Sodium Bicarbonate to Prevent Acute Kidney Injury in Children Undergoing Cardiac Surgery: A Randomized Clinical Trial

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PART A. Specific Aims

With over 1 million operations a year, cardiac surgery with cardiopulmonary bypass (CPB) appears to be the second most common major contributor to acute kidney injury (AKI) in developed countries (1). AKI is a common and serious postoperative complication of CPB in children (2, 3). The pathophysiology of AKI is complex and not yet completely understood. Multiple causes of AKI after CPB have been proposed and include ischemia/ reperfusion, generation of reactive oxygen species (ROS), hemolysis, and activation of inflammatory pathways (4,5) To date, no simple, safe and effective intervention to prevent cardiopulmonary bypass-associated acute kidney injury in a broad patient population has been found. Sodium bicarbonate has shown promise in animal and clinical studies in the prevention of AKI.

The proposed study will investigate the effect of sodium bicarbonate on the prevention of acute kidney injury in children undergoing cardiac surgery with cardio-pulmonary bypass. We hypothesize that the occurrence of acute kidney injury will be less in children treated with sodium bicarbonate in the perioperative period when compared to placebo. The specific aims of this proposal are as follows:

Specific Aims:

1. To institute a prospective, randomized, double-blinded, placebo-controlled trial in pediatric subjects undergoing cardiac surgery to determine the efficacy of sodium bicarbonate on prevention of acute kidney injury as measured by pRIFLE criteria.

2. To examine whether treatment with sodium bicarbonate modifies the duration of acute kidney injury, fluid balance, hospital length of stay, need for dialysis, and progression to kidney failure.

3. To determine the relevance of NGAL as a biomarker to predict development of acute kidney injury.

PART B. Significance, Background and Preliminary Studies

Acute Kidney Injury

Acute kidney injury is defined as the abrupt onset of renal dysfunction resulting from injurious endogenous or exogenous processes characterized by decrease in GFR and increase in serum creatinine. AKI leads to the inability to regulate acid and electrolyte balance and the inability to excrete waste and fluid. The exact incidence of AKI is unknown due to the heterogeneity of definitions of AKI reported in the literature. Recently, the pRIFLE criteria were developed to aid in the definition and classification of AKI in children (6).

In a heterogeneous group of about 3400 critically ill children in a tertiary PICU, Schneider et al. (Principal Investigator) identified AKI in about 10% of patients (2). AKI was found to be independently associated with prolonged PICU length of stay as well as length of mechanical ventilation. Further, AKI was independently associated with mortality, worsening with increasing degree of AKI.

Acute kidney injury is a common complication after cardiac surgery under cardiopulmonary bypass. In a retrospective chart review of 458 pediatric (<18 years of age) patients undergoing corrective surgery for congenital heart defects at Cohen Children's Medical Center of New York between 2006 and 2009, we demonstrated that 51% of patients developed AKI during their postoperative stay in the pediatric intensive care

unit. The incidence was even greater when limiting the analysis to neonates (<30 days of life), where 60% of patients developed AKI postoperatively (7). Li, et al, have also shown in a prospective multicenter analysis of children undergoing congenital heart corrective surgery that the incidence of AKI is 42%, but significantly higher in patients <2 years of age (8). AKI was identified as an independent risk factor for prolonged ICU and hospital length of stay as well as prolonged mechanical ventilation (7,8). To date, though, no study has identified a particular intervention or series of interventions (bundles) that can limit the development of this independent risk factor for poor outcomes in children undergoing CPB for corrective heart surgery. Pilot and laboratory data suggest that continuous infusion of sodium bicarbonate can decrease the incidence of AKI after adult CPB (9) or laboratory animal models of renal injury (10).

