Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Agus MSD, Wypij D, Hirshberg EL, et al. Tight glycemic control in critically ill children. N Engl J Med 2017;376:729-41. DOI: 10.1056/NEJMoa1612348

Supplementary Data, Figures, and Tables

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The following investigators were instrumental in trial design, oversight, and preparation of this manuscript.

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The following sites obtained approval from their institutional ethics review board to conduct the trial, screened patients for eligibility, but did not contribute subjects to the analyses presented in this manuscript.

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Pediatric Acute Lung Injury & Sepsis Investigators (PALISI)

PALISI (http://www.palisi.org) is a network of clinical researchers from 78 pediatric intensive care units across North America that develops multicenter trials to improve interventions and outcomes in the care of critically ill children. PALISI provided the HALF-PINT trial with meeting space and support at biannual national meetings for protocol training, trial management, and site recruitment.

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Cardiovascular failure (on intravenous vasopressors or inotropes, i.e., dopamine or dobutamine >5 mcg/kg/min, or any dose of epinephrine, norepinephrine, phenylephrine, milrinone, or vasopressin if used to treat hypotension)

   and/or

   Respiratory failure (acute mechanical ventilation via endotracheal tube or tracheostomy)
2. Age ≥2 weeks and corrected gestational age ≥42 weeks
3. Age <18 years (has not yet had 18th birthday)

Exclusion Criteria

1. No longer has cardiovascular or respiratory failure (as defined in inclusion criterion 1) or is expected to be extubated in the next 24 hours
2. Expected to remain in ICU <24 hours
3. Previously randomized in HALF-PINT
4. Enrolled in a competing clinical trial
5. Family/team have decided to limit or redirect from aggressive ICU technological support
6. Chronic ventilator dependence prior to ICU admission (non-invasive ventilation and ventilation via tracheostomy overnight or during sleep are acceptable)
7. Type 1 or 2 diabetes
8. Cardiac surgery within prior 2 months or during/planned for this hospitalization (extra-corporeal life support or non-cardiac surgery is acceptable)
9. Diffuse skin disease such that placement of a subcutaneous glucose sensor would be difficult to secure
10. Therapeutic plan to remain intubated for >28 days
11. Receiving therapeutic cooling with targeted body temperatures <34 degrees Celsius
12. Receiving a ketogenic diet
13. Ward of the state
14. Pregnancy

Early Stopping

The National Heart, Lung, and Blood Institute appointed a Data and Safety Monitoring Board (DSMB) to monitor data and oversee patient safety in the HALF-PINT trial. Data reports were reviewed by the DSMB in July 2013, February and November 2014, May and November 2015, and May and September 2016. Group sequential monitoring based on East, version 6.4 (Cytel), was used to assess potential early stopping of the trial due to efficacy or futility using O'Brien-Fleming boundaries.[1] Formal interim analyses were planned to occur after 50%, 67%, 83%, and 100% of intention-to-treat patient data had accrued. Interim analyses at other time points could also be accommodated. A sample size of 1,414 provides 80% power to detect a clinically important difference of 1.25 ICU-free days in a two-sided test.

For its meeting on September 13, 2016, the DSMB reviewed intention-to-treat data on the primary outcome, ICU-free days, from 698 patients (350 assigned to TGC-1, 348 assigned to TGC-2; 49% of the total horizon of 1,414 patients). They also reviewed additional analyses performed on a per-protocol basis for 683 patients (339 assigned to TGC-1, 344 assigned to TGC-2), excluding 10 patients withdrawn prior to the intervention due to a change in eligibility status and five whose guardians withdrew full consent.

At that time, the ICU-free days hazard ratio comparing TGC-1 vs. TGC-2 was 0.96 (95% confidence interval, 0.81 to 1.14, P=0.65) adjusting for age group and PRISM-III 12 score, where a hazard ratio <1.0 implies fewer ICU-free days for the TGC-1 group. Using East software, this first interim look with 698 patients gave stopping rules of P<0.0028 for efficacy and P>0.7017 for futility. The observed P=0.65 did not fall within either the efficacy or futility regions.

