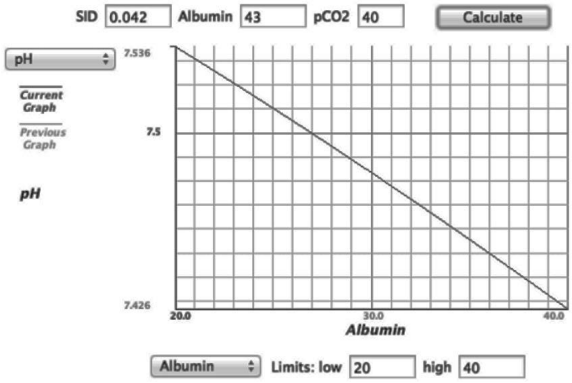

Fig. 11. Panel B. Effect of plasma (and thus also albumin) dilution on pH. Decreasing albumin from 40 to 20 g/L decreases the pH from 7.54 to 7.43 whilst keeping the other parameters constant.

Basic knowledge on the Stewart approach

The basic knowledge of fluids in general can be improved, ICU physicians need to be aware about the differences in oncoticity, tonicity, osmolality, the type of fluid, whether balanced or unbalanced and the Stewart approach.

The Stewart approach is really not difficult although it is often perceived as being very cumbersome (www.acidbase.org). It is not necessary to be a mathematician to use the Stewart approach at the bedside, Stewart makes it easy to see why physiologic salt solutions are quite pathologic. The plasma SID is close to 42mMol while the SID of normal saline is zero. Saline infusion therefore leads to a lower SID. The only rules that one needs to remember are listed below (see also Figure 11):

1. If SID goes down, the H+ goes up (and pH goes down)
2. If total acid content goes down, H+ goes down
3. If pCO_2 goes down, H+ goes down
4. SID can be approximated by [Na+] minus [Cl-]
5. And the acids are mainly albumin (so hypoalbuminemia leads to metabolic alkalosis)

Stewart basically says that lower SID solutions cause acidosis, and so does saline. Metabolic acidosis may cause decreased cardiac contractility, arterial and pulmonary vasoconstriction, decreased O2 binding to haemoglobin, protein wasting, insulin resistance, free radical formation and gut barrier dysfunction. Lung protective ventilation is much harder in face of metabolic acidosis. Stewart allows us to prevent delayed diagnosis and treatment. However in the literature, studies do not differentiate between the effects on hyperchloremia and hypo[SID]emia… Low SID and high chlorine levels cause numerous effects on cell function, cytokine production, renal function, gut barrier function and coagulation. Table 1 lists the major effects of a low SID.

The deleterious effects of saline have long been described by Harvey Cushing in 1901 [1]. Saline 0.9% has no convincing historical basis and it is dissimilar to most solutions used in the past (like Latta, Ringer or Hartmann), it is in no way "physiological" or "normal". Therefore our current practice may be based on historical misconception. A recent study in African children with severe infection showed that administration of saline boluses increases mortality compared to no bolus [2]. Hyperchloremia is also associated with increased mortality [3]. More recently Shaw et al. demonstrated that saline 0.9% resulted in more complications, postoperative infection, renal failure requiring dialysis, blood transfusion and electrolyte disturbances when compared to the balanced plasmalyte solution in patients after open abdominal surgery [4].

Colloids vs crystalloids

Do we need to make a choice between colloids and crystalloids? In the study on fluid boluses in African children, it was shown that regardless of the type of fluids given (saline *vs* albumin) the deleterious effects were the same [2]. In a recent survey on the use of colloids *vs* crystalloids, the highest proportion of all fluid resuscitation episodes was done with crystalloids in New Zealand (60%), the United States

