Direct Peritoneal Resuscitation in Gastroschisis

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Study Title:	**Direct Peritoneal Resuscitation in Gastroschisis**
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Abbreviations

ACH – Arkansas Children's Hospital
ACRI – Arkansas Children's Research Institute
AE – Adverse Event
AKI – Acute Kidney Injury
ALT – Alanine Aminotransferase
APGAR Score – Appearance, Pulse, Grimace, Activity, and Respiration
AST – Aspartate Aminotransferase
BP – Blood Pressure
CBC – Complete Blood Count
CFR – Code of Federal Regulation
CHND – Children's Hospital National Database
CRF – Case Report Form
d – Day
Diff - Differential
DPR – Direct Peritoneal Resuscitation
GGT – Gamma-Glutamyl Transferase
GI – Gastrointestinal
G-Tube – Gastrostomy Tube
HR – Heart Rate
INR – International Normalized Ratio
IV – Intravenous
JP drain – Jackson-Pratt drain
KDIGO – Kidney Disease: Improving Global Outcomes
kcal – kilocalorie
kg – kilogram
LAR – Legally Authorized Representative(s)
MAP – Mean Arterial Blood Pressure
mL – milliliter
mm – millimeter
MRN – Medical Record Number
NEC – Necrotizing Enterocolitis
NICU – Neonatal Intensive Care Unit
OB/GYN – Obstetrics & Gynecology
OG Tube – Orogastric Tube
PI – Principal Investigator
PTN – Pediatric Trials Network
RR – Respiratory rate
SAE – Serious Adverse Event
SoC – Standard of Care
SpO_2 – Pulse Oximetry
TPN – Total Parenteral Nutrition
UAMS – University of Arkansas for Medical Sciences

Background and Rationale

Gastroschisis is a clinical condition characterized by a defect in the normal development of the abdominal wall. The defect is present to the right of the umbilicus leading to *in utero* bowel evisceration and exposure to amniotic fluid. After birth and prior to operation, the usual treatment consists of covering the bowel with an impermeable plastic bag to prevent additional fluid losses and bowel desiccation. Subsequent operative intervention occurs either in the operating room or in the neonatal intensive care unit. Two surgical options include primary closure of the abdomen or placement of a silastic silo followed by subsequent closure several days later as a staged procedure. The main reason the abdominal wall is not closed initially is due to fear of abdominal compartment syndrome, a condition caused by high intra-abdominal pressures leading to respiratory and circulatory compromise. The key points of the initial surgery involve examining the intestine for any signs of atresia, bowel compromise, and either placement of the bowels back into the abdomen or a spring-loaded silo.

Arkansas Children's Hospital (ACH) has one of the highest rates of gastroschisis patients in the country and therefore has extensive experience managing these patients. We currently do not know why ACH has one of the highest rates of gastroschisis, but it has been postulated it may be due to some factor more common in low socioeconomic status population. ACH is the only pediatric hospital in the state of Arkansas. Quarterly, reviews of the Children's Hospital National Database (CHND) are performed to track the institutions progress in comparison to national trends. ACH's current surgical practice is to place nearly all patients in a silastic silo for staged reduction. Rarely are patients with gastroschisis treated with primary surgical closure at our institution. Serial reductions are performed and once the abdominal contents are at the level of the fascia the abdomen is closed in the operating room. Previous data indicates an average of five days from birth for final reduction and closure. After closure, there can be significant intestinal dysmotility with a prolonged ileus and a delayed return of bowel function. Generally, those with uncomplicated gastroschisis spend approximately 26 days in the neonatal intensive care unit before discharge home.

From historical CHND data, we know our patients with simple gastroschisis have an average length of stay of 29 days, average of 5 days until abdominal wall closure, average of 7 days until start of enteral feeding after abdominal wall closure and average of 10 days until meeting 100 kcal per kg per day enteral feeds.

Direct Peritoneal Resuscitation

The University of Louisville has been at the forefront of research for Direct Peritoneal Resuscitation (DPR). This technique uses clinically available peritoneal dialysis solution instilled into the abdomen with an initial bolus of 500 mL followed by a rate of 1.5 mL/kg/h in adults undergoing closure of the abdominal wall after traumatic injuries [1].

The aforementioned lab has also studied DPR in a rat model of hemorrhagic shock. The model has shown decreased mortality and increased intestinal and liver blood flow [2-5]. The group further investigated the use of DPR in a rat model of Necrotizing Enterocolitis (NEC) and discovered that 1.5% and 2.5% peritoneal dialysis solutions used as DPR improved intestinal blood flow, and with the 1.5% solution, there was less hyperglycemia than in the group treated with the 2.5% solution [6-10].

DPR has also been studied in the treatment of severely injured trauma patients and has shown a decrease in days until closure with improved outcomes [10, 11]. A randomized controlled study of 103 subjects requiring damage control surgery, i.e. open abdominal cavities, found that peritoneal resuscitation reduced the time to definitive abdominal closure, reduced intra-abdominal infections and reduced mortality [11].

Exposure of the abdominal viscera and its placement in a silo puts the neonate in a metabolically stressed state. Using DPR has been shown to counteract the systemic inflammatory response, leading to dilation of arterioles in the intestine resulting in reduced organ ischemia and cellular hypoxia [12].

Several case series have demonstrated safety of peritoneal dialysis in infants with recent abdominal surgery and intestinal perforation [13-15]. In pediatric patients, peritoneal resuscitation has been used in two infants with perforated NEC who were too unstable to undergo laparotomy. Both survived and went on to undergo laparotomy [16].

We consider the patient with gastroschisis as an equivalent to the general surgery patient with the open abdomen and that adjunctive DPR treatment may be able to accelerate abdominal closure and improve outcomes.

Ultrasounds

Optimal timing to begin feeds in neonates with gastroschisis remains unclear. A previous study performed by our research group concluded that bedside ultrasound is a feasible tool to detect return of bowel function in neonates with gastroschisis [17].

Study Summary

This is a prospective double-arm study designed to evaluate the tolerability of direct peritoneal resuscitation (DPR) in neonates with gastroschisis. The experimental arm (DPR group) will receive adjuvant DPR with standard treatment for gastroschisis (staged silo closure). The control arm (SoC group) will receive standard treatment for gastroschisis without DPR. The objectives are (1) to determine if subjects treated with DPR will have a more benign hospital stay as measured by time to full enteral feeds of 100 kcal/kg/day and (2) to monitor the effect of Dianeal 1.5% dialysis solution on the hemodynamics, serum electrolytes, lactic acid, respiratory function, and other parameters.

Hypothesis

Hypotheses: We hypothesize that the DPR group will have a more benign hospital course as measured by time to full enteral feeds of 100 kcal/kg/day. We will also assess time to abdominal wall closure, time on TPN, length of hospital stay and intestinal motility post-closure using bedside ultrasounds. Secondly, we hypothesize that there will be no deleterious effects related to introducing the peritoneal dialysis solution into the silo.

Study Objectives

Primary Objectives:

1. To demonstrate that subjects treated with DPR will have a more benign hospital course as measured by time to full enteral feeds. The primary outcome measure will be time to full feeds of 100 kcal/kg/day. Secondary outcomes will include length of time until abdominal wall closure, time on TPN, time to intestinal motility, and total days in the hospital.