Sodium Bicarbonate

Acidic urine may enhance the generation and toxicity of reactive oxygen species (ROS) generated by cardiopulmonary bypass. The beneficial effect of increasing tubular pH by urinary alkalinization, achieved for example with the use of sodium bicarbonate infusion, was protective in a rat model of acute renal failure (10). Report from a pilot double-blind, randomized controlled clinical trial conducted by Haase et al. suggested that sodium bicarbonate infusion with preoperative intravenous loading to achieve urinary alkalinization attenuates incidence of AKI associated with CPB in cardiac surgical patients (9). The findings of this pilot study justify further investigation provided by government sponsored clinical trials. In contrast, Herringlake et al found in a retrospective cohort study, that bicarbonate loading did not alter the incidence of AKI in adults (11). This study had several limitations. Given the extensive co-morbidities found in adults, it is quite possible that an intervention found not to be effective in the adult population would be effective in the pediatric population. Accordingly, we hypothesize that urinary alkalinization might protect kidney function in pediatric patients at increased risk of acute renal dysfunction undergoing cardiopulmonary bypass.

Further evidence for the beneficial effect of sodium bicarbonate is the data concerning the prevention of AKI due to IV contrast. Increasing urinary pH - in combination with *N*-acetylcysteine (12) or without (13) - has been reported to attenuate acute renal dysfunction in patients undergoing contrast- media infusion. In a recent meta-analysis of 19 clinical trials consisting of 3,609 patients, pre-procedural hydration with sodium bicarbonate was associated with a significant decrease in the rate of contrast induced AKI (odds ratio [OR] 0.56; 95% confidence interval [CI] 0.36-0.86; P=0.008). The authors concluded that sodium bicarbonate-based hydration is superior to sodium chloride in preventing AKI of patients undergoing exposure to iodinated contrast media (14).

PART C. Drug Information

Sodium Bicarbonate (reference Lexicomp 2010-2011)

Mechanism of Action: Dissociates to provide bicarbonate ion which neutralizes hydrogen ion concentration and raises blood and urinary pH.

Dose: Subjects in the intervention arm will receive NaHCO3 as a continuous infusion of D5% 1/3NS + 100 meq/L NaHCO3 + 20 meq/L KCl at maintenance IVF (1500 ml/m2/day). The solution contains ~154 meq of sodium which is equivalent to normal saline. The strength of NaHCO3 is based on a dose of150 meq/m2/day. Per Lexicomp, the dose for prevention of hyperuricemia secondary to tumor lysis syndrome (urinary alkalinization) in infants and children is sodium bicarbonate IV 120-200 mEq/m^2/day diluted in I.V. fluids of 3000 mL/m^2/day. 3000 ml/m2/day is two times normal maintenance IVF. Given that this protocol is for cardiac patients, there is a risk of fluid overload with two times maintenance IVF. Therefore, we have chosen a lower dose of sodium bicarbonate 150 meq/m2/day to be diluted in one times maintenance IVF (1500 ml/m2/day). The study drug will be obtained from the CCMC pharmacy. This dosing regimen will be tested in the first 10 subjects, see Section V.g.

Dosage Forms: Injection, solution: 4.2% [5 mEq/10 mL] (10 mL); 8.4% [10 mEq/10 mL] (50 mL) Neut®: 4% [2.4 mEq/5 mL] (5 mL) [contains edetate disodium] 1 mEq $NaHCO_3$ is equivalent to 84 mg; each g of $NaHCO_3$

provides 12 mEq each of sodium and bicarbonate ions; the osmolarity of 0.5 mEq/mL is 1000 mOsm/L and 1 mEq/mL is 2000 mOsm/L

Monitoring Parameters: Serum electrolytes including calcium, urinary pH, arterial blood gases

Pharmacodynamics: Onset of action: I.V.: Rapid Duration: I.V.: 8-10 minutes

Pharmacokinetics: Elimination: Reabsorbed by kidney and <1% is excreted in urine

PART D. Experimental Design and Methods

I. Overview of Study Design

A prospective, randomized, double-blinded, placebo-controlled trial in children undergoing cardiac surgery with cardio-pulmonary bypass will be conducted to determine the effect of sodium bicarbonate on the prevention of acute kidney injury. A total of 132 subjects will be enrolled (66 subjects in each arm) at a single pediatric tertiary hospital, Cohen Children's Medical Center of New York, over a two year time period.

Treatment Arm: At the start of the surgery, the patient will receive NaHCO3 as a continuous infusion of D5% 1/3NS + 100 meq/L NaHCO3 + 20 meq/L KCl at maintenance IVF (solution contains ~154 meq of sodium which is equivalent to normal saline). The NaHCO3 infusion will continue for the first 24 hours after the discontinuation of CPB. After 24 hours of receiving the NaHCO3 infusion, the IVF administered to the patient will be the standard solutions used in the PICU at CCMC.

