Acetate Ringer's solution versus 0.9% saline for septic patients: study protocol for a multi-center parallel controlled trial

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Study protocol

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Abstract

**Background:** Previous study drew different conclusions on significant differences between saline and balanced crystalloid solution infused in critical illness but both the statistical difference in sepsis subgroup. Thus, we will specifically focus on septic patients in this study to compare the effects of saline and balanced solution. We hypothesize that effects of saline on acute kidney injury (AKI) are related to the underline AKI severity and total volumes of infusion.

**Methods/design:** The investigators designed a pragmatic, multi-center parallel controlled trial recruiting 312 patients who are diagnosed with sepsis/septic shock in the intensive care unit (ICU) and will be assigned with either acetate Ringer’s solution or saline in the corresponding month. Patients with an end-stage renal disease (ESRD) or who need renal replacement therapy (RRT) prior to or at the time of enrolment are excluded. Enrolled patients will be regarded as with mild, moderate or severe sepsis on the basis of the severity of their illness, and will be divided into subgroups according to their initial renal function and various intravenous infusion volumes when being analyzed. The primary outcome is major adverse kidney events within 28 days (MAKE28), including the composite of in-hospital death, receipt of new renal replacement therapy, or persistent renal dysfunction. Secondary outcomes include 28 days-mortality, internal environment disturbance, incidence and duration of vasoactive drug treatment, duration of mechanical ventilation, duration of RRT and ICU and hospital length of stay.

**Results and conclusions:** To our knowledge, this study will be the first to focus on septic patients and provide credible and evident data on the comparison of outcome between acetate Ringer’s solution and saline for intravenous infusion in adult septic patients on the basis of baseline renal function and infusion volumes taken into consideration.

**Trial registration:** ClinicalTrials.gov, identifiers: NCT03685214. Registered on August 15th, 2018.
https://clinicaltrials.gov/ct2/show/NCT03685214

Background And Rationale

Sepsis, a common problem in the intensive care unit (ICU) with high morbidity and mortality(1-4), is the main cause for acute kidney injury (AKI) in critically ill adults(5). Septic AKI accounts for nearly half of all kinds of AKI(6), and increases mortality six to eight fold(6,7). Fluid resuscitation plays a vital role in the treatment of sepsis and septic shock(8, 9), which attaches great significance to the type of solution infused during fluid management. Saline is not a “normal” fluid with high level of chloride which may be related to AKI and mortality(10,11), but it is still commonly administered on a global basis so far(12). Meanwhile, a preference for balanced crystalloid solution on venous transfusion is emerging(13,14).

Until now, the choice of crystalloid for critically ill patients has not been confirmed(15, 16). The SPLIT (Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy) study conducted in four New Zealand ICUs(15)concluded with no difference neither in the primary outcome of the incidence of AKI nor in secondary outcomes of RRT use and mortality between the use of a buffered crystalloid and saline.
However, this study was criticized for the relatively small volume of fluid as it may have been too low to cause detectable renal toxicity(16). Another trial comparing saline to buffered crystalloids solutions (lactated Ringer's solution and Plasma-Lyte A) in a single ICU, the SALT (Isotonic Solution Administration Logistical Testing) study, demonstrated no difference in the overall incidence of AKI or major adverse kidney events (MAKE30) including death from any cause, new receipt of renal replacement therapy (RRT), or persistent renal dysfunction within 30 observational days. However, notably, there was a difference on MAKE30 in septic patients who received larger volume of crystalloids in subgroup analysis. The study showed a dose-response relationship(16). A recent multiple-crossover trial in critically ill adults in 5 ICUs demonstrated that the use of balanced crystalloids resulted in a lower rate of MAKE30 than the use of saline(17)though it showed no significant difference in the incidence of AKI and mortality respectively. It also showed difference in sepsis subgroup, but the potential dose-response relationship related with infusion volumes in the subgroup was not clarified(18). Both of the 2 studies implied that it is necessary to investigate further in septic patients as they are more prone to fluid damage. It still remains uncertain whether balanced crystalloid is superior than saline in septic patients, whether it is related to their initial renal function, and whether there is a dose-response relationship between fluids and outcomes. Thus, we carry out this study for further investigations.