2. To demonstrate that the use of DPR in neonates with gastroschisis treated with staged silo closure will result in no significant changes in commonly measured clinical and laboratory safety parameters. This will be measured with more frequent clinical and laboratory assessments for the DPR group. Vital signs and strict intake and output will be monitored every 6 hours for 48 hours after the maximum dialysate infusion volume has been reached, then every 12 hours. Sodium, potassium, blood glucose and lactate levels will be monitored every 6 hours via heelstick, central/arterial line or venipuncture

per NICU standard practice for 24 hours after the maximum dialysate infusion volume has been reached, then every 12 hours through Post-Closure Day 1.

Investigational Product

Dianeal PD-2 1.5% is a sterile, nonpyrogenic, hypertonic peritoneal dialysis solution containing dextrose, a monosaccharide, as the primary osmotic agent. Routine peritoneal dialysis in neonates and infants utilizes up to 40 mL/kg of dialysate per dwell. It will be administered via a 10 mm flat JP drain as a bolus infusion every 6 hours until the abdominal wall is closed (generally 3-5 days), but not to exceed 7 days maximum. The initial bolus infusion will be 10 mL/kg of Dianeal 1.5%. If tolerated, each subsequent infusion will be increased by 10 mL/kg of Dianeal 1.5% up to a goal infusion of 40 mL/kg (to a maximum volume of 100 mL) as tolerated.

The investigational product will be kept in a secure, limited-access storage in the ACRI research pharmacy under the direction of the research pharmacists who will be responsible for maintaining the supply according to the manufacturer's specifications, dispensing the drug for administration, and maintaining all drug accountability logs.

Study Population

We will prospectively enroll all neonates with the diagnosis of gastroschisis presenting to ACH within 12 hours after birth for whom consent is signed by the parent(s)/LAR. We anticipate enrolling 40 subjects at Arkansas Children's Hospital. All subjects that have their abdominal wall defect closed will be defined as having completed active participation in the study.

Eligibility Criteria

Inclusion criteria:

- Diagnosis of Gastroschisis
- Male or Female, any ethnicity
- Neonates [18]

Exclusion criteria:

- Primary gastroschisis repair
- Vanishing gastroschisis
- Encapsulating peritoneal sclerosis
- Infants < 2 kg and < 34 weeks gestation
- Infants > 12 hours at enrollment
- Severe hypotension, defined as either:
  - Mean arterial blood pressure (MAP) < gestational age in weeks, or
  - Systolic blood pressure (BP) < 45 or diastolic BP < 20
- Severe Hypertension defined as Systolic BP > 90 or diastolic > 60
- Culture-positive sepsis
- Known or strongly suspected inborn errors of metabolism
- Significant cardiac disorders, including cyanotic congenital heart disease, ductal-dependent congenital heart disease, and critical congenital heart disease (lesions requiring surgery or catheter-based intervention in the first year of life)
- Respiratory failure, defined as any requirement of positive pressure ventilation at the time of enrollment, or FiO2 > 50%

- Any other condition, that, in the opinion of the investigator, might interfere with the safe conduct of the study or place the subject at increased risk
- Lactic acidosis with at least one or more of the following:
  - Characterized by increased blood lactate levels (> 5 mmol/L) on two occasions at least 6 hours apart
  - Severe metabolic acidosis with an arterial pH ≤ 7.0
  - Bicarbonate < 14 or CO_2 < 12
  - Base excess of > -10 mEq/L
- Neonatal Acute Renal Failure, defined as serum creatinine > 2.0 mg/dL with anuria in the first 12 hours of life
- Neonatal Acute Hepatic Failure, defined as INR $\geq$ 3 [19]
- Liver function test abnormalities defined as AST > 200, ALT > 200, GGT > 100 [19]
- Electrolyte abnormalities, defined as:
  - Sodium < 130 or > 150 mEq/L
  - Potassium < 3.0 or > 6.5 mEq/L
- Hyperglycemia (> 150 mg/dL) or hypoglycemia (< 40 mg/dL)

Note: Potentially eligible subjects may be randomized and the silo placed according to the assigned study arm before all laboratory results are available. Laboratory values will be verified for eligibility prior to administration of DPR. Any ineligible subjects will be withdrawn from the study and may be replaced.

Randomization

The randomization schedule will be generated by the biostatistics department and the Principal Investigator (PI) will maintain a randomization log listing the subjects' ID and study arm assignment. Subjects will be randomized to either the DPR group or SoC group. If the subject is assigned to receive DPR, the ACRI Research Pharmacist will dispense the 1.5% Dianeal solution. The PI will calculate the dose to be distributed based on the subject's weight at the time of enrollment and administer the appropriate volume of 1.5% Dianeal solution as per instructions in the *Investigational Product* section.

Study Design and Procedures

This is a prospective double-arm study designed to evaluate the tolerability of direct peritoneal resuscitation (DPR) in neonates with gastroschisis. The experimental arm (DPR group) will receive adjuvant DPR with standard treatment for gastroschisis (staged silo closure). The control arm (SoC group) will receive standard treatment for gastroschisis only. All subjects will be placed in a silo shortly after birth and within 2 hours of admission to the NICU and subsequently serially reduced in silo with umbilical tape until the bowel contents are at the level of fascia and deemed suitable for closure.

A. SoC Group

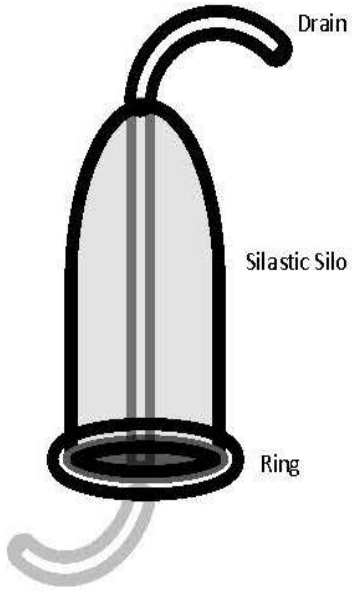
The SoC group will be placed in silo within 2 hours of admission to the NICU per standard practice. These subjects will have no change in current clinical management by the neonatologists or pediatric surgeons and will not receive peritoneal dialysis fluid.

B. DPR Group

The DPR group will be placed in a silo within 2 hours of admission to the NICU with a drain placed at the top of the silo as described below. At the time of silo placement for staged procedure, the JP drain will be placed intra-abdominally beneath the fascia at the base of the small bowel mesentery. Subjects will be treated with adjuvant direct peritoneal resuscitation (DPR) until the abdomen is closed, which is usually four to five days. No additional incisions will be made.

Set-up of Silo

The silo will be placed within 2 hours of admission to the NICU as per standard of care. Through the top of the silo a flat 10 mm JP drain will be placed and secured with suture and sterile, adhesive tape at the top of the silo to create a seal. This drain will allow for aspiration of peritoneal fluid for specimen collection and instillation of Dianeal 1.5% (DPR group only).



Drain manipulation

The JP drain will be sterilely placed through top of the silo at time of the silo placement into abdominal cavity. A closed system will be created using Medline One-link Needle-free IV connector to the drain to allow for sterile placement of the dialysate. There will not be any planned drain replacements. If the drain or silo replacement is necessary due to unforeseen circumstances, the abdomen will be prepped in standard sterile fashion and the silo with drain will be replaced in same manner as when it was initially placed. There will be no increased risk of underlying infection with placement of the silo or drain.

