Special Article

The Rise and Fall of the Third Space: Appropriate Intraoperative Fluid Management

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Keywords: *Perioperative fluid therapy, Intracellular fluid, Extracellular fluid, Third space, Fluid shifts*

J Med Assoc Thai 2013; 96 (8): 1001-8
Full text. e-Journal: *http://jmat.mat.or.th*

Perioperative fluid therapy has received considerable attention recently as the adverse effects of both fluid overload and restriction are realized in different settings. Formulae for type, quantity, or timing of fluids in diverse situations are lacking. In addition, can we, as perioperative physicians, influence outcome or has that already be predetermined by the patient's condition, as many would believe? Many studies address these issues. Conflicting results have been reported. Critical review of clinical trials reveals that current standard fluid therapy is hardly evidence-based and has been challenged for years[1]. Almost a century ago, Cannon pointed out that the administration of fluids before operative control of an injury was ineffective[2]. In the trauma arena Bickell emphasized the benefit of surgical correction before resuscitation noting that fluids and restoration of blood pressure could dislodge a soft clot and cause more bleeding[3]. However, during both the Korean and Vietnam campaigns, large fluid volume resuscitation was advised by the United States military to maintain renal perfusion (and the Da Nang lung was born).

The Fluid Compartments

Intracellular fluid (ICF) makes up approximately 60 to 65% of body water, and extracellular fluid (ECF), makes up the other 35 to 40% of body water (for all practical purposes, the only solvent in the body is water). In essence there is an intravascular and an extravascular space. The third space is some space in the body where fluid does not normally collect in large amounts, or where any significant fluid collection is physiologically non-functional.

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Fluid shifts occur when the body's fluids move between these compartments. Physiologically, this effect occurs by a combination of hydrostatic and osmotic pressure gradients. Water moves from one chamber into the next passively across a semi-permeable membrane until the hydrostatic and osmotic pressure gradients balance each other. Many medical conditions can cause fluid shifts. When fluid moves out of the intravascular space (the blood vessels), blood pressure can drop to dangerously low levels, endangering critical organs such as the brain, heart and kidneys. When fluid shifts out of the cells (the intracellular space), cellular processes slow down or cease from intracellular dehydration. Fluid shifts into brain cells can increase intracranial pressure or into the lungs and decrease adequate respiration and gas exchange. Fluid shifts may be compensated by fluid replacement in the case of dehydration or diuretics if there is overload or pump (heart) failure.

Third spacing has been suggested as the physiological phenomenon by which body fluids accumulate in the third space, a space where this fluid has no effect or useful activity. The term is commonly used with regard to burns, major trauma, pancreatitis, or ileus. In these latter two conditions, fluid leaks out into the abdominal cavity. The term also can refer to ascites and pleural effusions. Patients who are operated, especially when the surgery is long and the incision extensive are said to collect third-space fluids and become intravascularly depleted despite large volumes of intravenous fluid and/or blood replacement. However, extensive tissue swelling, (edema), occurs when the third space fills with excess fluid as may be seen in any dependent parts or in the intestinal walls or the lungs. The actual volume of fluid in a particular patient's third space is difficult to quantify accurately because identification of this space is difficult. Indeed, the "space" may be anywhere. About the operative experience, the third space is said to be related to the surgical experience and thus requires special attention. It came into being more than 50 years ago.