Table 1. Deleterious effects of a low SID

>40% of the acid load in resuscitated septic dogs
lower mean survival time in septic rats
increased IL6/IL10 ratio and NF-kB in cell cultures
increased expression of cytokines in normotensive septic rats
renal vasoconstriction n humans
reduced GFR in humans
longer time to micturition in volunteers
reduced urine output after major surgery in the elderly
increased NGAL after cardiac surgery in elderly
decreased renal blood flow and creatinine clearance in septic rats
higher incidence of hyperkalaemia (compared to ringer's)
more abdominal discomfort in healthy volunteers
higher tonometric CO2 gap after major surgery in elderly patients
more intestinal injury in rats
impaired gastropyloric motility in pigs.
worse 2 week survival in hemorrahgic rats
prolongation of time to cloth formation in trauma patients
abnormal thromboelastography after major surgery

and Germany (both around 50%), while colloids were most often used in Great Britain (75%), China (60%) and Australia (55%). Blood products were most often given in Sweden, USA and Denmark (all around 40%) [5]. Some reasons to give colloids could be faster shock reversal in the setting of early goal directed therapy and administration of less volume, so decreased risk for intra-abdominal hypertension (IAH) and acute respiratory distress syndrome (ARDS)[6—8]. Reasons not to give colloids could be increased cost and possible more side effects like acute kidney injury and coagulopathy. A recent Cochrane collaboration overview concluded that the review of trials found no evidence that colloids reduce the risk of dying compared with crystalloids [9]. However, there was much ado about the VISEP study with regard to lack of good protocolised care and cumulative doses of HES 10% of more than 250ml/kg [10]. Other recent randomized controlled clinical trials could also not demonstrate a benefit for colloids over crystalloids, like the 6S, CRYSTMAS and CHEST trials [11—13]. So that the debate has been opened as to whether hydroxyl ethyl starches 130/0.4 are safe to use [14]? Colloids seem to be related to increased risk for acute kidney injury and longer duration of RRT [10, 12, 15, 16]. The VISEP study on the other hand did not show a statistical significant difference [10]. Table 2 lists the effects of different studies on kidney function. When this paper went to press the final results of the CHEST trial just had been published: showing no difference on outcome but crystalloids were associated with less AKI and less renal replacement therapy although the risk for renal failure was the same [17]. It remains to be proven whether these observations can be extrapolated to the new balanced starches.

Table 2. Summary of effects of colloids on renal function

Study	Population	Colloid	AKI
Cittanova	Kidney donor	HES 200	Yes
Schortgen	Severe sepsis	HES 200	Yes
VISEP	Severe sepsis	HES 130	No diff
CRYSTMAS	ICU	HES 130	No diff

Starches vs gelatins

Two recent Cochrane analyses came to the following conclusions [18, 19]: 1. there is no evidence that one colloid solution is more effective or safe than any other, 2. since there is no evidence from RCT's that colloids reduce the risk of death, it is hard to see how their continued use can be justified. There are some possible explanations why we can't see the difference between the different types of colloids [20]: the end point of mortality is unjustified, there are methodological limitations in the sparse RCTs, the risks of hypervolemia are underestimated, the direct costs for colloids are overestimated, fluid monitoring and target values used are often inappropriate, and the risks-benefits balance is inadequate. However intensivists must be aware that there are clear differences between starches and gelatines and between old (200/0.5) and new (130/0.4) and waxy maze and potato starches. Gelatins have an unclear effect on kidney function, carry an anaphylactic potential, and have limited volume effect compared to HES [21, 22]. Tetrastarches are superior to gelatins with regard to the effects on stroke volume and cardiac output (resulting in less vasopressor use and better hemodynamic stability) [23—26]. With regard to effects on microcirculation and inflammation, tetrastarches sustain and improve pulmonary gas exchange [27—29]. Both 6% tetrastarch and gelatine seem to have neutral effects on kidney function [15, 30, 31]. Hexastarch 6% and pentastarch 10% however lead to accumulation and kidney toxicity [10]. The use of tetrastarches result in less blood loss and less packed cell transfusion when compared to pentastarches. In a head-to-head comparison, the blood loss is similar after tetrastarch and gelatin [32]. Finally, one must be aware that waxy maize-derived HES and potato-derived HES are not bioequivalent, since there is clear difference in the area under the curve (AUC) and plasma clearance, resulting in different effects on the gut mucosal microcirculation [20, 33]. Tetrastarches are approved in children where they have the best cost-effectiveness and safety profile [34]. Some colloids thus are more equal than others, so our choice does matter: our choice on the type of drug, the timing and the dosing. Tetrastarch 6% is "4-times more equal" than gelatin when it comes to efficacy and safety. More information can be found at the website www.perioperativebleeding.org.

