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# 3rd International Fluid Academy Days

## Abstracts of the invited lectures

### Omega-3 fatty acids ("fish oil") in parenteral nutrition

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***Introduction*** Omega-3 fatty acids (O3FA) are a family of highly unsaturated fatty acids. The parent O3FA alpha-linolenic acid is synthesised in plants and is essential for humans. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are n-3 fatty acids found in oily fish and fish oil supplements. These fatty acids are able to inhibit partly a number of aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid, production of inflammatory cytokines and T cell reactivity. ***Methods*** Review of the relevant literature. ***Results*** EPA and DHA are biologically active metabolic derivatives of alpha-linolenic acid, although synthesis of EPA and DHA is poor in humans. EPA and DHA are found in oily fish and in fish oils. EPA and DHA share a number of unique and important biochemical and physiological functions that result in improvements in cell and tissue function. For example, they play important roles in cell membrane structure and function, in cell signalling and regulation of gene expression, and in the control of production of lipid mediators involved in inflammation and blood coagulation. Thus there is a strong rationale for inclusion of EPA and DHA in intravenous (iv) nutrition from where they could exert effects increasing the likelihood of improved patient outcome. Indeed iv O3FA, in the form of fish oil, have been shown to have benefits in surgical patients, in patients in the ICU, and in parenteral nutrition-induced liver disease and the iv route may be advantageous where rapid delivery of O3FA is required. A number of trials of iv O3FA have been conducted in surgical patients (mainly gastrointestinal surgery) and these show consistent effects on inflammation and immune function linked with shorter hospital stay. ***Discussion*** These effects are demonstrated through several recent meta-analyses. The few studies in critically ill patients do not produce consistent findings but there is evidence for better gas exchange and decreased length of ICU and hospital stay. Findings of the trial by Barbosa et al. published in Critical Care in 2010 will be described [1]. Meta-analyses published in 2012 and 2013 of intravenous O3FA in the ICU and critical illness produce favourable findings with regard to ventilation requirement, length of hospital stay and mortality [2, 3]. ***Conclusion*** Since effects of iv fish oil are dependent upon the dose of EPA and DHA delivered it is important to recognise that not all preparations are equivalent in this regard.

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### The abdomen as a therapeutic target: managing abdominal hypertension

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***Learning objectives*** To describe the role of the abdomen in severe illness, to describe the pathophysiology in IAH, and to review strategies that target the abdomen. ***Introduction and background*** The abdominal compartment contains vital organs – that are also relevant during critical illness. But hen it comes to

therapy, the abdomen is the forgotten compartment in the ICU [1—4]. ***Methods*** Review of contemporary literature ***Results and main message*** There is a considerable body of evidence that IAH impairs abdominal and intestinal perfusion. This has been studied for the liver, GI tract and splanchnic organs with increased GI leakage and bacterial translocation demonstrated in animal studies. The abdominal perfusion pressure (APP) is the mean arterial pressure minus the intraabdominal pressure (MAP-IAP=APP) – a concept comparable to cerebral perfusion pressure in the intracranial cavity. Studies have identified low APP as associated with mortality – which in its end stage is of course to be expected. Whether APP can be a therapeutic target remains to be demonstrated. In case of severe IAH, strategies to decrease IAP may prove better treatment options until the advantage of increasing MAP with vasoactive drugs has found to be beneficial. Surgical decompression in that respect is the most efficient way to increase APP by reducing IAP. When treating patients with an open abdomen, negative pressure therapy is increasingly used as it is a convenient method for open abdomen management with added advantages such as increased abdominal closure rates. In experimental studies, NPT has been found to dampen inflammation, a mechanisms that is incompletely been understood, but evacuation of ascites and reducing interstitial oedema are probably involved in this. ***Key messages*** IAH impairs abdominal perfusion. Low perfusion pressures are bad. APP as a therapeutic target is attractive but targets have not been established. Abdominal decompression improves abdominal perfusion. Negative pressure therapy, dampens inflammation in experimental settings.

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## Bringing Stewart to the bedside


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***Introduction*** The Stewart approach to acid-base balance is fascinating and is increasingly being used throughout the medical community and especially in intensive care units. Invented by the late Peter Stewart around 1980, the approach completely demystifies any acid base disturbance [1]. ***Methods*** Review of the relevant literature. ***Results*** One of the key concepts of the Stewart approach is that bicarbonate, or HCO3-, does not play any role in acid-base balance. This is usually very intimidating and counterintuitive to most clinicians as the commonly used Henderson Hasselbalch dictates otherwise. Interestingly, Stewart does not deny the value of the Henderson Hasselbalch equation. In fact, this equation is actually one of the six equations that Stewart proposes to describe acid-base equilibrium. This implies that both approaches are mathematically compatible and that the Stewart approach may provide the bigger picture. According to the Stewart approach there are only three independent variables that determine the concentration of H+ and thus pH in any fluid, including plasma. These variables are the partial pressure of carbon dioxide (PCO2), the total amount of not completely dissociated weak acids (Atot, mainly albumin) and the so-called Strong Ion Difference (SID). The strong ion difference is the sum of all positively charged fully dissociated ions (mainly Na+) minus the sum of all negatively charged fully dissociated ions (mainly Cl). If PCO2 goes down, the patient will become more alkalotic. If Atot goes down, the patient will become more alkalotic. If SID goes down the patient will become more acidotic. Thus, while HCO3- may follow a change in one of these independent variables it can never cause a change in pH by itself. One of the most fascinating aspects of the Stewart approach is that it becomes very easy to see how fluid therapy may alter acid base status. Normal concentrations of plasma sodium and chloride are about 140 mEq/L and 100 mEq/L. This implies a normal strong ion difference of 40 mEq/L. If we now infuse normal saline, which contains 154 mEq/L of Na+ and Cl- with an SID of 0 mEq/L, it becomes obvious that plasma SID will go down, which causes acidosis. ***Conclusion*** At first glance, the Stewart approach may appear difficult, especially because it involves a number of equations. However, in our workshop we will show you that the Stewart approach is actually very easy to use and understand. We will focus on a number of difficult cases and solve these interactively. We will give you the tools to apply the Stewart approach at the bedside. After the workshop you will be able to fully understand, quantify and diagnose any acid base disturbance you may encounter in daily clinical practice.

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## FAST, e-FAST and basics of thoracic and abdominal ultrasound in emergency and intensive care medicine

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***Introduction*** After many years of just being a fancy gimmick for a few enthusiasts, echography is now fast moving into the mainstream teaching about almost any area of medicine, vastly extending the range of diagnostic capabilities of the dedicated bedside clinician. It is easily integrated into the clinical examination and decision making process. For some applications like the short trauma echography known as FAST (Focussed Assessment Sonography in Trauma) or e-FAST (extended FAST) the learning curve is steep, for others such as haemodynamic evaluation or that of the parenchymatous abdominal organs a larger experience base is required. ***Objectives*** These talks are to cover the basics of ultrasound applications in the initial emergency assessment and the daily chores of an ICU physician. It is to encourage the newcomers to choose some easily learnt techniques first, while cautioning about the complexities in other applications, as in the evaluation of vena-cava-inferior-dynamics in different haemodynamic and respiratory settings. ***Methods*** The presenter draws mainly from his collection of ultrasound images and clinical experience. While not being a researcher, he can honestly claim to have been one of the first physicians to use echography in daily ICU work, now being able to look back on more than 20 years of experience with this. ***Results*** From the point of view of an emergency room or intensive care physician, echography is an integral part of the patient assessment from the first physical examination to advanced treatment in the ICU, being an extension of his or her physical senses much like the stethoscope, and, ideally, just as naturally being carried around. Point-of-care ultrasound makes a substantial difference in daily patient care. Physicians do need some training, though, and many find it hard to get over the initial threshold of not daring to use this tool.

## Infusion fluids — current topics

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***Learning objectives*** During the talk an overview will be given on the current status and knowledge of different types of resuscitation fluids. ***Isotonic saline issue*** The use of isotonic saline for fluid resuscitation is much more widespread than clinically justified. More than 50% of the infusion fluids sold in 0.5 and 1.0 L fluid bags in Europe consist of isotonic saline [1] and the situation is the same in many Asian countries. Numerous studies show that balanced crystalloid fluids are to prefer with regard to the acid-base balance, kidney function and patient well-being. Vomiting probably remains the only indication for saline, as the low sodium content and the hypo-osmotic properties of the Ringer solutions has been solved with the composition in Plasma-Lyte. With regard to hypertonic saline, new studies show that hypertonic saline does not improve survival or neurological damage in prehospital care [2, 3]. ***Tips when infusing crystalloid fluids*** With the use of colloid fluids being increasingly questioned, the following tips are useful if turning to crystalloid electrolyte fluids as the mainstay of fluid resuscitation: (A) Using arterial pressure as the target for the infusion easily results in overhydration. Drug-induced hypotension cannot be reversed by fluid. If one fluid bolus does not raise the pressure, lighten the anaesthesia and/or use a vasopressor [4]. (B) Evaporation during surgery is often overrated. An open abdominal wound with liberal exposure of the organs is associated with loss of only 30 mL/h [5]. (C) Plasma volume expansion from crystalloid fluid is much greater than commonly believed as long as the infusion is continued. This is due to the fact that equilibration of infused fluid between the plasma and interstitial fluid space, in whole-body man, requires 30 minutes to be completed. The half-time of the distribution process is about 8 minutes [6]. This means that the infused fluid expands to plasma volume by about 60% of the infused amount during a standard operation [7]. (D) In anaesthesia-induced hypotension, crystalloid and colloid fluids are equally effective plasma volume expanders. With a reduction of the mean arterial pressure by 20% or more the distribution of fluid from the plasma to the interstitial fluid space becomes arrested [6]. All the infused fluid remains in the bloodstream until a new Starling equilibrium has developed. This may take 30 minutes and probably depends n the rate of infusion and the severity of the hypotension. (E) Anaesthesia and surgery greatly retard the rate of elimination of crystalloid fluid. Anaesthetists are happy if 50—100 mL is excreted as urine per

