Balanced Crystalloid vs Normal Saline in Pediatric Acute Gastroenteritis

with Statistical Analysis Plan

Unique Protocol ID: ADUPEDFluid | **Ethics:** 2026/185 (ADÜ KAEK, 14.05.2026)
NCT: Pending
Date: 18.05.2026 | **Status:** Recruiting

PART 1 — PROTOCOL SUMMARY

Study Identification

Organization's Unique Protocol ID
ADUPEDFluid

Brief Title
Balanced Crystalloid vs Normal Saline in Pediatric Acute Gastroenteritis

Study Type
Observational

Official Title
Comparison of Early Biochemical and Clinical Outcomes of Balanced Versus Unbalanced Isotonic Crystalloid in Children Aged 6 Months to 5 Years Who Require Intravenous Rehydration for Acute Gastroenteritis: A Single-Center Prospective Observational Cohort Study

Secondary IDs
—

Study Status

Record Verification Date
May 2026

Overall Recruitment Status
Recruiting

Study Start Date
May 15, 2026 — Actual

Primary Completion Date
January 2027 — Anticipated

Study Completion Date
March 2027 — Anticipated

Sponsors and Collaborators

Responsible Party
Principal Investigator

Investigator
Aykut Çağlar, MD — Professor — Aydin Adnan Menderes University

Sponsor
Aydin Adnan Menderes University

Collaborators
None

Oversight

U.S. FDA-Regulated Drug / Device
No / No

Board Status
Approved

Approval Number
2026/185

Board Name
ADÜ Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu

Board Affiliation
Aydin Adnan Menderes University Faculty of Medicine

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Data Monitoring Committee
No

Study Description

Brief Summary
Acute gastroenteritis (AGE) is among the most common reasons for paediatric emergency visits. Children with significant dehydration often require intravenous (IV) fluid therapy. Two main types of IV crystalloid solutions are currently used in clinical practice: 0.9% sodium chloride (normal saline, NS) and balanced crystalloids such as Isolyte-S, which contain acetate and gluconate as bicarbonate precursors.

Normal saline has a high chloride content (154 mEq/L), which may worsen the metabolic acidosis already present in many children with acute gastroenteritis. Balanced crystalloids have a chloride content closer to that of plasma (98 mEq/L) and additionally contain acetate and gluconate, which are metabolised in peripheral tissues to consume hydrogen ions and thereby raise serum bicarbonate — a mechanism distinct from simply avoiding chloride overload.

This study prospectively observes and compares early biochemical and clinical outcomes in children with acute gastroenteritis who receive one of these two fluid types as part of their routine clinical care. The treating physician independently decides which fluid to use; the

research team does not influence this decision and does not order any additional tests or procedures. Laboratory values used as outcomes are drawn solely from blood tests obtained as part of standard care.

The primary aim is to determine whether, at approximately 4 hours after IV fluid start, serum bicarbonate has changed more in children who received a balanced crystalloid compared with those who received normal saline. Secondary aims include comparing blood pH, chloride levels, need for additional IV boluses, time to first oral fluid intake, hospitalisation rate, and 72-hour return visits.

Detailed Description

Background and Scientific Rationale

Acute gastroenteritis causes gastrointestinal bicarbonate loss through diarrhoea, combined with reduced oral intake and, in severe cases, lactate accumulation from hypoperfusion, resulting in metabolic acidosis. The conventional choice, 0.9% sodium chloride (NS), carries a supraphysiological chloride load (154 mEq/L versus plasma reference of 98–103 mEq/L). This reduces the strong ion difference (SID), independently precipitating hyperchloraemic metabolic acidosis and failing to correct pre-existing acidosis.

Isolyte-S has a chloride content of 98 mEq/L and contains acetate (27 mEq/L) and gluconate (23 mEq/L) as bicarbonate precursors. Acetate is rapidly metabolised in cardiac muscle, skeletal muscle, and renal cortex independently of hepatic function (half-life approximately 30 minutes) via: $CH_3COO^- + O_2 + H^+ \rightarrow 2CO_2 + 2H_2O$, consuming 1 mEq of H^+ per mEq of acetate. Gluconate undergoes hepatic oxidation via the pentose phosphate pathway with analogous H^+ consumption. The total buffer capacity of Isolyte-S is 50 mEq/L — approximately twice that of Ringer's lactate (28 mEq/L). This active acid-neutralisation capacity is mechanistically distinct from simply avoiding chloride overload.