Set-up for DPR

The dialysate fluid will be placed in syringe under sterile conditions in the Research Pharmacy. The syringe will then be connected to the JP drain via a needle free IV connector. The connector will be cleaned with an alcohol wipe at the time of fluid instillation into the JP drain.

1. Instillation of fluid - Process will be repeated every 6 hours (± 30 minutes) until abdomen is closed.
    a. Fluid will be warmed at bedside using dry heat not to exceed 37°C/98°F.
    b. An initial bolus of 10 mL/kg of Dianeal 1.5% via the JP drain will be given. If tolerated, each subsequent bolus will be increased by 10 mL/kg of Dianeal 1.5% up to a goal infusion of 40 mL/kg of Dianeal 1.5% (to a maximum volume of 100 mL) as tolerated via the JP drain.
    c. The maximum dose that will be administered, based on a historical data (CHND), is 100 mL.
    d. Dialysate will dwell for 1 hour after instillation of fluid. Any excess fluid will then be removed via JP drain.
2. Data for DPR
    a. Blood samples will be obtained at the same time that routine laboratory values are performed. Supplementary research safety labs will require additional blood samples.
        i. Complete CBC, sodium, potassium, bicarbonate/CO_2, chloride, BUN, creatinine, calcium, phosphate, albumin, glucose and magnesium
        ii. Labs per standard of care are drawn each morning.
        iii. Monitoring of additional labs will be per the discretion of the NICU team if necessary for pertinent patient care and monitoring.
        iv. Heart rate, respiratory rate, blood pressure and pulse oximetry recordings will be recorded as part of the routine patient care. We will collect these measurements every 6 hours (± 30 minutes) at the time peritoneal fluid is infused.
    b. Volume of fluid instillation and removal (date/time) will be documented in the medical record.
    c. IV Fluids given

Antibiotic regimen for both treatment groups

- 5 days of ampicillin and gentamicin will be given.
- No additional doses beyond 5 days unless clinically indicated.
- Ampicillin Sodium: Q8H, IV (100 mg/kg q8)
- Gentamicin Sulfate: Q24H, IV (4 mg/kg q24)

No additional antibiotics will be given as part of standard care. Post-surgical antibiotics will be administered at the discretion of the surgeon as required.

Standardized treatment algorithms

To minimize inter-subject management variation and bias in the interpretation of the results the following standardized criteria or algorithms are provided:

i. Timing of abdominal closure/determination of readiness for closure
   - Serial reductions are performed with silastic silo placement for staged reduction using umbilical tape ties. The silo is assessed daily on morning rounds by the surgical team. Once the abdominal contents are at the level of the fascia, the abdomen is closed in the operating room. The average day to closure historically from CHND data is 5 days (Appendix C).

ii. Initiation and advancement of enteral feeds
   - Enteral feeding is begun after orogastric (OG) tube output has stopped and a bowel movement has occurred. OG tube output is checked at least every 4 hours (± 30 minutes) and/or before each feeding per NICU standard practice. Initiation of feeds is a clinical decision based on decreased gastric tube output, abdominal x-rays, and passing of stool. The initiation of enteral feeds is assessed daily on morning rounds by the neonatology team. Feedings start at an average of 7 days following abdominal wall closure. The advancement of enteral feeds will be based on standard practice at Arkansas Children's Hospital (Appendix D). Most feedings are started every six hours and advanced to every three hours as tolerated.

iii. Tapering of parenteral nutrition
   - Tapering of the parenteral nutrition is congruent with the increase in enteral feeding, which is calculated based on the amount of nutrition and calories needed. The combination of parenteral nutrition and enteral feeding will be 100 kcal/kg/day. As the enteral feeding is increased, the TPN will be reduced proportionately. This is assessed once daily on morning rounds by the neonatology team.

iv. Management of IVF/nutrition during DPR (i.e., changes in maintenance fluid or TPN rate during infusion)
   - The amount of IVFs is dependent on the subject's weight and calculated based on the volume of enteral feeds required to meet the subject's caloric needs. This is assessed daily on morning rounds by the neonatology team. IVF management changes will be made when clinically indicated by the neonatologists and guided by the subject's laboratory values. The current practice is not to replace the fluid lost during silo placement due to bowel edema often seen in these patients; thus, no additional changes are planned for the management of IVFs or nutrition during the intervention. The amount of dialysate fluid given will be documented in the medical record; it will dwell for 1 hour and then any remaining fluid will be removed.

Routine Laboratory Tests for both treatment groups

To reduce the risk of iatrogenic anemia and assure that excessive amounts of blood are not collected from any patient, the maximum allowable blood draw volumes are established per single phlebotomy collection. During routine daily lab draws, up to 1 mL of blood will be obtained for standard medical care.

All other standard care laboratory tests will be performed at the discretion of treating neonatologists. Routine daily labs for gastroschisis patients include:

- Complete Blood Count (CBC) with differential
- Magnesium
- Renal function panel (sodium, potassium, chloride, bicarbonate/CO_2, BUN, creatinine, calcium, phosphate, albumin, glucose)

Research Laboratory Tests

Additional research labs for safety monitoring will be drawn via heelstick, central/arterial line or venipuncture per NICU standard practice. The first capture of research labs should coincide with routine labs to avoid repeat blood draws. Up to 2 mL of blood for research may be drawn each day in addition to the routine daily labs.

SoC Group

A research lab for lactate only will be drawn every 24 hrs (± 30 minutes) through Post-Closure Day 1.

DPR Group

Additional research labs will be drawn every 6 hrs (± 30 minutes) for 24 hours after the maximum dialysate infusion volume is reached, then every 12 hrs (± 30 minutes) through Post-Closure Day 1. Research labs include:

- Lactate
- Sodium
- Potassium
- Glucose

Glucose via heelstick, central/arterial line or venipuncture per NICU standard practice will also be obtained within 1 hour prior to infusion and 1 hour (± 15 minutes) post-infusion for the first day of treatment.

The total amount of blood to be withdrawn per day, accounting for the additional research labs above for safety monitoring, will be up to 3 mL.

Ultrasound

We will perform trans-abdominal ultrasound imaging on all enrolled subjects from the time of abdominal wall closure until feedings have commenced. Additional imaging will be performed if the neonatology team has warranted a stop to feeding the neonate. This noninvasive modality will be used to determine categorization of intestinal motility. Abdominal ultrasound will be performed each morning at the bedside by the PI or other trained study personnel.

We will document the presence of intestinal motility with continuous recording of ultrasound in all four quadrants for 30 seconds. Clips will be stored from each abdominal quadrant with the linear probe. If bowel motility is not recognized by 3 weeks post-operative, then the imaging will be terminated. A separate computer workstation connected to the image server will be used for image viewing and data analysis. Images and videos will be reviewed for quality and assessment of motility. To assess motility, the investigators will identify all distinct bowel loops visualized in the video clips and count movements in each of the bowel loops identified in the clip to determine a motility count for each quadrant. Videos will be classified as poor, fair or good. Motility will be quantified as the total number of distinct peristaltic movements visualized in each abdominal quadrant over 30 seconds. Cumulative motility (CM) will be

calculated as the sum of motility from all four abdominal quadrants. Mean motility (MM) will be calculated as the mean number of distinct peristaltic movements per patient on each day of life imaged. A global descriptive score of bowel activity will also be assigned for each quadrant with the following categories: no, low, normal, or hyperactive peristalsis [20].

Data to be obtained (No. 1-13 are already obtained and available as part of the neonates' medical records):

All data collected as recorded by the NICU for the Children's Hospital Network Database (CHND) will be reviewed for the research. Data with an asterisks (*) are not included in the standard CHND database.

