

Use of the Selective Cytopheretic Device with Continuous Renal Replacement Therapy in Children: A Comparison of Contemporary Cohorts

Natalja L. Stanski^{a,b} JangDong Seo^c Todd Jenkins^c Kelli A. Krallman^d
Shina Menon^e H. David Humes^f David J. Askenazi^g Rajit K. Basu^h
Ayse Akcan-Arikanⁱ Stuart L. Goldstein^{a,d} Katja M. Gist^j
on behalf of the WE-ROCK Investigators

^aUniversity of Cincinnati College of Medicine, Cincinnati, OH, USA; ^bDivision of Critical Care Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; ^cDivision Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; ^dDivision of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; ^eDivision of Nephrology, Department of Pediatrics, Stanford University and Lucile Packard Children's Hospital Stanford, Palo Alto, CA, USA; ^fDepartment of Medicine, University of Michigan, Ann Arbor, MI, USA; ^gUniversity of Alabama at Birmingham, Birmingham, AL, USA; ^hDivision of Critical Care Medicine, The Ann and Robert Lurie Children's Hospital of Chicago, Chicago, IL, USA; ⁱDepartment of Pediatrics, Divisions of Critical Care Medicine and Nephrology, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA; ^jDepartment of Pediatrics, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Aurora, CO, USA

Keywords

Acute kidney injury · Continuous renal replacement therapy · Pediatrics · Mortality · Sepsis

Abstract

Introduction: The selective cytopheretic device (SCD) is a cell-directed extracorporeal therapy approved for use in children with acute kidney injury (AKI) receiving continuous renal replacement therapy (CRRT) with sepsis/sepsis-like conditions. We compared outcomes for children treated with SCD to a contemporary cohort of children treated with CRRT alone. **Methods:** Secondary analysis and comparison of patients ≤ 22 years old and ≥ 10 kg from a multicenter registry of patients receiving CRRT for AKI and/or fluid overload (WE-ROCK; 2015–2021) to patients from two multicenter, prospective, interventional studies of children with AKI and multiple organ dysfunction (MODS) receiving SCD

(SCD-PED-01/SCD-PED-02; 2016–2022). **Results:** Eighteen patients in the SCD cohort were compared to 178 in the CRRT cohort. There were no differences between cohorts at CRRT \pm SCD initiation. SCD patients had shorter CRRT duration (6 [3, 11] vs. 10 [5, 18] days, $p = 0.013$) and shorter ICU length of stay (LOS) in survivors (16 [11, 25] vs. 27 [16, 46] days, $p = 0.012$). Survival to ICU discharge or day 60 was 94% in the SCD cohort vs. 74% in the CRRT cohort ($p = 0.079$). A Bayesian analysis demonstrated a $>99\%$ probability of improved survival with SCD. A sub-analysis in septic patients demonstrated greater survival (100% vs. 69%, $p = 0.032$), shorter CRRT duration (5 [3, 7] vs. 11 [6, 17] days, $p = 0.006$) and reduced ICU LOS in survivors (21 [10, 25] vs. 27 [16, 45] days, $p = 0.027$) in SCD-treated patients. **Conclusions:** The addition of SCD therapy in children with AKI and MODS receiving CRRT may be beneficial, though larger prospective studies are needed.

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Introduction

Acute kidney injury (AKI) is common in the ICU, with recent data suggesting 1 in 3 critically ill children develop AKI [1]. Characterization of AKI epidemiology has also revealed its independent association with poor outcomes, including increased risk of death with worsening severity [1]. Because there are no disease-modifying therapies, continuous renal replacement therapy (CRRT) is a potentially life-saving bridge to recovery; however, it does not modify the underlying pathophysiology. As a result, outcomes for children receiving CRRT are poor, with associated morbidity and mortality rates nearing 50% [2–5]. There is a need to identify therapies that improve outcomes for this population.

The selective cytopheretic device (SCD) is a cell-directed extracorporeal therapy that targets activated leukocytes, a key driver of the inflammatory process involved in developing AKI and other organ failures in critical illness (online suppl. Figure 1; for all online suppl. material, see <https://doi.org/10.1159/000549111>) [6–9]. It recently received a Humanitarian Device Exemption from the US Food and Drug Administration for the treatment of patients ≥ 10 kg and ≤ 22 years of age with AKI due to sepsis/sepsis-like condition receiving CRRT (QUELimmune™). Pediatric studies have demonstrated the safety and probable efficacy of the SCD, including 77% survival and 100% renal recovery in survivors [7, 8]. A recent comparison of children with AKI and multiple organ dysfunction (MODS) receiving CRRT+SCD to a historical cohort receiving CRRT alone (Prospective Pediatric CRRT Registry, 2001–2005) demonstrated a 98% probability of improved survival with SCD [8]. However, a more contemporary comparison is needed. We leveraged the Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) registry to compare outcomes between critically ill children with AKI and MODS receiving CRRT+SCD to those receiving CRRT alone.