Hypertonics

The setting of cardiopulmonary bypass is a great model for simulating large volume shifts. Gelatins

Table 3. Summary of effects of albumin on renal function

Study	Population	Colloid	AKI
SAFE	ICU	Alb 4%	No diff
EARSS	Sepsis	Alb 20%	No diff
Cirrhosis	HRS	Alb 20%	Improved
Cirrhosis	SBP	Alb 20%	Improved

Table 4. Osmotic power of different solutions (COP of plasma is 25 mmHg, and for Voluven 36 mmHg)

Solution	Sodium (mEq/L)	Osmol (mosm/L)	COP (mmHg)
Normal saline	154	308	5944
Lactated Ringer	130	275	5307
Mannitol(20%)	-	1100	21230
Mannitol(25%)	-	1375	26537
3% Saline	513	1026	19802
7.5% Saline	1283	2400	46320
23.4% Saline	4004	8008	154554

may have a natural advantage in that they are balanced due to the gelatin content that is negatively charged and acts like the acetate, malate or lactate content in other balanced solutions [35, 36]. Negatively charged starches could, however, be formed through the linkage of carboxymethyl rather than hydroxyethyl groups to the starch backbone. Compared to crystalloids, colloids (and especially hypertonic solutions) are able to limit weight gain after major surgery by keeping the perioperative fluid balance "in balance"[35]. Moreover fluid shifts into the interstitial space need to be kept to a minimum. There can be 2 types of shifts: type 1 is a physiologic shift of colloid-free fluid; while type 2 results from dysfunction vascular barrier (endothelial glycocalyx capillary membrane) due to surgical manipulation, reperfusion injury and inflammatory mediators, or due to iatrogenic hypervolemia (less volume effect) [37]. Early goal directed therapy must focus on maintaining normovolemia whilst avoiding fluid shifts to the interstitium. Hypertonic solutions can have spectacular results due to the osmotic power, NaCl 7.5% for instance has a Na-content of 1283 mEq/L, an osmolality of 2400 mosm/L and a COP of 46320 mmHg (Table 4)! Small volume resuscitation with 4 ml/kg or 250 cc (eg Hyperhaes) as initial bolus over 5—10 min can acutely reset oversized fluid spaces via different mechanisms of action: 1. it shifts water out of RBCs and endothelium into plasma, 2. it shifts water out of interstitium and tissue cells; 3. it generates a rapid but transient improvement in intravascular volume; 4. it improves global hemodynamics; 5. endothelial cell shrinkage decreases capillary hydraulic pressure and improves perfusion [38]. The use of SVR is preserved for 1. pre-hospital treatment in (penetrating) trauma for pre-emptive shrinking interstitial and intracellular compartment; 2. treatment of high intracranial pressure (ICP) in hypotensive patients; 3. the setting of cardiac arrest as a last "chance" in moribund patients with severe shock; and 4. burn patients [39—44].

Albumin

Although albumin use was associated with increased mortality in the SOAP study, the SAFE study investigators showed no difference on outcome between albumin 4% and saline [45]. Moreover, a later subgroup analysis in those patients with septic shock showed a significant (p=0.03) adjusted odds ratio in favour of albumin of 0.71(0.52—0.97) [46]. On the other hand there is ample data that albumin should not be used in traumatic brain injury patients [47]. Albumin has neutral or favourable effects on kidney function (Table 3). A recent meta-analysis showed that hyperoncotic albumin resulted in less AKI and better survival when compared to controls, hyperoncotic HES on the contrary resulted in worse outcomes [48]. Besides a plasma expanding effect that is 0.8 for albumin 4%, 1 for albumin 5% and times three for albumin 20%, albumin has numerous other properties [49]: maintenance of colloid osmotic pressure (COP), no effect on other serum proteins, binding and transport of drugs (frusemide, antibiotics) and toxins, free radical scavenging, immunological stimulation or inhibition, anti- and procoagulatory effects, inhibition of platelets aggregation, inhibition of factor Xa by ATIII, the thromboelastography shows early hypocoagulable effects, vascular sealing (due to negative charge) but also increased vascular permeability related to "overalbuminisation", aluminum toxicity, hypotension (vasoactive peptides) and myocardial depression (related to Ca binding as shown in animal studies).