1. Demographics
    a. MRN, admit date, birth date, re-admission, gender, mother's zip code, birth weight, admit weight, gestation, birth head circumference
2. Transport and admission
    a. Referral source
    b. Morbidities and diagnoses present at admission
    c. Lines, tubes, and drains present at admission
3. Maternal, prenatal, perinatal (This is part of the neonates' medical record and will be abstracted from the neonates chart.)
    a. Maternal race/ethnicity, age, prenatal care, prenatal vaccination history* (as available) [21], any congenital anomalies that were diagnosed prenatally, maternal substance use history, infant or maternal toxicology screen results, maternal infection history* (including risk factors for infections (as available)) [21], maternal antenatal conditions, antenatal steroids, antenatal magnesium, prenatal ultrasound findings, obstetric antenatal conditions, multiplicity of births, delivery type, APGAR score, indications for C-section
4. Infection
    a. Blood stream infection, total ventilation days, surgical site infection, and ventilator-associated pneumonia, drain or catheter-related infections
5. Surgery
    a. Respiratory mode support with surgical time frame, lab values with surgical time frame, complications associated with surgical time frame, surgical procedures, complications
6. Interventions during this admission as recorded by the NICU for the Children's Hospital Network Database
7. Date of discharge from NICU
    a. Discharge disposition
8. Patients discharge to home/foster care
9. Mortality
10. GI
    a. Did this infant have functional or structural short gut syndrome at the time of discharge?
    b. Classification of gastroschisis at time of silo placement - Imaging to be taken at time of initial evaluation.
        i. Simple
        ii. Complex: atresia, stenosis, perforation, volvulus
        iii. Appearance

1. Pristine
2. Matted bowel with peel
3. Staining of amniotic fluid
4. Staining of bowel serosa

c. # of days of empiric antibiotics
d. Type/Staging of closure of gastroschisis
e. Complications associated with closure
f. Additional closure techniques(s)
g. Closure timing

11. Other complications
    a. Bacterial overgrowth, late ischemia, NEC, stricture, volvulus, malabsorption, transfer for bowel or liver transplant
12. Feeding and medications
    a. Medications and immunizations [21]
    b. Hyperalimentation
    c. Enteral feedings
        i. Route of feeding at initiation
        ii. Reached 100 kcal/kg/d
        iii. Route of feeding when reached 100 kcal/kg/d
            1. Type of gavage/gastrostomy tube feeding
        iv. Type of enteral nutrition when reached 100 kcal/kg/d
        v. Change in feeding regimen
            1. Date change was made
            2. Why change was made
13. Ultrasound
    a. Cumulative motility
    b. Mean motility
14. Additional data
    a. Gastrostomy tube residuals: date, time, and cc
    b. X-ray reads daily by radiology
    c. Reason and time of change in feeding regimen
    d. Stool output
15. Adverse events*
    a. The durability of treatment effectiveness as well as potential longer-term adverse events will be assessed via chart reviews of pediatric follow-up visits or follow-up phone calls up to 90 days after discharge.

Timeline

We estimate that after approval, it will take approximately 2-3 years to accrue and follow subjects as a single-site study and 6 months to analyze data and prepare manuscripts.

Calendar of Procedures and Assessments

Assessment	Screening (Day of Birth 0-12 hrs)	Staged Reduction (Day of Birth 0-24 hrs)	Day of Life 1-7	Day of Closure	Post-Closure Day 1	Post-Closure Day 2 until Discharge	Day of Discharge	Post-Discharge Follow-Up (up to 90 days)
Informed Consent	X							
Randomization	X							
Silo/JP Drain placement[1]	X							
Verify lab values for eligibility		X						
Vitals (HR, RR, BP/MAP, SpO2)	X[2]	X[2]	X[2]	X[2]	X[3]	X[3]	X[4]	
Weight	X	X	X	X	X			
Routine Labs[5]	X		X	X	X	X		
Research Labs[6 7]	X	X	X	X	X			
G-tube placement[4]	X[3]							
Instill DPR[8]		X	X					
Intake/Output		X[2]	X[2]	X[2]	X[3]	X[4]		
Glucose pre- & post-infusion[9]		X	X					
Bedside ultrasound					X	X[10]		
AE assessment[11]		X	X	X	X	X	X	X
Remove OG-tube & Initiate EBM/Formula[4]						X		
Chart Review or Phone Call								X

[1] Silo placement only or silo and JP drain placement per randomized group assignment
[2] Q6 hrs (± 30 min) for 48 hrs after maximum volume, then Q12 hrs (± 30 min)
[3] Q12 hrs (± 30 min)
[4] Per NICU Standard Practice
[5] All: CBC w/ Diff, Magnesium, Sodium, Potassium, Chloride, Bicarbonate/CO_2, BUN, Creatinine, Calcium, Phosphate, Albumin, Glucose, Q24 hrs (± 30 min)
[6] SoC Group: *Lactate only*, Q24 hrs (± 30 min) same time as Routine Lab
[7] DPR Group: *Lactate, Sodium, Potassium, Glucose*, Q6 hrs (± 30 min) for 24 hrs after maximum volume, then Q12 hrs (± 30 min)
[8] DPR Group: Q6 hrs (± 30 min), dwell for 1 hr, then remove excess fluid - 10 mL/kg initial bolus, then increase by 10 mL/kg up to 40 mL/kg (100 mL maximum volume)
[9] DPR Group only: Glucose within 1 hr prior to every infusion and 1 hr (± 15 min) every post-infusion for the first day (24hrs) of treatment
[10] Daily bedside ultrasound will be performed from post-closure Day 1 to time of full feeds and if feeds are stopped for any reason
[11] The clinical course of each AE should be followed until resolution, stabilization, or until it has been determined that the study treatment is not the cause.

Schedule of Procedures and Assessments

Screening (Day of Birth from 0-12 hours)

- Informed Consent
- Randomization
- Silo placement (within 2 hours of admission to the NICU)
  - JP drain placed and secured per randomization
- Vital signs: heart rate (HR), respiratory rate (RR), MAP/BP, pulse oximetry (SpO_2)
- Weight
- Routine Daily labs per NICU standard practice:
  - Complete CBC
  - Magnesium
  - Renal Function Panel (sodium, potassium, chloride, CO_2, BUN, creatinine, calcium, phosphate, albumin, glucose)
- Research lab (both groups):
  - Lactate
- G-tube placement per NICU standard practice

Staged Reduction Day 1 (Day of Birth from 0-24 hours)

- Verify laboratory values for eligibility
- Instill DPR for DPR group every 6 hrs (± 30 minutes)
- Blood glucose within 1 hour prior to infusion and 1 hour (± 15 minutes) post-infusion for the first 24 hrs of DPR
- Vital signs every 6 hrs (± 30 minutes): HR, RR, MAP/BP, SpO_2
- Weight
- Strict intake/output every 6 hrs (± 30 minutes)
- DPR Group research labs every 6 hrs (± 30 minutes):
  - Sodium
  - Potassium
  - Glucose
  - Lactate
- Adverse events