Methods

Study Design

We compared two cohorts of critically ill children with AKI and MODS receiving CRRT \pm SCD. The SCD cohort is comprised patients from two prospective studies (SCD-PED-01: NCT02820350, SCD-PED-02: NCT04869787) performed at four US centers from 2016–2022. The CRRT cohort was derived from a multicenter registry (WE-ROCK) of patients receiving CRRT for AKI and/or fluid overload from 2015–2021. Methodologic details from these studies have been published and are summarized in online sup-

plementary Methods [7, 8, 10]. The Institutional Review Board (IRB) at each center approved SCD-01/SCD-02 with a requirement for written informed consent (online suppl. Material 1). For WE-ROCK, each site received IRB approval with a waiver of informed consent (online suppl. Material 2). Personnel adhered to the ethical standards outlined in the 1975 Declaration of Helsinki and its later amendments.

Patient Selection

Patients were eligible for inclusion in SCD-PED-01/SCD-PED-02 if they were ≥ 10 kg, ≤ 22 years of age, had Kidney Disease Improving Global Outcomes-defined AKI [11] and MODS (additional requirement of invasive mechanical ventilation or a continuous vasoactive infusion), and were receiving CRRT as part of clinical care [7, 8]. For this study, all were included in the SCD cohort unless they were receiving extracorporeal membrane oxygenation, a WE-ROCK exclusion. CRRT cohort inclusion/exclusion criteria were selected to align with the SCD cohort. Patients were included if they were ≥ 10 kg, ≤ 22 years old, treated at a US center, had MODS at CRRT initiation, and CRRT duration was ≥ 3 days; they were excluded if they had an active malignancy, history of transplant, or had missing data (online suppl. Figure 2). No patients in the CRRT cohort received SCD. Full inclusion/exclusion criteria for parent studies are listed in online supplementary Methods.

Outcomes and Definitions

The primary outcome for was survival to ICU discharge or day 60 (whichever came first), chosen based on data availability across studies. Secondary outcomes included CRRT duration, ICU length of stay (LOS), and 90-day dialysis dependence in survivors. A subgroup analysis was performed in patients with sepsis. Further details are outlined in online supplementary Methods.

Statistical Analysis

Demographics, clinical characteristics, and outcomes were described using medians, interquartile ranges, frequencies, and percentages. Comparisons were performed using Wilcoxon rank-sum, chi-square, or Fisher's exact test. Multivariable logistic regression was performed to assess the association between SCD treatment and the primary outcome after adjustment for a priori selected covariates (age, sex, severity of illness by Pediatric Risk of Mortality [PRISM] III Score [12], and use of vasoactives at CRRT \pm SCD initiation). Bayesian logistic regression was used to estimate the probability that the log odds of the primary outcome in the SCD cohort exceeded that observed in the CRRT cohort (online suppl. Methods) [8]. All analyses were performed using R (version 4.4.2; brms package version 2.22.0).

Table 1. Clinical characteristics and outcomes of patients with acute kidney injury treated with CRRT in the WE-ROCK cohort compared to the SCD cohort (CRRT+SCD)