**Objectives**

This trial is the first to focus on septic patients and verify if acetate Ringer's solution is superior to saline, especially in the patients with septic AKI. It is aimed to provide credible and evident data and clarify if (1) there is a significant difference in the overall outcome between acetate Ringer's solution and saline in septic patients, (2) the effect is dependent on the baseline renal function, and (3) there is a dose-response effect by subgroup analysis.

**Methods/design**

The study is a multi-center, interventional, prospective, pragmatic, unblinded, and parallel controlled trial. This protocol is designed in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines(19). All the data will be collected at each time spot as shown in the Standard Protocol Items [Fig.1]. The study flow is described in Figure 2.

**Study sites and period**

The study is planned to be conducted from March 1st 2019 to February 28th 2022 in 2 centers including the ICU of Zhongnan Hospital of Wuhan University and the ICU of Wuhan Central Hospital of Tongji Medical College, Huazhong University of Science and Technology. The above 2 hospitals are both tertiary hospitals integrating clinical, scientific research and teaching. Participating ICUs began enrolment sequentially over the first year of the study. Each ICU will enroll participants for an equal number of acetate Ringer's solution and saline months for at least 12 months.

**Registration, ethical considerations, and monitoring**
The study was registered on ClinicalTrials.gov before the participants' enrolment started (identifiers: NCT03685214) (Table 1). This study follows the principles of the Helsinki Declaration 2013. The whole protocol has been reviewed and approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (Clinical Ethical Approval No. 2018010) and the Ethics Committee of Wuhan Central Hospital of Tongji Medical College, Huazhong University of Science and Technology (Hospital Ethical Approval No. 201904). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial. The DSMB is independent of the trial and is comprised of two academic intensivists, professor Jianguo Li and professor Bo Hu, who are experienced in the conduct of clinical trials in critical illness and outside the study, being able to pause the trial to investigate or give suggestions on potential safety issues to improve our design and implement. The DSMB follows the charter of the Ethics Committee of Zhongnan Hospital of Wuhan University.
Participant patients

Participants’ inclusion criteria are as follows:

1. At the age of 18 to 80;
2. Diagnosed as sepsis (a possible or specific proof for infection plus Sequential Organs Failure Assessment (SOFA) scores ≥ 2).
Participants’ exclusion criteria are as follows:

1. Patients once having received RRT;
2. Patients requiring RRT prior to enrolment;
3. Patients possessed with only one kidney;
4. Patients with a medical history of renal transplant;
5. AKI caused by permanent kidney artery embolism or surgery injury to kidney artery;
6. AKI caused by glomerulonephritis, interstitial nephritis or vasculitis;
7. AKI caused by postrenal obstruction;
8. Hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura;
9. Patients having received fluid resuscitation over 1000ml within 6 hours prior to ICU;
10. Patients with serum chloride more than 120mmol/L;
11. Pregnant women;
12. Patients enrolled into another clinical trial at the same time.

Study treatments

The intervention of treatment lies in fluid management. To exclude the possible difference caused by different balanced crystalloid solution, acetate Ringer’s solution is chosen for balanced crystalloids infusion. After patient screening and grouping, participants will be assigned with acetate Ringer’s solution or saline for intravenous infusion accordingly. The volume, infusion rate and additive content (e.g., potassium chloride) of the fluid will be determined by responsible clinicians. The intervention will last for 5 days after patients’ enrolment. Other solutions are permitted to be used as carrier fluids for the infusion of any drug on the occasion when neither acetate Ringer’s solution nor saline is considered compatible. Medication use except fluids will not be restricted in the study.

