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JOURNEY TO MAGNET EXCELLENCE
AMERICAN NURSES CREDENTIALING CENTER

Treating infants in the NIH Clinical Center: The GM1 Experience

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&

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NIH Clinical Center Research Hospital Board
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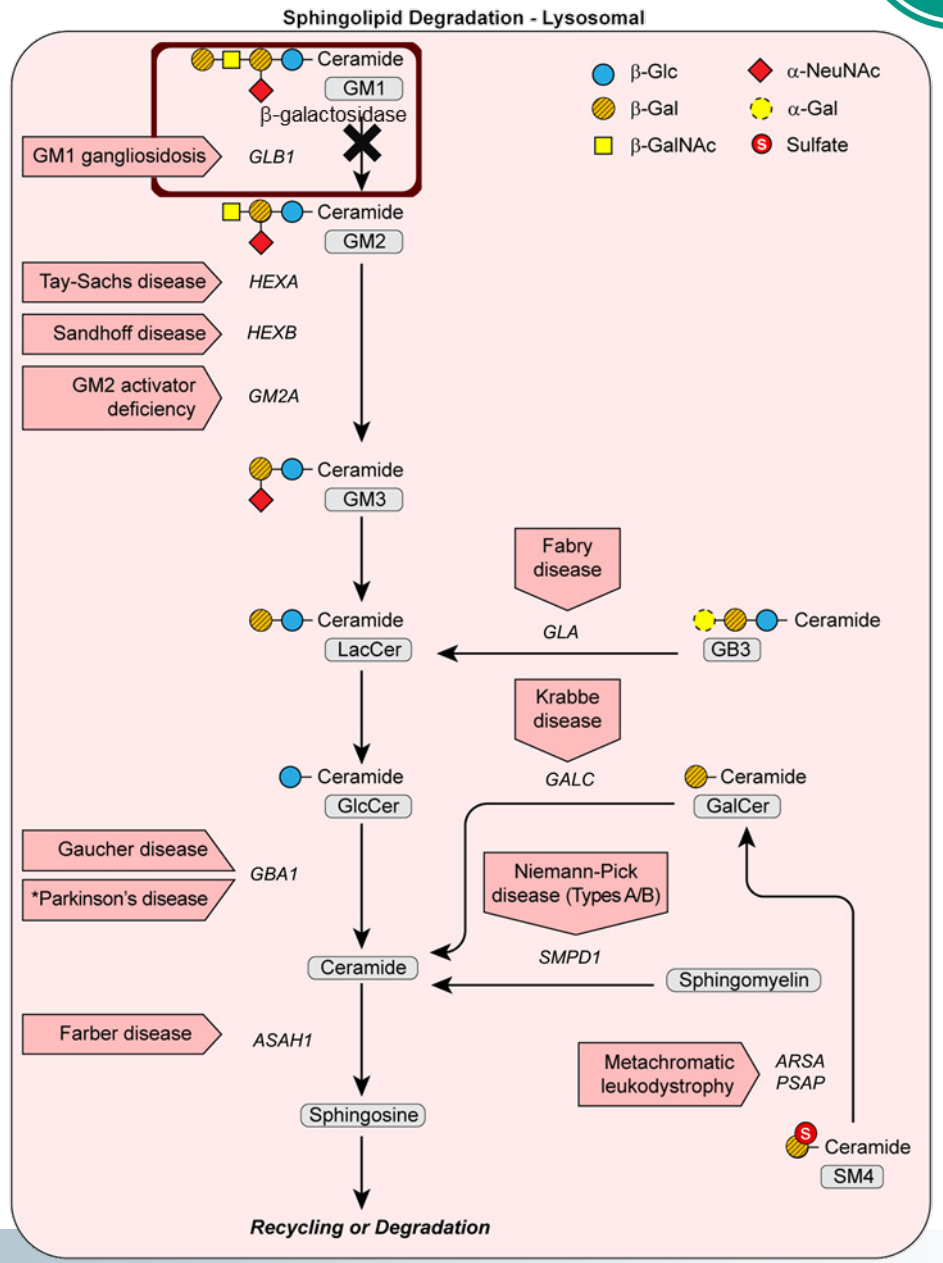
Lysosomal Storage Disorders

- Multisystem diseases characterized by lysosomal dysfunction
- There are more than 70 LSDs
- LSDs are inherited, most are autosomal recessive
- Most LSDs have a progressive neurodegenerative clinical course
- LSDs have symptom onset in infancy, childhood and some into adulthood
- LSDs are individually rare but collectively affect 1 in 5,000 live births

