What's in your fluid? Does it matter?

Lauren Hernandez, PharmD
PGY1 Pharmacy Resident
Department of Pharmacy, University Health System, San Antonio, Texas
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center,
University of Texas Health Science Center at San Antonio

May 3, 2013

Learning Objectives

1. Discuss the current use and indications for fluid therapy
2. Describe the distribution and composition of fluids
3. Identify potential complications of different types of fluids
4. Evaluate the clinical significance of adverse outcomes associated with fluid therapy

Why are fluids used?

I. Intravenous fluid therapy one of the most common interventions in medicine[1]
   A. Use began in 1830s after being the first successful treatment for cholera
   B. Estimated 10 million liters of 0.9% sodium chloride (0.9% NaCl) infused annually
   C. Commonly used for critically ill patients presenting with shock[2]
      1. Shock: inadequate oxygen and blood supply to meet tissue metabolic demand[3]
         a. Can progress to multi-organ failure and death if not treated immediately
         b. Present with hypotension and/or hypoperfusion
         c. Four types of shock
            i. Cardiogenic
            ii. Hypovolemic
            iii. Distributive
            iv. Obstructive
      2. Management of shock[3]
         a. Initial therapy: fluid resuscitation
         b. Additional therapy dependent on response and etiology
            i. Vasopressors
            ii. Inotropes
         c. Address underlying cause

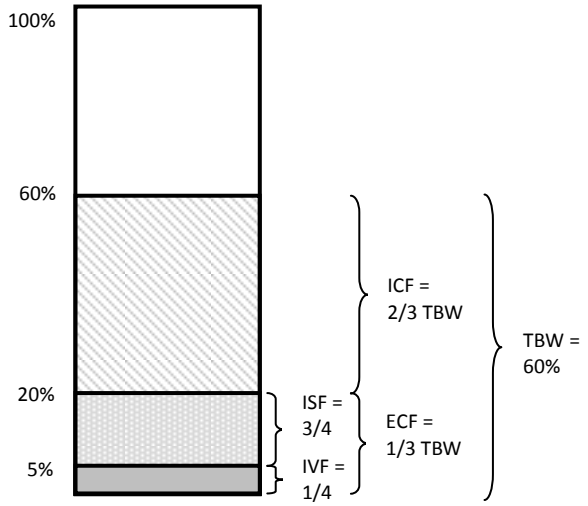
II. Fluid resuscitation[4]
   A. Increases intravascular volume to restore blood pressure and tissue perfusion
   B. Large volumes of fluids infused over 10 to 15 minutes followed by assessment
      1. Crystalloids (i.e. 0.9% NaCl) 20-30 ml/kg[4]
      2. Colloids[5]
         a. Albumin 5% 0.5-1 g/kg
         b. Hydroxyethyl starch (HES) 6% up to 20 ml/kg/day

III. Common areas fluid resuscitation prescribed
   A. Emergency department (ED)[6]
   B. Intensive care units (ICUs)[7]
      1. Administered in approximately 40% of patients
      2. Prompted by impaired perfusion/low cardiac output (CO) and abnormal vital signs
   C. Operating room[8]
      1. Surgical patients at risk for hypovolemia and reduced tissue perfusion
      2. Risks
         a. Preoperative dehydration
         b. Anesthesia-induced hypotension
         c. Hemorrhage due to surgical procedure

How do fluids work?

I. Total body water (TBW) distribution[2]
   A. Total body water (TBW) approximately 60% of body weight in adults
   B. Divided into two major compartments
      1. Intracellular fluid (ICF) and extracellular fluid (ECF)
      2. ECF further divided
         a. Intravascular fluid (IVF) and interstitial fluid (ISF)
         b. Adequate IVF needed to maintain blood pressure and tissue perfusion

Figure 1. Total Water Distribution for a 70 kg Person



Adapted from Fallick C, et al. Circulation. 2011;4:672.

C. Factors influencing fluid distribution and management[2,9]
   1. Osmolarity
      a. Measurement of solutes per liter of solvent (mOsm/L)
      b. Blood osmolarity: 285-295 mOsm/L
   2. Tonicity
      a. Compares osmolarity between two solutions separated by semipermeable membrane (i.e. extracellular and intracellular space)
      b. Movement of water dependent on tonicity
      c. Classifications
         i. Hypertonic: Greater solute concentration
         ii. Isotonic: Equal solute concentration
         iii. Hypotonic: Lesser solute concentration
   3. Plasma oncotic pressure
      a. Driving force for movement of water into intravascular space
      b. Decrease in oncotic pressure can cause fluid to accumulate in the tissues

II. Types of fluids[9]
   A. Crystalloids
      1. Composed of water, electrolytes, and/or sugars
      2. Composition of crystalloids

Table 1. Crystalloids[9,10]

	mEq/L								g/100 ml	mOsm/L
	Na^+	K^+	Cl^-	Ca^{2+}	Mg^{2+}	Lactate	Acetate	Gluconate	Dextrose	Osmolarity
0.9% NaCl	154	0	154	0	0	0	0	0	0	308
Lactated Ringer's (LR)	131	5	111	2.7	0	29	0	0	0	273
Hartmann's[a]	129	5	109	4	0	29	0	0	0	278
Ringer's Acetate[a] (RA)	130	5.4	112	0.9	1	0	27	0	0	276
Plasma-Lyte®[a]/Normosol-R®	140	5	98	0	3	0	27	23	0	280
Dextrose 5% in water	0	0	0	0	0	0	0	0	5	250