Albumin 20% can be very useful in ALI and ARDS patients resulting in better P/F ratios in combination with frusemide [50, 51]. This was also recently shown in a matched cohort study in combination with PEEP [6]. Another indication could be in patients with or at risk for hepatorenal syndrome, spontaneous bacterial peritonitis and in cirrhotics after large volume paracenthesis, in the latter the combination with terlipressin seems to improve outcome even further [52, 53].

The microcirculation

Fluids must be considered as a drug: as with medications, when giving fluids to a patient one can observe changes in the blood flow (distribution), the pO2, the haemoglobin content and the haematocrit level, the acid-base status and the SID, the osmotic balance and volume status, the blood sheer stress, (auto) regulation, the blood viscosity, and finally, the metabolic and inflammatory status. If a patient

looses colloids or crystalloids, then the administration of colloids or crystalloids seems justified, however that is rarely the case, more likely patients are losing blood as is the case in traumatic haemorrhagic shock. In a retrospective study of almost 6000 patients, Sakr et al. demonstrated that higher hemoglobin concentrations ($p<0.001$) and blood transfusions ($p=0.031$) were independently associated with a lower risk of in-hospital death, especially in patients aged from 66 to 80 years, in patients admitted to the ICU after non-cardiovascular surgery, in patients with higher severity scores, and in patients with severe sepsis [54].

When it comes to protecting the microcirculation, NaCl and Cl containing colloid solutions should be avoided. Balanced salt solutions are better in this respect. Of the starches, 130kD HES is best for the microcirculation

Too much or too little fluids are bad [55]. Don't forget tissue oxygenation. Oxygen delivery and microcirculatory flow are key targets for fluid therapy and can be clinically monitored. New clinical parameters may provide such tools for optimizing fluid therapy.

Conclusions

With an average score of 26.6±17.4% after the first vote *vs* 48.7±21.8% after the second vote, this survey demonstrates that there is a general lack of knowledge on fluids and fluid management. Since correct fluid management and early intervention with goal directed therapy can reduce morbidity and mortality in critically ill patients, further educational efforts should be directed towards improving this knowledge. This can be done by organising state of the art lectures and evaluating acquired knowledge with a voting system to detect a positive learning curve.

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References

1. Cushing H: Concerning the poisonous effect of pure sodium chloride solutions upon the nerve muscle preparation. Am J Physiol 1901;6:77—90
2. Maitland K, Kiguli S, Opoka RO, et al.: Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364:2483—2495
3. Boniatti MM, Cardoso PR, Castilho RK, Vieira SR: Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. Journal of critical care 2011;26:175—179
4. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA: Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Annals of surgery 2012;255:821—829
5. Finfer S, Liu B, Taylor C, et al.: Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Critical care 2012;14:R185
6. Cordemans C, De laet I, Van Regenmortel N, et al.: Aiming for negative fluid balance in patients with acute lung injury and increased intra-abdominal pressure: A pilot study looking at the effects of PAL-treatment. Annals Intensive Care 2012;2:S15
7. Cordemans C, De laet I, Van Regenmortel N, Schoonheydt K, Dits H, Huber W, Malbrain ML: Fluid management in critically ill patients: The role of extravascular lung water, abdominal hypertension, capillary leak and fluid balance. Annals Intensive Care 2012;2:S1
8. Malbrain ML, Cordemans C, Van Regenmortel N: Fluid overload is not only of cosmetic concern (Part II): Results from a meta-analysis and practical approach. ICU Management 2012;12:34—37
9. Perel P, Roberts I: Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2011;16:CD000567
10. Brunkhorst FM, Engel C, Bloos F, et al.: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. The New England journal of medicine 2008;358:125—139
11. Perner A, Haase N, Guttormsen AB, et al.: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. The New England journal of medicine 2012;367:124—134
12. Guidet B, Martinet O, Boulain T, et al.: Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 *vs* 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. Critical care 2012;16:R94
13. Myburgh J, Li Q, Heritier S, Dan A, Glass P: Statistical analysis plan for the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST). Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine 2012;14:44—52
14. Haase N, Perner A: Is hydroxyethyl starch 130/0.4 safe? Critical care 2012;16:116
15. Schortgen F, Lacherade JC, Bruneel F, Cattaneo I, Hemery F, Lemaire F, Brochard L: Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. Lancet 2001;357:911—916
16. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P: Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 1996;348:1620—1622
17. Myburgh JA, Finfer S, Bellomo R: Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. The New England journal of medicine. 2012
18. Bunn F, Trivedi D, Ashraf S: 2011 Colloid solutions for fluid resuscitation. Cochrane database of systematic reviews 2011: CD001319
19. Perel P, Roberts I: Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane database of systematic reviews 2011: CD000567
20. Westphal M, James MF, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H: Hydroxyethyl starches: different products--different effects. Anesthesiology 2009;111:187—202
21. Ertmer C, Rehberg S, Van Aken H, Westphal M: Relevance of non-albumin colloids in intensive care medicine. Best practice & research Clinical anaesthesiology 2009;23:193—212
22. Schramko AA, Suojaranta-Ylinen RT, Kuitunen AH, Raivio PM, Kukkonen SI, Niemi TT: Comparison of the effect of 6% hydroxyethyl starch and gelatine on cardiac and stroke volume index: a randomized, controlled trial after cardiac surgery. Perfusion 2010;25:283—291