Evidence Base

The 2023 Cochrane systematic review (Florez et al., 5 RCTs, 465 children) demonstrated improved bicarbonate and pH with balanced crystalloids but judged certainty as low to very low and explicitly called for new adequately powered studies. The meta-analysis by Lehr et al. (2022) reported a pooled delta-HCO_3 of +1.60 mmol/L (95% CI 0.04–3.16) favouring balanced fluids in critically ill children. The only RCT using Plasma-Lyte A versus NS in paediatric AGE (Allen et al., 2016) reported delta-HCO_3 of +1.6 versus 0.0 mEq/L at 4 hours (p=0.004) but was underpowered for clinical outcomes. No published study has investigated Isolyte-S specifically in children with AGE.

Study Design

Single-centre, prospective, non-interventional observational cohort study. No randomisation, allocation, or investigator-initiated prescribing occurs. The treating physician's independent clinical decision determines group assignment before research consent and enrolment.

Statistical Framework

Sample size: 180 total enrolments, yielding 126 evaluable participants assuming 70% T4 laboratory availability. Power calculation: MCID delta = 1.5 mmol/L, SD = 3.0 mmol/L, alpha = 0.05 (two-sided), power = 0.80. Primary analysis: PS-IPTW combined with IPOW to simultaneously address confounding by indication and informative T4 laboratory missingness. Pre-specified mechanistic mediation analysis (ACME/ADE) partitions the total effect on delta-

HCO3 into the indirect effect via delta-Cl and the direct effect attributable to acetate/gluconate buffering. Reporting: STROBE. Software: R ≥ 4.3.

Data Collection

Data are recorded on a standardised case report form at T0 (baseline), T4 (3–6 hour window, only if routine laboratory results available), and 72 hours (electronic health record review). No study-mandated procedures or tests are added to the routine care pathway.

Conditions

Conditions or Focus of Study

- Gastroenteritis Acute
- Dehydration
- Acidosis, Metabolic
- Diarrhea
- Vomiting

Keywords

balanced crystalloid | normal saline | bicarbonate | metabolic acidosis | pediatric emergency | Acute Gastroenteritis | Dehydration

Study Design

Observational Study Model

Cohort

Time Perspective

Prospective

Biospecimen Retention

None Retained

Enrollment

180 — Anticipated

Number of Groups/Cohorts

2

Groups and Interventions

Group A — 0.9% Sodium Chloride

Children with acute gastroenteritis who received 0.9% sodium chloride (Na+ 154, Cl- 154 mEq/L) as the initial IV crystalloid, as independently selected by the treating physician. No research-directed intervention.

Group B — Balanced Crystalloid (Isolyte-S)

Children with acute gastroenteritis who received an acetate/gluconate-buffered balanced isotonic crystalloid (Isolyte-S: Na+ 141, K+ 5, Mg2+ 3, Cl- 98, acetate 27, gluconate 23 mEq/L)

as the initial IV crystalloid, as independently selected by the treating physician. No research-directed intervention.

Outcome Measures

Primary Outcome Measure

1. Change in Serum Bicarbonate (Delta-HCO3)

Change from baseline in serum bicarbonate concentration (mmol/L) at approximately 4 hours after IV fluid initiation. Defined as HCO3(T4) minus HCO3(T0), where T4 is the routine blood gas or electrolyte measurement obtained 3 to 6 hours after IV fluid start. Analysis performed only in participants for whom T4 laboratory results are available as part of routine clinical care. No additional blood sampling is performed for research purposes.

[Time Frame: Approximately 4 hours (3-6 hour window) after IV fluid initiation]

Secondary Outcome Measures

2. Change in Blood pH (Delta-pH)

Change from baseline in arterial or capillary blood pH at approximately 4 hours. Calculated as pH(T4) minus pH(T0). Obtained from routine blood gas analysis only. [Time Frame: 3-6 hours after IV fluid initiation]

3. Change in Base Excess (Delta-BE)

Change from baseline in base excess (mmol/L) at approximately 4 hours. Calculated as BE(T4) minus BE(T0). Obtained from routine blood gas analysis only. [Time Frame: 3-6 hours after IV fluid initiation]

4. Change in Serum Chloride (Delta-Cl)

Change from baseline in serum chloride (mEq/L) at approximately 4 hours. Calculated as Cl(T4) minus Cl(T0). Serves as the mediator variable in the pre-specified causal mediation analysis. [Time Frame: 3-6 hours after IV fluid initiation]

5. Additional IV Fluid Bolus Requirement

Binary outcome: whether the treating physician administered one or more additional IV fluid boluses within 6 hours of initial IV fluid start, as documented in the routine clinical record. [Time Frame: Within 6 hours of IV fluid initiation]

6. Time to First Tolerated Oral Intake

Time in hours from IV fluid initiation to first documented tolerated oral fluid intake. Censored at 24 hours or at hospital admission, whichever occurs first. Analysed using weighted Cox regression. [Time Frame: 0 to 24 hours]