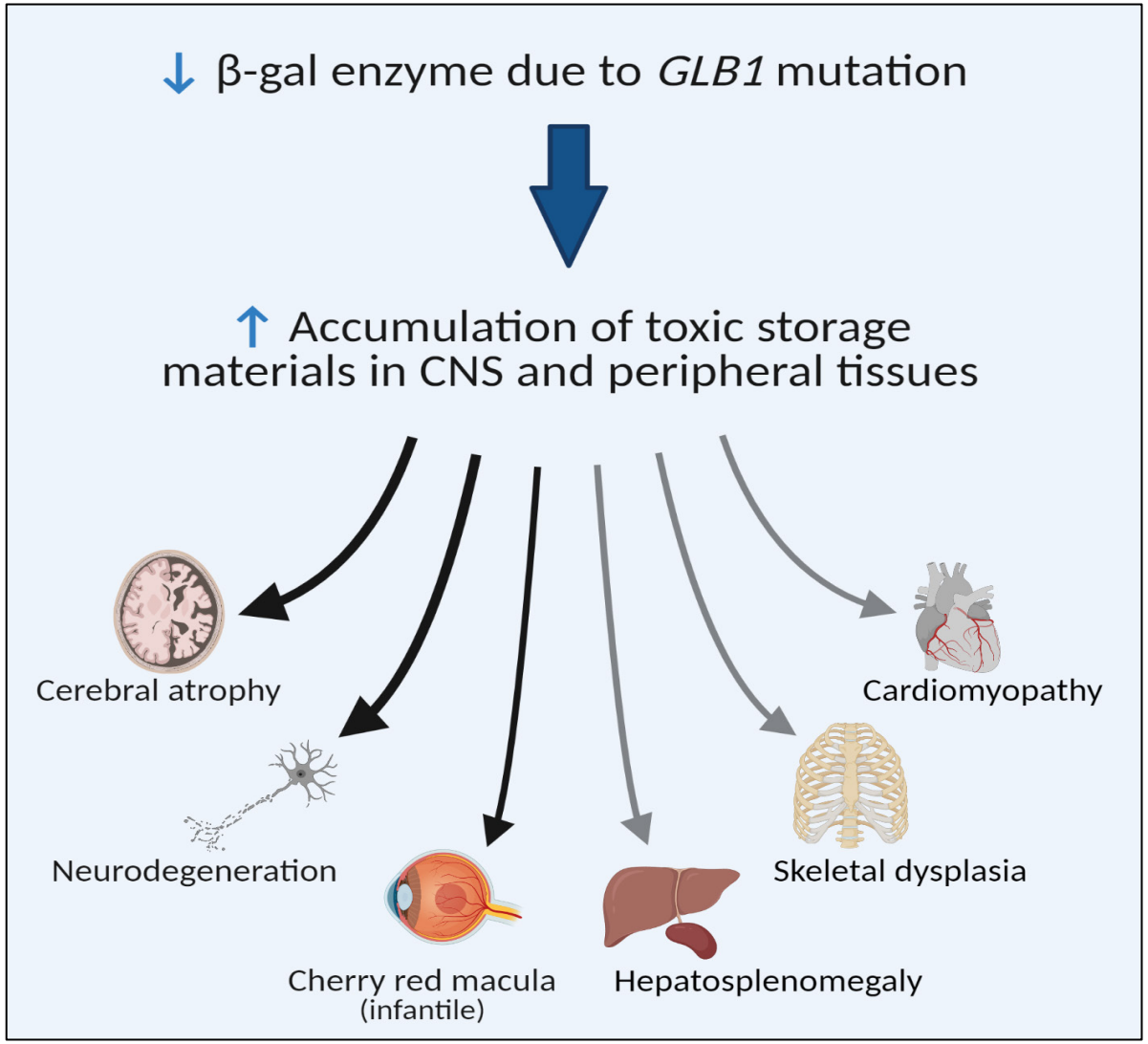
Platt, F.M. *et al*. (2018) Lysosomal storage diseases*Nat. Rev. Dis. Primers* doi.org/10.1038/s41572-018-0025-4

GM1 gangliosidosis

- GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by biallelic mutations in *GLB1* producing a deficiency in the hydrolytic enzyme lysosomal β-galactosidase
- Like its more well-known cousin, Tay-Sachs disease, GM1 gangliosidosis is a rare, uniformly fatal, neurodegenerative disorder that has no approved therapies
- The disorder is pan-ethnic, with an incidence of ~1 per 200,000 live births and more common in isolates in Malta, Brazil and among the Roma where there are founder mutations
- Newborn screening is not yet available for GM1



GM1 gangliosidosis is a multi-system disorder but predominantly affects the CNS



GM1 gangliosidosis is a disease continuum

Residual enzyme activity

Disease severity

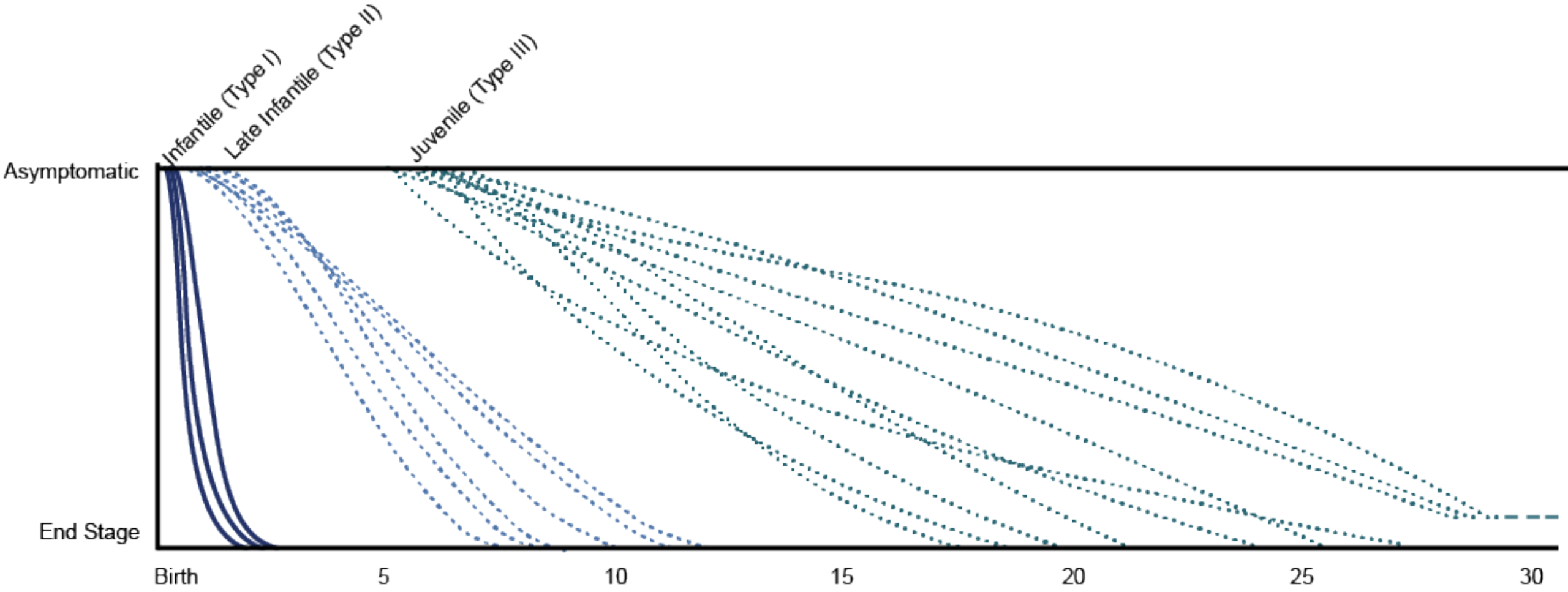
Type I (Infantile)
- Onset <6 months
- Hypotonia
- Developmental arrest
- Hepatosplenomegaly
- Cherry red macula
- Seizures
- Skeletal changes
- Death at <2 years