23. Van der Linden P, Ickx BE: The effects of colloid solutions on hemostasis. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2006;53:S30—S39
24. Niemi T, Schramko A, Kuitunen A, Kukkonen S, Suojaranta-Ylinen R: Haemodynamics and acid-base equilibrium after cardiac surgery: comparison of rapidly degradable hydroxyethyl starch solutions and albumin. Scandinavian journal of surgery: SJS: official organ for the Finnish Surgical Society and the Scandinavian Surgical Society 2008;97:259—265
25. Choi YS, Hong SR, Lee YM, Song KW, Park MH, Nam YS: Studies on gelatin-containing artificial skin: II. Preparation and characterization of cross-linked gelatin-hyaluronate sponge. Journal of biomedical materials research 1999;48:631—639
26. Choi YS, Hong SR, Lee YM, Song KW, Park MH, Nam YS: Study on gelatin-containing artificial skin: I. Preparation and characteristics of novel gelatin-alginate sponge. Biomaterials 1999;20:409—417
27. Heckel K, Winkelmann B, Strunden MS, Basedow A, Schuster A, Schumacher U, Kiefmann R, Reuter DA, Goetz AE: Tetrastarch sustains pulmonary microvascular perfusion and gas exchange during systemic inflammation. Critical care medicine 2012;40:518—531
28. Rittoo D, Gosling P, Burnley S, et al.: Randomized study comparing the effects of hydroxyethyl starch solution with Gelofusine on pulmonary function in patients undergoing abdominal aortic aneurysm surgery. British journal of anaesthesia 2004;92:61—66
29. Allison KP, Gosling P, Jones S, Pallister I, Porter KM: Randomized trial of hydroxyethyl starch versus gelatine for trauma resuscitation. The Journal of trauma 1999;47:1114—1121
30. Mahmood A, Gosling P, Vohra RK: Randomized clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatine during aortic aneurysm surgery. The British journal of surgery 2007;94:427—433
31. Godet G, Lehot JJ, Janvier G, Steib A, De Castro V, Coriat P: Safety of HES 130/0.4 (Voluven(R)) in patients with preoperative renal dysfunction undergoing abdominal aortic surgery: a prospective, randomized, controlled, parallel-group multicentre trial. European journal of anaesthesiology 2008;25:986—994
32. Lindroos AC, Schramko A, Tanskanen P, Niemi T: Effect of the combination of mannitol and ringer acetate or hydroxyethyl starch on whole blood coagulation in vitro. Journal of neurosurgical anesthesiology 2010;22:16—20
33. Lehmann GB, Asskali F, Boll M, Burmeister MA, Marx G, Hilgers R, Forster H: HES 130/0.42 shows less alteration of pharmacokinetics than HES 200/0.5 when dosed repeatedly. British journal of anaesthesia 2007;98:635—644
34. Saudan S: Is the use of colloids for fluid replacement harmless in children? Current opinion in anaesthesiology 2010;23:363—367
35. Himpe D: Colloids versus crystalloids as priming solutions for cardiopulmonary bypass: a meta-analysis of prospective, randomised clinical trials. Acta anaesthesiologica Belgica 2003;54:207—215
36. Himpe D, Neels H, De Hert S, Van Cauwelaert P: Adding lactate to the prime solution during hypothermic cardiopulmonary bypass: a quantitative acid-base analysis. British journal of anaesthesia 2003;90:440—445
37. Strunden MS, Heckel K, Goetz AE, Reuter DA: Perioperative fluid and volume management: physiological basis, tools and strategies. Ann Intensive Care 2011;1:2