Day of Life 1 - Day of Life 7

- Instill DPR for DPR group every 6 hrs (± 30 minutes) until abdomen is closed
- Blood glucose within 1 hour prior to infusion and 1 hour (± 15 minutes) post-infusion for the first 24 hrs of DPR
- Vital signs every 6 hrs (± 30 minutes) for 48 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes): HR, RR, MAP/BP, SpO_2
- Weight
- Strict intake/output every 6 hrs (± 30 minutes) for 48 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes)
- Routine daily labs per NICU standard practice:
  - Complete CBC
  - Magnesium
  - Renal Function Panel (sodium, potassium, chloride, CO_2, BUN, creatinine, calcium, phosphate, albumin, glucose)

- SoC Group research lab (every 24 hrs (± 30 minutes) at the same time as routine daily labs:
  - Lactate
- DPR Group research labs every 6 hrs (± 30 minutes) for 24 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes):
  - Sodium
  - Potassium
  - Glucose
  - Lactate
- Adverse events

Day of Abdominal Closure (generally 3-5 days, up to Day 7)

- Vital signs every 6 hrs (± 30 minutes) for 48 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes): HR, RR, MAP/BP, SpO_2
- Weight
- Strict intake/output every 6 hrs (± 30 minutes) for 48 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes)
- Routine daily labs per NICU standard practice:
  - Complete CBC
  - Magnesium
  - Renal Function Panel (sodium, potassium, chloride, CO_2, BUN, creatinine, calcium, phosphate, albumin, glucose)
- SoC Group research lab (every 24 hrs (± 30 minutes) at the same time as routine daily labs:
  - Lactate
- DPR Group research labs every 6 hrs (± 30 minutes) for 24 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes):
  - Sodium
  - Potassium
  - Glucose
  - Lactate
- Abdominal closure per surgical standard practice
- Adverse events

Post-Closure Day 1

- Vital signs every 6 hrs (± 30 minutes) for 48 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes): HR, RR, MAP/BP, SpO_2
- Weight
- Strict intake/output 6 hrs (± 30 minutes) for 48 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes)
- Routine daily labs per NICU standard practice:
  - Complete CBC
  - Magnesium
  - Renal Function Panel (sodium, potassium, chloride, CO_2, BUN, creatinine, calcium, phosphate, albumin, glucose)
- Bedside ultrasound
- SoC Group research lab (every 24 hrs (± 30 minutes) at the same time as routine daily labs:
  - Lactate

- DPR Group research labs every 6 hrs (± 30 minutes) for 24 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes):
  - Sodium
  - Potassium
  - Glucose
  - Lactate
- Adverse events

Post-Closure Day 2 until Day of Discharge

- Vital signs every 12 hrs (± 30 minutes): HR, RR, MAP/BP, SpO_2
- Strict intake/output per NICU standard practice
- Routine labs per NICU standard practice
- Removal of OG-tube and initiation of EBM/Formula per clinical decision and NICU standard practice
- Bedside ultrasound until full feeds are achieved and if feeds are stopped for any reason
- Adverse events

Day of Discharge

- Vital signs: HR, RR, MAP/BP, SpO_2
- Hospital Discharge
- Adverse events

Post-Discharge Follow-up (up to 90 days following hospital discharge)

- Chart review or phone call
- Adverse events

Risks and Benefits

Both groups will have the same underlying risks secondary to gastroschisis repair, anesthesia and surgery independent of the silo placement. These risks include allergic reaction to medicines, breathing problems (including problems requiring intubation and ventilation), bleeding, infection, inflammation of peritoneum, organ injury, problems with digestion and malabsorption, dysmotility, and abdominal wall hernia.

As this is a novel procedure, the risk for infection secondary to placement and retention of the JP drain, for the DPR group, is unknown. However, given that the JP drain will be sterilely placed and secured to the silo bag under sterile conditions, we estimate that the risk of JP drain placement and retention in the silo would not be appreciably higher than the risk of infection secondary to standard gastroschisis repair (12.5%). Additionally we estimate that the risk for infection secondary to placement and retention of JP drain within the peritoneum beneath the fascia at the base of the small bowel mesentery would not be substantially higher than the risk of infection secondary to standard gastroschisis repair (12.5%).

Subjects may also have the risk of potential for loss of confidentiality. Measures to protect the confidentiality of study participants will be implemented as described in the Data Handling and Recordkeeping section below.

Additional risks for babies who undergo DPR treatment may include electrolyte imbalances, which will be monitored via laboratory values.

Babies in the DPR group are at risk for Encapsulating Peritoneal Sclerosis, allergic reaction to corn (including anaphylaxis), and possible reactions with insulin or other concomitant medications and treatments.

Other possible adverse reactions may include lactic-acidosis, fungal peritonitis, peritonitis bacterial, catheter-related infections, hypovolemia, hypervolemia, fluid retention, hypokalemia, hyponatremia, dehydration, hypochloremia, hypotension, hypertension, dyspnea, peritonitis, peritoneal cloudy effluent, vomiting, diarrhea, nausea, constipation, abdominal pain, abdominal distension, abdominal discomfort, Stevens-Johnson syndrome, urticaria, rash (including pruritic, erythematous and generalized), pruritus, myalgia, muscle spasms, musculoskeletal pain, generalized edema, pyrexia, malaise, infusion site pain, and catheter related complication.

Potential benefits for these subjects include earlier closure, fewer ventilator days, earlier feeding and decreased length of stay.

There will be no direct benefits to the study participants in the SoC group; however, knowledge gained from the study could potentially benefit subjects in the future as it guides us in best practices for pediatric patients with gastroschisis.

Subject Withdrawal from Study

Subjects' parent(s)/LAR may choose to withdraw from the study for any reason. Additionally, the investigator may choose to remove subjects from the study. This may occur for the following reasons:

- Serious adverse event believed to be related to investigational product
- Intolerable side effects
- Clinically significant laboratory abnormalities
- The investigator believes it is in the best interest of the subject to discontinue the study

Any subject withdrawing their consent to participate in the study or their authorization to use their protected health information will be withdrawn from the study. Neonates who are withdrawn from the study will no longer undergo any study-related procedures or data collection. Standard of care treatment will be continued.

Reasons why subjects are discontinued from the clinical trial will be documented on the Study Termination Form.

Safety Monitoring

Given the risk for fluid and electrolyte imbalances, close monitoring will be provided for the DPR group by using more frequent clinical and laboratory assessments in addition to standard NICU monitoring. Vital signs and strict intake and output will be monitored every 6 hrs for 48 hours after maximum dialysate infusion volume (100 mL) is reached, then every 12 hrs (± 30 minutes). Sodium, potassium, blood glucose and lactate levels will be monitored every 6 hours (± 30 minutes) via heelstick, central/arterial line or venipuncture per NICU standard practice for 24 hours after the maximum dialysate infusion volume is reached, then every 12 hrs (± 30 minutes) through Post-Closure Day 1.

