Objectives: to investigate the hypothesis that "balanced crystalloids would result in earlier hospital discharge and a lower incidence of major adverse kidney events than saline." (p. 820)

Methods: This single-center, pragmatic, unblinded, multiple-crossover trial was conducted in the ED at Vanderbilt University between January 1, 2016 and April 30, 2017. Consecutive adult (18 years or older) patients receiving at least 500 mL of intravenous isotonic crystalloid in the ED who were later admitted to a non-ICU bed were enrolled. The type of crystalloid administered was "randomized" based on calendar month, alternating between saline and balanced crystalloids. During months when balanced crystalloids were administered, clinicians could choose to administer either lactated Ringer's solution or Plasma-Lyte A. Clinicians could also choose to administer off-protocol fluids if they were felt to be indicated. Selection of fluids administered after hospital admission was at the discretion of the admitting team.

The primary outcome being analyzed was hospital-free days to day 28. Patients who died were considered to have 0 hospital-free days. Secondary outcomes included: 1) major adverse kidney events within 30 days, defined as death, need for new renal replacement therapy, or a final serum creatinine $\geq 200\%$ of baseline at hospital discharge or 30 days (whichever came earlier); 2) acute kidney injury of stage 2 or higher; and 3) in-hospital death. Patients who were already on renal replacement therapy at presentation were not eligible to meet renal outcomes.

A total of 19,949 patients were treated with isotonic crystalloid in the ED during the study period; after excluding patients who received less than 500 mL of fluid and those admitted to the ICU, there were 13,347 patients in the final analysis, of whom 6708 (50.3\%) were assigned to receive balanced crystalloids and 6639 (49.7\%) were assigned to receive saline. The median age in the two groups was 54 and 53 years respectively, and 52.3\% and 50.9\% were female. The median crystalloid volume administered in the ED was just over 1 liter; 95.3\% of patients in the balanced fluid group received lactated Ringer's solution. Baseline creatinine values were not available for 4666 (35.0\%) patients.
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<td>I. Are the results valid?</td>
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<tr>
<td>A. Did experimental and control groups begin the study with a similar prognosis?</td>
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<tr>
<td>1. Were patients randomized?</td>
<td>No. &quot;the type of isotonic crystalloid was assigned according to calendar month, with all patients in the trial emergency department during the same month assigned to the same fluid, either balanced crystalloids or saline.&quot; (p. 821) This type of quasi randomization does not allow for <strong>blinding</strong> of interventions and is subject to systematic bias.</td>
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<td>2. Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be “randomized” to a particular group?</td>
<td>N/A as the study was not randomized.</td>
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<td>3. Were patients analyzed in the groups to which they were randomized?</td>
<td>Yes. &quot;Patients who received off-protocol fluids were included in the primary analysis according to <strong>intention-to-treat principles.</strong>&quot; (p. 821) A total of 88.3% of patients received only the assigned crystalloid.</td>
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<td>4. Were patients in the treatment and control groups similar with respect to known prognostic factors?</td>
<td>Mostly yes. Patients were similar with respect to age, gender, race, comorbidities, admission service, baseline creatinine (when available), and initial serum electrolytes. Details on the reason for admission were not provided and hence cannot be assessed.</td>
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<td>B. Did experimental and control groups retain a similar prognosis after the study started?</td>
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<td>1. Were patients aware of group allocation?</td>
<td>Yes (in theory), however it is unlikely that knowledge of fluids being received would affect the outcomes.</td>
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<td>2. Were clinicians aware of group allocation?</td>
<td>Yes. This study was not randomized and hence it was impossible to blind clinicians to fluid choice. As a result, <strong>performance bias</strong> may have affected the outcomes.</td>
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<td>3. Were outcome assessors aware of group allocation?</td>
<td>Yes. There is no mention of blinding of outcome assessors. While this could potentially lead to <strong>observer bias</strong>, the outcomes were fairly objective.</td>
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### Was follow-up complete?
Yes. As all outcomes measures were made during hospitalization, no patients were lost to follow-up.

### What are the results?

1. **How large was the treatment effect?**
   - There was no difference in the primary outcome, number of hospital-free days, between the balanced crystalloid and saline groups: median 25 days in each group; adjusted OR 0.98 (95% CI 0.92-1.04).
   - Patients in the balanced crystalloid group had a lower incidence of the composite of major adverse kidney events within 30 days: adjusted OR 0.82 (95% CI 0.70-0.95).
     - There was, however, no difference in the incidence of death or new need for renal replacement therapy.
     - There was also no unadjusted difference in the incidence of a final creatinine ≥ 200% of baseline (RR 0.86, 95% CI 0.73-1.01).

2. **How precise was the estimate of the treatment effect?**
   - See above.

### How can I apply the results to patient care?

1. **Were the study patients similar to my patient?**
   Yes. This study was conducted in a large, urban, tertiary care center with what is likely a similar mix of medical, surgical, and trauma patients. This was, unfortunately, a single-center study, and its results are less generalizable than a multi-center study would be.

2. **Were all clinically important outcomes considered?**
   No. The authors considered the most relevant outcomes (mortality, hospital LOS, and renal impairment), but did not look at cost or need for electrolyte repletion. The driving component of the secondary outcome (doubling of baseline creatinine) is of uncertain clinical relevance and is more a surrogate outcome than a patient-centered outcome.

3. **Are the likely treatment benefits worth the potential harm and costs?**
   No. This study demonstrates that choice of crystalloid has no significant effect on any clinically meaningful outcome when administered in relatively small volumes. The extremely small effect seen on the secondary outcome should be looked at in context: a NNT of ~100 was found when using a composite of unbalanced outcomes—the sole driving
component being of uncertain clinical relevance—and required statistical adjustment to even achieve statistical significance.

Limitations:

1. This was not a randomized controlled trial. Instead, group allocation was dictated by the month in which the patient presented.

2. Neither patients, clinicians, nor outcome assessors were blinded to group allocation, raising the possibility of performance bias and observer bias.

3. The secondary outcome (the only one to achieve statistical significance) was a composite outcome whose individual components did not achieve statistical significance. Additionally, the reported odds ratio for the composite outcome has been adjusted for certain prognostic factors and does not represent the raw results.

4. The driving force behind the positive results for the secondary outcome was a doubling of baseline creatinine. This is problematic because:

   a. This is a surrogate outcome rather than a patient-centered outcome, the clinical significance of which is unknown. The authors did not follow patients to see if creatinine values normalized following discharge.

   b. Baseline creatinine values were not available for 4666 (35.0%) patients.

Bottom Line:

This unblinded, single-center, pseudo-randomized study demonstrated no difference in hospital-free days among noncritically ill patients receiving balanced crystalloids versus normal saline. A small difference in the composite secondary outcome was seen with a number needed to treat of approximately 100. This was based on a statistical adjustment of the raw data and was driven entirely by a difference in the doubling of baseline creatinine, which is of uncertain clinical relevance and is more a surrogate outcome than a patient-centered outcome.