The Third Space; Discovery

A surgical team in Texas studied two groups of patients in an attempt to understand more closely the acute changes that determine the perioperative management of fluids and electrolytes[4]. The control group consisted of five patients undergoing minor surgery with general anesthesia (cyclopropane and ether) involving minimal tissue trauma and blood loss and the second group (13 patients) had elective major surgical procedures (cholecystectomies, gastrectomies, and colectomies). Plasma volume, red blood cell mass and extracellular fluid volumes were measured in all patients on two occasions during the operative period by using I 131 tagged serum albumin, chromate 51 red blood cells and sulphur 35 tagged sodium sulphate, a method that had previously been used to measure extracellular fluid volume[5]. Simultaneously blood sampling was made from opposite arms. Samples were taken at 10, 20, and 30 minutes after each injection and at 20-minute intervals between injections. Sponges and urine were also collected. Suction blood and all specimens were analyzed for isotopes and hemoglobin content. During this time no fluids or electrolytes were given. In the first group, the extracellular fluid loss was calculated at only 1.4% more than the expected decrease in this space from the actual measured and calculated plasma loss. The loss of extracellular fluid volume in group 2 was calculated as 0% to 28% of the original total body extracellular water. Based on these findings of a decrease in functional extracellular fluid in group 2, the authors concluded that there was internal redistribution of fluid associated with surgery (that is, the third space), which should be replaced by fluid administration. These findings were "confirmed" in an exsanguinated dog model, which did better with immediate fluid rather than only blood replacement[6]. Dogs in which only shed blood was replaced died. The authors concluded that a deficit in extracellular fluid occurred that was not alleviated by blood alone or by expansion with plasma; rather a balanced salt solution should be given in addition to blood to replace this deficit. Arguing against this position, Moore (a surgeon from Boston) had postulated some two years before that a metabolic response to surgical stress caused sodium and water retention and perioperative fluid restriction was indicated[7]. In a four-part treatise published in the New England Journal of Medicine, Moore described the several water and electrolyte changes that occurred during injury, surgery and several diseases, particularly those that related to renal problems. He advised that acute water intoxication is encountered in postoperative patients during a period of postoperative antidiuresis. In other words, secretion of antidiuretic hormone in response to stress results in the accumulation of water and additional saline or other electrolyte solutions is detrimental. Moore also noted that anesthetics, degree of surgical acuity, time, stress, and co-morbidities should also be taken into account. The debate prompted an editorial by the two combatants both of whom urged moderation[8]. Previous regimes had advised either no fluids or copious fluids[6]. However, Shires studies, while emphasizing a need to replace sodium and water, did recommend moderate replacement.

Fluid Formulae

Nevertheless, the excessive fluid doctrine to replace the "third space" won. Protocols were developed that calculated deficits based on degree of trauma, insensible losses and a host of other "variable" fluid decreases, all of which were to be replaced with balanced salt solutions. The 4:2:1 "rule", is found in all major anesthetic and surgical textbooks, where it appears with gospel-like intonation, (1^{st} 0-10 kg requires 4 ml/kg, next 11-20 kg 2 ml/kg, then >21 kg is 1 ml/kg). The explanation for the "rule" is that "it segments the curvilinear relationship between body weight and metabolic rate into 3 linear parts"[9]. The original description of the 4:2:1 rule was derived from a paper by Holliday and Segar who, in an attempt to simplify fluid requirements devised an arbitrary 100-50-20 scheme as a baseline for children[10]. They compared their system to three others[11-13], which considered in turn that:

1. Surface area is a good estimate of water expenditure,

2. Caloric expenditure is based on age, weight, activity and food intake (comparing a rat and a steer) and

3. Urinary volume and insensible losses relate to age.

However, if fluid requirements are proportional to metabolic rate and if basal metabolic rate is related to body surface area then formulae should take into account other factors including neurologic, endocrine, pharmacologic, and cardiovascular status, not to mention other pathologic conditions and the effects of anesthetic agents as Moore had suggested. The concept of preoperative deficit also enters the equation. The case for preoperative fluid loading is based on several assumptions:

1. The preoperative fasted patient is hypovolemic,

2. Insensible perspiration increases with surgery,

3. Fluid shifts to the third space must be replaced and

4. The kidneys can regulate any fluid overload.

After fasting for eight to 10 hours, the normal state after sleep, requirements in the non-comatose individual may be little more than one to two cups of fluid (240-480 ml). Very few patients are likely to require 1,500 to 2,000 ml fluid within the first one to two hours of surgery and perhaps a total of three to six liters over four to five hours, even with a 2-unit blood loss. Pre-operative fasting causes a slight decrease in extracellular fluid while maintaining intravascular volume. Current fasting requirements encourage clear fluids up to two hours before anesthesia. The use of evanescent agents ensures a rapid return to consciousness and the ability to drink. In addition, insensible losses are decreased with laparoscopic incisions and by constant irrigation of the wound. Finally, antidiuretic hormone release during anesthesia severely curtails the ability of the kidneys to remove excess fluid.