The DSMB also requested that conditional power analyses be performed for their September 13, 2016, meeting. Conditional power is the probability that final study results would reach statistical significance, given the data observed to date and specific assumptions about the patterns of the remaining data to accrue. Given non-normally distributed ICU-free days and the use of adjusted proportional hazards regression, we resorted to simulations to approximate conditional power. In particular, we sampled (with replacement) from the observations obtained to date to simulate new observations. Future TGC-2 patients were sampled from the TGC-2 patients to date. Future TGC-1 patients were sampled from the TGC-1 patients to date, with the same distribution to date or with adjusting future TGC-1 subjects to have more ICU-free days. These future simulated subjects were added to the data accrued to date. We ran

[1] O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35(3):549-56.

2,000 simulations and calculated the proportion of times that we reached statistical significance at the two-sided P<0.05 level (see table below).

Assumed Future Improvement in ICU-Free Days in the TGC-1 Group	Percent of Times TGC-1 is Significantly Better than TGC-2 (exact 95% confidence interval)	Percent of Times TGC-2 is Significantly Better than TGC-1
0	0% (0% to 0.2%)	3.5%
0.4	0% (0% to 0.2%)	1.5%
0.8	0.2% (0% to 0.4%)	0.7%
1.2	0.9% (0.5% to 1.4%)	0.3%
1.25	0.9% (0.5% to 1.4%)	0.2%
2.2	4.2% (3.4% to 5.2%)	0%
5.2	65.4% (63.2% to 67.4%)	0%

Thus, even under an anticipated improvement of 1.25 ICU-free days in the remaining TGC-1 patients, the conditional power, or chance of the TGC-1 group being statistically significantly better than the TGC-2 group, was approximately 1%.

At the September 13, 2016, DSMB review of unblinded outcome and safety data from the first 698 subjects, formal O'Brien-Fleming stopping boundaries for efficacy or futility, and conditional power estimates, the DSMB unanimously recommended that the study should be discontinued based on their review of the totality of the data and the low likelihood of being able to achieve a statistically significant result for the primary outcome variable if the study had progressed further. The National Heart, Lung, and Blood Institute stopped the trial on September 14, 2016. Two subjects on study at that time had their study treatment discontinued and are not included in data analyses. Subjects already through the study protocol were assessed for 28-day and 90-day hospital mortality as planned. The final sample size accrued was 713 for intention-to-treat analyses and 698 for per-protocol analyses.