Parallel control and allocation

Patients will be divided into 2 parallel groups: acetate Ringer’s solution versus saline. Crystalloids for enrolled patients is assigned according to the number of the month. Once assigned, the solution will be applied for the first 5 days during the patients’ stay in ICU. The assignment remains during change of month. The solution applied in the beginning month in each ICU is determined randomly by Excel2016 of Microsoft Office to make sure that stratified patient groups will be randomized to receive either acetate ringers or saline solution, followed by a monthly rotation of fluids, so that any potentially observed difference in renal function is not due to other confounding factors such as use of nephrotoxic medication or contrast media. According to the Excel2016-generated random numbers, Acetate Ringer’s solution will be applied in the odd month and saline will be applied in the even month both in the 2 centers. The random number table is operated by the primary investigator alone and clinicians are not involved in the process.
Study fluid distribution and logistics

The acetate Ringer’s solution is manufactured by Heng Rui Pharmaceutical Company Limited of Jiangsu Province with trade name of Le Jia, which has volume sizes of 250ml and 500ml, while the saline is produced by Baxter Healthcare with different volume sizes of 250ml and 500ml. Components of these two crystalloids are presented below [Fig.3]. The study is an open-label study, thus the exact solution used is known to investigators, clinicians and patients. Since the study is non-blind and two fluids used in this study have already been widely applied in the daily care of patients in the above ICUs, there are not problems of logistics.

Study outcomes

The primary outcome is MAKE28 (major adverse kidney events)(23)-a composite of in-hospital death, new renal-replacement therapy or persistent renal dysfunction (defined by an estimate glomerular filtration rate (eGFR) lower than 60 ml/min/1.73 m$^2$ for at least 3 months(24, 25)) within 28 observational days.

Secondary outcomes will include:

1. 28 days-mortality;
2. Electrolytes disturbance, including hypernatremia, hyperchloremia and hyperkalemia as well as hyponatremia, hypochloremia and hypokalemia;
3. Changes of renal functions based on the biomarkers measured from the participants' plasma and urine samples collected in the first 3 days after
4. Other clinical outcomes: ICU-stay days, ventilator days, vasopressor days, and RRT

Pre-specified subgroups for primary and secondary outcome analyses will include:

1. With or without kidney injury (defined as baseline creatinine concentration at least 1.5 times above the upper limit of normal for the local laboratory);
2. With or without septic shock;
3. Low versus high severity of sepsis: mild, moderate and severe (defined by SOFA scores and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores)
4. Intravenous infused volumes of the assigned

Sample size and statistical power

The sample size was calculated based on the occurrence of MAKE30 on septic patients, which was around 35%(17). With a noninferiority limit of 1.5%, a total of 312 study participants (156 in each group) would result in a power of at least 80% with a one-sided type-1 error rate ($\alpha$) of 2.5%, allowing a 20% withdrawal rate in each group.
**Statistical analysis**

Measurement data that conform to normal distribution will be described as mean ± SD, while ones that do not will be reported as the median and inter quartile range (IQR). Count data will be notified as frequencies and proportions. As for single factor analysis, the difference of measurement data will be compared with T-test between two groups or with one-way analysis of variance among three groups. Chi-square test and Fisher’s exact test will be used for rate comparison. As for multi-factor analysis, variables which showed a significant difference in the univariate analysis will be processed by logistic multivariate regression analysis. Multiple linear regression analysis will be used to demonstrate the linear relationship between variables. P value <0.05 will be considered statistically significant. SPSS 24.0 will be used to complete data processing and statistical analysis.

**Analytic rationale**

This study will recruit participants with a wide range of baseline risk factors of the primary outcome who are exposed to the study intervention and can be divided into subgroups of distinct renal function or received crystalloid volumes. The baseline and secondary analysis will figure out whether the intervention makes a difference to patients’ prognosis.