Control Arm: At the start of surgery, patients in the control arm will receive D5% Normal Saline + 20 meq/L KCl at maintenance IVF. After 24 hours, standard IVF, not containing NaHCO3 or Na acetate will be administered for the duration of the PICU stay as required, determined by the clinicians primarily caring for the patient postoperatively.

Primary Outcome Measure: The efficacy of sodium bicarbonate on prevention of AKI will be tested by comparing the proportion of subjects in each of the treatment arms who progress to AKI as measured by the Pediatric Risk, Failure, Loss of Function, and End-Stage Renal Disease (pRIFLE) criteria or an absolute increase in creatinine of 0.3mg/dl.

Secondary Outcome Measures:

1. Duration of acute kidney injury
2. Cumulative fluid balance
3. Hospital and intensive care unit length of stay
4. Need for dialysis
5. Progression to pRIFLE criteria F
6. Association of NGAL as a biomarker to predict development of acute kidney injury
7. Length of mechanical ventilation
8. Change in acid-base status

II. Study Sites

Subjects will be recruited from the Cardiothroacic Surgery Division of the Cohen Children's Medical Center of New York of North Shore-LIJ Health Systems (CCMC) in New Hyde Park, New York

III. Study Subjects

Patients from CCMC come from a large geographic area with a diverse racial composition. There are currently 150 children ≤18 years that undergo cardiac surgery with cardiopulmonary bypass per year at CCMC. Consecutive patients scheduled for cardiac surgery who meet eligibility criteria will be invited to participate in the study.

Eligibility criteria include:

Inclusion Criteria

1) Subjects age ≤18 years
2) Subjects scheduled for cardiac surgery with cardiopulmonary bypass

Exclusion Criteria

1) Subjects with abnormal creatinine clearance (<90 ml/min/1.7m2) as measured by the Schwartz formula
2) Subjects with known cystic kidney disease or posterior ureteral valves (subjects with solitary kidney, single multicystic/dysplastic kidney, hydronephrosis will not be excluded if renal function is preserved)
3) Subjects with known metabolic disorder
4) Premature infants born <30 weeks gestation and <30 days old due to risk of intraventricular hemorrhage

Subjects in severe cardiogenic shock post-operative requiring extra-corporeal membrane oxygenation (ECMO) or left ventricular assist device (LVAD) will be withdrawn from the study.

IV. Randomization and Blinding

Subjects will be randomized to the treatment group or control group in a 1:1 ratio to receive sodium bicarbonate (treatment group) or placebo (control group). Allocation will be based on random, computer-generated numbers in permutated blocks of 10. Study drug and placebo will be prepared and dispensed by the pharmacy according to randomization. The treatment will be administered in an identical fashion to subjects in both arms. The investigators involved in the study, clinicians and study subjects will be blinded to the treatment assignment.

V. Study Procedures

The outline of study procedures is as follows:

Study Procedures										
	Screening	**Pre-Operative**		**Intra-Operative**	**2 hr**	**4 hr**	**12 hr**	**24 hr**	**48 hr**	**30 days**
Review Inclusion/Exclusion Criteria	x		I N T E R V E N T I O N							
Informed Consent/Assent	x									
Randomization		x								
Demographics/Medical History	x									
Height and Weight	x	x								x
Serum creatinine/BUN	x	x			x	**x**	x	x	x	**x**
Serum electrolytes	x	x		x*	x	**x**	x	x	x	**x**
Urine pH		**x**		**x***	**x**	**x**	**x**	**x**	**x**	
CBC with differential	x	x								
Serum NGAL		**x**			**x**	**x**	**x**	**x**	**x**	
Serum pH		**x**		x*	x	**x**	x	x	x	
Urine Output Monitoring		x		x	x	x	x	x	x	

* Serum and urine pH and serum electrolytes will be done at the discretion of anesthesia and bypass team as per protocol.