Supplemental Figures

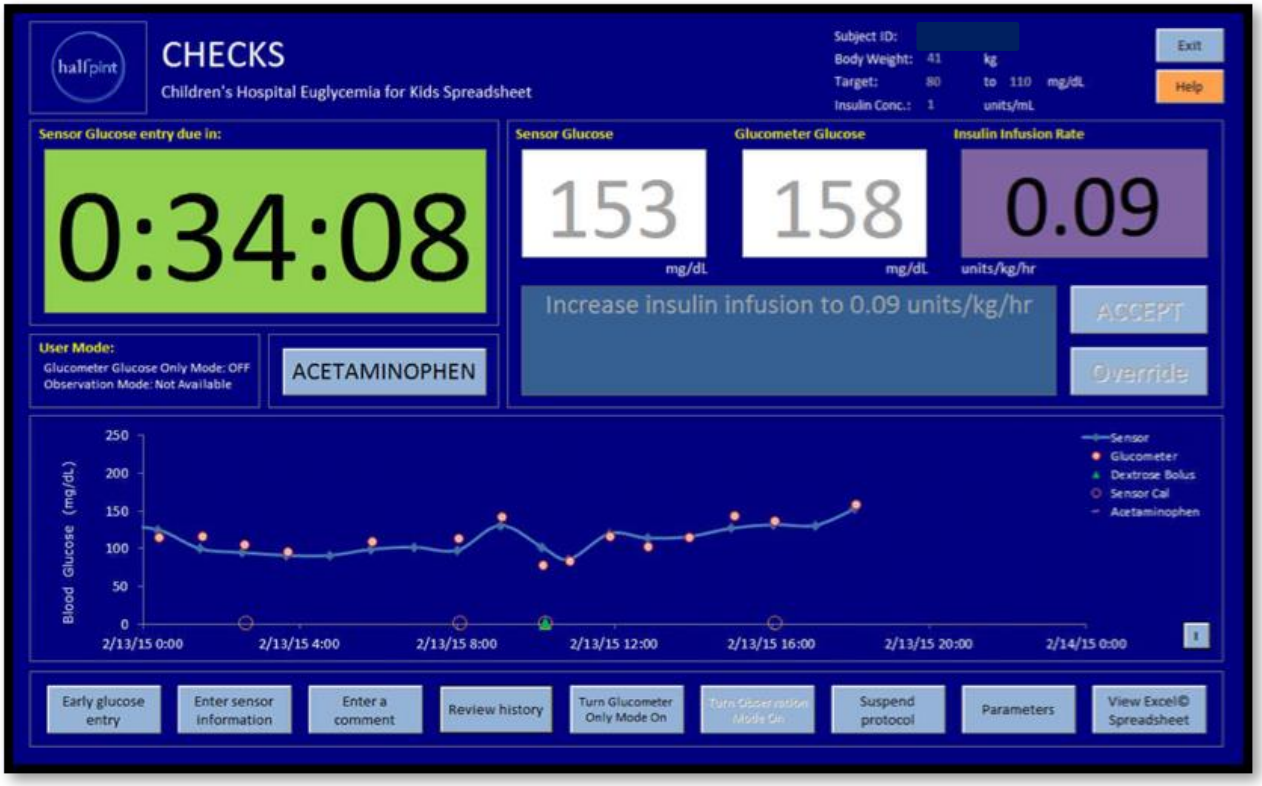

Figure S1. Children's Hospital EuglyCemia for Kids Spreadsheet (CHECKS) interface.
Children's Hospital EuglyCemia for Kids Spreadsheet (CHECKS) is a Microsoft Excel® spreadsheet with additional VBA programming designed by authors GMS, JLA, ELH, and MSDA to recommend insulin infusion rates, dextrose rescue boluses if needed, and timing of blood glucose measurements and glucose sensor calibration. All dosing recommendations are made based upon glucose meter measurements of blood glucose, with the timing of the next measurement guided by sensor glucose measurements obtained from a continuous glucose monitor that reports interstitial glucose concentrations every 5 minutes.