Subject will also be monitored for the following potential adverse events:

1. Hypokalemia: If the potassium falls to <3.0, additional potassium will added to the IV fluid at the discretion of the treating and study physicians.
2. Lactic acidosis: Lactate levels will be monitored with laboratory checks at least every 12 hours during the treatment phase. Continued monitoring of lactic acidosis will include laboratory checks, fluid replacement, and stopping infusion of the dialysate fluid.
3. Hyperglycemia: During the first day (24 hrs) of treatment, blood glucose will be obtained within 1 hour prior to infusion and 1 hour (± 15 minutes) post-infusion in addition to routine daily assessments. The neonatologists will change IVFs to contain less dextrose as needed.
4. Hypovolemia: This will be treated with fluid replacement. Blood pressure monitoring and urine output assessment will guide management for amount of fluid replacement needed.
5. Peritonitis: This will be evaluated daily by examination of the effluent dialysate for any cloudiness. Cloudy fluid will be sent to the laboratory for cell count, gram stain, and culture. If the cell count is elevated, the subject will receive antibiotics as indicated. Subjects with confirmed peritonitis will be withdrawn from the study.
6. Definite (culture positive) sepsis: Neonates with active clinical sepsis will be excluded from the study by the hemodynamic parameter exclusion criteria (hypotension, hyper/hypoglycemia, lactic acidosis, etc.). During the dialysate infusion period, subjects who develop definite (culture positive) sepsis will be withdrawn from the study.
7. Acute Kidney Injury (AKI): AKI will be staged using the "Neonatal AKI KDIGO Classification" Table below (Selewski *et al* [22]). Subjects who develop AKI > Stage 2 will be withdrawn from the study.

TABLE 1 Neonatal AKI KDIGO Classification

Stage	SCr	Urine Output
0	No change in SCr or rise <0.3 mg/dL	≥ 0.5 mL/kg/h
1	SCr rise ≥ 0.3 mg/dL within 48 h or SCr rise ≥1.5–1.9 × reference SCr[a] within 7 d	<0.5 mL/kg/h for 6 to 12 h
2	SCr rise ≥2.0–2.9 × reference SCr[a]	<0.5 mL/kg/h for ≥ 12 h
3	SCr rise ≥3 × reference SCr[a] or SCr ≥2.5 mg/dL[b] or Receipt of dialysis	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

Differences between the proposed neonatal AKI definition and KDIGO include the following:
[a] Reference SCr will be defined as the lowest previous SCr value.
[b] SCr value of 2.5 mg/dL represents <10 mL/min/1.73m^2.

Individual Subject Discontinuation

If a subject develops any of the individual subject discontinuation criteria below, the study drug will be immediately discontinued:

- Positive blood culture
- Documented peritonitis
- Lactic acid > 5 mmol/L
- pH < 7.1
- Sodium < 125 mEq/L or > 150 mEq/L
- Potassium < 2.5 mEq/L
- Continued hyperglycemia > 250 for more than 12 hours
- Definite (culture positive) sepsis
- Stage 3 AKI [22]

Subjects who develop any of the individual subject discontinuation criteria will be evaluated and monitored until resolution of the adverse events and laboratory values have returned to baseline. These subjects will no longer receive DPR, but will continue with assessments per the schedule of procedures and assessments.

Study Discontinuation

The study will be stopped if more than 3 subjects in the DPR group develop any one of the individual subject discontinuation criterion above.

Adverse Events

For purposes of this study, the following will be considered adverse events of special interest if they occur before study completion:

1. Bradycardia: defined as a heart rate < 100 bpm for ≥ 20 seconds
2. Desaturation: defined as SpO_2 < 80% for ≥ 20 seconds
3. A sustained apnea event defined as lasting ≥ 20 seconds and coinciding with at least one of the following:
   - HR < 100 bpm
   - Desaturation (oxygen saturation < 80%)
4. Other AES of special interest have been adopted from England *et al.*'s adverse event tables for the Pediatric Trials Network (PTN) [23] (Appendix E).
5. Infections [21]

Definitions

Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious AE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Serious AE (SAE) means any untoward medical occurrence at any dose: An event is "serious" if it involves considerable detriment or harm to one or more persons (who may or may not be participants), or required intervention to prevent one or more persons from experiencing considerable detriment or harm. SAEs include:

- Death
- Life-threatening experience – Disease or condition where the likelihood of death is high unless the course of the disease/condition is interrupted or diseases/conditions with potentially fatal outcomes where the endpoint of the clinical trial analysis is survival
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in participant's offspring

- Any other important medical event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

Related

An event is "related" if more likely than not it was caused by the research activity.

Unexpected

An event is "unexpected" when its specificity, nature, severity or incidence is not accurately reflected in the consent form, protocol, or investigator's brochure previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe than initially expected.

Study Period

All AEs will be recorded by the Investigator from the time of the start of study drug through the end of the designated follow-up period. All AEs will be recorded on the AE CRF. All relevant historical medical conditions that are known/diagnosed prior to the administration of study drug(s) are to be recorded.

Abnormal Laboratory Values Defined as AEs

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Requires treatment, modification of study drug dose, or any other therapeutic intervention
- Is judged by the Investigator to be of significant clinical impact/importance
- Grade 3 or Grade 4 lab abnormalities regardless of significance

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an AE. If the laboratory abnormality was not a part of a diagnosis or syndrome, then the abnormality should be recorded as the AE.

Monitoring, Recording and Reporting of AEs

All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. SAEs that are still ongoing at the end of the study period must be followed for up to 30 days to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately to the Sponsor.

All subjects will be monitored for AEs during the study. Assessments may include monitoring the subject's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination; or other appropriate tests and procedures.

AE data collection and reporting, which are required as part of every study, are done to ensure the safety of subjects enrolled in the studies and those who will enroll in future protocols. AEs are to be reported in a routine fashion at scheduled times during the trial, such as with the annual continuing review to the IRB. Certain AEs must be reported in an expedited fashion to allow for timely monitoring of subject safety and care.

The reporting of these events depends on the characteristics of the event:

1. Seriousness (grading of event)
2. Relatedness to study treatment
3. Expectedness

Steps to Determine if the Event Requires Expedited Reporting:

1. Determine whether the adverse event is related to the investigational drug. Attribution categories are as follows:
   - Unrelated
   - Unlikely
   - Possible
   - Probable
   - Definite
2. Determine expectedness of event. Expected events are those previously identified resulting from administration of the agent. An adverse event is considered unexpected when the type or severity of the event is not listed in the package insert, protocol, or consent form.

Note: This includes all events that occur within 30 days of the last dose/use of protocol treatment. Any event occurring more than 30 days after the last dose that is possible, probably, or definitely attributable to the investigational drug must be reported according to the instructions above.

Expedited Reporting of AEs

Institutional Review Board Reporting

Only adverse events meeting the UPIRTSO (Unanticipated Problem Involving Risks to Subjects or Others) will need to be reported to the UAMS IRB within the required 10-day allotment of being notified of the event. UPIRTSO requires that an unanticipated problem meet the following qualifications: a) unanticipated or unexpected; b) related to the research; and c) involves new or increased risk to the subject(s). All other adverse events should be recorded and reported to the UAMS IRB at continuing review.

Sponsor Reporting

The Sponsor will be promptly notified of all SAEs that are related to the study intervention and unanticipated/unexpected. These SAEs will be reported to the Sponsor using the FDA MedWatch 3500A. All other SAEs will be reported to the Sponsor and FDA in the Annual Progress Report. The Sponsor will report events to FDA in accordance with 21 CFR 312.

Deaths that are related to research will be reported to the Sponsor immediately upon Investigator notification. A death due to a terminal condition of the research participant would be considered anticipated and not related to the research. THE SPONSOR WILL REPORT DEATHS TO FDA IN ACCORDANCE WITH 21 CFR 312.

Monitoring

Clinical site monitoring will be conducted by the UAMS Office of Research Regulatory Affairs (ORRA) to ensure that the rights and well-being of trial participants are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and applicable regulatory requirements.

Monitoring specialists from ORRA will conduct periodic on-site, comprehensive monitoring as determined by a protocol-specific monitoring plan, which will be provided by the ORRA Monitoring Unit.

