Crystalloids, colloids and the appeal for balanced solutions. What's the evidence and does it really matter?

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Professor and Chief
Division of Cardiothoracic Anesthesiology
Vanderbilt University Medical Center

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2015 Disclosures

- **Consultant for Grifols – manufacturer of colloid (albumin) products**
- **Consultant for Baxter – manufacturer of crystalloid and colloid products**
- **No off label comments**

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Is fluid *amount* important ?

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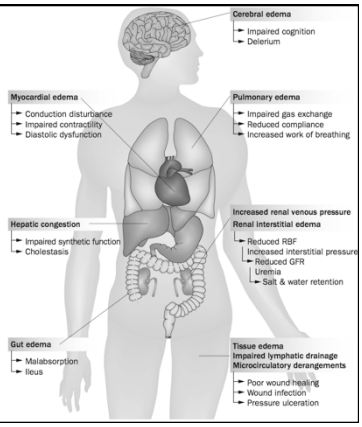
Organ function effects of volume overload



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Is fluid *amount* important ?

- **Excess fluid leads to adverse outcomes**
- **When fluid given is blinded – the ratio of crystalloid : colloid is generally 1.3 : 1**
- **NOT 3:1 as is widely believed**
- **Why are fluids not afforded the same respect as other intravenous drugs?**

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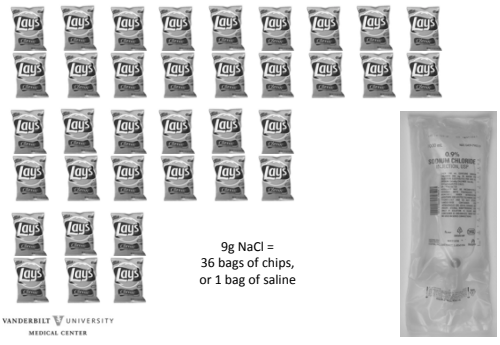
Is *crystalloid type* important ?



9g NaCl =
36 bags of chips,
or 1 bag of saline

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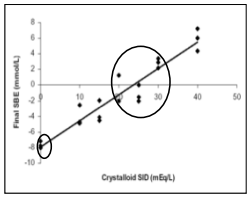
Fluid Therapy Basics

Not all IV Fluids are created equal…

- **A "balanced" fluid has the physiological electrolyte composition of plasma**
- **Balanced fluids do not cause the hyperchloremic acidosis associated with 0.9% saline**



•Base excess after infusion is determined by the strong ion difference (SID) of the fluid infused.

•The red circle represents 0.9% NaCl, the blue circle represents balanced crystalloid

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Abnormal Saline

- **0.9% saline contains Na and Cl in equal amounts (154 meq/l)**
- **Unlike plasma**
- **Adding NaCl to plasma increases the relative Cl concentration more than that of Na**
- **0.9% saline reduces plasma SID and leads to hyperchloremic metabolic acidosis**

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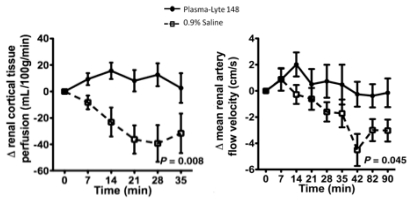
2L of Saline versus Balanced Crystalloid in Healthy Volunteers



Chowdhury et al (2012) Ann Surg

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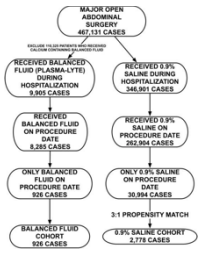
FEATURE

Major Complications, Mortality, and Resource Utilization After Open Abdominal Surgery

0.9% Saline Compared to Plasma-Lyte

Andrew D. Shaw, MB, FRCA, FCCM, Sean M. Bagshaw, MD,† Stuart L. Goldstein, MD,‡ Lynette A. Scherer, MD,§ Michael Duan, MS,‖ Carol R. Schermer, MD,¶ and John A. Kellum, MD#*

- **Retrospective analysis of a prospectively collected data asset (Premier database)**
- **Major (non cardiac) surgery**
- **>30,000 patients who received 0.9% saline or balanced crystalloid alone on day of surgery**



(*Ann Surg* 2012;00:1–9)

