Crystalloid Fluid Choice and Clinical Outcomes in Pediatric Sepsis: A Matched Retrospective Cohort Study

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Objective To test the hypothesis that resuscitation with balanced fluids (lactated Ringer [LR]) is associated with improved outcomes compared with normal saline (NS) in pediatric sepsis.

Study design We performed matched analyses using data from 12 529 patients <18 years of age with severe sepsis/septic shock at 382 US hospitals between 2000 and 2013 to compare outcomes with vs without LR as part of initial resuscitation. Patients receiving LR were matched 1:1 to patients receiving only NS (NS group), including separate matches for any (LR-any group) or exclusive (LR-only group) LR use. Outcomes included 30-day hospital mortality, acute kidney injury, new dialysis, and length of stay.

Results The LR-any group was older, received larger crystalloid volumes, and was less likely to have malignancies than the NS group. After matching, mortality was not different between LR-any (7.2%) and NS (7.9%) groups (risk ratio 0.99, 95% CI 0.98, 1.01; $P = .20$). There were no differences in secondary outcomes except longer hospital length of stay in LR-any group (absolute difference 2.4, 95% CI 1.4, 5.0 days; $P < .001$). Although LR was preferentially used as adjunctive fluid with large-volume resuscitation or first-line fluid in patients with lower illness severity, outcomes were not different after matching stratified by volume and proportionate LR utilization, including for patients in the LR-only group.

Conclusions Balanced fluid resuscitation with LR was not associated with improved outcomes compared with NS in pediatric sepsis. Although the current practice of NS resuscitation is justified, selective LR use necessitates a prospective trial to definitively determine comparative effectiveness among crystalloids. *(J Pediatr 2017;182:304-10).*

Fluid resuscitation is the cornerstone of acute management for hypovolemia and shock, but there remains uncertainty as to the most appropriate fluid to restore blood volume and optimize organ perfusion.[1-3] Isotonic crystalloid fluids are generally preferred, except in cases of hemorrhage, as they are inexpensive, easy to store, and available in a wide variety of settings.[4,5] Sepsis guidelines for adults and pediatrics recommend initial crystalloid fluid resuscitation.[6,7]

Crystalloid fluids can be categorized as either nonbuffered/nonbalanced (eg, 0.9% normal saline [NS]) or balanced (eg, lactated Ringer [LR], Hartmann, Plasma-Lyte, Baxter, Deerfield, Illinois) solutions. Although balanced fluid have a more physiologic electrolyte composition and strong ion difference closer to plasma than NS, these fluids have not been preferentially used for sepsis resuscitation.[4,5,8] However, large amounts of NS can induce a hyperchloremic metabolic acidosis and have been associated with adverse effects on kidney injury, coagulation, and death.[9-12] Alternatively, balanced crystalloids have been associated with improved outcomes and decreased renal replacement therapy compared with NS in adult sepsis.[11,13]

In pediatric sepsis, there are limited data comparing clinical outcomes following LR vs NS resuscitation. Although Carcillo et al[14] demonstrated the importance of early fluid resuscitation in pediatric septic shock, there was no differentiation between use of NS or LR. In a randomized trial of 4 fluid regimens in children with dengue fever, patients receiving LR were slower to recover from shock compared with NS, but the study was not powered for morbidity or mortality outcomes.[15] The largest study of fluid resuscitation in children with severe infections restricted crystalloid fluids to NS.[16] Consequently, guidelines for pediatric sepsis are unable to provide evidence-based recommendations to choose among available crystalloid solutions even despite emerging data questioning the relative safety of NS in adults.[6] Because crystalloid fluids are so commonly used, even

AKI	Acute kidney injury
ICD-9-CM	*International Classification of Diseases, Ninth Edition, Clinical Modification*
LOS	Length of stay
LR	Lactated Ringer
NS	Normal saline
PICU	Pediatric intensive care unit

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a small benefit attributable to type of fluid resuscitation could provide a substantial public health impact with only a minor shift in practice. We, therefore, sought to test the hypothesis that balanced fluid resuscitation is associated with improved outcomes in pediatric sepsis.

Methods

We conducted a matched retrospective cohort study of pediatric patients <18 years of age with severe sepsis or septic shock across 382 geographically diverse US hospitals between January 2000 and December 2013. Patients were identified from the Premier Healthcare Database, an administrative database established by the Premier healthcare alliance that contains itemized daily logs of all patient charges. The Premier Healthcare Database is the largest acute care database in the US with a complete census of all inpatients from more than 600 hospitals, of which approximately three-quarters are nonteaching hospitals. Pediatric data is contributed through a combination of community-based and specialty children's hospitals. The study was considered exempt from human subjects research oversight by The Children's Hospital of Philadelphia Institutional Review Board because only deidentified data were used.