Data Handling and Recordkeeping

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a file on a password-protected computer in the principal investigator's locked office. The data files will be kept in a separate file on the password-protected computer in the principal investigator's locked office. The only individuals who will have access to the code and information that identifies the subject in this study will be limited to investigators on this study. All data will be de-identified after analysis is complete by destroying the code key. De-identified data will be maintained as per UAMS and ACRI policy (currently all data will be kept until the last subject is 21 years of age plus 2 years) and destroyed per institutional guidelines.

All ultrasound studies will be transferred and stored on a secure image server located in the PI's office. The studies will be labeled prior to performing the study with a coded identification number based on the patients MRN. A separate computer workstation connected to the image server will be used for image viewing and data analysis. The ultrasounds will be reviewed on this separate password-protected computer only viewed by study personnel. All data will be de-identified after analysis is complete by destroying the code key. De-identified data will be maintained as per UAMS policy (currently seven years after publication) and destroyed per institutional guidelines.

Data Analysis

Demographic variables will be assessed for differences between groups. Categorical variables will be examined using Fisher's Exact Test or Chi Square Test. Continuous data will be examined using Students' T-test. All tests will be two-sided assuming a significance level of 5%. The dependent variable will be tested to ensure the assumption of normality is met.

The primary outcome measure is time to full enteral feeds of 100 kcal/kg/day. Using a two-sample t-test, we estimated that a sample size of 20 in each of the two groups will yield at least 80% power to detect a 6-day difference in mean time to goal enteral feeds (100 kcal/kg/day) assuming a common standard deviation of 7 and a two-sided significance level of 5%.

The proposed data analyses and sample size calculations were conducted with the support of statisticians at ACRI using SAS® Software, Version 9.4[24].

Ethical Considerations

This study is to be conducted according to applicable government regulations and Institutional research policies and procedures.

The parent(s)/LAR of each potential subject identified as meeting inclusion criteria for this study will be approached to discuss participation in this study by trained study personnel. The person obtaining consent will go over the informed consent comprehensively with the parent(s)/LAR. The risks and rationale of this study will be outlined and all questions will be answered. The volunteer natures of this project will be emphasized, including uninhibited withdrawal from the study at any time. No coercion or undue influence will be used in the consent process. A copy of the signed consent will be given to the subject's parent(s)/LAR, and the informed consent process will be documented in each subject's research record in a separate process note.

Ways of consenting parent(s)/LAR:

1. Mother or father (if mother and father are married)/LAR consented prenatally in OB/GYN clinic.
2. Mother or father (if mother and father are married)/LAR consented after birth via faxed consent to the OB unit and returned to PI. The faxed consent will then be witnessed by bedside nurse.
    a. The person obtaining consent will fax a consent form to the OB unit and conduct the consent process conversation by phone once the mother or father/LAR has the form in hand.
    b. After the person obtaining consent has verified that all questions have been answered, the mother or father/LAR will sign the consent and it will be faxed back.
    c. The person conducting the consent process will then sign the form, and a signed copy of this form will be given/sent to the mother or father/LAR.
    d. No research-related activities will be performed until the signed and witnessed consent form is received by ACH study personnel.
3. Consent obtained at bedside from mother or father (if mother and father are married)/LAR.

Dissemination of Data

This clinical trial will be registered at ClinicalTrials.gov, and information will be updated in a timely manner.

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant.

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Appendix A

Dianeal Solution

Dianeal PD-2 Peritoneal Dialysis Solutions are sterile, nonpyrogenic and contain no bacteriostatic or antimicrobial agents or added buffers.

Each 1000 mL of Dianeal Peritoneal Dialysis Solution contains:

Components	Contents
Glucose, BP	1.5 **%** - 15.0 g
Sodium Chloride, BP	5.38 g
Sodium Lactate	4.48 g
Magnesium Chloride Hexahydrate, BP	50.8 g
Calcium Chloride Dihydrate, BP	PD-2 257 mg
Water For Injections, BP	QS

Dianeal PD-2 Peritoneal Dialysis Solution with 1.5% Glucose:

Components	Contents
Glucose .H2O	76 mmol/L
Sodium	132 mmol/L
Calcium	1.75 mmol/L
Magnesium	0.25 mmol/L
Chloride	96 mmol/L
Lactate	40 mmol/L
Approximate Osm	346 mOs

Appendix B

Gastroschisis

Initial Treatment

Place infant right side down
- Replogle to LIS
- Cover lower body with bowel bag
- Antibiotics: Ampicillin & Gentamicin

Admission labs

Silo Placement at Bedside

Preparation
- Ensure there are no perforations, ischemic bowel, atresias
- Make sure Replogle is in place and functional
- Lay patient on right side if bowel appears ischemic

Equipment
- Gather from the OR: Concept battery powered pencil cautery.
- Gather from NICU: Betadine, umbilical artery catheterization tray, and silos size 3-6 (box in NICU).

Technique Tips
- Splay mesentery to avoid kinking
- If opening fascia, inject lidocaine first
- Cauterize fascia on top of the back end of a forcep
- Open fascia upward first about 0.5 cm
- Try not to cut skin unless needed
- Measure defect & pick silo size resulting in 1 cm overlap
- Lubricate silo with sterile saline
- Caution during placement → Liver & Spleen
- Ensure contents move easily within silo and are viable
- Consider milking meconium distally out of colon, succus proximally into Replogle and emptying bladder with palpation.

Silo Reduction
- Carefully apply umbilical or trach tape to silo sequentially daily.
- Do not clamp bowel
- Once at level of fascia, patient is taken to operating room for closure.

Post-Closure

a. When Replogle output clears and decreases, start formula or EBM and follow NICU protocols.
b. Continue Zantac or Prevacid
c. Glycerin enemas BID until stooling spontaneously

Failure to tolerate initiated diet 3-4 wks after closure → Contrast Enema to rule out atresia or meconium plugs.

Appendix C

NICU Feeding Protocols

Arkansas Children's Hospital
Recommended Neonatal Enteral Feeding Guidelines
Approximately >1500 grams and > 32 weeks

Patient Name: _____

Date of Birth: _____

Birth Weight: _____

Day of Feeds	Date	Weight	Composition	Volume
1			20 BM/20 PF	20 mL/kg/d
2			20 BM/20 PF	40 mL/kg/d
3			20 BM/20 PF	60 mL/kg/d
4			20 BM/20 PF	80 mL/kg/d
5			22 BM/22 PF	80 mL/kg/d
6			22 BM/22 PF	100 mL/kg/d
7			24 BM/24 PF	100 mL/kg/d
8			24 BM/24 PF	120 mL/kg/d
9			24 BM/24 PF	140 mL/kg/d
10			24 BM/24 PF	150 mL/kg/d

BM = Breast Milk
PF = Preterm Formula
B = Beneprotein
Goal is to begin trophic feeds by the first 2–7 days of life at the descretion of the neonatologist.