Type II (Late-Infantile)
- Onset 12-24 mos.
- Impaired ambulation
- Lack of, or regression of speech
- Decreased cognition
- Variable skeletal disease
- Seizures
- Death in mid-teens

Type II (Juvenile)
- Onset 3-6 years
- Impaired ambulation
- Progressive studdering or dysarthria
- Decreased cognition
- Variable skeletal disease
- Survival into 4th decade

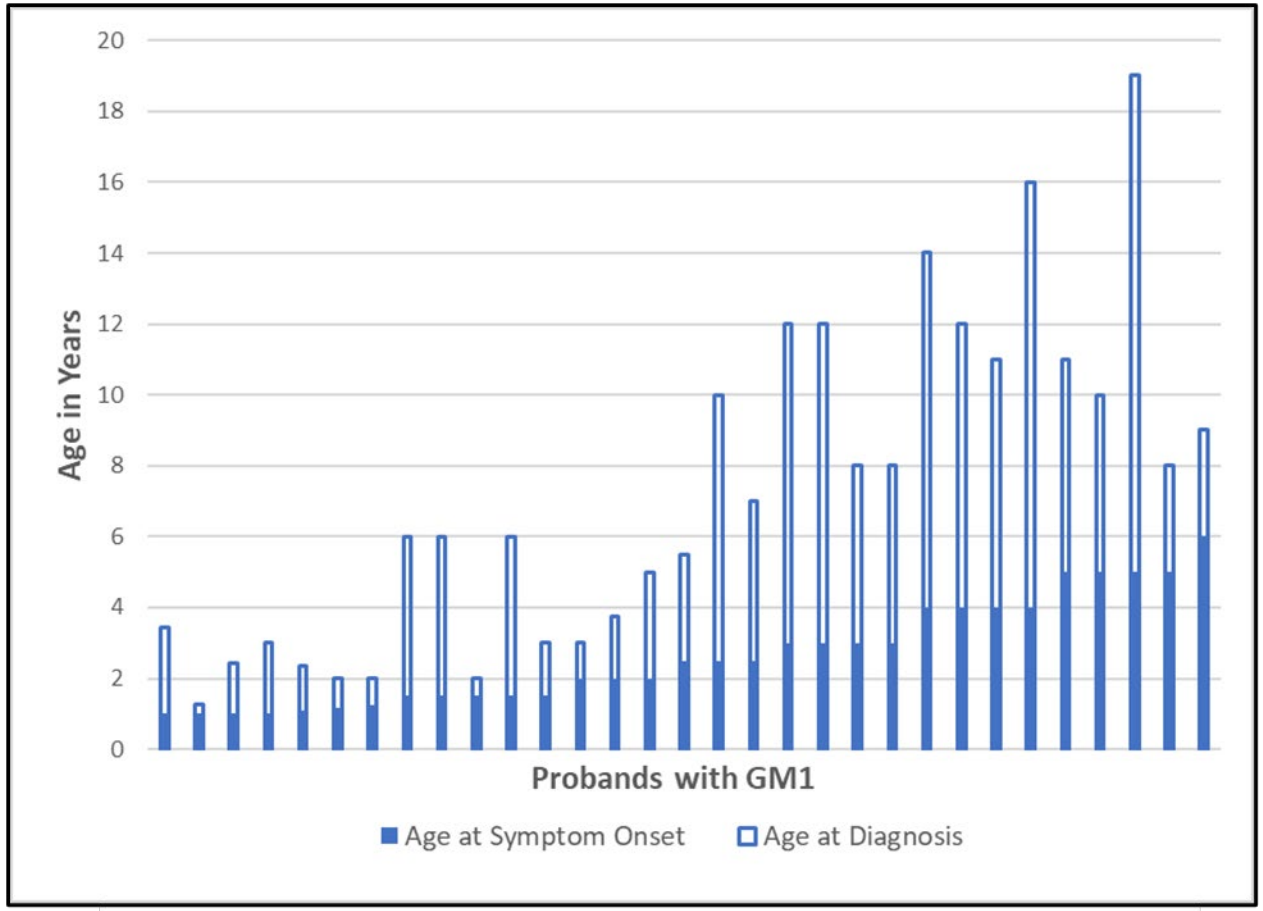
Type III (Adult)
- Gait disturbance
- Dystonia, dysarthria
- Decreased cognition
- Age at death variable

Later onset of disease means greater variability in disease progression



Natural history study at NIH over 10 years (02-HG-0107)

- **41 patients (30 probands)**
  - 17 late-infantile
  - 24 juvenile
- **Median time to diagnosis**
  - 17.5 months Late-infantile
  - 10 years Juvenile
- Adaptive behavior plateaus then declines over time
- Progressive brain atrophy tracks with declines in behavior and cognition
- Elevation of a unique penta-saccharide biomarker can provide a “read out” of treatment efficacy



AAV9*GLB1* Study Design: First-in-human, Phase 1/2 Study

Open-label, single-arm trial (NCT03952637, IND 18831)

STAGE 1: Dose Ranging

High-Dose
4.5×10^{13} vg/kg
(n=3)

Low-Dose
1.5×10^{13} vg/kg
(n=6)

Type II: Late-infantile/Juvenile:
- *3-year assessment*
- *2-year long term follow-up*

High-Dose
4.5×10^{13} vg/kg
(up to 3)

Low-Dose
1.5×10^{13} vg/kg
(n=2)