| Variable | CRRT only (n = 178) | SCD (n = 18) | p value |
|---|---------------------|-----------------|---------|
| <i>Demographics and admission characteristics</i> | | | |
| Age, years | 13.3 (5.4, 16.5) | 9.7 (4.3, 15.8) | 0.40 |
| Sex (male), n (%) | 83 (47) | 12 (67) | 0.11 |
| Weight, kg | 42 (19, 67) | 30 (17, 68) | 0.73 |
| PRISM III | 14 (11, 19) | 10 (7, 14) | 0.002 |
| <i>CRRT±SCD start characteristics</i> | | | |
| Sepsis at CRRT start (yes), n (%) | 105 (59) | 11 (61) | 0.86 |
| Fluid accumulation at CRRT start, % | 10 (4, 21) | 7 (3, 15) | 0.42 |
| Time from ICU admit to CRRT start, days | 2 (1, 6) | 3 (1, 5) | 0.99 |
| IMV at CRRT start (yes), n (%) | 131 (88) | 17 (94) | 0.70 |
| Vasoactive(s) at CRRT start (yes), n (%) | 136 (77) | 11 (61) | 0.16 |
| <i>Outcomes</i> | | | |
| Total CRRT duration, days | 10 (5, 18) | 6 (3, 11) | 0.013 |
| ICU length of stay (survivors), days | 27 (16, 46) | 16 (11, 25) | 0.012 |
| Survival to ICU discharge or day 60 (yes), n (%) | 132 (74) | 17 (94) | 0.079 |
| Day 90 dialysis dependence (survivors) (yes), n (%) | 21 (17) | 0 (0) | 0.075 |

Continuous variables presented as median (IQR). PRISM III, Pediatric Risk of Mortality III Score; CRRT, continuous renal replacement therapy; IMV, invasive mechanical ventilation.

Results

Eighteen patients were included in the SCD cohort and 178 in the CRRT cohort (online suppl. Figure 2). There were no demographic differences between cohorts, though CRRT patients had higher PRISM III at ICU admission (Table 1). CRRT ± SCD initiation occurred a median of ≥2 days from ICU admission in both cohorts and there were no differences in clinical characteristics at that time (Table 1). The SCD cohort had shorter duration of CRRT (6 [3, 11] vs. 10 [5, 18] days, $p = 0.013$), shorter ICU LOS in survivors (16 [11, 25] vs. 27 [16, 46] days, $p = 0.012$), and 94% survival to ICU discharge or day 60 (vs. 74% in WE-ROCK cohort, $p = 0.079$) (Table 1). There was no difference in day 90 dialysis dependence, though all surviving SCD patients were dialysis independent at day 90 (Table 1).

On multivariable regression, receipt of SCD was not independently associated with survival to ICU discharge or day 60 (Table 1). Given the small sample size, we undertook a Bayesian logistic regression analysis for the primary outcome (online suppl. Table 2). The distribution of the predicted probabilities for the primary outcome obtained from the posterior samples is shown in Figure 1. The log odds of

surviving to ICU discharge or day 60 for the SCD cohort was greater than the CRRT cohort in >99% of the posterior samples, though the credible interval was wide suggesting uncertainty of the model (online suppl. Table 2).

A subgroup analysis of patients with sepsis at CRRT ± SCD initiation is shown in online suppl. Table 3. Septic SCD patients ($n = 11$) had lower PRISM III but initiated CRRT a median of 4 days (IQR 2–5) from ICU admission; no differences existed between cohorts at CRRT ± SCD start. Septic SCD patients had greater survival to ICU discharge or day 60 (100% [$n = 11$] vs. 69% [$n = 72$], $p = 0.032$), shorter duration of CRRT (5 [3, 7] vs. 11 [6, 17] days, $p = 0.006$) and shorter ICU LOS in survivors (21 [10, 25] vs. 27 [16, 45] days, $p = 0.027$). Multivariable regression was not undertaken given the small sample size.

Discussion

In this contemporary comparison of children with AKI and MODS receiving SCD to those receiving CRRT alone, we demonstrate possible benefits from SCD therapy. While there were no differences seen in survival to ICU