hour after infusing 1.5—2 L of crystalloid, while a conscious volunteer would excrete >1 L the first hour. Ringer´s acetate in a conscious volunteer has a half-life of 30 minutes while the half-life is 200—300 minutes during laparoscopy [6,8]. In short, patients in this setting haev very difficult ot excrete fluid overload, and monitoring the urinary excretion can only provide information about the presence of marked hypovolaemia, not hypervolaemia. This slow elimination might account for the fact that crystalloids and colloids appear to have the same plasma volume expanding effect in intensive care [8]. ***Colloid fluids*** In contrast to the crystalloids, colloid fluids have various degrees of allergic properties and their half-life in plasma is longer, usually 2—3 hours (compared to 8 minutes). Combining crystalloid and colloid fluid may have unforeseen effects. Recently it was shown that hydroxyethyl starch has a capacity to displace crystalloid fluid to the interstitium, thereby prolonging its half-life by withholding the crystalloid from renal excretion [9]. The current criticism of colloid fluids are mostly related to the risk of kidney injury associated with starch preparations in the intensive care setting. Meta-analyses have not supported the existence of such risks when used in the operating room [10, 11]. The recent CRISTAL study found no increased mortality after using colloids as the initial resuscitation fluid hypovolaemic shock treated in the intensive care unit [12]. At 90 days, the data rather showed a benefit. Other issues relate to problems in identifying advantages of choosing a colloid compared to a crystalloid. In the mind of this author, the use of colloid fluid should be restricted to the treatment of more apparent hypovolaemia while minor haemorrhage (up to 500 mL) can be safely treated with a balanced crystalloid. Thereafter, there is a "window" until the transfusion trigger is reached where further use of crystalloid fluid will result in interstitial oedema and, in particular, is likely to have undesired effect on gastrointestinal function and wound healing. As a rule, crystalloid fluid administration should not exceed 3.5 L during abdominal surgery [13] and this target is easily exceeded if major haemorrhage is replaced by crystalloid fluid. ***Conclusions*** Fluids should be seen as drugs and as such the dose makes the poison. Fluids have indications and contraindications as well as adverse effects and should be dealt with as any other drug we administer to our patients.

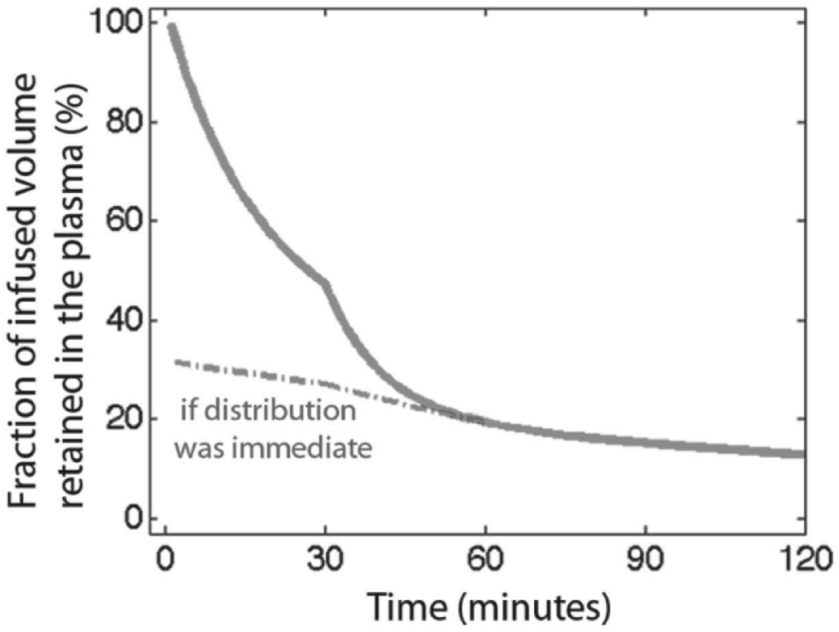


Fig. 1. The plasma volume efficacy of a 30-min infusion of Ringer´s acetate illustrates the importance of distribution for the plasma volume expansion.

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## Optimal administration of fluids can be achieved by targeting the microcirculation.

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***Learning objectives*** 1) Understand the physiology of oxygen transport to tissue in relation to fluid therapy. 2) To appreciate the importance of targeting the microcirculation in this respect. 3) To understand the distinction between convective and diffusive oxygen transport and the way in which fluids affect these physiological variables responsible for oxygen transport to tissue. 4) To review methods for direct observation of the microcirculation. 5) To introduce the latest recently developed vital microscope (Cytocam) based on and a computer controlled image sensor able to automatically analyze images. ***Introduction*** The condition in shock and sepsis where despite correction of systemic oxygen delivery variables, signs of hypoxia regional dysoxia and a deficit in oxygen extraction persist represent the true challenge in the hemodynamic management of the critically ill patient today. ***Methods*** Review of the relevant literature [1—13]. ***Results*** Current evidence shows that the origin of circulatory failure in such patients is not found in alterations in systemic variables, rather in the failure of microcirculatory to transport and the mitochondria to utilize adequately oxygen. These insights have gained clinical acceptance by our introduction of bedside microcirculatory observations using hand held microscopes, initially Orthogonal Polarized Spectral (OPS; commercialized by Cytometrics USA) and later Sidestream Dark Field (SDF commercialized by Microvision Netherlands and KK technologies UK) imaging. The latest generation of these hand held microscopes is and image sensor based computer--controlled device based on Incident Dark Field imaging (the Cytocam; Braedius Medical). Fluid therapy is regarded as the corner stone of hemodynamic support of septic shock patients. However, optimal titration of fluid therapy has remained a challenge, where both composition of fluids and the hemodynamic target to be reached are a source of ongoing debate. Recently identifying hypovolemic patients responsive to fluid therapy by observation of slow perfusion in the sublingual microcirculation was found to be more sensitive than using clinical indicators of hypovolemia. In a porcine study Xu et al recently showed that microcirculatory perfusion to be more effective as a resuscitation target than correction of systemic hemodynamic variables following shock. From these studies it is clear that targeting the microcirculation in fluid therapy may be a much better hemodynamic target than targeting systemic variables such as stroke volume or blood pressure variables or changes therein which can lead to fluid overload. In this way we envisage, that as the study of Pranskunas shows that, patients with low convective flow identify themselves as being hypovolemic in need of fluid therapy. Fluid responsiveness would be defined as the observation that microcirculatory flow increases in response to the administration of fluids. Once maximum functional capillary density has been achieved with optimal convective flow, adequate optimal fluid administration would have been achieved. Too much fluid would be indicated by an excessive reduction of viscosity and loss of capillaries resulting in a reduction in functional capillary density with increased diffusion distances and a reduction of the oxygen delivery capacity of the microcirculation. Such a theory for optimal fluid administration will have to be tested in clinical settings. However routine clinical use of hand held microscopes has not been realized and using the current first (OPS imaging) and second (SDF imaging) generation devices mainly due to their technical limitations and inability to automatically analyze images at the bedside needed for diagnosis and titrating therapy and they have mainly been used for research purposes. Recently, however, a third generation hand held microscope based on Incident Dark Field imaging has been introduced by Braedius Medical with a computer controlled high-resolution high-pixel density digital camera able to instantly analyze and quantify images. This development opens the way for implementation of quantitative microcirculatory imaging for routine clinically use. ***Conclusions*** It is concluded that bedside microcirculatory diagnostics will form an important addition to functional hemodynamic monitoring bringing important missing physiology to the bedside of the critically ill patient.