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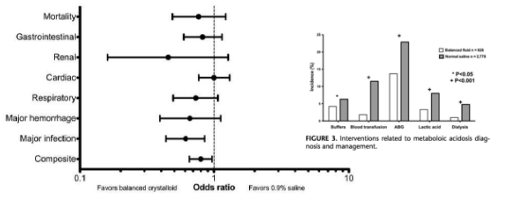
Risk adjusted major complications and resource use - All patients



Shaw et al (2012) Ann Surg

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Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis

Karthik Raghunathan, MD, MPH[1,2]; Andrew Shaw, MB, FRCA, FFICM, FCCM[1]; Brian Nathanson, PhD[3]; Til Stürmer, MD, PhD[4]; Alan Brookhart, PhD[4]; Mihaela S. Stefan, MD[5]; Soko Setoguchi, MD, DrPH[6]; Chris Beadles, MD, PhD[2]; Peter K. Lindenauer, MD, MSc[7]

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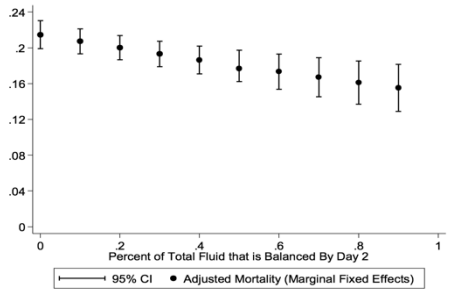
Raghunathan et al (2014) Crit Care Med

Mortality Dose Response



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Raghunathan et al (2014) Crit Care Med

Yunos et al 2012

PRELIMINARY COMMUNICATION

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

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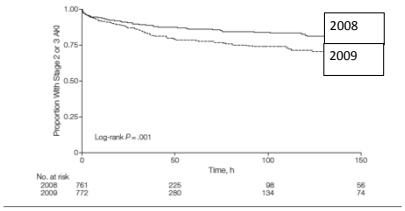
Yunos et al (2012) JAMA

KDIGO 2&3

Figure 1. Development of Stage 2 or 3 Acute Kidney Injury (AKI) While in the Intensive Care Unit (ICU)



Stage 2 or 3 defined according to the Kidney Disease: Improving Global Outcomes clinical practice guideline.

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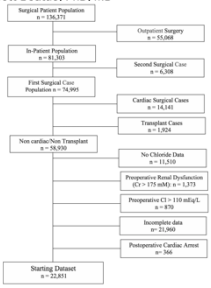
Yunos et al (2012) JAMA

Hyperchloremia After Noncardiac Surgery Is Independently Associated with Increased Morbidity and Mortality: A Propensity-Matched Cohort Study

Stuart A. McCluskey, PhD, MD,* Keyvan Karkouti, MSc, MD,*† Duminda Wijeysundera, PhD, MD,* Leonid Minkovich, PhD, MD,* Gordon Tait, PhD,* and W. Scott Beattie, PhD, MD*

- **Observational cohort study**
- **Major (non cardiac) surgery**
- **23000 patients**
- **4266 of 4955 who developed high serum chloride propensity matched to patients who did not**



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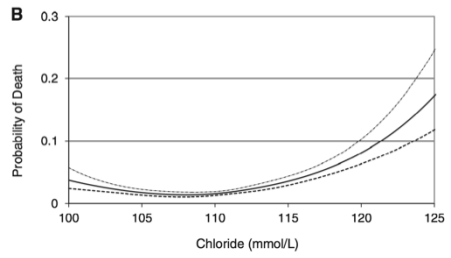
Chloride and mortality



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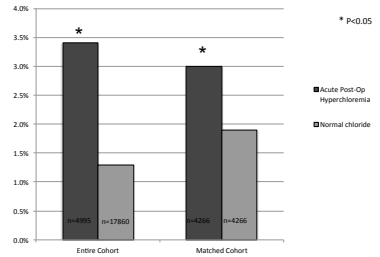
CME

Hyperchloremia After Noncardiac Surgery Is Independently Associated with Increased Morbidity and Mortality: A Propensity-Matched Cohort Study

Stuart A. McCluskey, PhD, MD,* Keyvan Karkouti, MSc, MD,*† Duminda Wijeysundera, PhD, MD,* Leonid Minkovich, PhD, MD,* Gordon Tait, PhD,* and W. Scott Beattie, PhD, MD*



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Anesth Analg 2013;117:412–21

Intensive Care Med
DOI 10.1007/s00134-014-3505-3

ORIGINAL

Andrew D. Shaw
Karthik Raghunathan
Fred W. Peyerl
Sibyl H. Munson
Scott M. Paluszkiewicz
Carol R. Schermer

Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS

- **109,836 adult patients with SIRS from Cerner health facts database**
- **Baseline risk adjustment as well as APS included in outcomes model**
- **Effect of volume adjusted chloride load on mortality**

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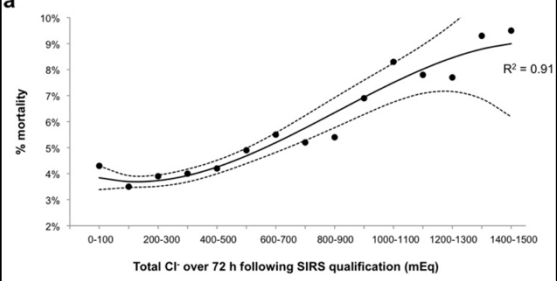
Shaw et al (2014) Int Care Med

Administered chloride



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Shaw et al (2014) Under review

Systematic review

Meta-analysis of high- *versus* low-chloride content in perioperative and critical care fluid resuscitation

M. L. Krajewski[1], K. Raghunathan[1,2], S. M. Paluszkiewicz[3], C. R. Schermer[4] and A. D. Shaw[5]

[1]Department of Anesthesiology, Duke University Medical Center, and [2]Anesthesiology Service, Durham VA Medical Center, Durham, North Carolina, [3]Boston Strategic Partners, Boston, Massachusetts, [4]Baxter Healthcare Corporation, Deerfield, Illinois, and [5]Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee, USA
Correspondence to: Professor A. D. Shaw, Division of Cardiothoracic Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee 37232–8274, USA (e-mail: andrew.shaw@vanderbilt.edu)

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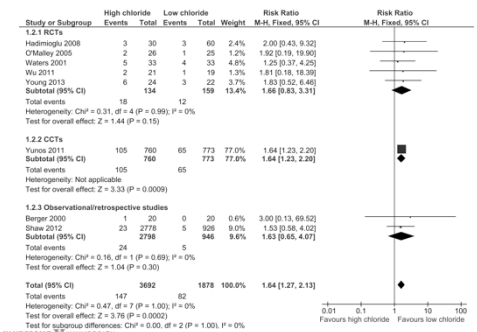
Krajewski et al (2014) Brit J Sur

AKI



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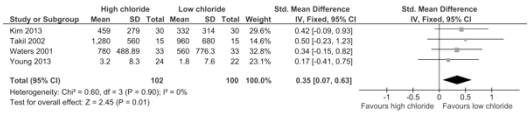
Krajewski et al (2014) Brit J Sur

Blood transfusion volume



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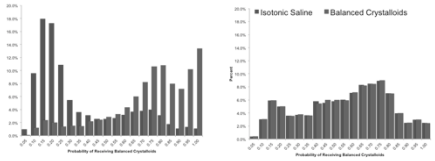
Krajewski et al (2014) Brit J Sur

New cardiac surgery data (1)

Choice of Intravenous Crystalloid Therapy and Major In-hospital Outcomes among Adult Patients Undergoing Cardiac Surgery

- **Cerner Healthfacts Database**
- **5641 on-pump patients receiving 0.9% saline PS matched with 5641 receiving balanced fluids during first 72 hours**



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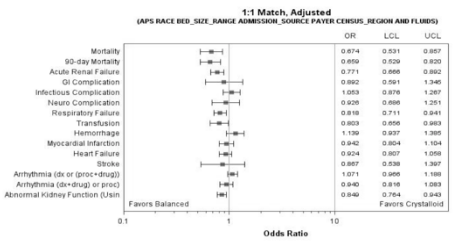
New cardiac surgery data (1)

Choice of Intravenous Crystalloid Therapy and Major In-hospital Outcomes among Adult Patients Undergoing Cardiac Surgery



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New cardiac surgery data (2)

TITLE: THE ASSOCIATION BETWEEN CHOICE OF BALANCED INTRAVENOUS CRYSTALLOID AND SUBSEQUENT MAJOR IN-HOSPITAL OUTCOMES AMONG ADULT PATIENTS UNDERGOING CARDIAC SURGERY

Raghunathan K [1]; Khangulov VS [2]; Peyerl FW [2]; Shaw AD [3]

[1] Department of Anesthesiology, Division of Veterans Affairs. Duke University, Durham, NC, USA; [2] Boston Strategic Partners, Inc., Boston, MA, USA; [3] Department of Anesthesiology, Cardiac Division, Vanderbilt University Medical Center, Nashville, TN, USA

- **299 patients receiving Plasmalyte or Normosol matched with 299 who received LR**
- **OR for 90 day death 0.96 (0.94-0.97)**

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When should we give abnormal saline?