Fluid Therapy

There is increasing agreement that excess fluid infusion should be avoided after an initial resuscitation phase and efforts made to keep patients in neutral or negative balance[1,14-16]. Indeed, a critique of fluid bolus therapy (20-40 ml/kg) indicated weak physiological and limited experimental support and is at odds with emerging observational data in critically ill patients or those undergoing major abdominal surgery[17]. Studies indicate that over generous fluid infusions contribute to complications such as pulmonary edema or extravascular lung water, myocardial dysfunction, bacterial translocation and development of sepsis, wound infection, and multiorgan failure[18,19]. Weight gain has been linked to increased mortality and morbidity including acute renal failure, a greater need for postoperative ventilation and longer hospital stay[20]. Even patients who have undergone relatively simple operations but who have received 3-4 liters of fluid over a short period may find that it takes many days to return to a normal weight. Wedding rings may become very tight, for example, requiring that they be cut off before ischemia of a finger sets in. Patients who developed postoperative blindness after lumbar surgery also had a very large positive fluid balance[21]. Tissue oxygenation is increased by supplemental oxygen and not by excess fluids[22]. Comparison of the standard (>3L, normal saline) versus restricted (<2L, 0.45 normal saline) protocols for postoperative fluids after hemicolectomy indicated significantly more complications in the standard group and longer hospital stay[23]. Rather, intravenous fluid therapy does not result in extracellular volume distribution expected from Starling's original model of semi-permeable capillaries subject to hydrostatic and oncotic pressure gradients within the extracellular fluid[24,25]. Other studies have reported a reduction of airway complications with fluid management fluid protocols (reduction form 6l-4l) during cervico decompression and fusion surgeries[26]. During free flap surgery, flap survival is improved when a regimen of decreased fluid administration with anticoagulant therapy is instituted[27]. Fluid overload in the presence of an epidural anesthetic has been shown to be deleterious in the healing of colonic anastomosis[28].

The contribution of the endothelial glycocalyx to vascular permeability must be considered. Glycocalyx is a general term referring to extracellular polymeric material (glycoprotein). While this sugar coating material is found in many parts of the body, its presence in the vascular system is crucial to the integrity of that system[29]. The glycocalyx is located on the apical surface of vascular endothelial cells that line the lumen. Conventional electron microscopy shows a small, irregularly shaped layer extending approximately 50-100 nm into the lumen of blood vessels. The glycocalyx also consists of a wide range of enzymes and proteins that regulate leukocyte and thrombocyte adherence, since its principal role in the vasculature is to maintain plasma and vessel wall homeostasis. Because the glycocalyx is so prominent throughout the cardiovascular system, disruption to this structure has detrimental effects including fluid imbalance, and edema as shedding of the glycocalyx leads to a drastic increase in vascular permeability. It is disadvantageous for vascular walls to be permeable, since that would enable passage of some macromolecules or other harmful antigens. In fact, maintenance of the glycocalyx is crucial to the health of the cardiovascular system. The structure is easily and rapidly disrupted in sepsis, diabetes, by direct contact with catheters and by large fluid infusions leading to an extravasation of albumin and fluid and tissue edema[30].

Which Fluids?

The choice of fluid has received much attention. During short, ambulatory cases with low surgical risk, it may be of little importance. Intravenous crystalloids remain in the intravascular space for short periods, redistributing quickly to soft and damaged tissue and dependent areas (gut, lungs, and larynx). Edema in the gut wall increases the inflammatory response and retards forward movement. A more serious complication is abdominal compartment syndrome causing respiratory and renal dysfunction and increased epidural bleeding during spine surgery[31]. Excessive crystalloids also increase coagulation abnormalities (dilutional or hypercoagulation), the need for more blood transfusion and delayed wound healing through increased cutaneous edema[32].