7. Hospital Admission Decision

Binary outcome: whether the treating physician decided to admit the child (observation unit, ward, or ICU), as documented in the electronic health record. [Time Frame: During the emergency department visit]

8. 72-Hour Emergency Department Return Visit

Binary outcome: unplanned return to the emergency department within 72 hours of discharge, regardless of cause, as identified through electronic health record linkage. [Time Frame: Within 72 hours of discharge]

Eligibility

Accepts Healthy Volunteers
No

Sex
All

Age Limits
Minimum: 6 Months | Maximum: 5 Years

Inclusion Criteria
- Age: 6 months to 5 years (60 months) inclusive
- Clinical diagnosis of acute gastroenteritis: acute diarrhoea (3 or more loose stools per 24 hours) with or without vomiting; symptom duration 7 days or less
- Clinician-initiated indication for intravenous rehydration
- IV fluid order placed and treatment initiated independently by the treating physician, without research team influence
- Written informed consent obtained from parent or legal guardian

Exclusion Criteria
- Chronic systemic disease (congenital heart disease, chronic kidney disease, chronic lung disease, inborn errors of metabolism, primary immunodeficiency)
- Hypernatraemic dehydration (serum sodium >= 150 mEq/L at baseline)
- Diabetic ketoacidosis, primary metabolic crisis, or suspected surgical abdomen
- Bloody diarrhoea or suspected invasive enteric infection requiring alternative management algorithm
- Hypoglycaemia (blood glucose < 60 mg/dL) at presentation
- Symptom duration exceeding 7 days
- Receipt of 20 mL/kg or more of IV fluid in the 24 hours preceding enrolment

Study Population Description
Consecutive eligible children aged 6 months to 5 years presenting to the paediatric emergency department of Aydin Adnan Menderes University Hospital with acute gastroenteritis and a clinician-initiated indication for intravenous rehydration. Enrolment is prospective and observational; the treating physician independently determines IV fluid type and dose based on clinical judgment, without involvement from the research team.

Sampling Method
Non-Probability Sample

Contacts and Locations

Central Contact
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Location
Aydin Adnan Menderes University Hospital, Department of Pediatric Emergency Care

Aydın, Turkey 09100 | Status: Recruiting

Principal Investigator: Aykut Çağlar

IPD Sharing Statement

Plan to Share IPD
No

Plan Description
Individual participant data will not be publicly shared due to Turkish personal health data protection regulations (KVKK). De-identified aggregate summary data will be made available upon reasonable request to the corresponding author following publication.

References

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PART 2 — STATISTICAL ANALYSIS PLAN

1. Analysis Populations

Full Analysis Set (FAS)
All enrolled participants meeting inclusion/exclusion criteria with informed consent. Used for all demographic descriptions and secondary clinical outcome analyses.

Primary Analysis Set (PAS)

FAS subset with both T0 and T4 HCO3 measurements available. Used for the primary outcome and all biochemical secondary analyses. T4 laboratory results are not available in all participants because they are obtained only when ordered by the treating physician as part of routine care — this is a structural, non-random missingness. IPOW (see Section 6) is applied to correct for the resulting selection bias.

Per-Protocol Set (PP)

PAS subset where the T4 measurement falls within the 3.0–6.0 hour window and no fluid crossover occurred. Used in sensitivity analysis only.

2. Sample Size

Minimum clinically important difference (MCID): delta = 1.5 mmol/L — the most conservative of three published meta-analytic estimates (Florez 2023: +2.44; Lehr 2022: +1.60; Fernandez Montes 2025: +2.30 mEq/L). Standard deviation assumption: sigma = 3.0 mmol/L (Lehr 2022). Alpha = 0.05 (two-sided), power = 80%. Core sample: 63 patients per group = 126 evaluable patients. Assuming 70% T4 laboratory availability: target enrolment ≥180 records. The pilot phase (first 4–6 weeks) will verify the actual T4 availability rate and update the enrolment target if needed; the analysis plan will not change.

3. Primary Analysis — Delta-HCO3

Two pre-specified complementary models. The primary conclusion is based on Model 2; Model 1 is supporting.

Model 1 — Multivariable Linear Regression (supporting)

Delta-HCO3 regressed on exposure group and the pre-specified covariate list (Section 5). Robust standard errors (HC3). Output: beta coefficient, 95% CI, p-value.

Model 2 — PS-IPTW + IPOW Double Weighting (primary conclusion)

Corrects two distinct sources of bias simultaneously: IPTW addresses confounding by indication in fluid selection; IPOW addresses non-random missingness of T4 laboratory results. The combined weight (w_final = w_IPTW x w_IPOW) is trimmed at the 1st–99th percentile. Output: weighted mean difference (WMD), 95% CI, p-value; Love plot showing covariate balance before and after weighting.