- **Rarely**
- **Traumatic brain injury**
- **HCl loss (severe vomiting)**
- **i.e. Almost never in cardiac surgical practice**

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Is colloid dangerous?

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Hydroxyethyl starch

- **Most commonly prescribed colloid globally.**
- **Evidence for toxicity is emerging but is not universally accepted**
- **Evidence for adverse effects related to accumulation in RES**

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VISEP study

- **RCT, 537 patients**
- **Severe sepsis or septic shock**
- **2 x 2 factorial design**
- **10% pentastarch (200/0.5) or LR**
  - hyperchloremic, hyperoncotic
  - median cumulative HES dose 70 ml/Kg

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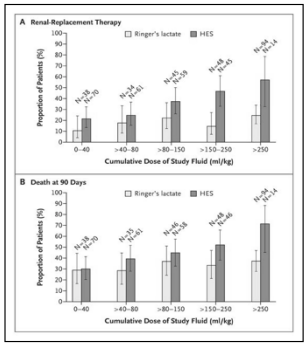
Brunkhorst et al. NEJM 2008; 358: 125-39



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Brunkhorst et al. NEJM 2008; 358: 125-39

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D.,
Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D.,
Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D.,
Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D.,

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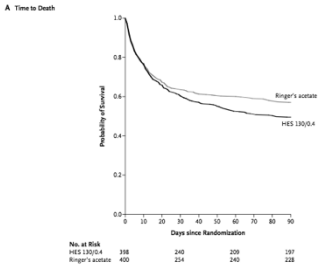
Perner et al (2012) NEJM

6S Survival



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Perner et al (2012) NEJM

CHEST

ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D.,
Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D.,
Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D.,
Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D.,
and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators
and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

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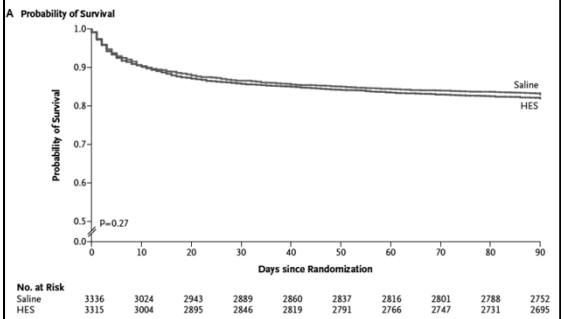
Myburgh et al (2012) NEJM

CHEST survival



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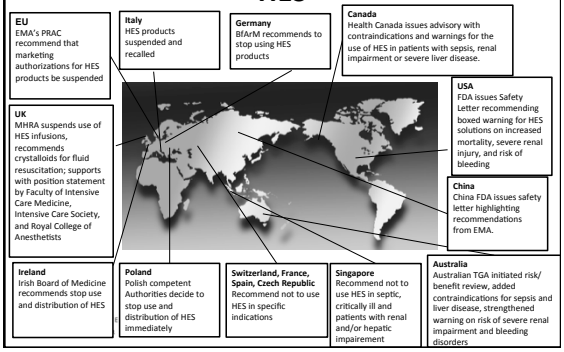
Recent Regulatory Activity Regarding HES



Colloid Alternatives to HES

- **Synthetic Colloid: Gelatin**
  - **Not associated with improved clinical outcomes**
  - **Risk of AKI and anaphylactic reactions**
- **Natural Colloid: Albumin**
  - **SAFE trial showed no increased risk of mortality in critically ill patients with use of albumin**
- **Dextrans**
  - **Not any more**

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Finfer 2004

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

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N Engl J Med 2004;350:2247-56.

SAFE in a nutshell

- **Albumin equivalent to saline in heterogeneous populations of ICU patients**
- **Unclear if saline is the ideal comparator though**
- **Albumin bad in head injury**
- **Albumin maybe good in sepsis**

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

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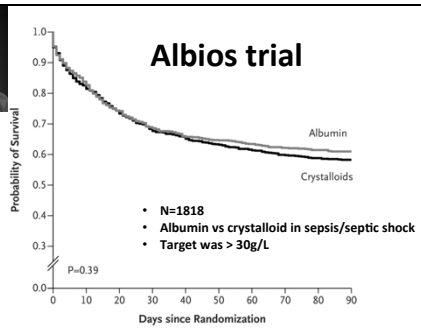
N Engl J Med 2014;370:1412-21.