3. Differences between crystalloids[2]
    a. Tonicity
        i. Hypotonic solutions: No role for intravascular replacement
        ii. Isotonic solutions: Useful for intravascular volume expansion
        iii. Hypertonic solutions: Utilized for traumatic brain injury patients
    b. Non-balanced and balanced[11,12]
        i. Determined by electrolyte composition
        ii. Non-balanced fluids
            a. Characterized by high chloride (Cl^-) content
            b. 0.9% NaCl or "normal" saline contains 40% higher chloride content than plasma
                1. Normal in terms of similar tonicity
                2. "Supra" physiological when referring to chloride
        iii. Balanced fluids
            a. Similar chloride concentration to plasma
            b. Contain additional electrolytes relative to plasma (i.e. K^+, Mg^+, Ca^{2+})
            c. Examples: LR, Hartmann's, RA, Plasma-Lyte®, Normosol-R®
        iv. Acid-base disturbances more associated with non-balanced fluids
4. Cost-effective and readily available

B. Colloids[2,9]
1. Composed of non-crystalline substances suspended in water-based diluents
2. Natural colloids
    a. Blood products
        i. Fresh frozen plasma
        ii. Packed red blood cells
        iii. Cryoprecipitate
    b. Albumin
        i. Major serum protein
        ii. Effective volume expander
        iii. Costly and limited resource
3. Synthetic colloids
    a. HES[13]
        i. Concentration
            a. 6% only available
        ii. Molecular weight (MW)
            a. High > 450 kiloDaltons (kDa)
            b. Medium ~200 kDa
            c. Low 70-130 kDa
        iii. Molar substitution (MS)
            a. Average number of hydroxyethyl residues per glucose subunit
            b. Value indicates starch name
                1. 0.7 = hetastarch
                2. 0.4 = tetrastarch
            c. Higher MS accumulates in plasma and tissue
        iv. Efficacy of volume expansion can vary by molecular weight
        v. More costly than crystalloids and less costly than albumin
    b. Dextrans used infrequently due to toxicities
    c. Gelatins not available in United States

4. Composition of colloids

Table 2. Colloids[9,10]

	kDa	mEq/L								mOsm/L
	MW/MS	Na^+	K^+	Cl^-	Ca^{2+}	Mg^{2+}	HCO_3^-	Lactate	Octanoate	Osmolarity
Plasma	0	140	5	100	2.2	1	24	1	0	280
Albumin 4%[a]	66	140	0	128	0	0	0	0	6.4	250
Albumin 5%	66	130-160	<1	130-160	0	0	0	0	0	309
Albumin 20%[a]	66	48-100	0	19	0	0	0	0	32	130
Albumin 25%	66	130-160	<1	130-160	0	0	0	0	0	312
Voluven® HES 6%	130/0.4	154	0	154	0	0	0	0	0	310
Volulyte®[a] HES 6%	130/0.4	137	4	110	0	1.5	0	34	0	286.5
Hextend® HES 6%	670/0.7	143	3	124	2.5	0.5	0	28	0	307
Hespan® HES 6%	670/0.7	154	0	154	0	0	0	0	0	309

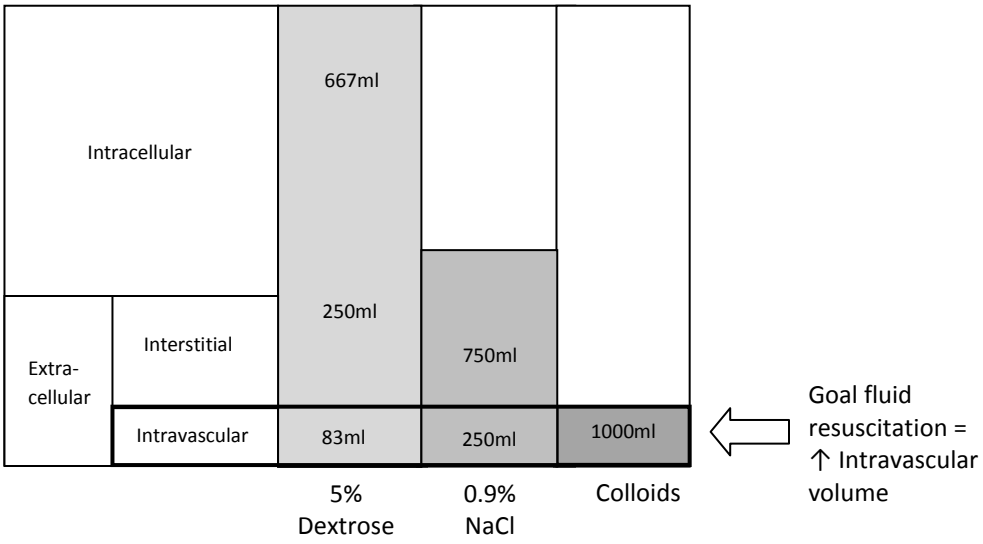
[a]Not available in the United States

5. Differences between colloids
    a. MW and MS for HES 6% products[13]
    b. Non-balanced and balanced[11,12]
        i. Non-balanced fluids
            a. Albumin 4%, 5%, 25% in high-chloride content fluid
            b. HES 6% products: Voluven®, Hespan®
        ii. Balanced fluids
            a. Albumin 20% in low-chloride content fluid
            b. HES 6% products: Volulyte®, Hextend®

III. Distribution of crystalloids and colloids[2]

1. Crystalloids
    a. Dextrose solutions distribute into extracellular and intracellular spaces
    b. 0.9% NaCl, Normosol-R distribute into extracellular space only (25% remains in intravascular space)
2. Colloids
    a. Distribute to extracellular space (~100% remains in intravascular space)
    b. Increase plasma oncotic pressure
3. Ideal solutions for fluid resuscitation
    a. Isotonic crystalloids
    b. Colloids

Figure 2. Distribution of 1 L Fluid[2]