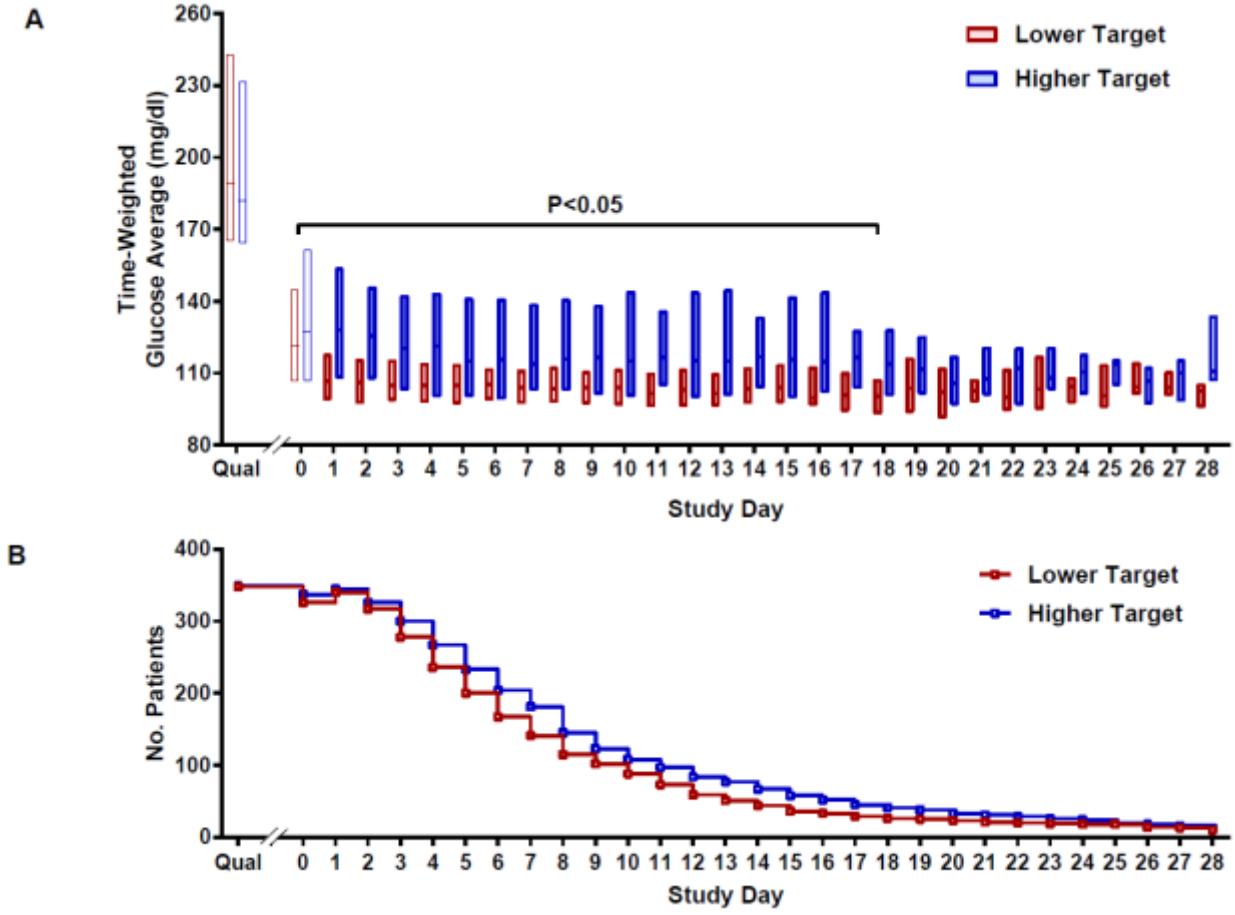

Figure S2. Time-Weighted Glucose Averages through Day 28, According to Study Group.

Data are for all 28 study days. Panel A shows time-weighted glucose averages obtained from linear interpolation of glucose values used to administer tight glycemic control protocol. Shaded bars indicate full study days (00:00 to 23:59); open bars indicate either partial study day (Day 0) or value used to qualify for study (Qual). Panel B shows total number of subjects receiving insulin therapy by day. P values for the comparison between groups were calculated with the use of Wilcoxon rank-sum tests (not adjusting for multiple comparisons).