**Primary analysis**

The primary analysis will be an intention-to-treat comparison of the primary outcome of MAKE28 between the saline and acetate Ringer’s solution. A generalized linear mixed-effects model will be used including fixed effects (sex, age, group assignment, principal diagnosis, mechanical ventilation days, vasopressor days, ICU stay days) and random effects. It is aimed to describe patients’ baseline characteristics and eliminate confounding factors.

**Main secondary analysis**

We presume that participants will receive a wide range of total crystalloid volumes and that the more fluid patients receive, the more significant difference will be performed between the two groups. Also, we presume that the outcome may be related with participants’ initial renal function. Based on these anticipations, in the main secondary analysis, patients will be divided into several groups according to different crystalloid infusion volumes and distinct initial renal function respectively. The proportion of patients experiencing the primary outcome will be compared between the same volume groups of saline and acetate Ringer’s solution respectively and between the same initial renal function groups, namely no AKI, AKI stage 1, AKI stage 2 and AKI stage 3, respectively. In this section, a logistic regression model with the primary outcome will be conducted to detect whether it differs significantly between saline and acetate Ringer’s solution infusion on renal outcome in the same volume group or the same initial renal function group, and then figure out whether the infused volume or initial renal function makes a difference.

**Additional secondary analysis**
Statistical methods mentioned in the statistical analysis will be applied according to the characteristics and distribution of the data.

1. Compare the secondary outcome between the two groups;
2. Subgroup analysis will include:
   a. Septic shock (yes/no)
   b. The APACHE II scores and SOFA scores at the day of enrolment
   c. Receipt of mechanical ventilation (yes/no) and ventilation days
   d. Receipt of vasopressor (yes/no), vasopressor category and max doses
   e. Receipt of RRT (yes/no) and RRT days
   f. Stage of AKI on the enrolment day (no AKI, AKI, chronic kidney disease without receiving RRT regularly)
   g. Main diagnosis at the time of admission to hospital (nervous system disease, respiratory system disease, cardiovascular system disease, digestive system disease, urinary system disease, hematologic system disease, endocrine system disease)
   h. Complications (Hypertension, diabetes, coronary heart disease, )

**Handing of missing data**

Of the primary outcome, data of the rate of AKI and the percentage of new receipt of RRT are not supposed to be missing for any patients. Nevertheless, some data of renal function may be missing due to protocol executive errors or record-keeping errors. Mean completer, hot deck imputation and filling manually will be taken to minimize the effects of these missing data as much as possible. For example, if the renal function values near the missing value are in the normal range or have the same trend, the missing data will be averaged or filled with proximity. Patients without a serum creatinine measurement between enrolment and hospital discharge who survive and do not receive new RRT will be considered as not having experienced MAKE. If the patients or authorized agents give up treatment due to little chance to survive predicted by clinicians, their outcome is considered to be death. Besides, in-hospital mortality may be missing due to patients or authorized agents giving up treatment or other unpredictable accidents when the illness is not that severe. Data may also be missing due to severe adverse events (SAEs) or patients quitting the trial. Under these circumstances, an intention-to-treat analysis will be conducted to deal with the missing data. Of other outcomes, deletion will be considered if the missing data is too large to fill. Indices with complete data after conservative imputation will be included in the statistical analysis.

**Data collection and management**

Patients’ demographic data, main diagnosis, comorbidities, assigned crystalloids, general vital signs, SOFA scores, APACHE II, infection indices and indices of multi-organ function including renal function, respiratory function, cardiac function, etc. at the time of enrolment will be collected as baseline data. Clinical information including infection indices (white blood cells count, procalcitonin, etc.), organ
function indices (renal function (creatinine, urea nitrogen, cystatin C, urine volumes, etc.), respiratory function (PO$_2$/FiO$_2$, ventilation situation, etc.), hepatic function (total bilirubin, etc.) and indices of internal environment (blood gas analysis) will be detected during the first 5 days in ICU, and treatments such as vasopressors, mechanical ventilation, RRT and electrolytes supplement will be recorded. These data and infused volumes of the assigned fluids will be collected for at least 5 days or until ICU discharge. ICU stay days, vasopressor days, RRT days and ventilation days will be counted during 28 days after enrolment. These data will be collected to assess and analyze primary and secondary outcomes. Besides, patients’ blood and urine samples within the first 3 days after enrolment will be collected and stored for testing possible biomarkers for identifying AKI at an early stage.