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## Fluids and traumatic brain injury (TBI)

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***Background*** Trauma is a leading cause of death worldwide and traumatic brain injury (TBI) is one of the commonest injuries. The need for urgent resuscitation is warranted for the prevention of secondary brain insult. The two most important physiological factors that stabilize the internal milieu of the brain are cerebral autoregulation and the blood brain barrier (BBB): both are frequently altered in severe TBI. This also results in misdistribution of osmoles and water within the brain [1—6]. ***Methods*** The purpose of this overview is to discuss fluid therapy in TBI: the most recent evidence on the use of colloids, crystalloids or hypertonic solutions is reviewed, with a specific focus on differences in safety and efficacy and how integration of monitoring parameters may be used to implement more personalized fluid treatment approaches. The key question is: does the type of fluid affects these variables and consequently the patient's neurological outcome? ***Results*** The early management of patients with sustained TBI is aimed at preventing secondary brain injury through avoidance of cerebral hypoxia and hypoperfusion. The goal of fluid management is to establish and maintain adequate intravascular euvolemia to moderate hypervolemia as also a negative fluid balance has been shown to be associated with an adverse effect on outcome. Moreover, intravascular volume depletion due to hemorrhage from associated injuries or polyuria secondary to diabetes insipidus, are common causes of hypotension in TBI patients. The incidence of hypotension in TBI patients is much more common due to extra-cranial injury rather than the isolated head injury. Hence the role of fluid resuscitation becomes crucial to overcome the hypotensive effects of the extra-cranial injury on cerebral hemodynamics and to avoid the development into shock. Moreover even patients with isolated TBI (without extra-cranial bleed) still require fluid resuscitation to preserve optimum cerebral perfusion pressure (CPP). In addition a negative balance of approximately 600 ml or more of the fluid was found to be an independent determinant of poor neurological outcome in severe TBI patients. This balance is delicate: inappropriate fluid administration to achieve intended CPP or MAP is also sometimes associated with hyperchloremic metabolic acidosis, fluid overload or ARDS. ***Discussion*** In general, hypotonic or isotonic crystalloids can aggravate the neuro-inflammatory responses and produce worsening of the cerebral edema and confer no neuroprotection; hypotonic solutions including glucose containing solutions should be avoided in the first 24 to 48 hours, unless the patient develops hypoglycemia in the absence of nutritional support. Isotonic crystalloids, specifically normal saline (NS) solution are the fluid of choice for fluid resuscitation and volume replacement. One study provides evidence that balanced solutions reduce the incidence of hyperchloraemic acidosis in brain-injured patients as compared with saline solutions. Blood and blood products may be used as appropriate. Management of electrolytes disturbances should follow complete volume restoration. Colloids offer a number of theoretical advantages over crystalloids. It is assumed that in severe head injury patients (with disrupted BBB), edema formation would be even worse with the further use of crystalloids. The high oncotic pressure of colloids may decrease the cerebral edema formation and might therefore be associated with improvement in the mean arterial blood pressure (MABP) and decreased neuronal death. However as opposed to this theoretical benefit, some colloids (e.g., hydroxyethyl starch solutions, dextrans) can have serious adverse effects, and albumin products entail higher costs. Few studies indeed report that the oncotic effect generated by colloids does not decrease the cerebral edema formation after TBI. In addition, the administration of colloids is generally not associated with either an increase in the cerebral oxygen delivery, improvement of the overall cerebral oxygenation or a decrease in the raised ICP. In fact some of the synthetic colloids even increase the blood viscosity and cause decrease in systemic rheological property. The results of the influential Saline Versus Albumin Fluid Evaluation (SAFE) trial and a subsequent SAFE subgroup analysis indicate that colloid therapy should even be avoided in patients with trauma and TBI: due to an

increased mortality risk relative to crystalloid therapy. A recent study suggests that the use of albumin for resuscitation in patients with severe TBI is associated with an increased ICP during the first week. Fluids like hypertonic saline-dextran combination have been shown to attenuate the inflammatory cascades involved in TBI. Especially in hypotensive patients, it has been postulated that hypertonic crystalloids and colloids might support mean arterial pressure more effectively by expanding intravascular volume without causing problematic cerebral edema. Hypertonic solutions (HSS) have been shown to decrease brain edema, to reduce elevated ICP and increase MAP and CPP. In one multicenter trial, all hyperosmotic solutions including 15% mannitol, 10% sodium chloride (NaCl), and hyper HES (7.2% NaCl combined with hydroxyethyl starch) were found to decrease the intracranial pressure in acute TBI patients. Among all the solutions, hyper HES had a significantly prolonged effect on reduction in ICP with possible favorable effects on both cerebral as well as hemodynamic parameters. Osmotic diuresis by using mannitol is also an effective method to decrease raised ICP after TBI but should be compensated by adequate fluid replacement with isotonic saline solution to maintain euvolemia. The beneficial effects of HSS are attributed to their unique oncotic property, which reduces the formation of cerebral oedema, and hemodynamic property which keeps the MABP in optimal range. Unfortunately, the overall results of HSS related studies are inconsistent and further clinical trials are needed to define their role. Nine randomized controlled trials and one cohort study have evaluated the effects of hypertonic solutions (with or without colloid added) for prehospital fluid resuscitation. None has reported better survival and functional outcomes over the use of isotonic crystalloids. The only trial of restrictive resuscitation strategies was underpowered to demonstrate its safety compared with aggressive early fluid resuscitation in head injured patients, and maintenance of cerebral perfusion remains the top priority. Conclusion Hypotension is the most amenable to prevention, and should be scrupulously avoided and aggressively managed. There is no evidence that the incidence of intracranial hypertension, morbidity, or mortality is increased by the active maintenance of CPP above 60 mmHg with normalizing the intravascular volume or inducing systemic hypertension. In the context of the published literature on this topic, it appears that the osmolality of an infusion solution rather than the colloid osmotic pressure per se represents the key determinant in the pathogenesis of cerebral edema formation. ***Take home message*** Rather than persisting in a standardized "one size fits all" approach to fluid therapy or continuing down the separate treats of goal directed therapy, one should think more in terms of "individualized therapeutic strategies" more focused on the specific requirements of each TBI patient by using multimodality monitoring of parameters. Until then, crystalloids remain the golden standard, colloids and albumin should be avoided and hypertonic solutions might be considered in TBI patients.

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## Applying the Surviving Sepsis Campaign Guidelines to Clinical Practice


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***Learning objectives*** Discuss updates in the new sepsis guidelines. Highlight implications of new guideline recommendations for clinical practice. Review the use of quality improvement strategies to improve sepsis care. ***Introduction*** Sepsis is a serious worldwide healthcare condition that is associated with high mortality rates, despite improvements in the ability to manage infection. New guidelines for the management of sepsis were recently released that advocate for implementation of evidence based practice care for both adult and pediatric patients. Implementing the new guidelines in clinical care requires a focused effort and has implications for all members of the ICU team to ensure that patients with sepsis receive therapies based on the latest scientific evidence. ***Methods*** The Surviving Sepsis Campaign (SSC) international guidelines are an update from the prior 2008 guidelines, and represent the work of a committee of 68 international experts representing 30 international organizations to outline evidence based recommendations for sepsis treatment. The guidelines use the Grades of Recommendation, Assessment, Development and Evaluation

(GRADE) system to establish the quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1) or weak (2). The updated guidelines outline 85 recommendations, including 62 adult and 23 pediatric suggestions for sepsis care management that have implications for emergency, unit/ward, and ICU care [1—3]. ***Discussion*** Among the new recommendations, specific aspects include a protocolized approach for sepsis resuscitation to ensure consistency in treatment; targeted vasopressor and inotropic therapy for hemodynamic support; broader goals for glycemic control; infection prevention measures; and new areas of focus including nutritional support, and on setting goals of care with patients and families, among other care recommendations. New to the 2012 guidelines is an emphasis on the performance improvement process in sepsis care. Data collection related to the 3 and 6 hour sepsis bundles as well as specific guideline recommendations can serve as a mechanism to improve sepsis care. Through decreasing clinical variation in patient care management, increasing adherence to the evidence based guidelines, monitoring processes, and measuring outcomes, the quality of sepsis care in emergency, unit/ward, and ICU can be improved. ***Conclusions*** The updated SSC guidelines advocate for implementation of evidence based practiced care for sepsis with a number of recommendations that have direct implications for clinical care. Implementing performance improvement strategies aimed at early recognition and targeted treatment can further improve sepsis care and patient outcomes. ***Take home message*** Clinical application of the new sepsis guidelines requires a quality improvement approach to improve the identification of severe sepsis and to implement the new guidelines, targeting multidisciplinary and multispecialty involvement, bridging emergency care, unit/ward, and ICU care.

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## Choice of fluids in trauma


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***Introduction*** In severe trauma macrocirculation, microcirculation, and tissue perfusion are impaired due to massive blood loss. Infusion strategy aims at restoring the volume of the intravascular space and, thereby, facilitating oxygen transport. The clinical questions include indication and differential indication of crystalloidal and colloidal fluids, clinical targets, and dosing. Material and methods Review of the relevant literature. ***Results*** Intravenous fluids are required in order to restore microcirculation and to prevent organ dysfunction and death in massive bleeding. Deliberate hypotension is recommended in uncontrolled traumatic hemorrhage [4]. In general pre-warmed fluids should be administered in order to prevent hypothermia-dependent coagulation disturbance [4]. In hemorrhagic shock with lactate acidosis, additional hyperchloremic acidosis due to saline-based infusions should be avoided by the use of chlorine-balanced solutions. Various crystalloidal and colloidal solutions are available. In a pathophysiology-driven approach crystalloids are indicated to replace extravascular deficits and colloids are indicated for intravascular volume replacement. The use of crystalloids only cannot fulfil a pathophysiology-driven fluid strategy because of high volume loss into the interstitial compartment [5]. Traditionally in countries with predominant crystalloid resuscitation, coagulation management is based on a 1:1:1 ratio concept of red blood cell concentrates *vs*. fresh frozen plasma (FFP) *vs* platelet concentrates. Ratio-based transfusion regimens deliver relevant amounts of volume (3 components together about 600 ml). The volume expanding capacity of the 8.5% protein solution in FFP, however, is unknown. Albumin is used in some countries as an endogenous colloidal solution in massive bleeding but both FFP and albumin also have their disadvantages, risks, and costs. Coagulation factor concentrate-based coagulation management deliver procoagulant activity in small carrier solutions (50 ml) and synthetic colloids with a context-sensitive volume expanding effect of around 100% are often used in this regimen [1]. Synthetic colloids, however, may aggravate trauma-induced coagulopathy by inducing intravascular dilutional coagulopathy [3]. Accordingly, maximum doses need to be considered. In acute bleeding the endothelial barrier is suggested to be intact. Dosing of fluids according to the targets of preload optimization and microcirculatory parameters would be useful but are often not applicable in the emergency setting of massive bleeding e.g. early in trauma management. Dosing of catecholamines and fluids according to heart rate and arterial blood pressure is still clinical reality but should be supplemented by repeated blood gas analyses. Head-to-head comparisons of fluid strategies in hemorrhagic shock are scarce but a recent trial comparison showed increased microcirculation and lactate clearance in colloid-treated trauma patients [2]. ***Conclusions*** Fluid strategy in hemorrhagic shock is heterogeneous throughout countries and continents. Studies comparing our traditional regimen are warranted.