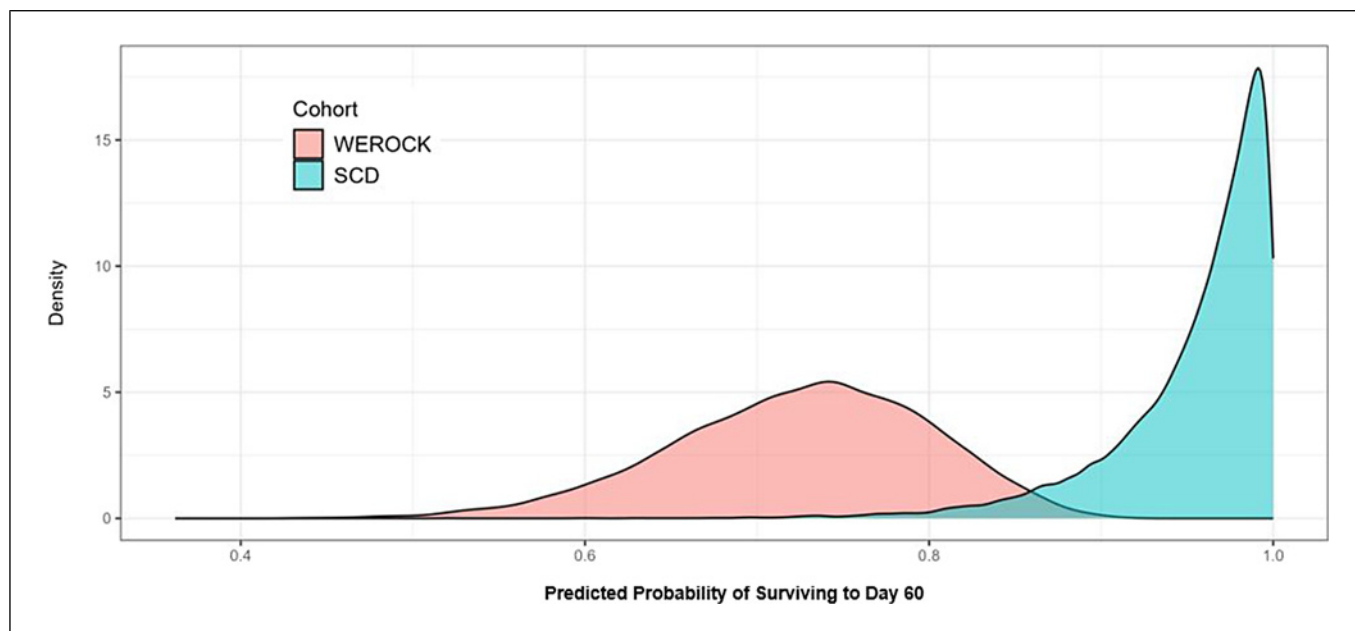


Fig. 1. Predicted probabilities of survival to ICU discharge or day 60. Predicted probabilities of survival to ICU discharge or day 60 obtained from the posterior samples for the SCD (blue) and CRRT (WE-ROCK) (red) cohorts. The CRRT cohort (WE-ROCK) (red) and the SCD cohort (blue) exhibit distinct distri-

butions, with the SCD cohort demonstrating a higher concentration of probabilities near 1.0, suggesting a greater likelihood of survival. The overlapping regions indicate areas of shared probability ranges, while the differences in peak density highlight variations in predicted outcomes between cohorts.

discharge or day 60 between cohorts employing traditional statistical techniques, SCD-treated patients had a greater probability of this outcome on Bayesian analysis. SCD-treated patients also had shorter CRRT duration and ICU LOS in survivors, and these associations appeared stronger when only sepsis patients were analyzed. However, the small number of patients treated with the SCD and potential differences in illness severity between cohorts necessitates caution in interpretation of these findings and highlights the need for larger studies.

Our study contributes to a growing body of literature suggesting potential benefits of SCD in critically ill patients [6–8, 13–15]. Mechanistically, the SCD selectively targets highly activated neutrophils and monocytes in the low-shear and low-ionized calcium environment of the device, deactivating, and reprogramming neutrophils for apoptosis while shifting monocytes to a less inflammatory, more reparative phenotype [14, 16] (online suppl. Figure 1). This cell-directed immunomodulatory effect is thought to promote organ recovery and is distinct from other extracorporeal CRRT adjuncts like cytokine adsorption filters. Similarly, pharmacological therapies are being studied for modulation of inflammation in pediatric MODS due to the previously demonstrated benefit of this approach [17]. Larger studies are needed to substantiate

these findings and explore the short- and long-term immunomodulatory effects of the SCD more comprehensively.

This study is limited by the small sample size and sparse data availability of the SCD cohort, with the former impacting power and validity and the latter likely resulting in unmeasured differences between cohorts. As a result, these findings should be viewed as preliminary and the basis for larger studies. Specifically, the reliance on admission PRISM III as a measure of illness severity (as opposed to something more proximate to CRRT \pm SCD therapy) should be addressed in future studies, which may allow for more rigorous statistical techniques like propensity matching. While the SCD studies' inclusion/exclusion criteria were applied to generate the CRRT cohort, it is possible that sicker patients who would not have been included in the SCD studies were inadvertently included in this analysis given the retrospective nature of WE-ROCK, biasing toward improved survival with SCD. Future prospective studies with more proximate markers of illness severity at the start of therapy (i.e., PELOD-2) should be performed to validate these findings. Importantly, these studies include only patients from resource-rich environments that offer CRRT, limiting generalizability to centers where this is unavailable. Our study is strengthened

by the fact that the cohorts received CRRT during the same era, reducing the likelihood that temporal differences in ICU care differentially impacted outcomes.