Colloidal expanders include albumin and hydroxyethylstarches (HES including Hespan®, Hextend®, Voluven®, and Volvulyte®). Albumin, 5%, or 25% supplied in 100 ml aliquots is derived from pooled human venous plasma, heated to 60 degrees for 10 hours to inactivate hepatitis viruses. It contains no isoagglutinins and thus the risk of adverse reactions is very low. Preparation charges make it significantly more expensive. HES in 0.9% sodium chloride is a synthetic polymer derived from a waxy starch composed of amylopetin. It is supplied in 500 ml bags. Dose related side effects include coagulopathy, renal failure and tissue storage the newer HES 130/0.4 (Voluven®) is said to have a lower risk of side effects[33], although these claims may not have been sufficiently validated[34]. An animal study indicated that goal directed colloid therapy improved tissue oxygen tension and increased microcirculatory tissue oxygen tension (pti02) in healthy and perianastomotic colonic cells significantly more than goal directed crystalloid therapy indicating improved microperfusion and less endothelial swelling[35]. However, several reports including the SAFE (saline versus albumin fluid evaluation) study which compared the use of albumin alone and saline resuscitation in head injured patients found a tendency to increased 24 month mortality in severely injured patients who received only albumin (up to 2 liters on the first day)[36]. Less severely compromised patients tended to do better with albumin. The same authors found that albumin resuscitation produced better survival rates in sepsis patients over saline[37]. In an ongoing attempt to determine the efficacy of colloids, Myburgh et al have mounted a 7,000 patient multicenter randomized controlled trial comparing the effects of 6% hydroxyethyl starch (130/0.4) to normal saline for fluid resuscitation in intensive care patients (CHEST)[38]. Two Cochrane database reviews were unable to determine that albumin reduced mortality when compared to saline in the resuscitation of patients with burns, trauma, or following surgery[39,40]. In a review of 3,456 patients with sepsis, administration of hydroxyethyl starch increased the need for renal replacement therapy and blood transfusion[41]. The VISEP trial that compared intensive insulin therapy with colloid resuscitation looked at 10% HES 200/0.5 and Ringer's Lactate resuscitation in severe sepsis[42]. The use of intensive insulin therapy placed critically ill patients with sepsis at increased risk of adverse events due to hypoglycemia. Colloid was shown to be harmful and its toxicity increased with accumulating doses, especially with regard to the renal system. Given that colloid is significantly more expensive than crystalloid, its use has been questioned. In all these investigations, colloid alone in significantly higher doses was compared to crystalloids. In addition, the study substance in many instances was albumin. The American Society of Anesthesiologists has advocated the combination of colloids and reduced crystalloids in the prevention of POVL[43]. The place of colloids may be as an adjuvant to crystalloid administration whereby the amounts infused of both may be reduced. But it is still not clear as to whether administration of colloids or a reduced volume of crystalloids results in improved patient outcome in all situations or only in certain subsets, or if the newer colloids are indeed harmful. The PRECISE RCT, now underway may provide light on these issues[44].

There is mounting evidence that blood transfusion carries many risks, not only of transmission of infection but also of antigen/antibody reactions among other consequences. Overall, adverse events from transfusions in the US account for about $17 billion- and in effect add more to the cost of each transfusion than acquisition and procedure costs combined[45]. While some complication risks depend on patient status or specific transfusion quantity involved, a baseline risk of complications simply increases in direct proportion to the frequency and volume of transfusion. As a result, many physicians have adopted a so-called "restrictive protocol" during "blood less surgery" -whereby transfusion is held to a minimum- due in part to the noted uncertainties surrounding storage lesion, in addition to the very high direct and indirect costs of transfusions, along with the increasing view that many transfusions are inappropriate or use too many red blood cell units[45]. However, a restrictive protocol is not an option with some especially vulnerable patients who may require transfusion to rapidly restore tissue oxygenation

Intra-operative hemoglobin determinations are far from reliable as an indicator of need to transfuse. Guidelines from the American Society of Anesthesiologists that note that transfusion is rarely needed if the Hb level is 7 gm do not take the patient's age, cardiovascular state or other co morbidities into account or even the rate of blood loss. (Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies. Last amended October 25, 2005).

A time-honored protocol has recommended the replacement of fluid:blood in a ratio of 3:1 ml. The basis for this regime may be found in the properties that allow fluids to leave the intravascular space quickly with less than 1/3 remaining after about 20 minutes. The extravasated fluid collects in dependent places, the abdominal wall, the lungs and all soft tissue areas where it is non-functional, rather creating what is a harmful situation in a third space. There is no rational for such replacement, rather lost blood should be replaced more appropriately by colloids, small amounts of crystalloids or blood (cell saver technique) if indicated by the patient's situation and co-morbidities.

Monitoring Fluid Requirements

Given that the purpose of fluid administration is to maintain vascular volume, cardiac function and tissue oxygenation, assessment of the adequacy of intravascular volume would seem essential in determining the amount, timing, and even type of fluid infused. Cardiac filling pressures and central venous pressures have been used to guide volume therapy but have not been shown to reliably predict volume therapy[46]. An endotracheal (ET) cardiac output monitor incorporated in the cuff of an endotracheal tube has been developed. Based on the principle that the electrical resistance of blood changes when it moves or changes in volume, flexible electrodes on the ET cuff utilize information from an arterial pressure line and thus continuously calculate stroke volume[47]. The transesophageal Doppler, supplying continuous real time objective data, also monitors preload conditions and helps optimize cardiac contractility and the effect of afterload impedance on left ventricular performance[48]. Stroke volume directed administration of hydroxyethyl starch or crystalloid in the sitting position craniotomy resulted in a 34% smaller volume of the colloid and less positive fluid balance, of importance in patients with decreased intracranial compliance[49].