In a pathophysiology-based concept chlorine-based crystalloids plus colloids are given individualized according to metabolic (and preload) parameters with monitoring for (dilutional) coagulopathy and active avoidance of overdosing and hypervolemia.

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## The art of de-resuscitation: Systematic review and meta-analysis on the impact of a positive cumulative fluid balance on intraabdominal hypertension and outcome in critically ill patients


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***Learning objectives*** Is fluid overload a cosmetic issue or just bad medicine? Oedema and derailed cumulative fluid balances: are they just collateral damage or do they put the patient in additional danger? What is best: restrictive versus liberal fluid strategies? What is the Ebb and Flow phase of shock? Is anasarc oedema just of cosmetic concern or is it harmful for the organs and eventually the patient? Maybe we need to rethink the 2 hit ischemia-reperfusion model and replace it by a 3 hit model, where unresolved shock will lead to the third hit, the global increased permeability syndrome? We need to move our targets and adapt our goals. Is there an additional effect of early removal of fluids or should we go from early goal directed treatment to late conservative treatment, to late goal directed fluid removal. How should we guide our fluids, should we use barometric or volumetric preload indices? Is there a place for PAL in the de-resuscitation phase? How can we get the right answers to the 4 basic questions: 1) when do I start giving fluids (this about the safety of fluids), 2) when do I stop giving fluids (this is about the risks of fluids), 3) when do I start to empty the patient (this is about the safety of removing fluids), and finally 4) when do I stop emptying the patient (this is about the risks of removing to much fluids)? Old habits die hard but does the good old central venous and capillary wedge pressures still hold against the new volumetric armamentarium? When are barometric indices of preload not working? Why are static filling pressures useless as resuscitation endpoint since they may lead to under- or futile over-resuscitation? Why are volumetric indices better in conditions of increased intrathoracic pressure? ***Introduction*** A positive daily and cumulative fluid balance has been associated with intraabdominal hypertension (IAH) and worse outcomes in adult critically ill patients. ***Methods*** We conducted a systematic review of published and unpublished studies. We searched MEDLINE, PubMed, EMBASE, Scopus, Web of Science, The Cochrane Database, Ovid, clinical trials registries and bibliographies of included articles. Two authors independently abstracted the data on study design, methodological quality, patient characteristics and outcome. ***Results*** Among all identified citations, 1 meta-analysis (albeit only published in abstract form), 10 randomized controlled clinical trials (of which 4 were blinded), 7 interventional studies, 28 observational studies, and 4 case series met the inclusion criteria. All together, a total of 23625 critically ill patients were studied and in 23 studies the intraabdominal pressure (IAP) was also measured. The cumulative fluid balance after one week of ICU stay was more positive in non-survivors with 4.5L (95%CI: 2.9—6.1, $p<0.0001$). Interventions aimed to obtain a restrictive fluid management resulted in a less positive cumulative fluid balance after 1 week of ICU stay with 5.3L (95%CI: 2.8—7.8, $p<0.0001$). Restrictive fluid management resulted in a decreased mortality of 22.2% (compared to 29.1% in patients treated with liberal fluid management), with an accompanying OR of 0.38 (95%CI: 0.28—0.53, $p<0.0001$). Patients with IAH had a more positive cumulative FB after 1 week of ICU stay with 2.9L (95%CI: 1.8—4, $p<0.0001$). Interventions to decrease fluid balance resulted in a decrease in IAP: an average total fluid removal of 6.8 L resulted in a drop in IAP from 21.5 mmHg (range 8—38) to 12 mmHg (range 5—18). ***Conclusions*** A positive cumulative FB is associated with worse outcomes. Interventions to limit a positive cumulative FB are associated with improved outcomes. A positive cumulative FB is associated with IAH. ***Key messages*** Traditional filling pressures are erroneously increased in situations of high intrathoracic pressures (related to IAP or PEEP). In this situation enddiastolic volumes are better preload indicators. Normal values of GEDVI and EVLWI in surgical and septic patients have been described in a recent meta-analysis. The PPV and SVV are not indicators of preload but rather markers of fluid responsiveness (in fully ventilated patients

with a tidal volume above 6ml/kg and in regular sinus rhythm). Pay attention to the fact that increased IAP may increase baseline values of SVV and PPV, so higher thresholds may be needed in order to define fluid responsiveness. Therefore one can start to give fluids when GEDVI (and GEF-corrected GEDVI) is low and PPV and SVV are high. However, before giving any fluids one must always assess fluid responsiveness with the passive leg raising (PLR) test or the end-expiratory occlusion (EEO) test taking into account that IAP may also have an impact on the interpretation of these tests. Measurement of flow (CI) alone does not allow you to discriminate between over- and underfilling. One must stop filling when GEDVI (or GEF corrected GEDVI), SVV and PPV return to normal or when EVLWI starts to increase above 10 mL/kg PBW. After the initial resuscitation phase an even more important question that needs to be answered is: "when to stop filling?" EVLWI can guide you to get rid of the excess fluids by initiating diuresis with frusemide or starting CVVH with ultrafiltration as was recently shown. So I start emptying my patient when IAP or EVLWI increase and when the daily or cumulative fluid balance is positive. Finally one must stop emptying the patient when IAP and EVLWI normalise, when cumulative fluid balance gets close to zero, or hen central venous oxygen saturation ($ScvO_2$) decreases. Off course if hepatosplanchnic perfusion is compromised (as evidenced by a low plasma disappearance rate of indocyanine green) one must stop emptying the patient since a dry liver leads to a dead patient!

## There is more to fluid responsiveness than a dancing curve: meet the experts

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***The heart-abdomen interactions*** In theory, the interactions between the abdomen and the heart might have three cardiovascular consequences. First, an increase in intraabdominal pressure might be transmitted to the thorax and thus to cardiac cavities through the diaphragm. Due to its high wall compliance, the right atrium is the cardiac cavity that is the most exposed to this pressure transmission. This might induce an increase in the right atrial pressure, which is the downstram pressure of venous return. Simultaneously, the increase in intraabdominal pressure might increase to a larger extent the mean systemic pressure, which is the driving pressure of venous return. In turn, this might increase the pressure gradient of the venous return and the cardiac preload. Nevertheless, in case of hypovolemia, the inferior vena cava might be collapsed by the increased intraabdominal pressure, what might preclude the increase in venous return and cardiac preload. Second, the increase in intraabdominal pressure might also be transmitted to the pulmonary vascular bed. The resultant increase in pulmonary artery pressure increases the afterload of the right ventricle. Third the increase in intraabdominal pressure increases the intramural pressure of the intraabdominal aorta. This might impede the left ventricular ejection, i.e. it might increase left ventricular afterload. Nevertheless, this latter mechanism might have significant consequences only in case of important intraabdominal hypertension. In practice, depending of their respective weight, the mechanisms detailed above might affect cardiac output in a way that is difficult to predict. This should incite to monitor hemodynamics in patients with intraabdominal hypertension. The condition of increased abdominal pressure might affect the markers and the tests that can be used to assess preload status and preload responsiveness. First, increased abdominal pressure increases the intramural right and left ventricular pressures, which overestimate their transmural pressures and thus cardiac filling pressures. In this regard, volumetric markers of preload are more relevant than pressures to assess preload in case of increased abdominal pressure. Second, increased abdominal pressure also affects preload responsiveness indices. The amplitude of the pulse pressure variation is increased and the cut-off that must be considered for detecting fluid responsiveness is increased. It has also been suggested that the passive leg raising test is less reliable in case of intraabdominal hypertension. Finally, since abdominal pressure is the downstream pressure for intraabdominal organs perfusion, the mean arterial pressure, which is the also upstream pressure for any organ perfusion must be targeted at a higher level in case of intraabdominal hypertension to maintain adequate perfusion of intraabdominal organs. ***The heart: monitoring and imaging techniques*** A complete cardiac monitoring should assess the three components of cardiac function: cardiac preload, contractility and afterload. Cardiac preload can be assessed by pressure markers (central venous pressure, pulmonary artery occlusion pressure, E and E' waves of the mitral flow) or volume markers (left ventricular end-diastolic dimensions with echocardiography and global end-diastolic volume with transpulmonary thermodilution). It must be pointed out that a functional dynamic approach is far more relevant than the static preload approach to make judicious decisions in terms of fluid management (see below). The reference technique for measuring cardiac contractility at the bedside is undoubtedly echocardiography. However, it must be remembered that the left ventricular ejection fraction is not a pure marker of cardiac contractility since it is also influenced by preload and afterload. In practice, this leads to an overestimation of cardiac contractility in case of arterial hypotension and vice versa. An inconvenient of echocardiography in the intensive care unit is