Type I: Early-infantile:
- *1-year assessment*
- *4-year long term follow-up*

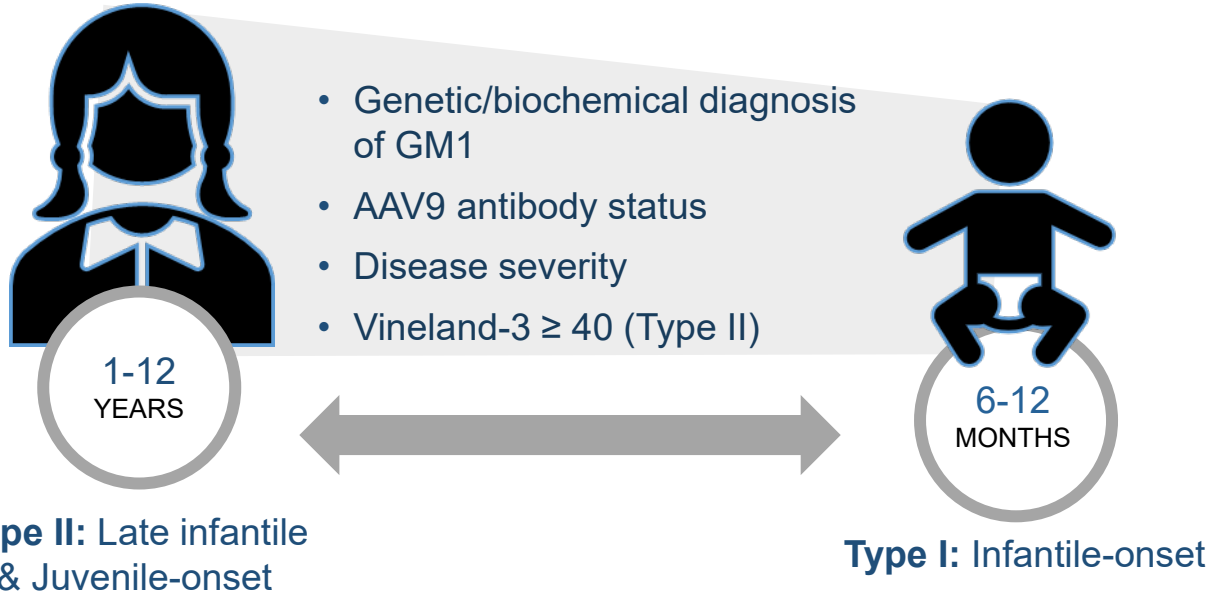
STAGE 2: Efficacy & Safety Study

Registrational Study using Optimal Dose from Stage 1

All patients received immune modulation with rituximab, sirolimus and glucocorticoids.

AAV9*GLB1* Study: Key Eligibility Criteria and Study Endpoints

Key Patient Eligibility Criteria



- Genetic/biochemical diagnosis of GM1
- AAV9 antibody status
- Disease severity
- Vineland-3 ≥ 40 (Type II)

Key Study Endpoints

- Safety and tolerability
- Disease severity by Global Clinical Impressions Scale
- Upright and Floor Mobility Scales
- Developmental changes assessed by the Vineland-3 Adaptive Behavior Scale and Bayley Scales of Infant Development
- Changes in brain volume by MRI and *N*-acetyl-aspartate (*NAA*) by MRS *(after 1 year)*[1]
- Biomarkers of disease (β-galactosidase enzyme activity in serum, GM1 ganglioside in CSF, and a pentasaccharide biomarker in serum, urine and CSF)

1. Regier, DS et. al. *Am J Med Genet A* 2016;170(3):634-44.

“First-in-Human” May 8, 2019

https://www.genome.gov/news/news-release/how-do-you-toast-a-gene-therapy-trial-with-tea

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Subject Demographics

Participants				Dose		Gene Transfer	
Demographics	**Disease Onset**	**Age at Diagnosis (months)**	**Genotype**	**Dosing Cohort**	**Dose (vg/kg)**	**Age (months)**	**Weight (kg)**
5/2019 to 6/2021 (N=9)							
EA: F/Asian	Juvenile	36	c.245C>T, c.367G>A	Low Dose	1.5×10^{13}	120	25.6
Pt1: M/White	Juvenile	12*	c.602G>A, c.481T>G	Low Dose	1.5×10^{13}	45	18.3
Pt2: M/Middle Eastern	Late infantile	23	c.967C>G, c.1479G>T	Low Dose	1.5×10^{13}	32	17.9
Pt3: M/White	Late infantile	44	c.75+1G>C, c.245C>T	Low Dose	1.5×10^{13}	68	17
Pt4: F/White	Late infantile	29*	c.75+1G>C, c.245C>T	Low Dose	1.5×10^{13}	47	14.9
Pt5: F/White	Late infantile	29*	c.75+1G>C, c.245C>T	Low Dose	1.5×10^{13}	47	14.4
Pt 6: F/White	**Juvenile**	**84**	**c.602G>A, c.622 C>T**	**High Dose**	**4.5×10^{13}**	**88**	**22.9**
Pt7: F/White	**Juvenile**	**52**	**c.602G>A, c622 C>T**	**High Dose**	**4.5×10^{13}**	**58**	**21.7**
Pt8: M/White[1]	**Juvenile**	**58**	**c.977C>T, c.1784G>C**	**High Dose**	**4.5×10^{13}**	**74**	**13.0**
To Date (N=11)							
Pt9: F/White	Infantile	7	c.1480-2A>G, c.622C>T	Low Dose	1.5×10^{13}	9	8.3
Pt10: F/White	Infantile	3*	c.176G>A, c.765G>C	Low Dose	1.5×10^{13}	7	6.5