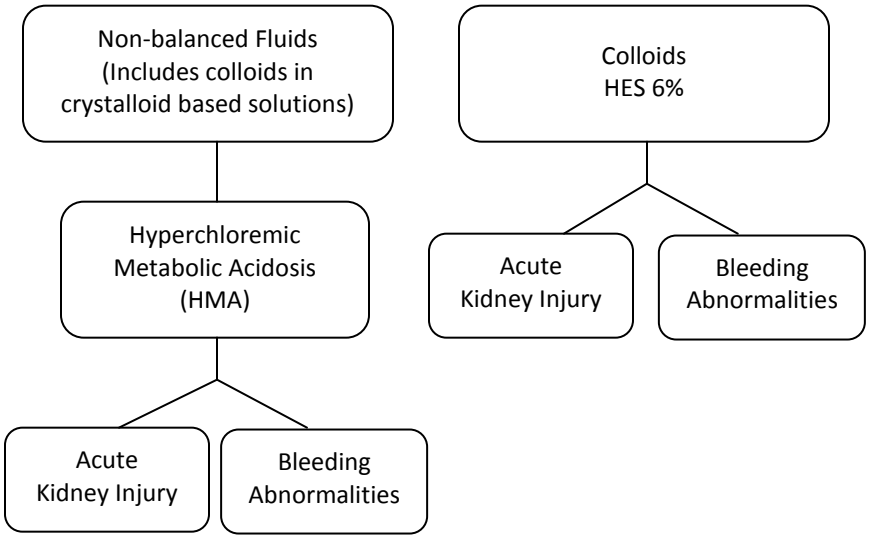


Which fluid should be used?

I. Crystalloids vs Colloids: Is the debate settled?
   A. Efficacy for resuscitation in critically ill has been an ongoing controversy[14]
   B. Colloids more effective plasma expanders than crystalloids[2]
      1. Increase plasma volume and oncotic pressure to restore intravascular volume
      2. Conflicting literature on safety and efficacy of albumin compared to crystalloids[14]
   C. Saline vs albumin fluid evaluation (SAFE) Trial 2004[15]
      1. Objective: To evaluate 28-day mortality from any cause with 4% albumin vs 0.9% NaCl for intravascular-fluid resuscitation
      2. Methods
         a. Randomized, double-blind, multi-center trial
         b. ICU patients who required fluid administration to maintain or increase intravascular volume
         c. Randomized to receive 4% albumin or 0.9% NaCl
      3. Primary outcome: Death from any cause within 28-days after randomization
      4. Results
         a. Albumin: n = 3497; 0.9% NaCl: n = 3500
         b. No difference in mortality at 28 days: 20.9% (albumin group) vs 21.1% (0.9% NaCl group) (0.99 RR 95% CI 0.91 to 1.09), p = 0.87
         c. No difference in new single-organ and multiple-organ failure or ICU, hospital, mechanical ventilation or renal-replacement therapy days
      5. Conclusion: Albumin showed equal safety and efficacy compared to 0.9% NaCl
   D. Current perspective for this ongoing debate[4,17]
      1. No direct survival benefit with colloids compared to crystalloids
      2. Crystalloids more cost-effective and preferred
      3. Albumin can be alternative when large volumes of crystalloids anticipated

II. Safety concerns with fluid choice
   A. Adverse outcomes associated with certain crystalloids and colloids

Figure 3. Adverse Outcomes with Crystalloids and Colloids[11,19]



B. HMA[9,18,19]
    1. Acid-base disturbance classified as a non-anion gap metabolic acidosis[20]
    2. Result of large quantities of saline-based infusions with high chloride content[18]
    3. Explanations behind HMA and 0.9% NaCl administration
        a. Dilutional acidosis[20]
            i. Excessive plasma volume expansion with fluids containing no bicarbonate
            ii. Causes relative decrease in bicarbonate (HCO_3^-) concentration
        b. Stewart's physiochemical approach[21]
            i. Acidosis due to significant increase in Cl^- concentration
                a. Adding 0.9% NaCl (154 mEq/L each) to water produces net balance of acid and base, with no effect on pH
                    1. $NaCl + H_2O \rightleftharpoons HCl + NaOH$
                b. 0.9% NaCl added to plasma increases Cl^- concentration more than Na^+
                c. Increased Cl^- shifts acid-base balance toward HCl leading to metabolic acidosis
            ii. Strong ion difference (SID)[18]
                a. SID calculation: $[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] – [Cl^-] – [lactate^-]$
                b. Cl^- major strong anion affecting SID
                c. ↓ SID = metabolic acidosis; ↑SID = metabolic alkalosis
                d. Normal plasma SID = 40-42 mEq/L
    4. Expected changes after infusions of non-balanced fluids[9,12,18]
        a. Chloride concentration increases
            i. Strong anion causes decrease in SID
            ii. Normal range: 95-106 mmol/L
        b. Bicarbonate concentration decreases
            i. Weak anion
            ii. Normal range: 20-29 mmol/L
        c. Base excess decreases
            i. Deviation of base from its normal value
                a. Positive value represents an excess
                b. Negative value represents a deficit (base deficit)
            ii. Normal range: -2 to +2
        d. pH decreases
            i. Measurement of H^+ ion activity
            ii. Plasma pH: 7.35-7.45 (< 7.35 = acidosis; > 7.45 = alkalosis)
    5. Hypothesized HMA-related adverse outcomes[11]
        a. Acute kidney injury
        b. Bleeding abnormalities
C. Acute kidney injury (AKI)[22]
    1. Variety of causes can lead to kidney's inability to maintain function
    2. Ranges in severity and may cause permanent and complete loss of renal function
    3. Defined by Risk, Injury, Failure, Loss, End-stage (RIFLE) Criteria[23] (See Appendix A, page 16)
        a. Changes in serum creatinine (SCr) from baseline
        b. Urine output (UO) per hour
    4. Incidence in ICUs[24]
        a. Overall: 20-50%
        b. Greater incidence in septic patients compared to surgical patients