Patients' information and clinical data will be collected from the Hospital Information System (HIS) of the hospitals involved in this study, and recorded in the Case Report Format (CRF) by the trial manager or trained personnel. An electronic password-protected excel, which will be applied for statistical analysis, will be created to summarize the data of all participants. All the data will be accessed by only investigators and authorized personnel to monitor the completeness and authenticity of the table. The confidentiality is secured and all the data will be preserved for the purpose of a secondary analysis or investigations by the investigators. To protect patients' privacy, their names will not appear on the CRF table. Every participant will only be recognized by their study ID.

Risk evaluation and adverse events

The trial is considered to pose a low risk. Firstly, saline and acetate Ringer's solution have already been widely used in the clinical practice of ICUs of the above hospitals. Secondly, it still remains controversial which fluid (saline or balanced crystalloid solution) is better for septic patients. Thirdly, clinicians are allowed to make clinical judgments and choose the other crystalloid for a specific patient if they think the assigned one may increase the risk of poor prognosis. Certainly, data of these patients will not be included in the final analysis. Therefore, the adverse events (AEs) of this trial may be minimal.

Still, during the entire observational 28 days from the beginning of the trial, possible AEs will be assessed and recorded in the CRF table. Investigators will evaluate the relationship between the events and our intervention by clinical judgment, and the events will be graded as mild, moderate and severe. SAEs should be considered if unexpected clinically significant critically ill diseases which may be resulted from fluid intervention happen. AEs, especially SAEs, must be reported to DSMB and followed until they are solved. At the end of the trial, AEs and their relationship to the study will be documented in a table and submitted.

Summary/discussion

Fluid resuscitation is the mainstream for the treatment of patients with sepsis/septic shock, and all the guidelines recommend crystalloids as the first choice. Normal saline, a very common crystalloid, poses hyperchloremia and probably worsens AKI which is always complicated by sepsis(26). However, it is
unknown if saline can be safely used in septic patients. Recent studies demonstrated different conclusions in kidney outcomes between saline and balanced solutions in overall critically ill patients (15-17), but showed a significant difference in septic patients by subgroup analysis (16,17). This enlightens us to study on a possible dose-response relationship in a high-risk population. Thus, we hypothesize that the harmful effects of saline are associated with the initial kidney function and infused volume of fluids. To confirm this hypothesis, we will carry out this study. As sepsis or septic shock is one of the most typical problems requiring large volume of fluids, this also makes it clinically practical significant to investigate. To our knowledge, this study will be the first to focus on septic patients and compare the effects on outcome between balanced crystalloid solution and saline. In light of this study, a particular comparison will be conducted between acetate Ringer’s solution and saline. Firstly, the patients recruited will be confined to septic/septic shock. Therefore, the conclusions will be applied specifically in septic population. Secondly, the analysis of the association between the due solution and outcome, especially the development of AKI, will be more in details. The infused volume and the baseline renal function will both be taken into consideration. If this trial demonstrates that balanced crystalloid solution or saline shows a priority over the other, it can provide an evidence for the guideline on fluid resuscitation for septic/septic shock. Therefore, the results of this study may be instructive and meaningful.

**Trial status**

This is the second version of the protocol which was reviewed and approved on April 20th, 2018. Patient recruitment has started on March 1st, 2019 and will be completed on February 28th, 2022.