However, perhaps of even greater and more practical value is goal directed fluid management based on pulse oximeter plethysmogram variations (pleth variability index; PVI). Decrease in the arterial pulse pressure variation induced by mechanical ventilation has been appreciated for decades as an indicator of hypovolemia. Computerized analyses have incorporated information from the pulse oximeter arterial wave- form to provide a continuous display of arterial pressures, stroke volume, cardiac output, pulse pressure variation, and stroke volume variation. In one study, PVI-guided fluid therapy resulted in less crystalloid administered perioperatively and significantly reduced lactate levels[50]. Thus, fluid versus vasopressor therapy can be tailored to individual patient's needs rather than general application of formulae. In a study of patients undergoing high-risk surgery, a multicenter study showed that fluid administration based on stroke volume variation and stroke volume was not only feasible but also decreased postoperative wound infection[51].

A critical complication of excessive fluid administration is the development of extravascular lung water. Quantification of non-hydrostatic pulmonary edema may be used to predict mortality and morbidity and be employed as a guide to fluid therapy and ventilator strategies[52-54]. Bedside assessments may be made using dilution methods and by ultrasonography, monitors that may soon become standard in ICU settings.

Nevertheless, clinicians continue to rely on central venous pressure (CVP) monitoring despite many studies indicating that it is insufficient as a surrogate parameter for assessing volume status and is unable to predict fluid responsiveness[55-57]. Only in situations of fluid overload may CVP be of minimal benefit[58]. Moreover, the closed claims analysis of the American Society of Anesthesiologists indicated that claims related to central catheters not only had increased significantly recently but also had a high severity of patient injury[59].

Concluding Statement

It would appear that in most cases there is a need to restrict and reevaluate perioperative fluid management. As fasting times are reduced and anesthetic agents more evanescent, pre-operative volume loading is rarely necessary. The classic "third space" does not exist. Both crystalloid and colloid overload have deleterious effects. Routine replacement of insensible losses is unnecessary. Demand related regimens should be followed rather than central pressures to improve patient outcome. Restricting excessive administration of fluids that are quickly redistributed outside the vascular space minimizes perioperative shifting. Fluid balance should be maintained. Excessive intravenous fluid therapy and positive fluid balances correlate directly with patient morbidity and mortality. Blood replacement should be undertaken with caution.

However, traditions die hard. Evidenced-based medicine is still in its infancy. We still believe (in spite of all the evidence to the contrary) that blood pressure, heart rate, urine output, blood loss can all be "optimized" by giving more fluid. So when parameters fall out of range, we tend to give more fluids, without looking further for other causes of the perturbations. Evidence against this action is mounting.

Potential conflicts of interest

None.

