Journal Club Eastern Virginia Medical School
Therapy Article

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CITATION:

Raghunathan K et al. Association between Initial Fluid Choice and Subsequent In-hospital Mortality during the Resuscitation of Adults with Septic Shock. Anesthesiology. 2015 Sep 28.

I. **WHAT IS BEING STUDIED?**	
1. Study Objective	To test the hypothesis that the specific mixture of IV fluids, colloids and different types of crystalloids, used during initial resuscitation, in severe sepsis, is associated with major hospital outcomes, particularly in-hospital mortality
2. Study Design	Retrospective cohort study of detailed "administrative and financial" data from hospital members of Premier healthcare alliance from January 2006-December 2010Used "standardized hospital discharge files and detailed itemized date stamped billing charges" Used 8 ICD9 codes to identify primary or secondary sepsis diagnosis
3. Inclusion Criteria	≥18 years old Principle or secondary diagnosis of sepsis Known in-hospital mortality outcome Hospital LOS > 2 days Admitted to ICU Receiving vasopressors by hospital day 2 Blood cultures drawn by day 2 3 consecutive days of antibiotics Received at least 2 L of crystalloids Of 654,844 who met inclusion criteria, 60,734 were included in analysis (8.2%)
4. Exclusion Criteria	Surgical patients Elective admissions Deceased or discharged prior to hospital day 2 Patients transferred from other facilities

5. Interventions Compared	Four patient exposure categories: - Received isotonic saline exclusively - Received isotonic saline and balanced crystalloids - Received isotonic saline and colloids - Received isotonic saline, balanced crystalloids and colloids
6. Outcomes Evaluated	Primary: - In-hospital mortality Secondary: - Hospital LOS - Costs per day
II. **Are the results of the study valid**	
1. Was the assignment of patients randomized?	Patients were not randomized.
2. Was randomization concealed (blinded)?	N/A
3. Were patients analyzed in the groups to which they were randomized?	N/A
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Differences taken into account in statistical models. Used a host of statistical models (propensity matched groups, hierarchal logistic regression) to account for unbalanced numbers 44,437 NaCl vs. 3,651pts in Bal +NaCL and baseline characteristics
III. **Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1. Were patients aware of group allocation?	NA.Retrospective study.
2. Were clinicians aware of group allocation?	Yes, as this was not an RCT, clinicians directed therapy completely.
3. Were outcome assessors aware of group allocation?	Not formally stated. No mention that outcome assessors were blinded to study hypothesis which would assist in decreasing bias

4. Was follow-up complete?	N/A. Seems data was extracted to in hospital mortality during index admission only.
IV. What were the results? Answer the questions posed below	
1. How large was the treatment effect? (Difference between treatment and control group).	Unadjusted Mortality (no CI's reported) Sal - 20.25% Bal + Sal- 17.64% Sal + Col- 29.94% Bal + Sal + Col- 25.15% Mortality with IPW-based risk adjustment: Sal – 20.19% Bal + Sal – 17.69% (p<0.001) Sal + Col – 29.94% (p<0.001) Bal + Sal + Col – 25.15% (p=0.401) Mortality with logistic regression model: Sal – 21.35% Bal + Sal – 18.83% (p<0.001) Sal + Col – 25.36%(p<0.001) Bal + Sal + Col – 19.97% (p=0.138) Relative Mortality Risk PSM: Bal vs. Sal (without Col) – 0.84 (p<0.001) Bal vs. Sal (with Col) – 0.79 (p<0.001) Col vs. Sal (without Bal) – 1.14 (p<0.001) Col vs. Sal (with Bal) – 0.99 (p=0.92) Relative Mortality Risk IPW: Bal vs. Sal (without Col) – 0.87(p<0.001) Bal vs. Sal (with Col) – 0.82(p<0.001) Col vs. Sal (without Bal) – 1.13(p<0.001) Col vs. Sal (with Bal) – 1.09 (p=0.119) Secondary Outcomes: Hospital LOS & Costs per day comparable between BAL & Sal however both were increased in those receiving colloids.
2. What was the estimated treatment effect at a 95% confidence interval? (Precision)	See *Table 2* – For adjusted mortality, CIs did not overlap with exception of Bal + Sal + Col group. For relative mortality risk, 95% CI did not cross 1 except for Col vs. Sal (with Bal)
V. **Will the results help me in caring for my patients? (Applicable?)**	
1. Were the study patients similar to my	In terms of general patient population –

patient?	yes. Data was collected from Premier healthcare alliance, which includes 3600 geographically diverse hospitals of varying sizes and types all in the USA.
2. Were all clinically important outcomes considered?	Yes. In-hospital mortality as primary endpoint.
3. Are the likely treatment benefits worth the potential harm and costs?	If association is in fact causative, there do not appear to be any harms or increased costs associated with balanced fluids over isotonic saline. Host of methodological issues make "association" questionable.

Limitations

1) Very large proportion of initial population meeting inclusion criteria was excluded (601,698 of 654, 844 = 92%). Many of the exclusions are not factors that can be known *a priori* when we are seeing these patients in the ED – such as whether they are in the ICU or receiving pressors by day 2 or if they have died before day 2. It seems quite possible including these patients could have substantially affected the results.
2) The authors state that they used three distinct statistical models for analysis including inverse probability weighting (IPW), propensity score matching (PSM) and hierarchical logistic regression methods. However, they only report results from two models (IPW and regression models) for risk-adjusted mortality and two models (PSM and IPW) for relative mortality risk.
3) There was no discussion of the total amount of fluids that patients received or the percent of balanced vs. isotonic fluids that those patients received, though the authors reported this was controlled for.
4) The authors reports that mortality decreased as the proportion of patients receiving balanced fluids increased. However, in figure 3, all of the 95% CIs overlap.
5) Though the statistical analyses attempted to compensate for the vastly different sample sizes amongst the four groups, there is still substantial risk of unaccounted for confounders in the data with such a large discrepancy (12x patients received saline alone vs. saline and balanced).
6) Dates f analysis coincide with Surviving Sepsis Campaign publication in 2005 and effects of practice changes (early AB's and recognition) may have confounded data.
7) Used nine ICD-9 codes as primary patient identifiers. This is prone to missing large groups of patients with incorrect diagnoses
8) No mention of blinding of data assessors, of the use of a standardized data extraction scheme, sampling of individual patient charts for accuracy and two or more data assessors with determination of kappa scores regarding agreement if individually assessed data.
9)

Clinical Bottom Line:

While this study suggests that there may be a small trend towards mortality benefit to balanced crystalloids over isotonic saline in resuscitation of patients with severe sepsis, a large, well-designed prospective RCT is needed to provide further evidence before a definitive fluid resuscitation strategy is recommended.