5. Renal replacement therapy (RRT) and mortality with AKI in ICUs[24]
    a. ~12% of patients with AKI require RRT
    b. Mortality dependent on severity according to RIFLE criteria
        i. Risk: 20.9%
        ii. Injury: 45.6%
        iii. Failure: 56.8%
6. Non-balanced crystalloids[11]
    a. Primarily linked with HMA
    b. Proposed by animal studies[25]
7. Synthetic colloids (HES 6%)[17]
    a. Shown with high MW and greater MS [i.e. HES 6% (>200/0.5)]
        i. Increased risk of AKI
        ii. Increased RRT requirement
    b. Possible mechanisms
        i. Uptake of starch into proximal renal epithelial cells
        ii. Tubular obstruction
        iii. Renal interstitial inflammation

D. Bleeding abnormalities[11,17]
    1. Hypocoagulation with increased bleeding tendency
    2. Non-balanced crystalloids linked with HMA
    3. Synthetic colloids (HES 6%) associated with
        a. Increased blood product transfusions
        b. Platelet dysfunction
        c. Interaction with coagulation cascade
        d. Decreased factor VIII and von Willebrand factor levels

Clinical Questions: Clinical significance of proposed safety concerns

I. Are the adverse outcomes with non-balanced vs balanced fluids clinically significant?
II. Is there an increased safety risk with low MW and MS HES 6% when used for fluid resuscitation?

Question I. Are adverse outcomes with non-balanced fluids clinically significant?

I. Adverse outcomes of HMA
   A. Decreased renal function[11,12]
      1. Animal studies linked HMA with associated effects[25]
         a. Renal vasoconstriction
         b. Increased renal responsiveness to vasoconstrictive agents
         c. Decreased glomerular filtration rate
      2. Human studies

Table 3. Human studies assessing HMA and decreased renal function

Study	Patients	Design	Intervention	Outcome in non-balanced group*
Wilkes et al. 2001[26]	Elderly surgical patients (n=47)	RCT	HES 6% in balanced fluid + Hartmann's vs HES 6% in 0.9% NaCl + 0.9% NaCl	↓ Urine output
Chowdhury et al. 2012[27]	Healthy volunteers (n=12)	RCT, double-blinded, crossover	2 L IV over 1 hr Plasma-Lyte or 0.9% NaCl 7 – 10 days apart	Cl^-: ↑ 6 mmol/L SID: ↓ by 4 mmol/L Renal artery blood flow velocity: ↓ 9% from baseline Renal cortical tissue perfusion: ↓ 11% from baseline

***Significantly different compared to balanced group (p <0.05)**
RCT: Randomized control trial

   B. Abnormalities in coagulation and bleeding[11,12]
      1. In-vitro studies
         a. Balanced fluids have fewer negative coagulation parameters
         b. Significant limitations with in-vitro
      2. Human studies

Table 4. Human studies assessing HMA and bleeding abnormalities

Study	Patients	Fluid	Outcome in unbalanced group
Gan et al. 1999[28]	Major surgery (n=120)	HES 6% in balanced fluid vs HES 6% in 0.9% NaCl	↑ time to onset of clot ↑ mean estimated blood loss
Waters et al. 2001[29]	Abdominal aortic aneurysm repair (n=66)	LR vs 0.9% NaCl	↑ volume of platelet transfusion ↑blood products No difference in blood loss

II. Literature review[30,31]

Table 5. Shaw AD, Bagshaw S, Goldstein S, et al. Major complications, mortality, and resource utilization after open abdominal surgery. 0.9% saline compared to Plasma-Lyte. *Ann Surg*. 2012;255:821-29.	
Objective	To compare the effect on clinical outcomes between 0.9% saline infusion and Plasma-Lyte (a balanced solution) in patients undergoing major abdominal surgery
Design	▪ Retrospective cohort study ▪ Inclusion o 18 years and older o Elective or emergency open general surgery o Exclusively received 0.9% or Plasma-Lyte on day of surgery (500 ml or 1000 ml) ▪ Exclusion o Patients undergoing major abdominal operations for traumatic injuries
Outcomes	▪ Primary: Composite of one or more major complications o Respiratory failure >24 hours postoperatively o Cardiac complications requiring intervention o Major gastrointestinal dysfunction (bleeding or perforated ulcer) o Infectious complications o Acute renal failure ▪ Secondary: Electrolyte disturbances, physician orders related to acidosis evaluation or management, rehospitalization within 30 days
Statistical analysis	▪ Baseline characteristics o t -test – continuous variables o Chi square – categorical variables ▪ Outcome models o (1) Ordinary logistic regression, (2) ordinary logistic regression including propensity score as model predictor and (3) ordinary logistic regression on sample of patients matched by propensity score 3:1, 0.9% saline to Plasma-Lyte o Elixhauser's algorithm – comorbidity score used to assess outcome
Results	▪ 271,189 patients received fluid on day of surgery o 30,994 in 0.9% saline arm vs 926 in Plasma-Lyte arm ▪ Baseline characteristics o ~70% patients >50 years of age, ~65% elective admission, ~30% emergent admission o Patients receiving 0.9% saline more likely to be minorities, ED admission, have presence of comorbidities such as heart failure, diabetes, and renal failure o Groups well matched on comorbidity parameters after propensity score ▪ Outcomes o Association with major complication was in favor of balanced fluid group o Developing major infection was significantly lower in the balanced fluid group o After multivariate analysis, emergency surgery group had adjusted odds of death 50% lower in balanced group vs 0.9% saline (OR 0.51; 95% CI 0.28-0.95) o After propensity matching, the 0.9% saline group had: ▪ More fluid (1976 ml vs 1658 ml, p <0.001) ▪ More buffer orders (6.3% vs 4.2%, p = 0.02) ▪ More transfusions (11.5% vs 1.8%, p <0.001) ▪ Increased ventilator days (3.0 days vs 2.5 days, p <0.001) ▪ A 5-fold greater chance of receiving dialysis (1% vs 4.8%, p <0.001) o Significantly more utilization of tests to evaluate acidosis in 0.9% saline group: arterial blood gases (22.3% vs 13.7%) and lactic acid (8% vs 3.3%); p < 0.001) o Balanced group had longer length of stay in the hospital (6.4 days vs 5.9, p < 0.001)
Authors' Conclusions	▪ Compared to physiologically balanced crystalloid solutions, saline associated with greater risk of complications and greater utilization of resources