References

1. Singer M. Management of fluid balance: a European perspective. Curr Opin Anaesthesiol 2012; 25: 96-101.
2. Cannon WB. The course of events in secondary wound shock. JAMA 1919; 73: 174-81.
3. Bickell WH, Shaftan GW, Mattox KL. Intravenous fluid administration and uncontrolled hemorrhage. J Trauma 1989; 29: 409.
4. Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. Ann Surg 1961; 154: 803-10.
5. Shires T, Williams J, Brown F. Simultaneous measurement of plasma volume, extracellular fluid volume, and red blood cell mass in man utilizing I-131, S-35-labeled sulfate, and Cr-51. J Lab Clin Med 1960; 55: 776-83.
6. Shires T, Coln D, Carrico J, Lightfoot S. Fluid therapy in hemorrhagic shock. Arch Surg 1964; 88: 688-93.
7. Moore FD. Common patterns of water and electrolyte change in injury, surgery and disease. N Engl J Med 1958; 258: 277-85, 325-33, 377-84, 427-32.
8. Moore FD, Shires T. Moderation. Ann Surg 1967; 166: 300-1.
9. Tonnesen AS. Crystalloids and colloids. In: Ronald MD, Miller D, editors. Anesthesia. 4th ed. New York: Churchill Livingstone; 1994: 1595-617.
10. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics 1957; 19: 823-32.
11. Crawford JD, Terry ME, Rourke GM. Simplification of drug dosage calculation by application of the surface area principle. Pediatrics 1950; 5: 783-90.
12. Darrow DC, Pratt EL. Fluid therapy; relation to tissue composition and the expenditure of water and electrolyte. J Am Med Assoc 1950; 143: 365-73.
13. Wallace WM. Quantitative requirements of the infant and child for water and electrolyte under varying conditions. Am J Clin Pathol 1953; 23: 1133-41.
14. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36: 296-327.
15. Doherty M, Buggy DJ. Intraoperative fluids: how much is too much? Br J Anaesth 2012; 109: 69-79.
16. Sadaka F, Juarez M, Naydenov S, O'Brien J. Fluid resuscitation in septic shock: the effect of increasing fluid balance on mortality [Internet]. J Intensive Care Med 2013 [cited 2013 Apr 3]. Available from: http://jic.sagepub.com/content/early/2013/02/27/0885066613478899.full.pdf
17. Hilton AK, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. Crit Care 2012; 16: 302.
18. Joshi GP. Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. Anesth Analg 2005; 101: 601-5.
19. Bajwa SS, Kulshrestha A. Diagnosis, prevention and management of postoperative pulmonary edema. Ann Med Health Sci Res 2012; 2: 180-5.
20. Gan TJ, Soppitt A, Maroof M, el Moalem H, Robertson KM, Moretti E, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002; 97: 820-6.
21. Grover V, Jangra K. Perioperative vision loss: A complication to watch out. J Anaesthesiol Clin Pharmacol 2012; 28: 11-6.
22. Kimberger O, Fleischmann E, Brandt S, Kugener A, Kabon B, Hiltebrand L, et al. Supplemental oxygen, but not supplemental crystalloid fluid, increases tissue oxygen tension in healthy and anastomotic colon in pigs. Anesth Analg 2007; 105: 773-9.

23. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet 2002; 359: 1812-8.
24. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth 2012; 108: 384-94.
25. Becker BF, Chappell D, Jacob M. Endothelial glycocalyx and coronary vascular permeability: the fringe benefit. Basic Res Cardiol 2010; 105: 687-701.
26. Hart RA, Dupaix JP, Rusa R, Kane MS, Volpi JD. Reduction of airway complications with fluid management protocol in patients undergoing cervical decompression and fusion across the cervico-thoracic junction. Spine (Phila Pa 1976) 2013 May 3. doi: 10.1097/BRS.0b013e31829914ed.
27. Brinkman JN, Derks LH, Klimek M, Mureau MA. Perioperative Fluid Management and Use of Vasoactive and Antithrombotic Agents in Free Flap Surgery: A Literature Review and Clinical Recommendations. J Reconstr Microsurg 2013 Apr 18. doi: 10.1055/s-0033-1343955.
28. Nessim C, Sideris L, Turcotte S, Vafiadis P, Lapostole AC, Simard S, et al. The effect of fluid overload in the presence of an epidural on the strength of colonic anastomoses. J Surg Res 2013 Mar 27. doi: 10.1016/j.jss.2013.03.030.
29. Reitsma S, Slaaf DW, Vink H, van Zandvoort MA, oude Egbrink MG. The endothelial glycocalyx: composition, functions, and visualization. Pflugers Arch 2007; 454: 345-59.
30. Chung FT, Lin HC, Kuo CH, Yu CT, Chou CL, Lee KY, et al. Extravascular lung water correlates multiorgan dysfunction syndrome and mortality in sepsis. PLoS One 2010; 5: e15265. doi: 10.1371/journal.pone.0015265.
31. McNelis J, Marini CP, Jurkiewicz A, Fields S, Caplin D, Stein D, et al. Predictive factors associated with the development of abdominal compartment syndrome in the surgical intensive care unit. Arch Surg 2002; 137: 133-6.
32. Roche AM, James MF, Bennett-Guerrero E, Mythen MG. A head-to-head comparison of the in vitro coagulation effects of saline-based and balanced electrolyte crystalloid and colloid intravenous fluids. Anesth Analg 2006; 102: 1274-9.
33. James MF. The role of tetrastarches for volume replacement in the perioperative setting. Curr Opin Anaesthesiol 2008; 21: 674-8.
34. Hartog CS, Bauer M, Reinhart K. The efficacy and safety of colloid resuscitation in the critically ill. Anesth Analg 2011; 112: 156-64.
35. Kimberger O, Arnberger M, Brandt S, Plock J, Sigurdsson GH, Kurz A, et al. Goal-directed colloid administration improves the microcirculation of healthy and perianastomotic colon. Anesthesiology 2009; 110: 496-504.
36. Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007; 357: 874-84.
37. Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med 2011; 37: 86-96.
38. Myburgh J, Li Q, Heritier S, Dan A, Glass P. Statistical analysis plan for the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST). Crit Care Resusc 2012; 14: 44-52.
39. Alderson P, Bunn F, Lefebvre C, Li WP, Li L, Roberts I, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev 2004; (4): CD001208.
40. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2013; 2: CD000567.
41. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ 2013; 346: f839. doi: 10.1136/bmj.f839.
42. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358: 125-39.
43. Practice advisory for perioperative visual loss associated with spine surgery: a report by the American Society of Anesthesiologists Task Force on Perioperative Blindness. Anesthesiology 2006; 104: 1319-28.
44. McIntyre L, Fergusson DA, Rowe B, Cook DJ, Arabi Y, Bagshaw SM, et al. The PRECISE RCT: evolution of an early septic shock fluid resuscitation