Conclusions

In children with AKI and MODS receiving CRRT, the addition of SCD therapy may be beneficial. Larger, rigorously designed prospective studies are needed to validate these findings.

Acknowledgments

All persons listed here specifically contributed to the tasks listed: protocol development and review, data collection, and drafting or reviewing the manuscript, as outlined. The contribution of each member of WE-ROCK is standard for each project if not listed as a byline author.

The following individuals served as collaborators and investigators for the WE-ROCK studies. They collaborated in protocol development and review, data collection, and participated in drafting or reviewing the manuscript, and their names should be citable by PubMed.

Emily Ahern CPNP, DNP¹, Ayse Akcan-Arikan MD² RELNO, Issa Alhamoud MD³, Rashid Alobaidi MD, MSc⁴, Pilar Anton-Martin MD, PhD^{5,6}, Shanthi S Balani MD⁷, Matthew Barhight MD, MS⁸, Abby Basalely MD, MS⁹, Ameer M Bigelow MD, MS¹⁰, Gabriella Bottari MD¹¹, Andrea Cappoli MD¹¹, Abhishek Chakraborty MD⁵, Eileen A Ciccio MD¹², Michaela Collins BA¹³, Denise Colosimo MD¹⁴, Gerard Cortina MD¹⁵, Mihaela A Damian MD, MPH^{16,17}, Sara De la Mata Navazo MD¹⁸, Gabrielle DeAbreu MD⁹, Akash Deep MD¹⁹, Kathy L Ding BS²⁰, Kristin J Dolan MD², Lama Elbahlawan MD²¹, Sarah N Fernandez Lafever MD, PhD¹⁸, Dana Y Fuhrman DO, MS^{13,22}, Ben Gelbart MBBS²³, Katja M Gist DO MSc¹²⁰ RELNO, Stephen M Gorga MD, MSc²⁴, Francesco Guzzi MD²⁵, Isabella Guzzo MD¹¹, Taiki Haga MD²⁶, Elizabeth Harvey MD²⁷, Denise C Hasson MD²⁸, Taylor Hill-Horowitz BS⁹, Haleigh Inthavong BS, MS², Catherine Joseph MD², Ahmad Kaddourah MD, MS²⁹, Aadil Kakjiwala MD, MSCI³⁰, Aaron D Kessel MD, MS⁹, Sarah Korn DO³¹, Kelli A Krallman BSN, MS¹³, David M Kwiatkowski MD MSc¹⁶, Jasmine Lee MSc²⁷, Laurance Lequier MD⁴, Tina Madani Kia BS⁴, Kenneth E Mah MD, MS^{16,32}, Eleonora Marinari MD¹¹, Susan D Martin MD³³, Shina Menon MD^{16,34}, Tahagod H Mohamed MD¹⁰, Catherine Morgan MD MSc⁴, Theresa A Mottes APRN⁸, Melissa A Muff-Luett MD³⁵, Siva Namachivayam MBBS²³, Tara M Neumayr MD¹², Jennifer Nhan MD, MS^{7,30}, Abigail O'Rourke MD⁹, Nicholas J Ollberding PhD¹³, Matthew G Pinto MD³⁶, Dua Qutob MD²⁹, Valeria Raggi MD¹¹, Stephanie Reynaud MD³⁷, Zaccaria Ricci MD¹⁴, Zachary A Rumlow DO^{3,24}, María J Santiago Lozano MD, PhD¹⁸, Emily See MBBS²³, David T Selewski MD, MSCR^{38,39}, Carmela Serpe MSc, PhD¹¹, Alyssa Serratore RN, MSc²³, Ananya Shah BS²⁰, Weiwen V Shih MD^{1,20}, H Stella Shin MD¹⁷, Cara L Slagle MD⁴⁰, Sonia Solomon DO^{36,41}, Danielle E Soranno MD⁴⁰, Rachana Srivastava MD⁴³, Natalja L Stanski MD¹³, Michelle C Starr MD, MPH⁴⁰, Erin K Stenson MD^{1,20}, Amy E Strong MD, MSCE³, Susan A Taylor MSc¹⁹, Sameer V Thadani MD², Amanda M Uber DO^{35,42}, Brynna Van Wyk ARNP,

MSN³, Tennille N Webb MD, MSPH⁴⁴, Huaiyu Zang PhD¹³, Emily E Zangla DO⁷, Michael Zappitelli MD, MSc²⁷.