Albios trial



- **N=1818**
- **Albumin vs crystalloid in sepsis/septic shock**
- **Target was > 30g/L**

No. at Risk										
Albumin	903	733	647	597	567	556	545	535	529	523
Crystalloids	907	729	652	598	676	551	538	521	511	504

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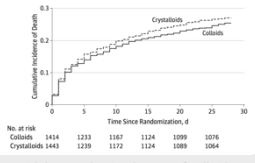
N Engl J Med 2014;370:1412-21.

Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock
The CRISTAL Randomized Trial



CONCLUSIONS AND RELEVANCE Among ICU patients with hypovolemia, the use of colloids vs crystalloids did not result in a significant difference in 28-day mortality. Although 90-day mortality was lower among patients receiving colloids, this finding should be considered exploratory and requires further study before reaching conclusions about efficacy.

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SAFE, 6S, CHEST, CRISTAL, ALBIOS

- None of these suggest a benefit for colloid over crystalloid
- Most people now believe there is a hazard associated with colloid use in the ICU
- Which leaves crystalloid – so if there are differences between them then we need to understand what that means.

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Albumin in heart surgery

Adam Kingeter MD[1], Sibyl Munson PhD[2], David Hayashida, BA[2], Martin Bunke MD[3], Andrew Shaw MD[1]

Title:

Albumin administration within one day of on-pump cardiac surgery is associated with improved survival when compared with crystalloid fluid therapy

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Kingeter et al (2015) SCA presentation

Kingeter et al (2014)

- 1526 adult on-pump CABG +/or valve surgery patients
- Propensity matched 1:1 for receipt of albumin or crystalloid only (n=763 each group)
- Primary endpoint in-hospital mortality
- Secondary endpoints organ dysfunction

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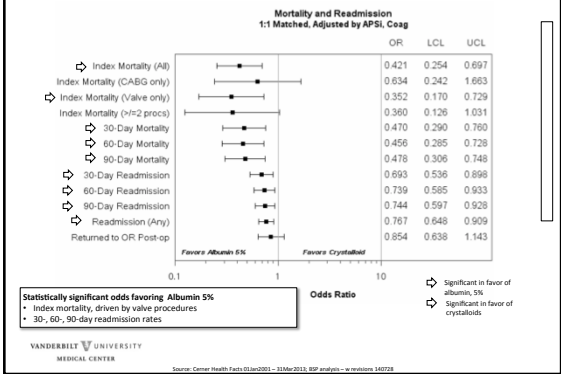
Kingeter et al (2014) AHA

A Mortality, Readmissions, Re-Operations



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Source: Cerner Health Facts 01Jan2001 – 31Mar2013; BSP analysis – w revisions 140728

Mortality

- OR for death in hospital: 0.48 (0.27 - 0.87)
- OR for death at 90 days: 0.58 (0.34 - 0.98)
- 52% relative risk reduction
- 2% absolute risk reduction
  - (4.46% crystalloid to 2.36% albumin)
- NNT of 50

  28 lives per year at Vanderbilt

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Kingeter et al (2014) AHA

Acute Kidney Injury

- KDIGO criteria used to define AKI
  - Any AKI (1, 2 or 3):- OR 0.78 (0.60 – 0.99)
  - Mod / Sev AKI (2 or 3): - OR 0.54 (0.31 – 0.93)
  - Sev AKI (stage 3):- OR 0.38 (0.18 -0.76)
- RRT used:- OR 0.29 (0.10 – 0.86)
- Association (protection?) signal gets stronger with specificity of diagnosis

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Kingeter et al (2014) AHA

Fluids in 30 seconds

- Hydroxyethyl starch
  - Probably hazardous
  - Most have stopped using (China hasn't…)
- Albumin
  - Safe but expensive
  - Not good for TBI
  - New data suggest possible benefit in heart surgery
- Crystalloid
  - 0.9% saline bad
  - Balanced solutions (including LR) good

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Conclusions

- The circumstantial evidence that high chloride solutions are harmful continues to mount
- There are no data suggesting 0.9% saline is beneficial
- New multicenter cardiac surgical data suggest balanced crystalloids (and possibly albumin) are the fluids of choice for cardiac surgical patients.

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Thank You

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