*Diagnosed based on sibling diagnosis

Teamwork

- 14 Departments
- Four Services
- Two Organizations
- One Research Team

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Gene Therapy Timeline

Weeks 3 to 4

Baseline testing: **3 OUTPATIENT days in 1NW Day Hospital**

Baseline testing: **2 INPATIENT nights on 1NW**

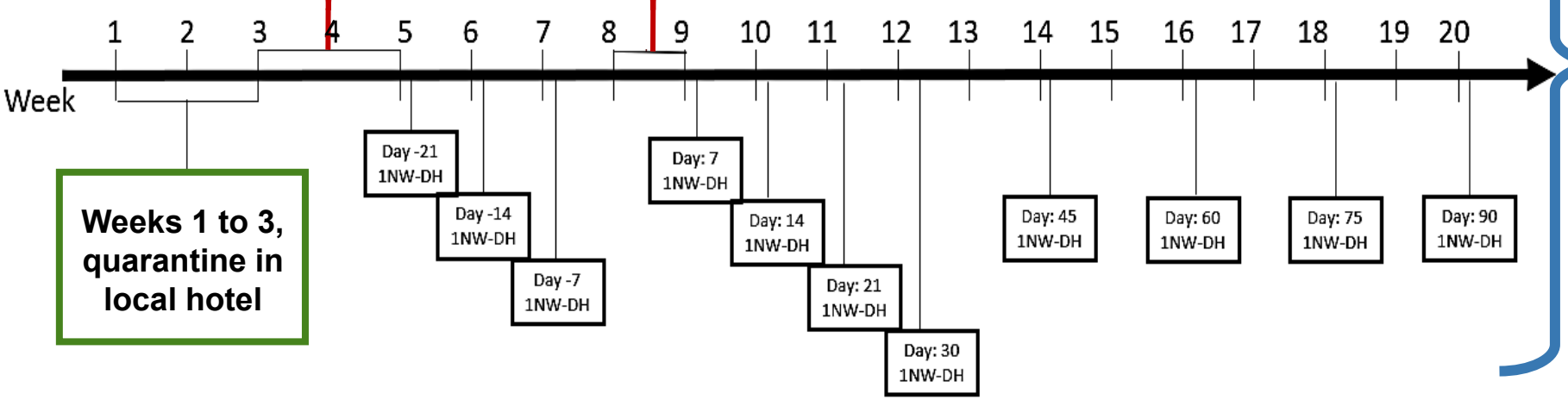
- Co-managed by PAC team
- Awake and extended overnight EEG
- Sedated procedures at the NIH
- Brain MRI w/ fMRI and MRS
- Abdominal MRI
- Lumbar Puncture

OUTPATIENT PICC line placement at CNMC

Weeks 8 and 9

at least 5 INPATIENT nights on 1NW

Day-1: Admit 1NW Inpatient Unit
Day 0: 1NW Inpatient Unit - Gene Transfer Agent Administration
Days 1-5: Co-managed with PAC team and monitored for 48 hours and while asleep during the remainder of the admission.
At day 5 the subject may remain inpatient until day 7 or discharged to outpatient at the discretion of the PI



Weeks 1 to 3, quarantine in local hotel

- Multiple blood draws
- Anesthesia
- Lumbar Punctures
- Rituximab IV infusions
- Sirolimus
- AAV9 GLB1 IV Infusion

Failure Mode Effect Analysis (FMEA)

- Pre-enrollment
- Pre-arrival

Area 1

Baseline Testing

Area 2

Procedures

Area 3

Immune Modulation Treatment

Area 4

Discharge to a local area

Area 5

Equipment

Area 6

Emergency Responses

Area 7

Education, training & competencies

Area 8

194 Potential risks

8 Major areas

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Failure Mode Effects Analysis

- Emergency Response
- System Review
- Department Preparedness
- Policies & Procedures
- Clinical Competence

Areas of Nursing Gaps

Area 6: Equipment

- Infant Emergency Supplies
- Infant Cart
- Infant Bottles
- Bottle Warmers
- Diaper Scales
- Breast Pumps
- Blood collection volume reduction strategies

Area 7: Emergency Response

- Didactic
- Training in care of infants
- New SOP/ Procedures
- High Risk Medications
- Nursing emergency Response

Area 8: Education, Training & Competencies

- Simulation in lab and in situ
- Hands on equipment training
- Team dynamics
- Communication
- Roles & Responsibilities

Area 6: Equipment

- Infant Supply Cart (1NW & ICU)
- Breast Pump
- IV start equipment
- Blood volume reduction strategies