that it does not allow a continuous monitoring. In this regard, transpulmonary thermodilution takes its advantage because of its ease to use. Through automatic calculation of the cardiac function index and the global ejection fraction, it allows to estimate the left ventricular ejection fraction and its changes over time and with treatments. The best marker of cardiac afterload is the mean arterial pressure. In practice in case of vasopressors administration, if the mean arterial pressure does not increase above its normal value, the left ventricular afterload cannot result in a decrease of cardiac output. The heart: fluid management and treatment options On the one hand, due to the shape of the Frank-Starling curve, volume expansion does not always result in the expected increase in cardiac output: all patients are not volume responders. On the other hand, it is now clearly demonstrated that overzealous fluid administration is deleterious, especially in patients with septic shock and acute respiratory distress syndrome. Thus, fluid management should include two types of indices: indices indicating when to start fluid administration and indices indicating when to stop fluid administration: indices predicting fluid responsiveness and indices assessing the risk of fluid administration. Concerning prediction of fluid responsiveness, it is now very clear that static markers of cardiac preload cannot indicate whether a patient will or not respond to volume expansion. The prediction should rather be based on dynamic indices, like the pulse pressure variation, the passive leg raising test or the end-expiratory occlusion test. Concerning indicators of the risk of fluid administration, they should take into account the degree of lung edema and the importance of the pulmonary capillary leak. Transpulmonary thermodilution is the unique method that allows a reliable estimation of extravascular lung water and of pulmonary vascular permeability at the bedside. If elevated, these indices should incite to refrain from using volume expansion for hemodynamic resuscitation. ***Acknowledgements*** Prof. Prof. Monnet and Teboul are members of the Medical Advisory Board of Pulsion Medical Systems.

## Evidence based medicine and hemodynamic monitoring: Live and let live!

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***Introduction*** Just because an idea can be proved doesn't mean it's true and just because an idea is true doesn't mean it can be proved (Lehrer J, The New Yorker, 2010). Critical care medicine is characterized by the careful monitoring and real-time analysis of many physiologic variables. In particular, hemodynamic monitoring is a key component of the management of the critically ill patients, in whom the hemodynamic status may be complex. The monitoring of vital cardiopulmonary variables may enable the identification of underlying pathophysiological processes, the selection of appropriate therapies and the continuous assessment of their impact. And yet, in contradistinction to the expert clinician's belief that hemodynamic monitoring may dramatically influence patient management, the evidence that such monitoring improves patient outcome is small, or more often, absent [1-3]. ***Learning objectives*** With the growing importance and influence of evidence-based medicine (EBM) in recent years, it seems imperative that we should understand if, and how, should this lack of evidence change our practice of hemodynamic monitoring at the bedside. ***Discussion*** Hemodynamic monitoring is used by clinicians as a mean to minimize the uncertainty that often surrounds the patient's hemodynamic status. Using reasoning that is based on pathophysiologic rationale, the collected data serve as a basis for decisions regarding patient management. EBM, on the other hand, advocates the use of current best evidence from clinical research in making decisions about the care of individual patients. Theoretically, this is an attractive concept as it offers a reliable way to cope with the every-day uncertainties of our practice. But in reality, rarely does epidemiology provide the information necessary to treat individuals. Moreover, EBM, per its own definition, de-emphasizes the importance of pathophysiologic rationale in making decisions at the bedside. This major claim of EBM stands in contradistinction to our daily clinical practice, in which pathophysiological rationale serves as the cornerstone of many of our decisions. The randomized controlled trial (RCT) is considered by EBM to provide the highest quality of evidence. However, in intensive care medicine there is a shortage of "gold standard" RCT's to support therapeutic decisions. Moreover, we are repeatedly witnessing the 'decline of truth' effect, namely, that the implementation of new protocols and guidelines that incorporate emerging evidence from the medical literature, is followed by their removal a few years later, when validation trials fail to confirm the initial results. The net effects of these "positive-negative" cycles are loss of faith in medical research, and, more importantly, exposure of patients to costly and potentially harmful treatments. Thus there is a growing realization that RCT's may have significant inherent limitations and that other study designs should be considered for the ICU. The limitations of EBM principles in guiding hemodynamic monitoring are best demonstrated by the example of pulse oximeters. Randomized controlled trials have shown that pulse oximetry does not prevent adverse events nor does it improve patient outcome. And yet, based on many personal daily observations, each clinician is convinced that these simple devices can be life-saving. This is supported by robust data about the significant decline of malpractice claims due to respiratory adverse events in the perioperative period since the introduction of pulse oximetry and capnography into routine monitoring during anesthesia. Hence, 'expert opinion', though lowest in the EBM hierarchy of evidence, may offer better guidance than RCT's,

which, as the case of pulse oximetry demonstrates, may be dangerously misleading. Another example is that of monitoring of cardiac output (CO) in critically ill patients, which, again, is not supported by evidence. If we believe that increasing CO may improve outcome in many of our patients, and if we vigorously apply therapy to achieve this goal, shouldn't the monitoring of CO be considered as a necessary step in achieving this improvement? It certainly makes more sense than relying on clinical examination and vital signs alone, a practice that does not have 'evidence' to justify it either. The automotive, aviation and other industries have introduced technological developments and improvements in order to improve safety and efficiency. And yet, had the speedometer ever been subjected to an RCT before its introduction into modern-day cars? The lack of evidence for our current practice of hemodynamic monitoring is not only due to the limitations of EBM but is also due to the limitations of hemodynamic monitoring itself. First and foremost, patient outcome is dependent on treatment decisions and not on the monitoring modality in and by itself. Secondly, each and every hemodynamic variable that we monitor has inherent limitations and confounding factors, and 'normalcy' does not necessarily mean 'adequacy'. The correct application of hemodynamic data necessitates integration of various variables, and may vary according to patient and situation. Last but not least, a few minutes of inattentive care may impact outcome more than long hours of appropriate diligent monitoring. ***Take home message*** When trying to reconcile EBM principles and our bedside practice of hemodynamic monitoring, we should adopt the recent official multi-society statement about the role of EBM in the practice of critical care medicine (Am J Resp Crit Care Med 2012;185:1117—1124): "The results of clinical research, pathophysiologic reasoning, and clinical experience represent different kinds of medical knowledge crucial for effective clinical decision making. Each kind of medical knowledge has various strengths and weaknesses. No single source of medical knowledge always takes precedence over the others." Disclosure The author is a member of the Medical Advisory Board of Pulsion Medical Systems, Germany.

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## Do we need care bundles in severe sepsis?


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***Introduction*** A large number of trials have demonstrated that protocol-based strategies can reduce variation and cost of critical care medicine and improve morbidity and mortality of critically ill patients. These include protocols for ventilator-weaning, sedation and analgesia, transfusion, and the prevention of ventilator-associated pneumonia and catheter-related blood stream infections. Several protocolized cardiovascular management algorithms have also been proposed for the care of hemodynamically unstable patients, mainly those who have severe sepsis or septic shock. These include the SCCM's practice parameters for hemodynamic support of sepsis in adult patients [4], a pulmonary artery catheter-based algorithm [7], and the Surviving Sepsis Campaign (SSC) 'bundle' for the initial hemodynamic resuscitation of severe sepsis or septic shock, which has been recently updated [1]. These noble efforts to standardize care of patients in septic shock need to be carefully examined because, due to the complexity of hemodynamics in sepsis, the goals of therapy are much more difficult to define with certainty than in other forms of shock. Learning objective This presentation will give a critical analysis on the recently published guidelines and bundles ***Discussion*** A central element in all the above-mentioned protocols is the reliance on specific values of filling pressure (either CVP or PAOP). This is especially true for the SSC 'bundle', which recommends aggressive fluid administration until a value of CVP of 8—12 mmHg is reached (12—15 in ventilated patients) as a first step in the management of shock. However, there is a vast evidence-based consensus that filling pressures are inadequate for the determination of the patient's need for fluids, and that reliance on these parameters may lead to either incomplete fluid resuscitation or to detrimental fluid overload. The second parameter that plays a major role in some of these algorithms is the central venous oxygen saturation ($ScvO_2$), which is regarded as "the gold standard for defining global adequacy of cardiovascular performance". The $ScvO_2$ is indeed an important cardiopulmonary parameter, and yet, a low ScvO2 value tells you that something is wrong but not what to do about it (fluids? inotropes?). The ScvO2 was included in the SSC 'bundle' following the Rivers study [8] in which the mean $ScvO_2$ value of septic patients on admission to the Emergency Department was exceedingly low. However, septic shock is characterized by a low oxygen extraction that is usually associated with misleading normal or high ScvO2 values in the presence of inadequate tissue oxygenation. Of note, none of the patients in the Rivers study had a high $ScvO_2$ and high lactate values, a commonly observed situation in septic patients in the ICU. The SSC resuscitation 'bundle' is still based on