trial. Transfus Med Rev 2012; 26: 333-41.
45. Shander A, Hofmann A, Gombotz H, Theusinger OM, Spahn DR. Estimating the cost of blood: past, present, and future directions. Best Pract Res Clin Anaesthesiol 2007; 21: 271-89.
46. Cavallaro F, Sandroni C, Antonelli M. Functional hemodynamic monitoring and dynamic indices of fluid responsiveness. Minerva Anestesiol 2008; 74: 123-35.
47. Wallace AW, Salahieh A, Lawrence A, Spector K, Owens C, Alonso D. Endotracheal cardiac output monitor. Anesthesiology 2000; 92: 178-89.
48. Chytra I, Pradl R, Bosman R, Pelnar P, Kasal E, Zidkova A. Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: a randomized controlled trial. Crit Care 2007; 11: R24.
49. Lindroos AC, Niiya T, Silvasti-Lundell M, Randell T, Hernesniemi J, Niemi TT. Stroke volume-directed administration of hydroxyethyl starch or Ringer's acetate in sitting position during craniotomy. Acta Anaesthesiol Scand 2013 Apr 3. doi: 10.1111/aas.12105.
50. Forget P, Lois F, de Kock M. Goal-directed fluid management based on the pulse oximeter-derived pleth variability index reduces lactate levels and improves fluid management. Anesth Analg 2010; 111: 910-4.
51. Scheeren TW, Wiesenack C, Gerlach H, Marx G. Goal-directed intraoperative fluid therapy guided by stroke volume and its variation in high-risk surgical patients: a prospective randomized multicentre study. J Clin Monit Comput 2013; 27: 225-33.
52. Maharaj R. Extravascular lung water and acute lung injury. Cardiol Res Pract 2012; 2012: 407035. doi: 10.1155/2012/407035.
53. Trezzi M, Torzillo D, Ceriani E, Costantino G, Caruso S, Damavandi PT, et al. Lung ultrasonography for the assessment of rapid extravascular water variation: evidence from hemodialysis patients. Intern Emerg Med 2011 May 18. doi: 10.1007/s11739-011-0625-4.
54. Michard F. Bedside assessment of extravascular lung water by dilution methods: temptations and pitfalls. Crit Care Med 2007; 35: 1186-92.
55. Janssens U, Graf J. Volume status and central venous pressure. Anaesthesist 2009; 58: 513-9.
56. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 2008; 134: 172-8.
57. Kuntscher MV, Germann G, Hartmann B. Correlations between cardiac output, stroke volume, central venous pressure, intra-abdominal pressure and total circulating blood volume in resuscitation of major burns. Resuscitation 2006; 70: 37-43.
58. Ji FH, Li WJ, Li J, Peng K, Yang JP, Liu H. Responsiveness of stroke volume variation and central venous pressure during acute normovolemic and hypervolemic hemodilution. Chin Med J (Engl) 2013; 126: 1838-43.
59. Domino KB, Bowdle TA, Posner KL, Spitellie PH, Lee LA, Cheney FW. Injuries and liability related to central vascular catheters: a closed claims analysis. Anesthesiology 2004; 100: 1411-8.