This form is not a permanent part of the medical record

Appendix D

Adverse Event Table – Laboratory Values [23]

	Adverse Event		Serious Adverse Event	
	Conventional Units	**International System (SI)**	**Conventional Units**	**International System (SI)**
Electrolytes				
Hyponatremia	120–124 mEq/L	120–124 mmol/L	<120 mEq/L	<120 mmol/L
Hypernatremia	150–159 mEq/L	150–159 mmol/L	>159 mEq/L	>159 mmol/L
Hypokalemia	2.0–2.5 mEq/L	2.0–2.5 mmol/L	<2.0 mEq/L	<2.0 mmol/L
Hyperkalemia	7–7.9 mEq/L	7.0–7.9 mmol/L	>7.9 mEq/L	>7.9 mmol/L
Bicarbonate: Low	12–14 mEq/L	12–14 mmol/L	<12 mEq/L	<12 mmol/L
Bicarbonate: High	35–45 mEq/L	30–45 mmol/L	>45 mEq/L	>45 mmol/L
Hypocalcemia (ionized)	4.1–4.2 mg/dL	0.7–1.05 mmol/L	<4.1 mg/dL	<0.7 mmol/L
Hypercalcemia (ionized)	5.4–5.7 mg/dL	1.3–1.6 mmol/L	>5.7 mg/dL	>1.6 mmol/L
Renal				
BUN	60–100 mg/dL	21.42–35.7 mmol/L	>100 mg/dL	>35.7 mmol/L
Creatinine	1.5–2.5 mg/dL	132.6–221 µmol/L	>2.5 mg/dL	>221 µmol/L
Endocrine				
Hypoglycemia	25–36 mg/dL	1.4–2 mmol/L	<25 mg/dL	<1.4 mmol/L
Hyperglycemia	250–500 mg/dL	13.9–27.8 mmol/L	>500 mg/dL	>27.8 mmol/L
Gastrointestinal				
Aspartate aminotransferase	200–1000 U/L	3.34–16.7 µkat/L	>1000 U/L	>16.7 µkat/L
Alanine aminotransferase	200–1000 U/L	3.34–16.7 µkat/L	>1000 U/L	>16.7 µkat/L
Alkaline phosphatase	1000–1400 U/L	16.4–23.4 µkat/L	>1400 U/L	>23.4 µkat/L
Conjugated bilirubin	3-10 mg/dL	51.3–171 µmol/L	>10 mg/dL	>171 µmol/L
Gamma-glutamyl transferase	100–125 U/L	1.7–2.1 µkat/L	>125 U/L	>2.1 µkat/L
Hypertriglyceridemia	500–1200 mg/dL	5.7–13.6 mmol/L	>1200 mg/dL	>13.6 mmol/L
Hematologic				
Leukopenia	0.5–2 × 103/µL	0.5–2 × 109/L	<0.5 × 103/µL	<0.5 × 109/L
Leukocytosis	30-50 × 103/µL	30-50 × 109/L	>50 × 103/µL	>50 × 109/L
Anemia: hemoglobin	7–9 g/dL	70–90 g/L	<7 g/dL	<70 g/L
Anemia: hematocrit	20–26%	0.24–0.26	<20%	<0.24
Polycythemia: hemoglobin	23–24 g/dL	230–240 g/L	>24 g/dL	>240 g/L
Polycythemia: hematocrit	66–70%	0.66–0.7	>70%	>0.7
Thrombocytopenia	50–100 × 103/µL	50–100 × 109/L	<50 × 103/µL	<50 × 109/L
Thrombocytosis	450–1000 × 103/µL	450–1000 × 109/L	>1000 × 103/µL	>1000 × 109/L
Prothrombin time	18–22 seconds	18–22 seconds	>22 seconds	>22 seconds
Activated partial thromboplastin time	79–101 seconds	79–101 seconds	>101 seconds	>101 seconds
Lactate	45.1–90.1 mg/dL	5–10 mmol/L	>90.1 mg/dL	>10 mmol/L
Musculoskeletal				
Creatine kinase	470–600 U/L	7.9–10 µkat/L	>600 U/L	>10 µkat/L
Respiratory				
Acidosis: pH	7.10–7.19	7.15–7.19	<7.10	<7.15
Alkalosis: pH	7.50–7.60	7.50–7.60	>7.60	>7.60
pCO_2: low*	25–30 mEq/L	25–30 mEq/L	<25 mEq/L	<25 mEq/L
pCO_2: high*	55–65 mEq/L	55–65 mEq/L	>65 mEq/L	>65 mEq/L
Base Excess: low*	-10 – -15 mEq/L	-10 – -15 mEq/L	>-15 mEq/L	>-15 mEq/L
Base Excess: high*	+5 – +10 mEq/L	+5 – +10 mEq/L	>+10 mEq/L	>+10 mEq/L

*Laboratory values added to the original table

Adverse Event Table – Clinical Entities [23]

	Adverse Event	Serious Adverse Event
Gastrointestinal		
Necrotizing enterocolitis		Bell Stage II or III
Intestinal perforation		Intra-abdominal free air without preceding pneumatosis
Musculoskeletal		
Fracture	Fracture treated with immobilization	Fracture with any surgical intervention needed or known lasting sequelae
Respiratory		
Respiratory failure		Initiation of mechanical ventilation or some defined change
Pneumothorax	Present but no intervention required	Intervention required (e.g., chest tubes, sclerosis therapy and/or operative)
Apnea		Requiring initiation of mechanical ventilation
Pulmonary hypertension		Present and initiation of medical therapy to treat pulmonary hypertension (e.g., nitric oxide, milrinone, sildenafil)
Neurological		
Seizure		Present and treated with anticonvulsant
Intraventricular hemorrhage		Grade 3-4
Periventricular leukomalacia		Present on imaging
Cardiology		
Hypotension		Requiring pressors
ECG QTc prolongation	460 – 485 ms	> 485 ms
Supraventricular tachycardia	Episode resolves spontaneously or with vagal maneuvers	Requiring medical drug therapy or electroconversion to revert to sinus rhythm
Infectious Disease		
Wound infection	Requiring only local intervention (e.g., topical antimicrobial)	Requiring systemic antimicrobial therapy or surgery
Urinary tract infection		Positive urine culture treated with systemic antibiotics or antifungals
Cellulitis	Requiring only local intervention (e.g., antimicrobial)	Requiring systemic antimicrobial therapy or surgery
Bloodstream infection		Positive blood culture requiring systemic antimicrobial
Meningitis		Positive cerebral spinal fluid culture requiring systemic antimicrobial
Ophthalmologic		
Conjunctivitis	Requiring only local intervention (e.g., topical antimicrobial)	Requiring systemic antimicrobial therapy or surgery
Retinopathy of prematurity	Any stage	Any stage requiring surgical or medical intervention
Otolaryngology		
Hearing impairment		Confirmed hearing loss, either unilateral or bilateral
Drug mediated		
Infusion related reaction	Mild transient reaction or reaction that responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids)	Prolonged reaction that does not respond promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids) or life-threatening reaction that requires urgent intervention
Infusion site extravasation	Erythema with or without associated symptoms (e.g., edema, pain, induration, phlebitis)	Significant tissue injury leading to ulceration, necrosis, operative intervention indicated, or urgent intervention indicated
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching, lipodystrophia, edema)	Significant tissue injury leading to ulceration, necrosis, operative intervention indicated, or urgent intervention indicated
Allergic reaction	Transient flushing, rash, drug fever that responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics)	Prolonged reaction that does not respond promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids) or life-threatening reaction that requires urgent intervention
Anaphylaxis	Acute onset of illness with skin and/or mucosal tissue manifestations and either respiratory compromise or hypotension that requires parental medication intervention	Acute onset of illness with skin and/or mucosal tissue manifestations and either respiratory compromise or hypotension that is life-threatening and requires urgent intervention