Limitations	▪ Retrospective, observational study ▪ Very small percentage of patients received only exclusively one fluid vs another ▪ Baseline comorbidities higher in non-matched cohort include congestive heart failure, renal failure, diabetes with complications, deficiency anemia ▪ Detecting major complications such as infection and renal failure by ICD-9 codes could provide some inaccuracies without objective patient data ▪ Increased arterial blood gas utilization could be attributed to increased ventilator days in 0.9% saline

Table 6. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308:1566-72.

Objective

- To determine the association between incidence and severity of acute kidney injury with a chloride-restrictive IV fluids strategy in critically ill patients compared to a chloride-liberal IV strategy

Design

- Prospective, open label, before and after pilot study in the ICU at a university-affiliated hospital in Australia
- Three sequential six month periods
  - Control period: Chloride-liberal strategy with clinician preference for IV fluids
  - Phase-out period: Education and preparation of all ICU staff
  - Intervention period: Chloride-restrictive strategy allowing chloride-rich fluids only when prescribed by attending for specific conditions (hyponatremia, traumatic brain injury [TBI], cerebral edema)
- Fluid options

Chloride Liberal		**Chloride Restrictive**	
Fluid	**Cl (mmol/L)**	**Fluid**	**Cl (mmol/L)**
0.9% saline	150	Lactated crystalloid solution (Hartmann)	109
4% succinylated gelatin	120	Balanced buffer (Plasma-Lyte 148)	98
4% albumin in NaCl	128	20% albumin	19

- Baseline collection data: age, sex, acute physiology and chronic health evaluation (APACHE) II and III, simplified acute physiology score (SAPS) II (Appendix B), multiple clinical characteristics
  - Serum Creatinine (SCr): pre admission and daily
  - RRT data

Outcomes

- Primary
  - Increase in SCr from baseline to peak ICU level
  - Incidence of AKI defined by the RIFLE criteria
- Secondary post-hoc analysis
  - RRT needed
  - Length of ICU and hospital stay
  - Survival

Statistics

- Baseline characteristics
  - Chi square, t-tests, Wilcoxon rank sum tests
- Primary outcomes
  - Logistic regression: Report OR with 95% CI for AKI and need for RRT
  - Cox proportional hazards & Kaplan Meier curve: Time-to-event analysis
- Multivariate sensitivity analysis: Sex, APACHE III scores, diagnosis, operative status, admission type (elective or emergency) and baseline SCr
- Nested cohort (n=100): Detail fluid data was collected to assess the relationship between chloride intake and changes in SCr
- Subgroup: time in ICU, APACHE score, risk of death, presence of sepsis and cardiac surgery
- 2-sided p value of 0.01 was used to indicate statistical significance

<table>
<tr><td>Results</td><td>
N = 1644 admissions in 1533 patients (n=760 in control, n=773 in intervention)
Table I: Baseline Characteristics: None were significantly different
Majority of patients were male, mean age was 60, post-operative admission, and had cardiovascular comorbidities
Changes in solute therapy
Chloride: 694 to 496 mmol/patient
Sodium: 750 to 623 mmol/patient
Potassium: 3.5 to 22 mmol/patient
Lactate: 18 to 220 mmol/patient
Primary Outcome
<table>
<tr><th></th><th>Control (n=760)</th><th>Intervention (n=773)</th><th>p value</th></tr>
<tr><td>SCr increase from baseline</td><td>0.26 mg/dL</td><td>0.17 mg/dL</td><td>p = 0.03,
p adj = 0.007</td></tr>
</table>
Incidence of AKI by RIFLE
<table>
<tr><th>Rifle Class</th><th>Control (n=760)
No. (%)</th><th>Intervention (n=773)
No. (%)</th><th>p value</th></tr>
<tr><td>Risk</td><td>71 (9)</td><td>67 (7.4)</td><td>0.16</td></tr>
<tr><td>Injury</td><td>48 (5.3)</td><td>23 (3)</td><td>0.002</td></tr>
<tr><td>Failure</td><td>57 (7.5)</td><td>42 (5.4)</td><td>0.10</td></tr>
<tr><td>Injury and failure</td><td>105 (14)</td><td>65 (8.4)</td><td><0.001</td></tr>
</table>
Secondary Post-Hoc
<table>
<tr><th></th><th>Control (n=760)
No. (%)</th><th>Intervention (n=773)
No. (%)</th><th>p value</th></tr>
<tr><td>RRT</td><td>78 (10%)</td><td>49 (6.3%)</td><td>p = 0.005</td></tr>
</table>
Outcomes remained significantly lower during intervention group after conducting multivariate analysis
</td></tr>
<tr><td>Authors' Conclusions</td><td>
Chloride restrictive fluid strategy compared to chloride liberal strategy led to significant reduction in increase of mean creatinine level from baseline, incidence of AKI and use of RRT
Similar findings after adjusting for baseline variables, subgroup analysis and nested cohort
</td></tr>
<tr><td>Discussion</td><td>
Strengths
Evaluated clinical outcomes (SCr, RIFLE criteria, RRT)
Attempted to control for temporal bias
Weaknesses
Unable to evaluate the primary factor causing difference in SCr increase, injury and failure AKI, and RRT because different use of fluids
Not randomized or blinded
Education and intervention period may have influenced outcomes seen in phase-out period
Volume use of fluid was not separated by indication (fluid replacement, resuscitation)
Lack of information on other medications/IV solutions that could affect outcomes
</td></tr>
</table>