Eligible patients were <18 years of age, diagnosed with severe sepsis or septic shock, received initial treatment at the Premier hospital, were not admitted to a neonatal intensive care unit (based on all patient refined-diagnosis related group codes), and were ordered to receive any combination of NS or LR fluid boluses during the first 3 days of hospital admission. To identify severe sepsis and septic shock, we used previously published combinations of *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) codes for either an invasive infection plus acute organ dysfunction (**Tables I** and **II**; available at www.jpeds.com) or the ICD-9-CM codes for severe sepsis (785.52) or septic shock (995.92).[17,18] To increase the likelihood that initial fluid resuscitation was related to sepsis, we restricted inclusion to patients with blood cultures and broad-spectrum antibiotics (**Table III**; available at www.jpeds.com) ordered within the first 3 hospital days. We excluded patients with unknown hospital disposition at day 30.

Exposure to LR or NS was defined by type and amount of fluid recorded over the first three hospital days. Only LR or NS ordered as bolus therapy was considered. Because balanced fluids other than LR (eg, Plasma-Lyte) were rare (0.3%), we limited our analysis to LR and NS. Fluid volumes were billed as 250, 500, or 1000 mL units. Although some patients likely received only a portion of a unit because of weight-based fluid dosing in pediatrics, we considered the entire unit to have been administered. Patients were categorized as exposure to only NS (NS group) or to varying amounts LR and NS (LR-any group), similar to the methodology published by Raghunathan et al.[13] We also performed a separate analysis of patients who received only NS vs only LR (LR-only group).

Demographics, month/site of admission, comorbid conditions, and intensive care therapies were obtained from the Premier Healthcare Database. Comorbid conditions were defined using pediatric complex chronic conditions.[19] Therapies included use of the following on hospitals days 1, 2, or 3: noninvasive and invasive mechanical ventilation, vasoactive infusions, albumin, blood products, furosemide, corticosteroids, use of a central venous catheter, arterial line, or bladder catheter, and extracorporeal membrane oxygenation. Because doses of vasoactive infusions were not available, we summarized this variable as the total number of vasoactive infusions. Blood products were defined as any combination of red blood cells, platelets, fresh frozen plasma, or cryoprecipitate.

Outcomes

The primary outcome was all-cause 30-day hospital mortality in the NS vs LR-any groups. To increase the likelihood that death was related to the initial sepsis episode requiring fluid resuscitation, we censored the primary outcome at 30 days after admission. Secondary outcomes included uncensored hospital mortality, hospital mortality plus hospice, acute kidney injury (AKI) with and without dialysis, and pediatric intensive care unit (PICU) and hospital length of stay (LOS). AKI was defined by the ICD-9-CM code 584.x and AKI with dialysis was defined as an ICD-9-CM code for AKI (584.x) with either (a) a procedure charge for a dialysis catheter (38.95) with a charge for dialysis (39.95) or (b) charge codes for dialysis supplies.[13] Patients with an ICD-9-CM code for end-stage renal disease already undergoing dialysis (ICD-9-CM 585.6) were excluded from the analysis of AKI with or without dialysis. All outcomes were also analyzed separately for patients in the LR-only group.

Statistical Analyses

Analyses were performed using R 2.13.1 (R Foundation) with mipmatch package[20] and Stata v 12.1 (StataCorp, College Station, Texas). Data are presented as medians (IQR) or proportions. We used mixed integer programming 1:1 matching to minimize the within-pair Mahalanobis distance for key covariates that were both available within Premier and had a biologically plausible or previously demonstrated association, including demographics, comorbidities, and therapies, with risk of death. The Mahalanobis distance is the difference in covariate values for patients in the LR vs NS groups divided by the covariates' SD.[21] Unlike propensity scores that can produce stochastic balance, integer matching ensures a more predictable and precise balance on specific covariates.[20] The specific patient-level covariates used for matching are listed in **Tables IV** and **V** (**Table IV**; available at www.jpeds.com). In addition, because LR use was likely to cluster by hospital, we also matched within site exactly except for hospitals that had ≤10 patients for which we allowed matching across sites. We also repeated the analysis excluding hospitals with ≤10 patients to ensure matching across low-volume hospitals did not impact our findings. Because prior studies have demonstrated differences in mortality for patients identified with specific severe sepsis/septic shock ICD-9-CM codes compared with