Items marked in **RED** indicate procedures being done specifically for the research study. Blood draws at 4 hours post-operatively are standard practice for certain patients, based on complexity of the surgical procedure, and will be done for

research purposes on some patients who had less complex surgeries. All other procedures represent standard practice for all patients undergoing cardiopulmonary bypass for correction of congenital heart lesions.

a. Screening Visit

Eligibility and demographic data will be collected on all children scheduled for cardiac surgery with cardio-pulmonary bypass during the study interval. Subject and disease characteristics will be recorded for all ineligible subjects and those declining participation. Potential subjects will be screened using the protocol inclusion and exclusion criteria. Pre-surgical testing laboratory data, collected as part of standard care, will be reviewed. Study subjects who meet the eligibility criteria will be asked to participate in the study in person by physicians known to them in clinic or in the hospital. Parental/guardian permission (informed consent) and, if applicable, child assent, will be obtained prior to any study related procedures being performed.

b. Perioperative Management

As part of their standard care, subjects will have baseline height, weight, comprehensive metabolic panel, complete blood count and serum pH done on the day of surgery at the time of IV and arterial line insertion. Subjects will then be randomized into one of the treatment groups and will receive the intervention at the start of surgery.

Clinical practices associated with cardiac surgery will not be modified for the purpose of the study and standard of care will be given to all patients. Intra-operative fluid management will be left to the discretion of the anesthesiologist and will be documented. Intra-operative serum pH will be monitored and subjects may receive sodium bicarbonate boluses regardless of treatment group as standard of care if needed (this is done infrequently). As part of the standard practice, all subjects will receive Ancef at the time of surgery and will be continued for three doses (vancomycin is used in cases of allergy). A foley catheter will be placed and urine output will be recorded. Any pre-operative electrolyte disturbances (i.e. hypokalemia, hypernatremia, hypocalcemia and acidosis) will be corrected prior to administration of NaHCO3. Serum and serum electrolytes will be done during surgery at the discretion of anesthesia and bypass team as per protocol. Electrolyte abnormalities will be treated by the anesthesiologist and will be documented.

c. Intervention

Treatment Arm: Patients randomized to the intervention of receiving NaHCO3 perioperatively will initially receive the current standard anesthetic and perfusion approach at CCMC, which includes a cardiopulmonary pump priming solution containing 0.2mEq per milliliter of crystalloid. At the start of the surgery, the patient will begin to receive NaHCO3 as a continuous infusion of D5% 1/3NS + 100 meq/L NaHCO3 + 20 meq/L KCl at maintenance IVF (solution contains ~154 meq of sodium which is equivalent to normal saline). The strength of NaHCO3 is based on a dose of 150 meq/m2/day (reference range 120-200mEq/m2/day [Lexicomp, 18th Ed., 2011-12]) and IVF maintenance of 1500 ml/m2/day. .While the patient is undergoing CPB, calculated base deficits more negative than -3 will be corrected by giving NaHCO3 according to the formula: base deficit * patient weight in kilograms/ 3. Tromethamine (THAM) may be used in the neonatal population while undergoing CPB if the serum sodium levels have increased to greater than 145 mEq/dL. Blood gas serum sodium, potassium and calcium will be monitored during the surgery and corrections will be made by the anesthesiologist. The NaHCO3 infusion will continue for the first 24 hours after the discontinuation of CPB (based on current data from CCMC PICU: 85% of patients who develop AKI do so in the first 24 hours, and duration of AKI is <48 hours in 75% patients (reference Aydin, Annals of Thoracic Surgery, 2012). After 24 hours of receiving the NaHCO3 infusion, the IVF administered to the patient will be the standard solutions used in the PICU at CCMC, notably a sodium concentration with dextrose along the spectrum of D5 0.33% NaCl through D5 0.45% NaCl, depending on the patient's serum electrolyte profile.