III. Take home points: non-balanced vs balanced
   A. HMA associated with decreased renal function and abnormalities with coagulation and bleeding
   B. Balanced solutions resulted in decreased use of blood products after surgery and RRT in ICU patients
   C. No difference in mortality or length of ICU or hospital stay

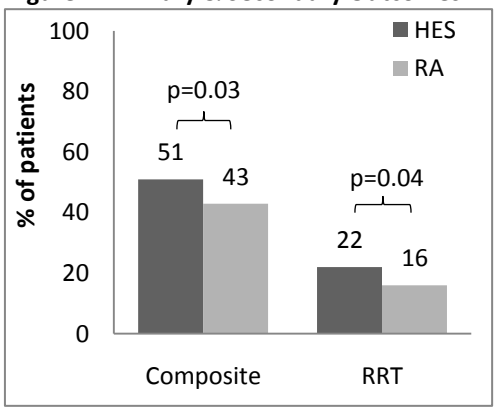
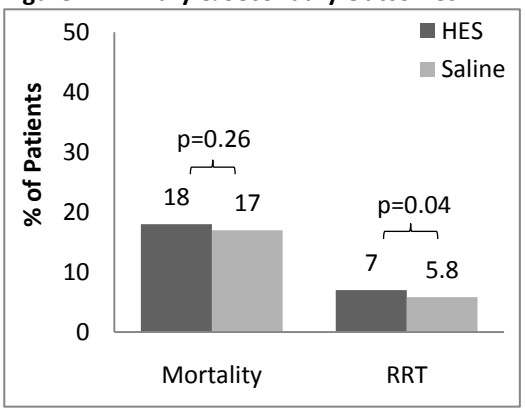
Question II. Is there an increased safety risk with low MW and MS HES when used for fluid resuscitation?

I. Renal injury effects are associated with HES[10,17]
   A. High MW (> 200 kD) and greater MS (> 0.4)
   B. HES dose administration exceeded recommendations
   C. Higher risk in septic patients
II. Conflicting literature on adverse renal effects[21]
   A. Low MW (≤ 130 kD)
   B. Lesser MS (0.4)
III. Literature review

Table 7. Safety of HES 6% for Fluid Resuscitation

Trial	**6S[32]**	**CHEST[33]**
Patient Population	• Severe sepsis in the ICU requiring fluid resuscitation	• Adult ICU patients requiring fluid resuscitation
Intervention	• 6% HES (130/0.42) in RA vs RA • Max dose of HES: 33 ml/kg	• 6% HES (130/0.4) in 0.9% saline vs 0.9% saline • Max dose of HES: 50 ml/kg/d
Primary Outcome	• Composite death or dependence on dialysis at 90 days	• All-cause mortality at 90 days
Secondary Outcomes	• Severe bleeding, allergic reactions • Repeat SOFA score • Renal outcomes (RRT, renal SOFA > 3, doubling SCr)	• Renal outcomes (RIFLE, RRT) • New organ failures • MV and RRT duration • Cause-specific mortality
Results	**HES (n = 398) vs RA (n = 400)**	**HES (n= 3358) vs 0.9% saline (n= 3384)**

	Baseline Characteristics: No differences
	• Source of ICU admission
	  ○ 44-49% general ward
	• SAPS II – median: 50-51
	• SOFA – median: 7
	• Shock : 84%
	• MV: 60-61%
		Baseline Characteristics: No differences
		• Source of ICU admission
		  ○ 27% ED & 23% elective surgery
		• APACHE II – median: 17
		• Sepsis subgroup: 28.4-29.2%
		• Use of vasopressor: 45.5 – 46.1%
		• MV: 64%

	Figure 1. Primary & Secondary Outcomes  • Severe bleeding: ↑ with HES vs RA	**Figure 2. Primary & Secondary Outcomes**  • RIFLE-R,I: ↑ in saline vs HES (p <0.05) • Post hoc analyzed SCr & UO separately: RIFLE ↑ in HES vs saline

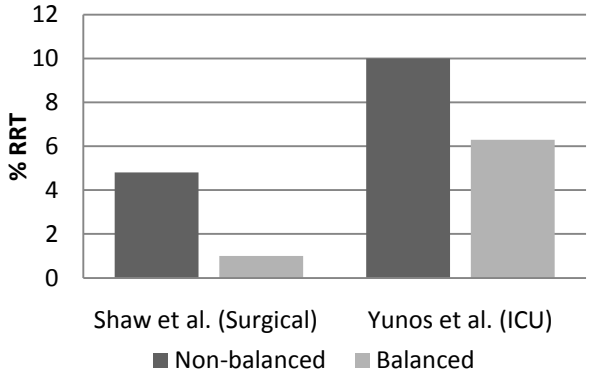
Comments	• Included severely ill septic patients • Composite primary endpoint ○ Results due to mortality • Identified AKI by increase in SOFA score + RRT or doubling of SCr	• Included all ICU patients • Sepsis subgroup showed similar results • Post hoc analysis revealed ↑ SCr & ↓ UO in HES group when evaluated separately
Conclusions	• Severe sepsis patients had an increased mortality and rate of RRT with HES 6% (130/0.4)	• ICU patients had an increased rate of RRT with HES 6% (130/0.4)
6S: Scandinavian Starch for Severe Sepsis/Septic Shock trial; CHEST: Crystalloid versus Hydroxyethyl Starch Trial; RA: Ringer's acetate; RRT: renal replacement therapy; MV: mechanical ventilation; SOFA:Sequential Organ Failure Assessment score; APACHE II: Acute Physiology and Chronic Health Evaluation II; SAPS II: Simplified Acute Physiology Score. Reference Appendix B for SOFA, APACHE II, SAPS II.		