¹Children's Hospital CO, Aurora, CO, USA; ²Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA; ³University of Iowa Stead Family Children's Hospital, Carver College of Medicine, Iowa City, IA, USA; ⁴University of AB, Edmonton, Canada; ⁵Le Bonheur Children's Hospital, Memphis, TN, USA; ⁶Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, PA, USA; ⁷University of Minnesota, Minneapolis, MN, USA; ⁸Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; ⁹Cohen Children's Medical Center, Zucker School of Medicine, New Hyde Park, NY, USA; ¹⁰Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH, USA; ¹¹Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; ¹²Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO, USA; ¹³Cincinnati Children's Hospital Medical Center; University of Cincinnati College of Medicine, Cincinnati, OH, USA; ¹⁴Meyer Children's Hospital, IRCCS, Florence, Italy; ¹⁵Medical University of Innsbruck, Innsbruck, Austria; ¹⁶Stanford University School of Medicine, Palo Alto, CA, USA; ¹⁷Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA, USA; ¹⁸Gregorio Marañón University Hospital; School of Medicine, Madrid, Spain; ¹⁹King's College Hospital, London, England; ²⁰University of Colorado, School of Medicine, Aurora, CO, USA; ²¹St Jude Children's Hospital, Memphis TN USA; ²²University of Pittsburgh Medical Center Children's Hospital of Pittsburgh, Pittsburgh, PA, USA; ²³Royal Children's Hospital, University of Melbourne, Murdoch Children's Research Institute, Melbourne, VIC, Australia; ²⁴University of Michigan Medical School, C.S. Mott Children's Hospital, Ann Arbor, MI, USA; ²⁵Santo Stefano Hospital, Prato, Italy; ²⁶Osaka City General Hospital, Osaka, Japan; ²⁷Hospital for Sick Children, Toronto, ON, Canada; ²⁸NYU Langone Health, Hassenfeld Children's Hospital, NY, NY, USA; ²⁹Sidra Medicine and Weil Cornell Medicine, Qatar, Doha, Qatar; ³⁰Children's National Hospital, WA, DC, USA; ³¹Westchester Medical Center, Westchester, NY, USA; ³²University of California, San Francisco, CA, USA; ³³Golisano Children's Hospital at University of Rochester Medical Center, Rochester, NY, USA; ³⁴Seattle Children's Hospital, University of Washington, Seattle, WA, USA; ³⁵University of Nebraska Medical Center, Children's Hospital & Medical Center, Omaha, NE, USA; ³⁶Department of Pediatrics, Westchester Medical center, Maria Fareri Children's, Valhalla, NY, USA; ³⁷Dalhousie University, Halifax, NS, Canada; ³⁸Medical University of South Carolina, Charleston, SC, USA; ³⁹Arkansas Children's Hospital, University of Arkansas for Medical Sciences, Little Rock, AR, USA; ⁴⁰Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN, USA; ⁴¹Department of Pediatrics, Nemours Children's Hospital, Wilmington DE, USA; ⁴²University of Utah School of Medicine, Primary Children's Hospital, Salt Lake City, UT, USA; ⁴³Mattel Children's Hospital at UCLA, Los Angeles, CA, USA; ⁴⁴Childrens of AL/University of Alabama at Birmingham, Birmingham, AL, USA,

Additional WE-ROCK contributors not meeting authorship criteria: T. Christine E. Alvarez MHI RN¹, Elizabeth Bixler BS², Erica Blender Brown MA, CRA³, Cheryl L Brown BS¹, Ambra Burrell BA⁴, Anwesh Dash BS⁵, Jennifer L Ehrlich RN MHA⁶, Simrandeep Farma HBSc⁷, Kim Gahring RN BSN, CCRN⁸, Barbara Gales RN⁹, Madison R Hilgenkamp¹⁰, Sonal Jain MS¹¹, Kate Kanwar BA MS⁴, Jennifer Lusk BSN RN, CCRN⁸, Christopher J. Meyer BA AA¹, Katherine Plomaritas BSN RN¹², Joshua Porter BS⁵, Jessica Potts BSN RN¹³, Alyssa Serratore BNurs, GDipNP(PIC), RN, MSc¹⁴, Elizabeth Schneider BS⁵, Vidushi Sinha BS⁵, PJ Strack RN, BSN, CCRN¹⁵, Sue