Control Arm: At the start of surgery, patients in the control arm will receive D5% Normal Saline + 20 meq/L KCL at maintenance IVF. The standard approach to perfusion for CPB, including the pump prime solution containing NaHCO3 as well as replacement of NaHCO3 for calculated base deficits will be administered as described above. After 24 hours, standard IVF, not containing NaHCO3 or Na acetate will be administered for

the duration of the PICU stay as required, determined by the clinicians primarily caring for the patient postoperatively.

d. Hospital Course

Serum creatinine, NGAL and urine pH will be monitored at 2, 4, 12, 24, and 48 hours. Urine pH will be collected and tested by a research nurse from the division of pediatric nephrology according to the study outline (see section V.). The research nurse will be blinded to whether the patients being evaluated are enrolled in the control or intervention arms. Data regarding patient urine pH will be identified by study-specific patient number, and stored in a password-protected electronic spreadsheet on the computer of the research nurse. Investigators will be blinded to the results of the urine pH, maintaining the double-blinded study design. Urinary output will be targeted to maintain urine flow >0.5 ml/kg/hr using furosemide, normal saline bolus and ionotropes as necessary. The use of nonsteroidal anti-inflammatory drugs and other nephrotoxic agents such as aminoglycosides will be avoided if possible, which is consistent with the standard of care of treating all critically ill children. The use of all medications and fluid boluses will be recorded.

e. Protocol for electrolyte imbalance

Metabolic derangements such as hypernatremia, hypokalemia, hypocalcemia or severe alkalosis will be treated as per standard of care in the PICUl. Severe alkalemia, defined as pH>7.6, can be associated with ventricular arrhythmias and seizures. Therefore, any subject with serum pH >7.55 will have the intervention fluids immediately discontinued. As per standard of care, electrolytes will be rechecked after any treatment intervention. Adverse events such as hypernatremia, hypokalemia and severe alkalosis will be monitored.

f. Follow up Visit

Subjects will be seen in the outpatient cardiothoracic clinic on Day 30, as is done routinely. Each subject will have height, weight, comprehensive metabolic panel and complete blood count measured as part of the research protocol.

g. Pilot study to test dose of Sodium Bicarbonate

To ensure that the chosen dose of sodium bicarbonate adequately alkalinizes the urine, we will briefly halt enrollment to blindly review urine pHs of the first 10 randomized subjects. The research nurse will be blinded to the patients' enrollment arm and the information regarding the results of the urine pH will not be available to the investigators until this interim analysis to assure appropriate blinding during the treatment of each patient. Since we have blocked randomization in groups of 10, we expect that half of the subjects will receive treatment with Sodium Bicarbonate. Therefore, we expect half of the subjects to have urine pH close to 7. If we find that urine is not adequately alkalinized, we will halt the study and submit a modification to the IRB to alter the dose of sodium bicarbonate.

VI. Study Outcomes

Demographic and Clinical Data

The medical record will be abstracted for the following variables: age, gender, diagnosis, previous surgical history, race, left ventricular ejection fraction on baseline echo, and current medications. Surgical parameters of cardio-pulmonary bypass time, ischemic time, surgical procedure, surgical complexity score, lowest temperature, use of circulatory arrest, use of cerebral perfusion, renal NIRS (measure of oxygen saturation of the renal vessels), medications administered, pH range, urine pH, surgical time, post-bypass time, estimated blood loss, and blood products administered will be measured. Cumulative fluid balance (daily Ins and Outs), hospital and intensive care unit length of stay, need for and duration of dialysis and medical complications will be recorded.

Serum NGAL is a biomarker of early AKI that often increases before serum creatinine. Specifically for this research study, serum NGAL and creatinine level will be drawn at the time of surgery and at 2, 4, 12, 24, and 48 hours.
As per routine care, creatinine will then be measured daily. pRIFLE level will be calculated on the maximum creatinine attained.

pRIFLE Criteria

	GFR	**Urine Output**
Risk	decrease by 25%	0.5 mL/kg/h for 8 hours
Injury	decrease by 50%	0.5 mL/kg/h for 16hours
Failure	decrease by 75% or GFR <35	0.3 mL/kg/h for 24 hours or anuric for 12 hours

Loss Persistent failure 4 weeks
End stage End-stage renal disease (persistent failure 3 mo)

Creatinine clearance will be estimated by the Schwartz formula (k x ht (cm)/ creatinine; k= 0.4 premature, k= 0.55 females and pre-pubertal males <13, k= 0.7 pubertal males). NGAL will be measured by enzyme-linked immunosorbent assay. Urine pH will be measured at 2, 4, 12, 24 hours post surgery, and as described above, the investigators will be blinded to these results. Serum pH and electrolytes will be measured at 2, 4, 12, 24 hours. NGAL and urine pH will be measured specifically for the purpose of performing this research study. Serum pH is routinely measured as standard practice in post-operative cardiothoracic surgery patients during surgery, and at hours 2, 12, and 24 hours post-operatively.