Monitoring equipment

IV & CVAD

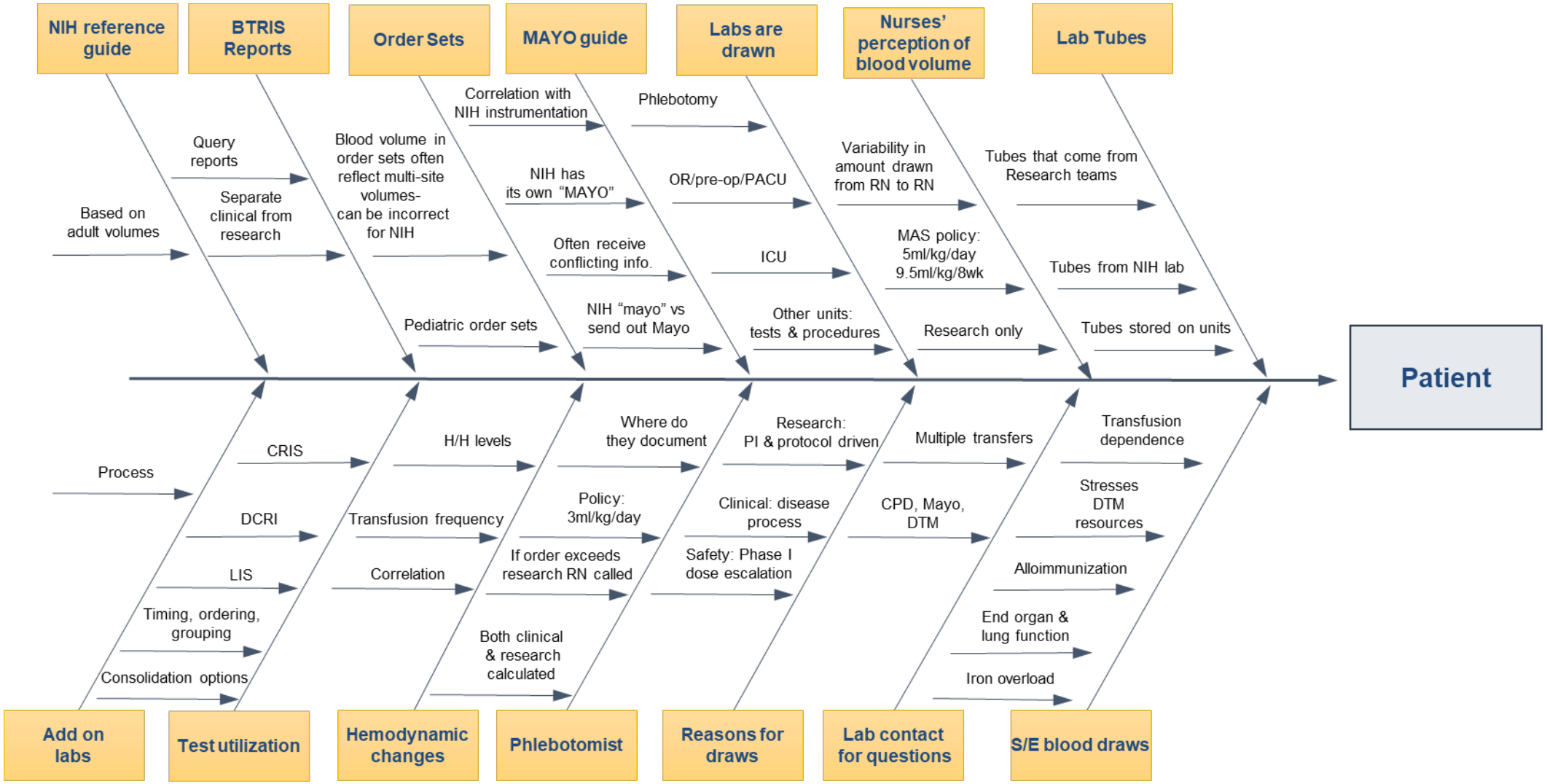
Suction Supplies

Respiratory/Airway

GI/GU/Feeding

Diapers/Linens

Blood collection reduction strategies



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Reduction Strategies

- Managing phlebotomy volumes by:
  - Monitoring duplicate & excessive ordering
  - Bundling scheduled tests
  - Advocating for blood volume reduction practices including use of:
    - Closed system collection devices
    - Small volume collection tubes
- Successful EBP QI projects:
  - Avoid duplicate testing
  - Frequent clinical evaluation of routine or repetitive testing
  - Adoption of excessive phlebotomy reduction strategies

(Eaton et al, 2017, Dolman et al, 2015, Jones et al, 2019 & Thakkar et al, 2015, Wu et al, 2020).

Choosing Wisely CELEBRATING OUR 7TH YEAR
An initiative of the ABIM Foundation

Surgery
Volume 158, Issue 4, October 2015, Pages 1083-1088
ELSEVIER
Central Surgical Association
Impact of minimizing diagnostic blood loss in the critically ill
Heather S. Dolman MD [a, b], Kelly Evans C-NP [c], Lisa Hall Zimmerman PharmD [d], Todd Lavery MD [a, b], Alfred E. Baylor MD [a, b], Robert F. Wilson MD [a, b], James G. Tyburski MD [a, b]
Get rights and content

Impact of an Educational Intervention on the Frequency of Daily Blood Test Orders for Hospitalized Patients
Rajiv N. Thakkar, MD,[1] Daniel Kim, MD,[1] Amy M. Knight, MD,[1] Stefan Riedel, MD,[2] Dhananjay Vaidya, MBBS, PhD, MPH,[1] and Scott M. Wright, MD[1]

Reducing Blood Loss by Changing to Small Volume Tubes for Laboratory Testing
Yu Wu [1], Aaron C Spaulding [2], Shalmali Borkar [2], Michelle M Shoaei [3], Maria Mendoza [4], Rhonda L Grant [5], Bruce W Barber [5], Gretchen S Johns [5], Pablo Moreno Franco [6]

Evidence-Based Guidelines to Eliminate Repetitive Laboratory Testing
Kevin P. Eaton, MD; Kathryn Levy, MD; Christine Soong, MD; Amit K. Pahwa, MD; Christopher Petrilli, MD; Justin B. Ziemba, MD; Hyung J. Cho, MD; Rodrigo Alban, MD; Jaime F. Blanck, MLIS, MPA, AHIP; Andrew S. Parsons, MD, MPH

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Blood collection reduction strategies

- Research team worked with lab to modify amount of research blood needed in each tube & combined tests
- Protocol modified
- Research blood collection volume reduced
- Blood volume for clinical labs unpredictable

DISCLAIMER: These blood draw volumes represent estimates and should not be interpreted as exact or absolute totals. These totals are calculated using actual tube size blood volume and do not take into account factors such as underfill, overfill, or waste. The volume for Research, Blood orders are from the CRIS Order. All other volumes are from those blood specimens scanned into SoftID.

Draw Limits (in mL)

Draw Limit Volume [Past 8-weeks + Today]	158.65	OVER DRAW LIMIT [over by 1671.35 mL]
Pediatric Daily Limit	N/A	IS A PEDIATRIC PATIENT

Most Recent Vitals/Results

* Collection Date	Weight (in kg)	HCT	HGB
07/11/2018 00:00:00	16.7 kg [07/11/2018 09:01]	24.2 [07/11/2018 04:23]	8.8 [07/11/2018 04:23]

* 'Collection Date' is the most recently identified blood draw collection. If 'Collection Date' is N/A, then no blood draws have been identified in the past 8-weeks.
* 'Collection Date' is used as the maximum date for identifiying the most recent Vitals/Results. If 'Collection Date' is N/A, today's date is used as the maximum date.

Blood Draw

	Past [8-weeks]		Today [07/11/2018]		Future [8-weeks]	
	# of Tubes Collected	Volume (in mL)	# of Tubes Collected	Volume (in mL)	# of Tubes Collected	Volume (in mL)
Non-research (from LIS)*	403	1819.00	3	11.00	N/A	N/A
Research (from SCM)†	0	0.00	0	0.00	0	0.00
Culmulative	403	1819.00	3	11.00	0	0.00
Culmulative [Past 8-weeks + Today]	-	-	406	1830.00		