Taylor RN¹⁶, Katherine Twombly MD³, Brynna Van Wyk MSN, ARNP CPNP⁶, Samantha Wallace MS¹⁷, Janet Wang BS⁵, Megan Woods BS⁵, Marcia Zinger RN¹⁸, Alison Zong BS⁵

¹Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; ²Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA; ³Medical University of South Carolina, Charleston, SC, USA; ⁴Nationwide Children's Hospital, Columbus, OH, USA; ⁵University of Tennessee Health Science Center College of Medicine, Memphis, TN, USA; ⁶University of Iowa Stead Family Children's Hospital, Carver College of Medicine, Iowa City, IA, USA; ⁷Hospital for Sick Children, Toronto, ON, Canada; ⁸Children's Hospital CO, Aurora, CO, USA; ⁹Mattel Children Hospital at UCLA, Los Angeles, CA, USA; ¹⁰University of Nebraska Medical Center, Children's Hospital and Medical Center, Omaha, NE, USA; ¹¹Seattle Children's Hospital, Seattle, WA, USA; ¹²University of Michigan, C.S. Mott Children's Hospital, Ann Arbor, MI, USA; ¹³Children's of AL/University of Alabama at Birmingham, Birmingham, AL, USA; ¹⁴Royal Children's Hospital, Melbourne, VIC, Australia; ¹⁵Children's Mercy Hospital, Kansas City, MO, USA; ¹⁶King's College Hospital, London, England; ¹⁷Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN, USA; ¹⁸Cohen Children's Medical Center, New Hyde Park, NY, USA.

Statement of Ethics

The study protocol for each of the parent studies was reviewed and approved by the appropriate Ethics Committee of each individual participating site. The Institutional Review Board (IRB) at each center approved SCD-01/SCD-02 with a requirement for written informed consent (online suppl. Material 1). Written informed consent was obtained from the participants prior to the study. For WE-ROCK, each site received IRB approval with a waiver of informed consent (online suppl. Material 2).

Conflict of Interest Statement

Dr. Stanski receives funding from the National Institute of General Medical Sciences (K23GM151444-02). Drs. Goldstein, Basu, and Askenazi received consulting fees from SeaStar Medical to assist with the application for a Humanitarian Device Exemption from the US FDA for selective cytopheretic device (SCD) technology; Dr. Goldstein continues to receive consulting fees from SeaStar Medical. Dr. Humes is a shareholder, scientific advisor, and consultant for SeaStar Medical. Drs. Menon and Gist receive funding from the Gerber Foundation for the evaluation of nutritional outcomes in children <10 kg requiring continuous kidney

replacement therapy for acute kidney injury and/or fluid overload (MINI-ROCKET Study). Dr. Gist is a consultant for BioPorto Diagnostics. Dr. Menon is a consultant for Medtronic, Inc. Dr. Askenazi consults for Nuwellis and is the Chief Scientific Officer at Zorro-Flow Inc. and has patent intellectual property rights for a female non-invasive urine collection device. Dr. Akcan-Arikan serves on the scientific advisory board of SeaStar Medical. Drs. Goldstein and Basu were members of the journal's Editorial Board at the time of submission. All other authors report no relevant conflicts of interest.

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Author Contributions

Data collection for the SCD studies was performed by Kelli A. Krallman, David J. Askenazi, Rajit K. Basu, and Stuart L. Goldstein. Data collection for the WE-ROCK registry was performed by Kelli A. Krallman, Natalja L. Stanski, and Katja M. Gist. Data curation for this study was performed by Natalja L. Stanski, Katja M. Gist, Todd Jenkins, and JangDong Seo. Analyses were performed by Natalja L. Stanski, Katja M. Gist, Todd Jenkins, and JangDong Seo. The first draft of the manuscript was written by Natalja L. Stanski. Natalja L. Stanski, JangDong Seo, Todd Jenkins, Kelli A. Krallman, Shina Menon, H. David Humes, David J. Askenazi, Rajit K. Basu, Ayse Akcan-Arikan, Stuart L. Goldstein, and Katja M. Gist commented on previous versions of the manuscript before reading and approving of the final manuscript and contributed to the study conception and design.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons, but de-identified summary data are available from the corresponding author upon reasonable request.

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