the 2001 single-center Rivers study which has never been replicated and which included an unusual subject pool, namely, a largely minority population with poor health status, who is typically sicker when it seeks care due to lack of medical insurance. The SSC claims that the reported improved survival following the adoption of its guidelines provides the necessary evidence for the efficacy of the hemodynamic resuscitation 'bundle'. However, as administered and studied to date, only the early administration of appropriate antibiotics was found to be independently associated with survival benefit, while the attainment of the CVP and $ScvO_2$ goals did not influence survival. Additionally, while the SSC guidelines have significantly increased, both in volume and in the number of references (135 in 2004, 341 in 2008 and to 636) in 2013, the section devoted to the initial hemodynamic resuscitation (including its 10 meager references has been only slightly updated. It is important to note that all the recommendations that the SSC has decided to include in the sepsis 'bundles' were chosen because they "can be converted into data elements that can be precisely defined, with clearly identified failure modes". According to the Institute of Healthcare Improvement (www.ihi.org), with whom the SSC partnered in order to promote the Campaign, “a bundle must be followed for every patient, every single time. There should be no controversy involved, no debate or discussion of bundle elements. Addition of other strategies not found in the bundles is not recommended”. This approach seems to be in line with other attempts to turn consensus statements into performance measures, pay-for-performance and other tools to critique the quality of physician care. However, even with this massive promotion, compliance with all bundle elements has not reached more than 25% even in those institutions that have actively participated in the data collection of the Campaign, which included more than 15000 patients. Following these sobering compliance rates, the leadership of the SSC has recently issued a statement saying that the new sepsis bundles deemphasize specific targets for CVP and $ScvO_2$, requiring only that those values be measured (!). The SSC leadership further stated that "the decision to give more fluid or add inotropes to the resuscitation should be based on the entire clinical picture", that "in some patients, reaching higher or lower values than these targets may be associated with better hemodynamics", and that "institutions that can bring more advanced technologies to the bedside may do so and use those measurements as part of the total clinical picture for decision making" [2, 3, 5, 6]. ***Take home message*** In conclusion, hemodynamically unstable septic patients should not be treated by a rigid protocol that includes specific targets of physiological parameters which may not be suitable for all patients. Any attempt to protocolize care in septic patients has to use more comprehensive hemodynamic monitoring and has to leave room for individualized clinical judgment. Disclosure The author is a member of the Medical Advisory Board of Pulsion Medical Systems, Germany.

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## Goal directed perioperative monitoring


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***Introduction*** The identification of the actual needs of perioperative fluids has been a persistent controversy among anesthesiologists, surgeons, and intensivists. The risk of inadequate fluid therapy include hypovolemia and end-organ hypoperfusion and congestive heart failure and the negative effects of oedema formation on respiration and wound healing [2—7]. The clinician typically is equipped with limited useful monitoring data and no consensus guidelines on the optimal fluid strategy. In recent years the concept of perioperative goal directed hemodynamic and volume therapy using advanced monitoring technology has shown promising results to answer some of the questions regarding the need for perioperative fluid prescription. ***Discussion*** The main objective of goal-directed fluid management is to maintain tissue perfusion and assuring organ function. Optimization of cardiac output (CO), resulting in the optimization of oxygen supply and demand as well as tissue oxygenation, should be performed at an early stage prior to appearance of organ dysfunction. It is ineffective or even harmful when performed later. The oxygen dept that can result during surgery leads

to a higher incidence of complication such as infections, organ failure and as a final consequence death. Various studies and meta-analyses showed the benefit of intraoperative goal-directed fluid management. A review by Dalfino et al. showed that goal-directed fluid therapy (GDT) is an effective tool in reducing the incidence of infectious complications, and, more specifically, that GDT significantly decreases the rate of surgical site infections, pneumonia and urinary tract infections [1]. During surgery, GDT, by preserving or increasing cardiac output, may protect patients against severe gut ischemia-reperfusion injury and thus decreases the incidence of postoperative infections. These findings could be found in a meta-analysis performed by Giglio et al [2]. They showed that GDT could decrease the incidence of postoperative gastrointestinal dysfunction by maintaining an adequate systemic oxygenation in patients undergoing major surgery. Besides the benefits of intraoperative GDT the profit of GDT during the immediate post-operative period showed reductions in complications and duration of hospital stay. Nevertheless, for a physiological point of view it seems to be obvious that the patient benefits from GDT that starts earlier to prevent intraoperative hypoperfusion, meaning that it should start intraoperatively. Due to the fact that more high-risk patients are undergoing surgery, the perioperative challenge to the anesthesiologist - concerning monitoring and fluid management - has increased and the benefits of goal-directed fluid therapy have become more evident. The technological achievements of hemodynamic monitoring encourage the anesthesiologist in using extended monitoring for this group of patients. However, further development of non-invasive monitoring devices will customize goal-directed fluid therapy for a greater group of patients to provide standardized fluid therapies in the perioperative setting. Nevertheless, there is still a lack of randomized controlled studies comparing the different concepts of fluid-management. ***Conclusion***s Further trials are needed to study the benefits in lower risk patients and long-term effects of perioperative, standardized fluid-management. Interesting research questions for the future will deal with the "right" fluid for goal directed volume optimization – crystalloids or colloids – and its effects on transfusion rate and coagulopathy as well as implementation of a universal scoring system for patient identification.

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## Basic Ultrasound principles principles and techniques


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***Introduction*** Basically, all ultrasound imaging is performed by emitting a pulse, which is partly reflected from a boundary between two tissue structures, and partly transmitted. The reflection depends on the difference in impedance of the two tissues. Basic imaging by ultrasound does only use the amplitude information in the reflected signal. One pulse is emitted, the reflected signal, however, is sampled more or less continuously (actually multiple times). As the velocity of sound in tissue is fairly constant, the time between the emission of a pulse and the reception of a reflected signal is dependent on the distance; i.e. the depth of the reflecting structure. The reflected pulses are thus sampled at multiple time intervals (multiple range gating), corresponding to multiple depths, and displayed in the image as depth. Different structures will reflect different amount of the emitted energy, and thus the reflected signal from different depths will have different amplitudes as shown below. The time before a new pulse is sent out, is dependent of the maximum desired depth that is desired to image. ***Learning objectives*** This talk will cover the basics of ultrasound. The attendant will: 1) Learn what ultrasound is, 2) Understand some ultrasound physics and essential concepts, 3) Understand how an ultrasound image is generated, 4) Understand when to use which transducer, 5) Become familiar with the different knobs on his US machine, 6) Learn to optimise image quality in B mode, and 7) Learn about relevant US artifacts. The course on vascular access ultrasound will cover the techniques of

ultrasound guided puncturing of arteries and veins: learn the different techniques and options, hand-eye coordination, training on 'dummies'.

## Choice of fluids in the critically ill. Where are we now?

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***Introduction*** The years 2012 and 2013 were exciting years for fluid specialists. After decades of treating fluid substitution as a mere method of stabilization, recent large and well-performed trials challenged the traditional way of using the many available solutions [1—6]. ***Results*** The 6S trial confronted the medical world with significant data showing that the use of solutions containing hydroxyethyl starch (HES) had a deleterious effect on kidney function and even mortality [4]. The CHEST-trial, a randomized controlled study looking at the use of crystalloids versus HES in a general ICU population of more than 7000 patients showed that more patients in the HES group were in need for renal replacement therapy [2]. The volume effects in these trials were also smaller than generally accepted (around 1:1.2 instead of 1:3). This lead to the decision by regulatory authorities like PRAC to restrict the use of these solutions to rather small groups of patients with well defined indications in the perioperative setting. Although data showing an advantageous effect of the colloids emerged in the meantime, e.g. in the French CRISTAL-trial, the suspicion is not likely to diminish soon. ***Discussion*** In this lecture we'll try to give a concise overview of the recent data and their consequences for our daily practice in treating the critically ill patient. We'll look at three categories of patients and try to answer three questions Can we still use HES? What are the alternatives? What is the best fluid strategy? First category of patients are those with sepsis, severe sepsis and septic shock. The data in this population are too overwhelming to be ignored, so the answer on the first question is no. This can probably be extended to every patient with (a risk for) acute kidney injury. Although the CHEST trial showed less robust proof in the septic subpopulation than the 6S trial, this can probably be explained by the higher mortality and severity of disease in the latter. Possible alternatives are normal saline, balanced crystalloids, older colloids like gelatins or human albumin. At this time a combination of balanced crystalloids (although no specific proof was delivered in the septic population) and human albumin (especially in the patient group with a higher SOFA score, as shown by the ALBIOS-trial) seems a pragmatic but the most logical choice. Even more emphasis than on the fluid choice needs to be put on the fluid strategy. This was nicely summarized by Myburgh and Mythen in a recent review article in the New England of Medicine in 2013 [3]. Avoiding fluid overload by a restrictive and goal-driven fluid regimen seems to be of paramount importance. Second category of patients concerns the general ICU population. This population was studied in the CHEST-trial, although the most important critique on this data was that colloids were used in an unrealistic way, namely in patients who were already resuscitated before entering the study and colloids being used for conditions beyond their typical indication (acute hypovolemia and tissue hypoperfusion). It is not clear whether this pragmatic approach makes the study less relevant, as it is probably safe to say that the use of colloids beyond this strict indication is (or was) widespread. Multiple meta-analyses and a Cochrane systematic review taking older data into account discarded the potential benefits of the colloids (greater volume effect, shorter time to hemodynamic stabilization,…) and concluded against the use of colloids in this setting. Regulatory authorities seem to follow the recommendations made. Alternatives are balanced crystalloids, e.g. PlasmaLyte, as Yunos and co-workers elegantly showed a reduction in acute kidney failure by banning chloride-rich solutions from the ICU [7]. There is a lack of data to stimulate the use of other colloids like gelatins or human albumin (except for specific situations in the latter case). Again a rather restrictive and goal-directed fluid approach is important. The third and last category is the perioperative setting. There are no hard data to extend the data on HES derived from the aforementioned trials to this population. A recent meta-analysis by Van der Linden et al. showed no indication that the use of tetrastarch during surgery induced negative effects on kidney function, blood loss, need for transfusion or mortality [6]. On the other hand there is a lack of data looking at the long-term effects of HES and this is the reason PRAC put emphasis on the long term follow up of patients' kidney function, although the practical consequences of this directive remain to be seen. Conclusions With the actually available data there is no reason to abandon the use of third generation tetrastarch in the strict indication of acute hypovolemia, blood loss or hypotension with proof of tissue hypoperfusion at the moment. Well performed trials are needed urgently. Possible alternatives are again the balanced crystalloids. In a retrospective study Shaw et al showed Plasmalyte to be superior over normal saline regarding morbidity and cost effectiveness. There is absolutely no proof that gelatins can overcome the problems of the starches and their short half-life has a negative impact on their practical use. Maybe there will be a role of iso- or hyperoncotic albumin preparations especially in surgery were high volume substitution is required (e.g. cardiac surgery), but evidence is missing at this time. Many studies on goal-directed perioperative optimization have proven in the mean-