Research lab collection volume reduction by 70%

BLOOD	Pre-Screen	Baseline NIH Day -36 to -22	Immune Modulation Day -21	Day -14	Day -7	Day -1	Gene Transfer Day 0
Acute care panel, mineral panel, hepatic panel, lipid panel, lipase, amylase, CRP, Iron and transferrin, Quantitative Immunoglobulins, GGT, TSH, and/or		4	*	2	2	2	
CBC with diff, reticulocyte count, sirolimus, TBNK, and/or ammonia		3	*	2	2	2	
D-dimer						3	
PT/PTT		3					
Cytokine Panel							
M. tuberculosis screening		**					
Anti-HAV, Anti-HBc, Anti-HBs, Anti-HCV Antibody		**					
HIV 1/2 Antibody Combo		**					
Anti-AAV9 Antibody Titer (Athena)	x	3					
Anti-AAV9 Neutralizing Antibody Titer (store for Axovant)							1
Total AAV9 Antibody Titer (UFL)							1
Beta-galactosidase Enzyme Levels (LabCorp)	x	**					
Beta-galactosidase Enzyme Levels (Greenwood)							1
PK Studies (store for Axovant and us, -> UF)							
PBMC's		***					
Pentasaccharide Biomarker (for us, -> Wash U)		2					
Beta-Galactosidase Antibody (store for Axovant)		2					
Biorepository Serum (store for us)		2					
Biorepository EDTA Plasma (store for us)		2					
Biorepository NaHep Plasma (store for us)		2					
TOTAL (mL)	0	23	0	4	4	7	3

Area 7: Emergency Response

- Code and Infusion sheets
- Infant equipment on code carts
- Children's National intensivist to run infant code if needed
- Team roles & responsibilities

10/14/2021 14:57
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National Institutes of Health
Clinical Center

Pediatric Emergency Drug Sheet (PEDS)

Generic Weight: 8 kg

ETT SIZE Cuffed: (age in years/4)+3.5 Size: _____ Uncuffed: (age in years/4)+4 Size: _____

RESUSCITATION MEDICATIONS	Dose	Pt. Dose	Dose (ml)
ADENOSINE (3 mg/mL)			
Initial dose: Give rapid IV push over 1-2 sec, follow by rapid NS flush	0.1 mg/kg	0.8 mg	0.27 mL
Repeat dose: (may repeat x 2)	0.2 mg/kg	1.6 mg	0.53 mL
AMIODARONE (50 mg/mL)***dose volume (mL) listed is undiluted drug*			
Pulseless VF/VT - Give IV push undiluted	5 mg/kg	40 mg	0.8 mL
Tachyarrhythmia with pulse - dilute with 24 mL D5W - infuse over 20-60 min	5 mg/kg	40 mg	0.8 mL
ATROPINE (0.1 mg/mL)			
	0.02 mg/kg	0.16 mg	1.6 mL
CALCIUM CHLORIDE 10% (100 mg/mL)			
Max infusion rate 100 mg/min; May repeat in 10 min if necessary	20 mg/kg	160 mg	1.6 mL
DEXTROSE 25% (250 mg/mL)**no dilution required*			
Use for weights <45 kg	500 mg/kg	4000 mg	16 mL
DEXTROSE 50% (500 mg/mL)- *Use undiluted for >=45 kg*			
Dilute 1:1 with NS for <45 kg **Dose volume (mL) listed is undiluted drug	500 mg/kg	4000 mg	8 mL
EPINEPHRINE			
IV/IO 0.1 mg/mL	0.01 mg/kg	0.08 mg	0.8 mL
ETT 1 mg/mL-dilute with 2-5 mL NS. Max single dose = 2.5 mg	0.1 mg/kg	0.8 mg	0.8 mL
LABETOLOL (5 mg/mL)			
May repeat every 10 min prn	0.2 mg/kg	1.6 mg	0.32 mL
	0.5 mg/kg	4 mg	0.8 mL
LIDOCAINE (20 mg/mL)			
IV. May repeat in 10-15 min	1 mg/kg	8 mg	0.4 mL
ETT dose	2 mg/kg	16 mg	0.8 mL

Area 8: Education, Training & Competencies

Who: ICU, Peds, PACU, IR nurses

What: Improve knowledge, skills, & confidence in infant emergency response

How: Infant-focused didactic, hands-on skills & interprofessional high-fidelity simulations

Education & Training Methodologies

Didactic

- Nursing: Pediatric, ICU, Post Anesthesia Care Unit & Interventional Radiology
- Infant Care
- Emergency Response
- Potential clinical risks

Skills Lab

- Emergency respiratory care, epinephrine IM
- Intraosseous placement, Rapid Sequence Intubation, fluid resuscitation, hemodynamic drips, & arrythmia management.

Simulation Lab

- Multidisciplinary NIH Teams
- Anaphylaxis
- Supraventricular Tachycardia (SVT)
- Seizure Management
- Shock

In Situ Simulation

- Multidisciplinary NIH Teams
- Children's National Intensivist & Respiratory Therapy
- Anaphylaxis
- SVT management
- Seizure management

Education & Training

- Phase I
  - 8 lectures
  - 8 skills stations
- Phase II
  - 24 integrated in-lab simulations with NIH CC providers
- Phase III
  - Five in-situ multidisciplinary simulations with National Children's Hospital providers

Competencies/Polices/Procedures/Standard of Practice

Reviewed existing CC policies/Procedures/Standards of Practice to identify gaps related to infant population

Venous Access

Placement and Management

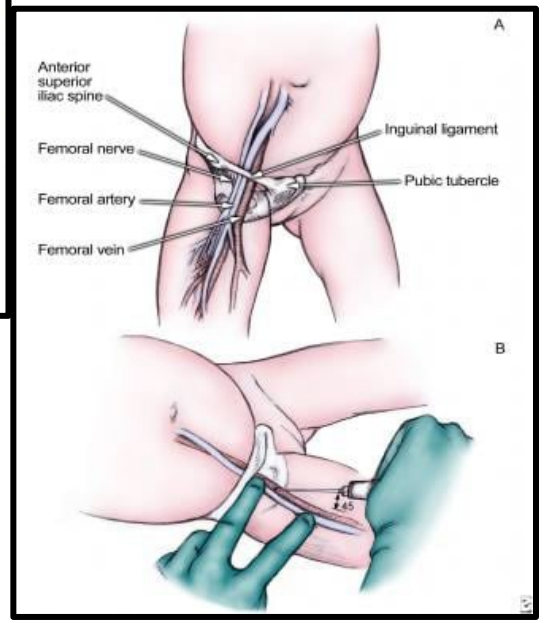
Chemotherapy/Biotherapy Administration of Rituximab in Infants