IV. Take home points: safety of low MW and MS HES 6%
   A. Both low and high molecular weight HES solutions result in increased use of RRT and mortality in severe sepsis
   B. Renal replacement therapy is increased when low molecular weight HES solutions are used in an ICU population

Summary and Recommendations

III. Question I. Are the adverse outcomes with non-balanced vs balanced fluids clinically significant?
   A. Summary of safety[11,30,31]
      1. Balanced fluids have better safety profile compared to non-balanced fluids due to decreased chloride intake
      2. Large observational and open-label pilot studies showed increased use of resources in a specified surgery population as well as mixed ICU population with non-balanced crystalloid use
         a. Surgical patients only: increased blood product transfusions
         b. Both surgical and ICU patients: increased RRT

Figure 5. Rates of renal replacement therapy[30,31]



      3. Hospital length of stay significantly longer in surgical patients with balanced crystalloids, but study design renders interpretation difficult
      4. Overall ICU length of stay and mortality similar between groups
   B. Other considerations
      1. The perfectly balanced solution[18]
         a. Experimentally, the SID needed to have neutral effect on acid-base balance after fluid administration is 24 mEq/L
         b. Currently available solutions do not have this specific SID
         c. Closest SID found with Hartmann's and Lactated Ringer's at ~27 mEq/L

2. Cost[10]

Table 8. Costs changes if switched from 0.9% NaCl to balanced formulas		
Fluid	Cost (Dollars/1 L)	Cost (Dollars/10 million L)
0.9% NaCl	1.03	10.3 million
Normosol-R	2.21	22.1 million
Lactated Ringers	0.94	9.4 million

C. Final recommendation
    1. Balanced or non-balanced crystalloids for volume resuscitation are acceptable
        a. Data does not support one fluid over another for this indication since length of study follow up ranged from immediately post-operatively to days and weeks
        b. Preliminary data shows HMA occurs after large volume infusions
            i. Need randomized, controlled trial data to evaluate the clinical significance when used for volume resuscitation
            ii. Determine effects of maintenance replacement fluids separately
        c. Studies lacked evaluation of confounding variables in the ICU on acute kidney injury events (i.e. nephrotoxic agents)
    2. Due to study design, differences in length of stay, and no difference in mortality, the cost increase that may result when switching to balanced solutions is not justified

II. Question II. Is there an increased safety risk with low MW and MS HES 6% when used for fluid resuscitation?

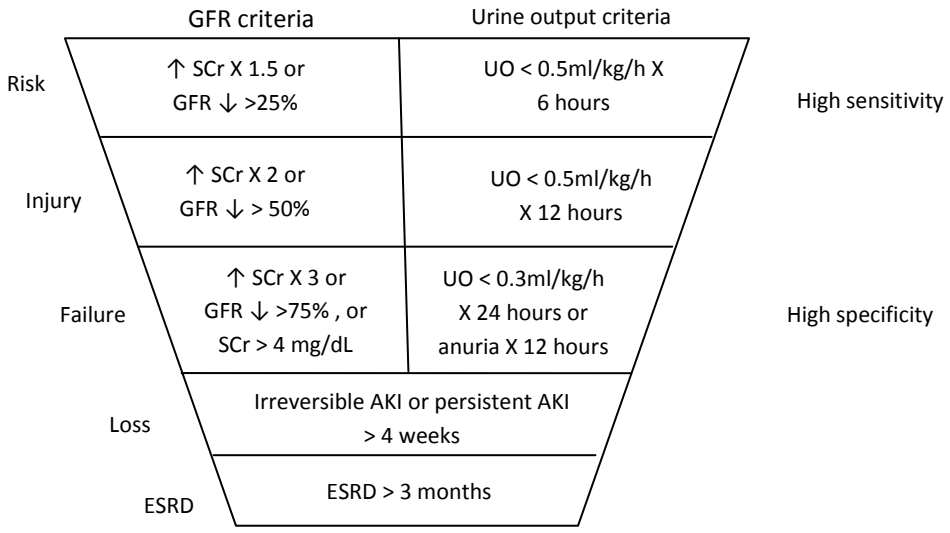
A. Summary[32,33]
    1. Low MW and low MS HES 6% products (MW 130, MS 0.4) showed adverse renal outcomes when compared to crystalloids for volume resuscitation
    2. Patient population
        a. Severe sepsis patients have increased need for RRT, bleeding risk and mortality when HES 6% (130/< 0.4) is used
            i. Surviving Sepsis Campaign Guidelines 2012 advise against HES 6% for volume resuscitation
        b. ICU patients
            i. Significant increase in need for RRT
            ii. No significant differences in mortality

B. Cost considerations
    1. Albumin 5% in 500 ml: $198
    2. HES 6% in 500 ml 0.9% NaCl: $61.06

C. Final recommendation
    1. For volume resuscitation in critically ill patients, do not recommend HES 6% 130/<0.4
        a. Supported by well-designed randomized, controlled trial showing increased need for RRT
        b. Although mortality did not differ in the ICU population studied, mortality was increased in severe sepsis patients
        c. Maximum daily doses
            i. Increased adverse outcomes (i.e. AKI, bleeding abnormalities) when exceeded
            ii. Once reached, crystalloids are recommended for resuscitation; will reduce the true benefit of less volume when using HES 6%
    2. Recommend albumin 5% as adequate alternative colloid

Appendices

Appendix A. RIFLE Criteria for AKI[23]