time that the ideal way to use any solution is to appreciate the effect of fluid challenges and administering fluid driven by the right parameter. ***Take home message*** To conclude, fluid substitution got the stepmother treatment for way too long and it is good to see this important part of our daily practice evolving from a tradition-based towards a scientific-driven approach.

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## All you ever wanted to know about nutrition after the ePanic attack


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***Learning objectives*** Define a reasonable strategy to optimize nutrition in the critical care setting. List key variables to consider in obtaining nutritional adequacy. Describe the evidence related to optimal amount of calories. ***Introduction*** Nutritional deficits will eventually lead to adverse outcomes and prolonged critical illness will eventually lead to a state of malnutrition. Important clinical level 1 studies and meta-analyses have been published in the past 2 years that assist the practicing intensivists in choosing a nutritional support plan for his patients. The current presentation will review a number of practical issues concerning nutritional support in the critically ill patient. ***Methods*** Review of peer reviewed publications in Pubmed [1—4]. ***Results and main message*** A nutritional screening process should always precede the provision of artificial nutrition. Scores, such as the Nutritional Risk Score or the Nutric score are imperfect options. The caloric target should be individualized, even though we do not really know if or how many exogenous macronutrients can prevent or correct a nutritional deficit in most of our patients. Indirect calorimetry has never been shown in level one RCTs to improve outcome. The methodology is neither applicable in most ICUs nor in many patients. Therefore, formulas for calculating caloric target are still the recommended albeit flawed tool. There is good evidence for preferring enteral nutrition (EN) over parenteral nutrition (PN) and there are sufficient scientific arguments to advocate early EN within 24 to 48 h of admission. The gastric residual volume is the most frequently used parameter for monitoring tolerance to EN. As compared to the past, threshold values for intolerance can definitely be relaxed to values of 300 ml and above. Controversy about the risks or benefits of hypocaloric versus normocaloric (feeding to target) feeding has been ongoing for decades. Strong evidence has emerged from three recent level 1 trials that at least for the first week of ICU stay there is no benefit from a normocaloric feeding strategy. A hypocaloric regime might even be advantageous for outcome. Key message The quality of clinical research aimed at optimizing nutritional strategies in the critically ill has improved significantly in recent years and is filling important knowledge gaps.

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## Advertorial: revolution in the world of fluids

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***Introduction*** The World of intravenous fluids is drastically changing. Over the last two centuries, fluid management was not the focus for most clinicians or researchers. Intravenous (IV) solutions were administered to patients without clear rules or education, simply out of habit. Fluids were not considered to be medication themselves. Crystalloids The use of IV solutions as part of a treatment began with crystalloids when T. Latta used IV saline in 1831 during the cholera epidemic in England [7]. Then, Ringer's work demonstrating that river water containing inorganic salts could replace blood for a time and had positive effects in many tissues [6]. Alexis Frank Hartmann developed the first balanced crystalloid, by adding sodium lactate to Ringer's solution [6], to act as a natural buffer. Other researchers subsequently developed newer solutions closer in characteristics to plasma, e.g Ringer's acetate, Plasma-Lyte 148 (pH=7.4). Colloids Among the colloid solutions, the modern use of albumin, naturally derived from plasma, was first documented in World War II to treat sailors severely burned during the attack on Pearl Harbor [8, 15], while synthetic colloids, such as gelatins were first administered to humans in 1915 [8], dextrans in 1956 during the Korean War [5, 8, 18], and hydroxyl-ethyl starch (HES) products in the 1970s in the United States [8]. In the 1990s, a prominent anaesthetist, Prof. Joachim Boldt, conducted several studies on HES solutions reporting their benefits compared to other IV solutions. The large number of positive studies published within a short time led other researchers to investigate their veracity. Steven Shafer highlighted concerns to a German state medical association [12,17] who prompted their re-examination. As a result, several studies were withdrawn from the medical literature in 2011 (11 focusing on HES; 88 of 102 in the area of anaesthesia in general) [12]. Clinical studies In 2008, Brunkhorst et al, in the VISEP study, a randomized controlled trial (RCT) of 537 patients with severe sepsis or septic shock who received either a 10% HES 200/0.5 solution or Ringer's lactate, reported no mortality difference between the groups at 28 days, but a trend towards higher risk of death at 90 days in the HES group [1]. This trend was associated with an increased risk of acute renal failure and renal replacement therapy (RRT). In 2012, in the 6S study, conducted in 798 patients with severe sepsis or septic shock randomised into two groups receiving either 6% HES 130/0.42 or a balanced crystalloid solution (Ringer's acetate), Perner at al, reported an increased risk of death at 90 days after randomisation, more bleeding and the patients were more likely to receive RRT than those infused with the balanced crystalloid [11]. Shortly following publication of the 6S study, the CHEST study, another RCT conducted in 7000 critically ill patients admitted to ICUs, also reported a higher risk of RRT, more hepatic failures and adverse events (pruritus, rash) in the HES group (6% HES130/0.40) than in the group receiving an unbalanced crystalloid, 0.9% sodium chloride [9]; however, contrary to the Scandinavian study [11], no differences in mortality were observed between the groups [9]. The outcomes of these three studies [1, 9, 11] led to debates among the scientific community and the Medicines Registration Agencies on the safety of HES products. Metaanalysis In 2013, five meta--analyses [3, 4, 10, 16, 19] confirmed a higher risk of mortality, kidney injury or bleeding in critically ill or severe septic patients receiving HES solutions versus comparators. The overall results of two of them having included Boldt analyses were not influenced whether studies in favour of HES published by Boldt were included or excluded [10, 19]. Contrary to this, a meta-analysis in patients during surgery reported no specific safety concerns with modern starches compared to other IV solutions, without any separate analysis of the potential influence of the results of the single study conducted by Boldt included in it [13]. ***Conclusions*** Based on the results of the VISEP, 6S and CHEST studies, the German Medicines Registration Agency (BfArM) requested a safety risk assessment on HES products for infusion by the European Medicines Agency (EMA) under Article 31 of Dir 2001/83/EC [14]. In June 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended to the EMA-CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human) to suspend all marketing authorisations for HES containing products in all indications (Pharmacovigilance Risk Assessment Committee (PRAC): Press release: PRAC recommends suspending marketing authorisations for infusion solutions containing hydroxyethyl starch, EMA/349341/2013 http://www.ema.europa.eu, accessed October 20th, 2013). This recommendation triggered differing local decisions around Europe, including the suspension of all HES-containing products in the United Kingdom (Medicines and Healthcare products Regulatory Agency (MHRA): Press release: MHRA suspends use of hydroxyethyl starch (HES) drips http://www.mhra.gov.uk, accessed Oct 20th 2013) and Italy (Agenzia italiana del farmaco, Comunicazione sul divieto di utilizzo cautelativo per i medicinali per uso infusionale contenenti amido idrossietilico http://www.agenziafarmaco.gov.it/it/content/comunicazione-sul-divieto-di-utilizzo-cautelativo-i-medicinali-uso-infusionale-contenenti-am, accessed October 20th, 2013). In the UK, the British Medicines and Healthcare products Regulatory Agency (MHRA) triggered then the Article 107i procedure for an urgent decision by the EMA. At the same time, some marketing authorisation holders requested the PRAC to re-examine the safety data for HES solutions. These procedures are still running in parallel - the final recommendation from PRAC is expected in October 2013, to be followed by the CMDh opinion and final decision, and finally by the European commission final decision, anticipated by early 2014. ***Key message*** In the meantime, in order to help clinicians choose appropriate alternatives, the Royal College of Anaesthetists,

with three additional British medical institutions, has published a position statement recommending using physiologically balanced solutions such as Hartmann's solution, Ringer's lactate or Plasma-Lyte 148 over 0.9% sodium chloride . It also mentions to the physicians who prefer to include colloids and who have been using HES until now, the alternative colloids, such as gelatins, highlighting the few and low-quality data showing that fluid resuscitation with gelatin is achieved with a lower volume than with crystalloid, and their risks of acute kidney injury and anaphylactic reactions . Finally, this paper supports the international Surviving Sepsis Campaign recommending, for patients with severe sepsis or septic shock, to use crystalloids as initial fluid of choice, suggesting the use of 4.5% human albumin solution for the patients with septic shock who require large volumes of crystalloid [2]. Following this position statement, the MHRA published a press release (http://www.mhra.gov.uk/NewsCentre/Pressreleases /CON287028, accessed Oct 20th 2013) referring to Professor J. Bion, Dean of the Faculty of Intensive Care medicine in the UK, supporting the position of the Royal College of Anaesthetists. ***Acknowledgements*** This information is accurate at the time of writing and the situation may change due to appropriate actions by regulatory authorities. At the time of submission of this paper, the final decision of the EMA-CMDh is pending.