PART E. Statistical Issues

I. Statistical Analysis

Statistical analyses will be done using SPSS 18.0 (SPSS Inc., Chicago, IL) statistical package. A two-tailed p-value < 0.05 is the criterion for statistical significance. Intention to treat analysis will be done. Descriptive statistics will be used to characterize outcome measures in subjects. Means, standard deviations, 95% confidence intervals, medians, and minimum and maximum values will be tabulated and reported for all continuous variables. Frequency counts and percentages will be used for categorical variables. The distributions of each outcome will be examined for normality. Baseline demographic and clinical data of the two arms will be examined. Differences in means in the treatment group will be compared to the control group using Student's t-test, or the Wilcoxon Rank Sum test if the data are not normally distributed. Differences in proportions will be assessed using the chi-square test.

Specific Aims:

1. To analyze the primary outcome, chi-square will be conducted to compare the proportion of subjects who develop AKI by pRIFLE criteria in the two groups.

2. Student's t-test or Wilcoxon Rank Sum test for non-normally distributed variables will be used to compare values of duration of acute kidney injury, fluid balance, hospital length of stay, need for dialysis, and progression to kidney failure between groups. Pearson correlation and linear regression will be used to examine the association between duration of acute kidney injury, fluid balance, hospital length of stay, need for dialysis, and progression to kidney failure and development of AKI. Regression analysis will be adjusted for sex, age and race. Variables may be log transformed to improve the fit of the models.

3. Pearson correlation and linear regression will be used to analyze the association of NGAL with development of AKI.

II. Sample Size Estimates

Sample size estimates were calculated for the primary outcome of proportion that develop AKI in each of the two groups. Sample sizes were considered based on various effect sizes. Assuming 50% risk of AKI from our previous work, a drop from 50% AKI to:

35% would need 170 per group
30% would need 93 per group
25% would need 66 per group
20% would need 44 per group

In the literature, studies have used reductions between 20-35%. We aimed for somewhere in between. The comparison of 66 subjects in the treatment group and 66 subjects in the control group provides 80% power ($\alpha = 0.05$) to detect a difference from 0.5 in the control group to 0.25 (that is a 50% reduction in AKI) in the treatment group. nQuery software was utilized to calculate sample size.

III. Limitations

The proposed study is limited by the small sample size and heterogenous population. Given these limitations, we believe the results of the proposed study will be able to be generalized to the pediatric cardiac surgery population.

PART F. PROTECTION OF HUMAN SUBJECTS

Risk to Subjects

a. Human Subjects Involvement and Characteristics

The proposed study will involve human subjects, in particular, children and adolescents aged ≤18 years of age. The purpose of the study is to examine cardiac surgery in a pediatric population, therefore, other age groups are excluded from this study. Other inclusion/exclusion criteria are listed elsewhere in the protocol. This vulnerable population will be protected. Assent will be obtained from the participants and participants may withdraw from the study at any time.

b. Potential Risks

Hypokalemia and hypernatremia are the most common complications. Administration of bicarbonate to induce alkaline diuresis results in alkalemia (an increase in blood pH or reduction in its hydrogen ion concentration). Severe alkalemia, pH >7.6 may result in ventricular arrhythmias and seizures. Alkalotic tetany occurs occasionally, but hypocalcemia is rare. Extravasation of concentrated NaHCo3 can lead to tissue necrosis due to the hypertonicity of $NaHCO_3$, but concentrated NaHCO3 boluses are not used in this study. NaHCO3 needs to be used with caution in patients with CHF or other sodium-retaining conditions and renal insufficiency. Rapid administration of hyperosmotic solution in neonates, infants, and children <2 years of age has led to hypernatremia, decreased CSF pressure, and intracranial hemorrhage. Rapid administration of sodium bicarbonate will not be used in this study. Most data are from premature and very low birthweight babies, which have been excluded in this study.