Appendix B. Severity scores

	Variables measured	Time Frame	Score range
Acute physiology and chronic health evaluation (APACHE II)[34]	▪ 12 physiological variables (age, GCS, temperature, blood pressure, heart rate, respiratory rate, FiO_2, PaO_2, pH, sodium, potassium, creatinine, hematocrit, WBC) ▪ 2 disease related variables (acute renal failure and severe organ system insufficiency or immunocompromised)	▪ Worst variables measured within 24 hours of ICU admission ▪ Not calculated after 24 hours of admission	▪ 0 to 71 ▪ Mortality equation takes into account reason for admission
Acute physiology and chronic health evaluation (APACHE III)[35]	▪ Similar to APACHE II ▪ 4 components: age, major disease category (reason for admission), acute physiology variables (added acid-base status and neurologic status) site prior to admission	▪ Worst variables measured within initial 24 hours in ICU ▪ Daily updates can be used to recalculate estimated mortality on daily basis	▪ Ranges 0 – 299 ▪ Equation to predict mortality
Simplified acute physiology score (SAPS II)[36]	▪ 12 physiological variables (age, heart rate, systolic blood pressure, temperature, PaO_2, FiO_2, urine output, BUN, WBC, potassium, sodium, bicarbonate, bilirubin, GCS) ▪ 3 disease-related variables (mechanical ventilation, chronic diseases, types of admission)	▪ Worst variables measured within initial 24 hours in ICU ▪ Not calculated after 24 hours of admission	▪ Ranges 0 -163 ▪ Predict hospital mortality
Sequential organ failure assessment (SOFA)[37]	▪ 6 variables; each representing organ system (respiration: FiO2, PaO2, MV; coagulation: platelets; liver: bilirubin; neurological: GCS; cardiovascular: MAP, vasopressors; renal: creatinine, urine output)	▪ Worst variables measured every 24 hours of ICU admission ▪ Can calculate during ICU admission beyond 24 hours	▪ Ranges 0 – 24 ▪ No conversion available to determine mortality ▪ Developed to determine organ dysfunction and morbidity

GCS: Glasgow coma scale; FiO_2: fraction of inspired oxygen; PaO_2: partial arterial oxygen; MAP: mean arterial pressure

References

1. Awad S, Allison S, Dillep L. The history of 0.9% saline. *Clin Nutr*. 2008;27:179-88.
2. Griffel MI, Kaufman BS. Pharmacology of colloids and crystalloids. *Crit Care Clin*. 1992;8:235-53.
3. Society of Critical Care Medicine. Chapter 5: Diagnosis and management of shock. Available at: http://www.sccm.org/SiteCollectionDocuments/HDM%20Course%20Chapter%205.pdf/. Accessibly verified April 15, 2013.
4. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013; 41:580-637.
5. DRUGDEX® System (electronic version). Thomson Reuters, Greenwood Village, Colorado, USA. Available at: http://www.thomsonhc.com.libproxy.uthscsa.edu. Accessed April 15, 2013.
6. Graham CA, Parke TR. Critical care in the emergency department: shock and circulatory support. *Emerg Med J*. 2005;22:17-21.
7. Finfer S, Liu B, Taylor C, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care*. 2010;14:R185.
8. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology*. 2008;109:723-40.
9. Kaplan L, Kellum J. Fluids, pH, ions, and electrolytes. *Curr Opin Crit Care*. 2010;16:323-31.
10. Bartels K, Thiele R, Gan T. Rational fluid management in today's ICU practice. *Crit Care*. 2013;17(suppl 1):S6.
11. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: Chloride in critical illness. *Crit Care*. 2010;14:226.
12. Guidet B, Soni N, Rocca G, et al. A balanced view of balanced solutions. *Crit Care*. 2010;14:325.
13. Westphal M, James MF, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H. Hydroxyethyl starches: different products—different effects. *Anesthesiology*. 2009;111:187-202.
14. Hartog CS, Bauer M, Reinhart K. The efficacy and safety of colloid resuscitation in the critically ill. *Anesth Analg.* 2011;112:156-64.
15. Finfer S, Bellomo R, Boyce N, et al. SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247-56.
16. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. 2013;2:CD000567.
17. Estrada C, Murugan R. Hydroxyethyl starch in severe sepsis: end of starch era? *Crit Care*. 2013;17:310.
18. Morgan TJ. The meaning of acid-base abnormalities in the intensive care unit – effects of fluid administration. *Crit Care*. 2005;9:204-11.
19. Gunnerson K, Kellum J. Acid-base and electrolyte analysis in critically ill patients: are we ready for the new millennium? *Curr Opin Crit Care*. 2003;9:468-73.
20. Adrogue H, Madias N. Management of life-threatening acid-base disorders. *N Engl J Med*. 1998;338:26-34.
21. Roche AM, James M. Colloids and crystalloids: does it matter to the kidney? *Curr Opin Crit Care*. 2009;15:520-524.
22. Case J, Khan S, Khalid R, Khan A. Epidemiology of acute kidney injury in the intensive care unit. *Crit Care Res Pract*. 2013; 479730.
23. Bellomo R, Ronco C, Kellum J, et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204-12.
24. Ostermann M, Chang WS. Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med*. 2007;35:1837-43.
25. Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest*. 1983;71:726-35.
26. Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg*. 2001;93:811-6.

27. Chowdhury AH, Cox EF, Francis S, et al. A Randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256:18-24.
28. Gan TJ, Bennet-Guerrero E, Phillips-Bute B, et al. Hextend, a physiologically balanced plasma expander for large colume use in major surgery: A randomized phase III clinical trial. *Anesth Analg*. 1999;88:992-8.
29. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson D. Normal saline versus lactated ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg*. 2001;93:817-22.
30. Shaw AD, Bagshaw S, Goldstein S, et al. Major complications, mortality, and resource utilization after open abdominal surgery. 0.9% saline compared to Plasma-Lyte. *Ann Surg*. 2012;255:821-829.
31. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308(15):1566-72.
32. Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group; Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124-34.
33. Myburgh JA, Finfer S, Bellomo R, et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901-11.
34. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985 Oct;13:818-29.
35. Knaus WA, Wagner DP, Draper EA, et al. The Apache III prognositic sytem. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100:1619-36.
36. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score based on European/North American multicenter study. *JAMA*. 1993;270:2957-63.
37. Vincent JL, de Mendoca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on"sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26:1793-800.