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## Advertorial: Plasma-Lyte 148, physiological balanced crystalloid, as an alternative to HES solutions

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***Introduction*** For many years, hydroxyl-ethyl starches (HES) have been preferred over crystalloids in fluid resuscitation as they remain longer in the intravascular space and rapidly restore normovolaemia. Crystalloids, which readily cross capillary membranes, increase the risk of interstitial oedema. Recently, this phenomenon has been explained by the primary role of the glycocalyx, a layer of polysaccharides and transmembrane proteins that coats the luminal membrane of the vascular endothelium, which retains colloids within the vessels [5, 7, 8, 11, 25]. Acting as a competent barrier between blood cells and endothelium, the intact glycocalyx can contribute to the prevention of interstitial oedema [11]. Nevertheless, in illness and injury [5, 7,16,25], e.g. stress [25], inflammation [7, 16], septic shock [6, 9, 18, 20], trauma [18] or after major surgery [6], the glycocalyx is impaired, allowing fluids to shift to the extravascular space, independent of molecule size or type of IV solutions [6, 16, 20]. The question, then, is how this may impact patients and IV fluid management. Clinical studies In the 6S study conducted in patients with severe sepsis or septic shock [17], similar quantities of 6% HES130/0.42 and balanced crystalloid (Ringer's acetate) were administered, meaning higher volumes of HES were used than would be anticipated in a population without severe sepsis. This suggests that the overload of HES could have been associated with the adverse effects reported by Perner et al, in which HES patients required more renal replacement therapy (RRT) use and had a higher mortality. In the discussion, the authors explain that these negative outcomes may have been due to the high

fraction of HES deposited in tissues and not metabolised, having then long-term toxic effects, causing the late deaths observed in this trial and in the VISEP trial [2]. Other studies, VISEP and CHEST, conducted in patients with severe sepsis or critical illness [2, 15] also report increased renal dysfunction or more need for RRT use in HES groups compared to crystalloid groups, despite lower administered volumes of HES than crystalloids. Consequently, further studies may be needed to confirm if the association between the negative outcomes and HES solutions is due to the HES itself or if the adverse outcomes can be solely attributed to the amount of volume infused, or if the risks are only found in certain populations. Results Due to the safety issues reported in these studies [2, 15, 17] and on demand of the German Health Authorities (BfArM), the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) performed a risk/benefits analysis of HES products, and recommended their suspension [21]. Until the European regulatory authorities make a definitive decision on the licensing of starch-based fluids, clinicians may wish to consider the position statement of the Royal College of Anaesthetists and other medical societies of the United Kingdom, recommending against the use of HES products and proposing alternatives in resuscitation [22]: "in most cases, fluid resuscitation should be undertaken with crystalloids containing sodium in the range of 130—154 mmol/L; the use of physiological balanced crystalloids, such as Hartmann's, Ringer's lactate or Plasma-Lyte 148 should be preferred over 0.9% sodium chloride". Alternatively, gelatins could be considered but need to be used while understanding the risk of acute kidney injury and anaphylactic reactions; For patients with severe sepsis or septic shock, the use of crystalloids is recommended as the initial fluid of choice, while 4.5% human albumin solution may be considered for the patients who require large volumes of crystalloid. Balanced solutions As recommended, physiological balanced crystalloids should be considered over unbalanced (0.9% sodium chloride). 0.9% sodium chloride contains the same amount of chloride as sodium, i.e. 154 mmol/L, and no buffers or additional electrolytes. Physiological concentrations of sodium and chloride in blood are 136—145 mmol/L and 98—106 mmol/L, respectively [10]. High concentrations of chloride perturb the acid-base balance, decreasing the strong ion difference (SID), as defined by Stewart as SID (mmol/L)=[Na+]+[K+]-[Cl–], inducing a hyperchloraemic metabolic acidosis [1, 10, 12]. Consequently, infusions of sodium chloride increase the serum chloride concentration [3, 4, 14, 23, 24], may exacerbate a pre-existing metabolic acidosis [4, 13] or slow its resolution [4], potentially impair renal function and induce more major complications (postoperative infections, renal failure requiring dialysis, need for more blood transfusion, electrolyte disturbance) when compared to Plasma-Lyte 148 [14]. Plasma-Lyte 148 is a physiologic balanced crystalloid. Its physiologic concentration of chloride (98 mmol/L) has been shown to minimise the risk of kidney injury in critically ill patients compared to chloride-rich solutions, such as 0.9% sodium chloride, 4% gelatin or 4% albumin 20. Because it does not contain lactate, a bicarbonate precursor predominantly dependent on hepatic metabolism, Plasma-Lyte 148 is not restricted in patients with liver dysfunction. Finally, the absence of calcium avoids potential citrate chelation, which could impact coagulation, and thus permits concurrent Plasma-Lyte 148 infusion with any blood transfusion. All IV solutions are not the same. Key message All i.v. fluids are medications; their composition directly affects patient outcomes. Low chloride concentrations have shown clear benefits in critically ill patients. New processes based on evidence, change of prescribing habits, and education of healthcare professionals need to be implemented. Plasma-Lyte 148, as a physiological balanced crystalloid, should be considered for fluid management in patients with mild to moderate metabolic acidosis as indicated in resuscitation (e.g. after burns, head injury, fracture, infection, and peritoneal irritation), intraoperative fluid replacement or for haemorrhagic shock and clinical conditions requiring rapid blood transfusions. ***Acknowledgements*** This information is accurate at the time of writing and the situation may change due to appropriate actions by regulatory authorities. At the time of submission of this paper, the final decision of the EMA-CMDh is pending.

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## Nutrition after an ePanic attack

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***Learning objective*** Inform about relevant publications for optimal critical care nutrition since the publication of the EPANIC trial in 2011. Inform about the effects of normocaloric versus hypocaloric feeding strategies. ***Introduction*** In critically ill patients the administration of parenteral nutrition almost guarantees the prevention of a caloric deficit. However, in 2011 the EPANIC trial showed that during the first week of ICU stay a substantial caloric deficit is not detrimental for outcome and thereby questioned the intrinsic value of PN in this time frame [1—9]. Indeed, withholding PN and not reaching the currently recommended caloric targets seemed to be of benefit for the vast majority of critically ill patients during the first 7 days. The current presentation will review relevant publications from the past 2 years and contrast them with the results of the EPANIC trial. ***Methods*** Review of peer reviewed publications in Pubmed [1—9]. ***Results*** Relevant studies addressing hypocaloric versus normocaloric feeding included the following. In a large, randomized trial (the EDEN trial, n=1000) conducted in critically ill patients with acute lung injury, Rice et al. compared "trickle enteral feeding" to "full enteral feeding" [9]. Trickle feeding resulted in a large cumulative energy debt (after 6 days a mean of 1300 kcal/d versus 400 kcal/d). However, morbidity and mortality were not different. Follow-up after one year also showed no difference for physical function, survival or multiple secondary outcomes. A second smaller (n=305) randomized trial assessed whether delivery of 100% of the energy target from day 4 to 8 in ICU with EN plus PN as opposed to only EN could optimize clinical outcome [4]. This controversial study concluded that optimizing individual energy delivery with the aid of indirect calorimetry could reduce nosocomial infections. A third randomized trial addressed early PN versus standard care in 1372 critically ill patients with relative contraindications to early EN [3]. In the standard care group 29.2 % of patients commenced with EN, 27.3% with PN and 40.8% remained unfed for variable periods of time. There was no significant difference between groups for either the primary endpoint (death by study day 60) or for ICU or LOS. Time on mechanical ventilation was significantly reduced by 0.47 days with early PN. Finally, subanalysis of the EPaNIC trial showed that a) tolerating a substantial macronutrient deficit early during critical illness did not affect muscle wasting but allowed for faster recovery from weakness and b) that caloric dose had a negative inverse relation with infectious morbidity [2,5]. Other relevant observations from RCTs of the past two years with potential impact for clinical practice include: early provision of glutamine or antioxidants did not improve clinical outcomes and not monitoring gastric residual volume did not increase the rate of VAP [6,8]. ***Conclusion*** Strong evidence from several RCTs supports the conclusion that tolerating a substantial caloric deficit in the first 5 to 7 days of ICU stay will influence mortality or length of stay. However, best evidence indicates that hypercaloric or even normocaloric feeding during this time frame will worsen morbidity.

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