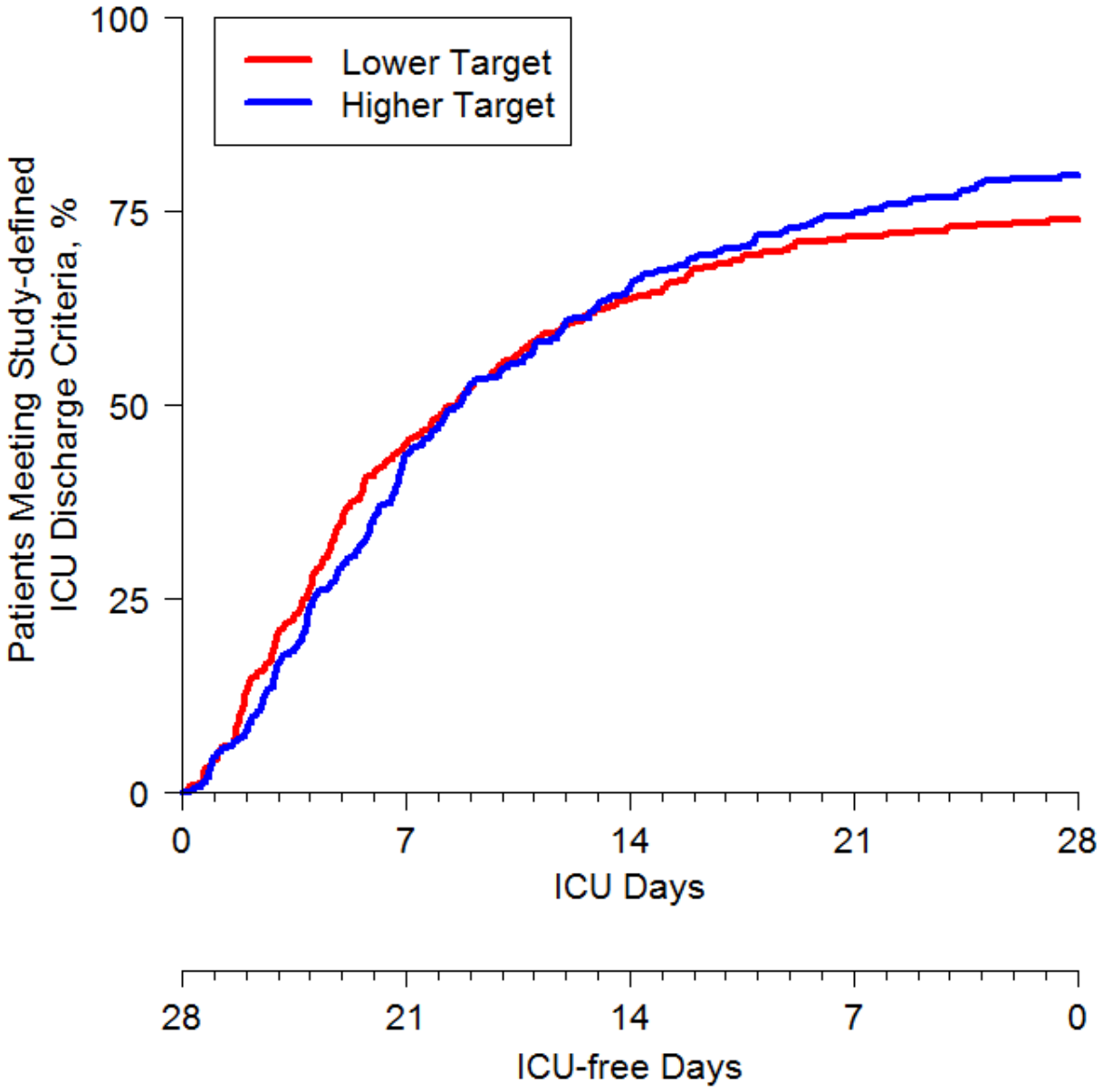

Figure S3. Time to Study-defined ICU Discharge in Intention-To-Treat Analysis of 713 Patients, According to Study Group.

Patients not meeting study-defined ICU discharge criteria by Day 28 (zero ICU-free days) were still receiving invasive mechanical ventilation, non-invasive ventilation that provides ≥5 cm H_2O pressure, or vasoactive infusions, were transferred to another hospital, or died. The P value for the comparison between treatment groups was 0.58, calculated with the use of proportional hazards regression with adjustment for age group and PRISM III-12 score. ICU denotes intensive care unit.

Supplemental Tables

Table S1. Reasons Patients were Ineligible or Guardian was not Approached.

Reason*	**N=19,750**
Patient never had BG >130 mg/dl (7.2 mmol/l) within 14 days of initial screening	9562 (48)
Patient had one or more exclusion criteria (more than one allowed)	7626 (39)
No longer has study-defined cardiovascular or respiratory failure, or is expected to be extubated in the next 24 hours	4918
Chronic ventilator dependence prior to ICU admission (non-invasive ventilation and ventilation via tracheostomy overnight/during sleep are acceptable)	1033
Family/team decision to limit/redirect from aggressive ICU technological support	645
Cardiac surgery within prior 2 months or during/planned for this hospitalization	440
Expected to remain in ICU <24 hours	295
Type 1 or 2 diabetes	170
Ward of the state	116
Enrolled in a competing clinical trial	81
Receiving therapeutic cooling with targeted body temperatures <34 °C	67
Current or planned ketogenic diet	65
Diffuse skin disease such that placement of a subcutaneous glucose sensor would be difficult to secure	57
Previously randomized in HALF-PINT	56
Therapeutic plan to remain intubated for >28 days	44
Pregnancy	1
Guardian was not approached	2562 (13)
Insufficient access for insulin and blood glucose measurements	666
Patient did not have two consecutive BG ≥150 mg/dl (8.3 mmol/l) within 14 days of initial screening	603
Systems or staff coverage issues	396
Attending physician did not allow approach for consent	258
Guardian unavailable	220
Study equipment not available	106
Language barrier	100
Patient died before consent	54
Previous guardian refusal to HALF-PINT or other study	38
Perceived or actual incompatibility with protocol	31
Enrollment ceased	30
Guardianship issues	28
Other**	32

* Data are no. (%).

** Other includes patient transferred to another ICU or hospital, pregnancy status could not be verified, and guardian unable to understand consent process.

Table S2. Reasons Patients were Consented but Not Randomized.

Reason*	**N=110**
Consent obtained when BG>130 mg/dl but BG never ≥150 mg/dl prior to ICU discharge or within 28 days, so were never eligible for randomization	77 (70)
Patient became ineligible after confirmatory BG ≥150 mg/dl	17 (15)
Clinician request due to situational concerns	11 (10)
Withdrawal of consent	5 (4)

* Data are no. (%).