Step-by-step weight calculation:

- PS model: logistic regression on FAS → estimated probability of receiving balanced crystalloid given covariates
- Stabilised IPTW: w_IPTW = marginal probability of treatment / conditional probability of treatment
- IPOW model: logistic regression on FAS → estimated probability of T4 lab being available given IPOW predictors (Section 6)
- IPOW weight: w_IPOW = 1 / estimated probability of T4 availability — applied to PAS patients only
- Combined weight: w_final = w_IPTW x w_IPOW; trimmed at 1st–99th percentile
- Weighted linear regression: Delta-HCO3 ~ exposure group (weight = w_final)

4. Secondary Outcome Analyses

- Delta-pH, Delta-BE, Delta-Cl: Models 1 and 2, identical format to primary analysis.
- Binary outcomes (additional IV bolus, hospital admission, 72-hour return visit): weighted logistic regression — OR, 95% CI.
- Time to oral intake: weighted Cox regression — HR, 95% CI; censored at 24 hours or hospital admission.

Secondary analyses are exploratory. No correction for multiple comparisons; all p-values reported unadjusted.

5. Pre-specified Covariate List

Applied identically to both Model 1 (regression) and the PS model (Model 2). Any change requires a formal protocol amendment.

- Age (months, continuous)
- Weight (kg, continuous)
- Sex (binary)
- Symptom duration (days, continuous)
- Vomiting at presentation (binary)
- Heart rate at T0 (bpm, continuous)
- Capillary refill time at T0 (seconds, continuous)
- Consciousness at T0 (AVPU, categorical)
- Baseline HCO3, pH, BE (continuous)
- Baseline Na, Cl, K (mEq/L, continuous, separate variables)
- Baseline glucose and creatinine (continuous)
- Pre-enrolment oral rehydration solution or IV fluid use (binary)
- Antiemetic use between T0 and T4 (binary)
- IV volume in first 2 hours (mL, continuous)
- Admission time category: daytime / night / weekend (categorical)

6. IPOW Predictors — T4 Lab Availability

The following predictors for the IPOW model are fixed prior to data collection and cannot be changed without a protocol amendment:

- Baseline acidosis: HCO3 <18 mEq/L or pH <7.30 (binary)
- Dehydration severity: capillary refill ≥3 seconds and/or age-appropriate tachycardia (binary)
- Hospital admission decision (binary)
- Admission time category: daytime / night / weekend

7. Missing Data

- Covariate missingness <5%: complete-case analysis.
- Covariate missingness >5%: multiple imputation (R: mice package, m ≥ 20 datasets; chained equations; Rubin's rules for combining estimates).

- T4 HCO_3 missingness is structural (not at random) and is addressed by IPOW; imputation is not applied to the outcome.
- Missingness mechanism assessed using Little's MCAR test.

8. Sensitivity Analyses

- Acidosis sub-cohort: patients with baseline HCO_3 ≤22 mEq/L.
- Time window restriction: T4 strictly within 3.0–6.0 hours (Per-Protocol set).
- As-treated: reclassification based on actual fluid received for patients with crossover.
- Alternative PS: 1:1 nearest-neighbour matching (caliper = 0.2 SD).
- E-value: quantification of unmeasured confounding threshold needed to explain away the observed association.
- Complete-case: without IPOW, restricted to patients with T4 lab available.
- IPTW only: without IPOW, to isolate the independent contribution of observation weighting.

9. Mechanistic Mediation Analysis

Research question: Of the total effect of balanced crystalloid on Delta-HCO_3, how much is mediated through Delta-Cl (hyperchloraemic mechanism) and how much reflects the direct buffering action of acetate and gluconate?

Method: Causal mediation analysis using the potential outcomes framework (R package: mediation; 1000 bootstrap replications for confidence intervals).

- Mediator model: Delta-Cl ~ exposure + covariates
- Outcome model: Delta-HCO_3 ~ exposure + Delta-Cl + covariates
- Outputs: ACME (average causal mediation effect = indirect effect via Delta-Cl), ADE (average direct effect = direct buffering action), total effect, proportion mediated; all with 95% bootstrapped CI.

This analysis is exploratory. Findings will be reported as mechanism-consistent associations; causal inference will not be claimed.

10. Software and Reporting

Software

R version 4.3 or later. Packages: WeightIt, MatchIt, mediation, tableone, mice, rms, sandwich.

Reporting standard

STROBE statement for observational studies.

Pre-registration

All analyses will be conducted after data lock. This SAP will be uploaded to the ClinicalTrials.gov record or time-stamped before data lock. No interim analyses are planned.