38. Tollofsrud S, Elgjo GI, Prough DS, Williams CA, Traber DL, Kramer GC: The dynamics of vascular volume and fluid shifts of lactated Ringer's solution and hypertonic-saline-dextran solutions infused in normovolemic sheep. Anesthesia and analgesia 2001;93:823—831
39. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J: Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA : the journal of the American Medical Association 2004;291:1350—1357
40. Rizoli SB, Rhind SG, Shek PN, et al.: The immunomodulatory effects of hypertonic saline resuscitation in patients sustaining traumatic hemorrhagic shock: a randomized, controlled, double-blinded trial. Annals of surgery 2006;243:47—57
41. Bender R, Breil M, Heister U, Dahmen A, Hoeft A, Krep H, Fischer M: Hypertonic saline during CPR: Feasibility and safety of a new protocol of fluid management during resuscitation. Resuscitation 2007;72:74—81
42. Tollofsrud S, Mathru M, Kramer GC: Hypertonic-hyperoncotic solutions in open-heart surgery. Perfusion 1998;13:289—296
43. Tollofsrud S, Noddeland H: Hypertonic saline and dextran after coronary artery surgery mobilises fluid excess and improves cardiorespiratory functions. Acta anaesthesiologica Scandinavica 1998;42:154—161
44. Tollofsrud S, Tonnessen T, Skraastad O, Noddeland H: Hypertonic saline and dextran in normovolaemic and hypovolaemic healthy volunteers increases interstitial and intravascular fluid volumes. Acta anaesthesiologica Scandinavica 1998;42:145—153
45. The SAFE Study Investigators: A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. The New England journal of medicine 2004;350:2247—2256
46. Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R: Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive care medicine 2011;37:86—96
47. Myburgh J, Cooper DJ, Finfer S, et al.: Saline or albumin for fluid resuscitation in patients with traumatic brain injury. The New England journal of medicine 2007;357:874—884
48. Wiedermann CJ, Dunzendorfer S, Gaioni LU, Zaraca F, Joannidis M: Hyperoncotic colloids and acute kidney injury: a meta-analysis of randomized trials. Critical care 2010;14:R191
49. Delaney AP, Dan A, McCaffrey J, Finfer S, (2011) The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Critical care medicine 39: 386-391
50. Martin GS, Mangialardi RJ, Wheeler AP, Dupont WD, Morris JA, Bernard GR: Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. Crit Care Med 2002;30:2175—2182
51. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR: A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med 2005;33:1681—1687
52. Fernandez J, Monteagudo J, Bargallo X, Jimenez W, Bosch J, Arroyo V, Navasa M: A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology Baltimore 2005;Med 42:627—634
53. Boyer TD, Sanyal AJ, Garcia-Tsao G, Blei A, Carl D, Bexon AS, Teuber P: Predictors of response to terlipressin plus albumin in hepatorenal syndrome (HRS) type 1: relationship of serum creatinine to hemodynamics. Journal of hepatology 2011;55:315—321
54. Sakr Y, Lobo S, Knuepfer S, et al.: Anemia and blood transfusion in a surgical intensive care unit. Critical care 2010;14:R92
55. Bellamy MC: Wet, dry or something else? Br J Anaesth 2006;97:755—757