**Abbreviations**

AKI: acute kidney injury; ICU: intensive care unit; ESRD: end-stage renal disease; RRT: renal replacement therapy; SPLIT: Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy; SALT: Isotonic Solution Administration Logistical Testing; MAKE: major adverse kidney events; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; KDIGO: Kidney Disease Improving Global Outcomes; DSMB: data and safety monitoring board; HUS: Hemolytic uremic syndrome; SOFA: Sequential Organ Failure Assessment; eGFR: estimate glomerular filtration rate; APACHE II: Acute Physiology and Chronic Health Evaluation II; IQR: inter quartile range; CRF: Case Report Format; AE: adverse events; SAE: severe adverse events.

**Declarations**

**Trial sponsor**

Trial Sponsor: Zhongnan Hospital of Wuhan University

Sponsor’s Reference: 12420000441435122B

Contact name: Professor Zhiyong Peng
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**Ethics approval and consent to participate**

This study follows the principles of the Helsinki Declaration 2013. The whole protocol and related documents (e.g. CRFs, informed consents, etc.) have been reviewed and approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (Clinical Ethical Approval No. 2018010) and the Ethics Committee of Wuhan Central Hospital of Tongji Medical College, Huazhong University of Science and Technology (Hospital Ethical Approval No. 201904) respectively. Investigators will give the written informed consent and inform patients about the purpose, intervention, benefits, and possible risks of this trial. Only participants who signed the written informed consent will be screened for enrolment.

**Consent for publication**

This protocol and findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.

**Availability of data and materials**

The CRFs and final dataset will only be accessible to the study investigators.

**Competing interests**

None declared.

**Funding**

The study is funded by Wu Jieping Medical Foundation (Project identifier: HRJJ20171026). The foundation has reviewed and approved this project, and the primary investigator is supposed to report the process of this study to the foundation. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

**Authors’ contributions**

FL, JZ, YZ, LS, YL, LH, LY, ZP designed this study; FL, JZ designed the statistical analysis plan; LS and LH wrote the bid for the research project and obtained permission from every ethics committee; FL, JZ, YZ, LY carried out this trial and draft this manuscript; ZP, LS, YL carefully reviewed the manuscript; All authors read and approved the final manuscript.

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References

1. Martin GS, Mannino DM, Eaton S, Moss The epidemiology of sepsis in the United States from 1979 through 2000. The New England journal of medicine. 2003;348(16):1546-54.
2. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, et Hospital Deaths in Patients with Sepsis From 2 Independent Cohorts. JAMA. 2014;312(1):90-2.
3. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et Sepsis in European intensive care units: results of the SOAP study. Critical care medicine. 2006;34(2):344-53.
4. Zhou J, Qian C, Zhao M, Yu X, Kang Y, Ma X, et Epidemiology and outcome of severe sepsis and septic shock in intensive care units in mainland China. PloS one. 2014;9(9):e107181.
5. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive care medicine. 2015;41(8):1411-23.
6. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et Acute renal failure in critically ill patients: a multinational, multicenter study. Jama. 2005;294(7):813-8.
7. Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration Critical care medicine. 2009;37(9):2552-8.
8. Levy MM, Evans LE, Rhodes The Surviving Sepsis Campaign Bundle: 2018 update. Intensive care medicine. 2018;44(6):925-8.
9. Liu V, Morehouse JW, Soule J, Whippy A, Escobar Fluid volume, lactate values, and mortality in sepsis patients with intermediate lactate values. Annals of the American Thoracic Society. 2013;10(5):466-73.
10. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey Chloride- liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. Intensive care medicine. 2015;41(2):257-64.
11. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive care medicine. 2014;40(12):1897-905.
12. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care Critical care (London, England).
13. Bellomo R, Kellum JA, Ronco C, Wald R, Martensson J, Maiden M, et Acute kidney injury in sepsis. Intensive care medicine. 2017;43(6):816-28.

14. Hammond NE, Taylor C, Saxena M, Liu B, Finfer S, Glass P, et al. Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and Intensive care medicine. 2015;41(9):1611-9.

15. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. Jama. 2015;314(16):1701-10.

16. Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED, et Balanced Crystalloids versus Saline in the Intensive Care Unit. The SALT Randomized Trial. American journal of respiratory and critical care medicine. 2017;195(10):1362-72.

17. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al. Balanced Crystalloids versus Saline in Critically Ill The New England journal of medicine. 2018;378(9):829-39.

18. Reverter E, Poch E, Fernández Balanced Crystalloids versus Saline in Critically Ill Adults. The New England journal of medicine. 2018;378(20):1949.

19. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158(3):200-7.

20. Khwaja KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Nephron Clinical Practice. 2012;120(4):c179-c84.

21. Ware JH, Hamel Pragmatic trials–guides to better patient care? The New England journal of medicine. 2011;364(18):1685-7.

22. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama. 2016;315(8):801-10.

23. Billings FT, Shaw Clinical trial endpoints in acute kidney injury. Nephron Clin Pract. 2014;127(1-4):89-93.

24. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney international. 2011;80(1):17-28.

25. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney 2005;67(6):2089-100.

26. Gómez H, Kellum Sepsis-induced acute kidney injury. Current opinion in critical care. 2016;22(6):546-53.
Table 1

| TIMEPOINT                        | STUDY PERIOD                        |
|----------------------------------|-------------------------------------|
|                                  | Enrollment & Allocation | On-study | Termination |
| ICU admission (Day 0)            | ×                                  |          | 28 days after enrollment |
| Eligibility screen              | ×                                  |          |              |
| Allocation                       | ×                                  |          |              |
| Interventions                    |                                    |          |              |
| Acetate Ringer’s solution        |                                    |          |              |
| Screening for contraindications  | ×                                  | ×        | ×            |
| 0.9% saline                      |                                    | ×        | ×            |
| Screening for contraindications  |                                    | ×        | ×            |
| Assessments                      |                                    |          |              |
| Baseline variables              | ×                                  |          |              |
| Intravenous fluid receipt       | ×                                  | ×        | ×            |
| Serum creatinine and blood gas analysis | ×        | ×        | ×            |
| Receipt of invasive support      | ×                                  | ×        | ×            |
| Clinical outcomes                |                                    |          | ×            |

**Figure 1**

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Baseline variables include: baseline renal function; main diagnosis and complications; severity of illness at enrolment; demographic characters; admission location. Intravenous fluid includes: saline; acetate Ringer's solution; other fluids. Receipt of invasive support includes: mechanical ventilation; receipt of RRT; vasopressors. Clinical outcomes include: vital status; vasopressor days, mechanical ventilation days, RRT days and serum creatinine at hospital discharge.
Figure 2

Study Flow Abbreviations: RRT, renal replacement therapy; AKI, acute kidney injury; HUS, hemolytic uremic syndrome; ICU, intensive care unit

| Components       | Acetate Ringer’s solution (mmol/L) | 0.9% Saline (mmol/L) |
|------------------|------------------------------------|----------------------|
| Na               | 140                                | 154                  |
| K                | 4                                  | -                    |
| Mg               | 1                                  | -                    |
| Ca               | 1.5                                | -                    |
| Cl               | 115                                | 154                  |
| Glucose          | 1%                                 | -                    |
| Buffer system    | Acetate 25                          | -                    |
| Osmotic concentration | 304                          | 286                  |

Figure 3

Patients excluded:
1. Age <18y or >80y;
2. Patients once having received RRT;
3. Patients requiring RRT prior to enrollment;
4. Patients with only one kidney;
5. Patients with a medical history of renal transplant;
6. AKI caused by permanent kidney artery embolism or surgery injury to kidney artery;
7. AKI caused by glomerulonephritis, interstitial nephritis or vasculitis;
8. AKI caused by postrenal obstruction;
9. HUS or thrombotic thrombocytopenic purpura;
10. Patients having received fluid resuscitation over 1000ml within 6 hours prior to the ICU;
11. Pregnant women;
12. Patients enrolled into another clinical trial at the same time.
Components of two crystalloids used in the trial.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- [SPIRITChecklist.doc](#)