Adequacy of Protection of Risk

a. Recruitment and Informed Consent

Study subjects who meet the eligibility criteria will be approached in person by physicians in the Cardiothoracic Clinic. Written informed consent from the participant, participant's parent or legal guardian and assent from the patients will be obtained before any study procedure is initiated. Participants who turn 18 years of age during the course of the study will be approached for informed consent. No study procedure will be continued in these participants unless informed consent is obtained. No advertisements will be used for recruitment of renal transplant patients.

b. Protection Against Risk

We will monitor for clinical adverse events throughout the study. We will report promptly report all unanticipated problems related to research to the IRB. Refer to DSMB section for specifics. Participation in all areas of the study is completely voluntary. Should the subjects become intolerant of any aspect of the study, their participation (or the specific procedure) will be discontinued. Subjects in severe cardiogenic shock post-operative requiring extra-corporeal membrane oxygenation (ECMO) or left ventricular assist device (LVAD) will be withdrawn from the study. Study investigators will be responsible for communicating to subjects' information arising from the study (on harm or benefit), or from other research on the same topic, that could affect subjects' willingness to continue the study. All other aspects of the study will be kept confidential. Data will be stored in a locked cabinet and password protected file.

c. Potential Benefits to Subjects and Others
One group might receive more effective treatment and/or have fewer side effects than the other treatment groups. This study has considerable future potential benefit for all children with cardiac surgery in preventing AKI.

d. Data Collection and Management
The Investigators are responsible for data management and accuracy of records. Data will be kept in a secure location in an office in the PICU. Each patient will have a separate folder with all data collected within. All data will be entered into a database by an investigator or study coordinator with unique identifiers attached to each patient. Data will be encrypted and password protected.

e. Confidentiality
All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

In order to keep protected health information from disclosure, subjects will be assigned unique identifiers known only to IRB approved study personnel..

Storing Documents in Hard Copy
If you are storing documents in hard copy:
Any documents that contain subjects' PHI (e.g., consent forms) will be stored in a locked cabinet within the office of study investigator's in the PICU, separately from any de-identified research data. IRB approved personnel will be the only individuals with access to the research data.

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Storing Documents Electronically
Any documents containing subjects' PHI will be stored in a password protected computer document/database that will be stored on a password protected computer network, separately from any de-identified research data files. IRB approved personnel will be the only individuals with access to subjects PHI. De-identified data files will be stored on a password protected computer network.

Storing Documents on Portable Electronic Devices
No research data containing PHI will be stored on any Portable Electronic Devices (e.g., laptops, tablets, flash drives, etc.)

Emailing Data
Any research data that will be emailed will be de-identified and encrypted. PHI will not be emailed to any commercial email addresses (e.g., gmail, yahoo, hotmail, etc.)

Storing Samples/Specimens

Participant samples/specimens will de-identified and stored with the subject's study ID number in a locked freezer located in the PICU.

The information collected as part of this study will be retained for at least 10 years after the study is completed. At that time, the research information will either be destroyed or all the information that identifies the subject will be removed from the study results and the key destroyed.

PART G. INCLUSION OF WOMEN AND MINORITIES
All subjects who meet the above inclusion criteria will be invited to participate in the study regardless of gender or race. The study will include females and minorities consistent with the demographics of the program.

PART H. DATA AND SAFETY MONITORING PLAN
An independent reviewer who is an experienced investigator not directly involved in the study will monitor the safety of this study. The reviewer will review the study when ¼, 1/2 , and ¾ th of the study population are enrolled. The independent reviewer will review adverse events, make recommendations concerning continuation or conclusion of the study, protection of the confidentiality of the trial data and the results of monitoring, review of data and study quality.

PART I. Payment to Subjects/Families
Subjects will not be compensated taking part in this study.

PART J. Publication Policy

We plan to publish the results (positive or negative) of this study in academic journals and/or national meetings. We will not disclose protected health information about this study. Any proven evidence of falsification of data will be dealt with to take appropriate action against such unacceptable procedures.

PART K. Conflict of Interest
James Schneider (PI), has no conflict of interest to disclose with respect to this research study**.**

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