Breast feeding and expressed breast milk

Venous Access Placement and Management

- Reviewed existing venous access device placement and maintenance documents
- Benchmarked with institutions that admit infants and place central venous access devices
- PICC placement (peripherally inserted central catheter)
  - Preferred placement location: femoral vein
  - PICC inserted at Children's National
  - Flush guidelines modified for infant and femoral placement
  - Document created regarding the care, maintenance, and troubleshooting of PICC in infants

Fig. 15.2 Tunneled femoral CVAD (used with permission T. Kleidon)



Chemotherapy/Biotherapy: Rituximab Administration

- Identify evidence-based practice standards for monitoring in infants
- Benchmarking conducted via the Association of Pediatric Hematology Oncology Nurses (APHON)
- Vital sign monitoring consistent with CCND documents
  - Baseline and with dose escalations
- Cardiac monitoring
  - Practice of placing infants on cardiac monitoring variable
  - Inpatient setting
    - Most placed on cardiac monitors
  - Outpatient setting
    - If available cardiac monitoring utilized
    - Pulse oximetry utilized

Breast Feeding and Expressed Breast Milk

- Mom's expressed desire to continue to breast feed their infants
  - Benefits of breast feeding
- Limited documents in the Clinical Center
  - 2300-640-1 - NIH Nursing Mothers Program (https://policymanual.nih.gov/2300-640-1)
  - Policy applies to
    - Any nursing mother personnel, contractors, fellows, and visitors choosing to express breast milk to take home for their infant(s)

Creation of Expressed Breast Milk Documents

Input was obtained from various departments

Nutrition

HES

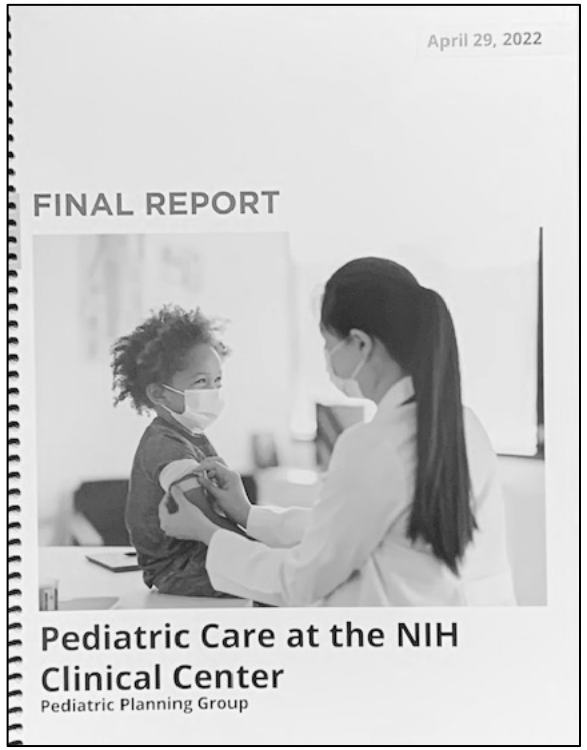
Lactation Room Coordinator

Biomed

Nursing

Future Implications

- Impact of the teamwork
- Transferrable model
- Blood Volumes
- Pediatric Planning Group



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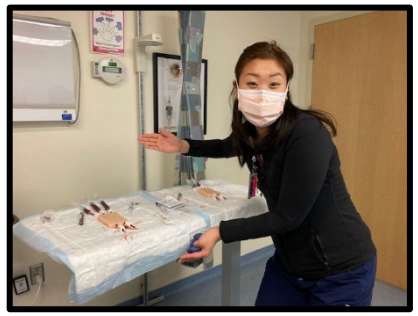
Many thanks to the bedside nurses and PCTs who…

Provided clinical care to infants and caregiver

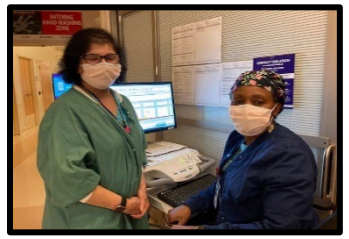
Embraced a new population through learning

Shared their experiences

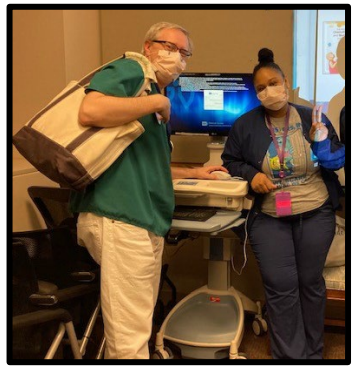
Provided feedback to assist in refinement and improvement of resources

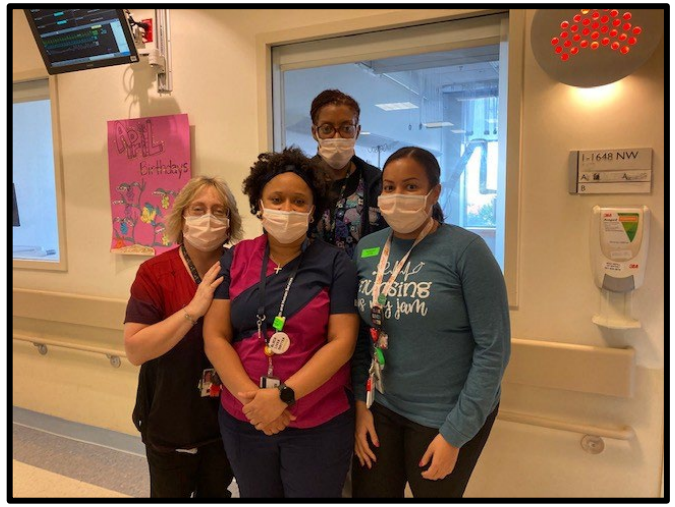


Collaboration



Maintained research study integrity and provision of safe care





1NW Inpatient Nursing Staff

It Takes a Village

3 SWS ICU Nursing Staff

1NW Day Hospital Nursing Staff

1HPED Nursing Staff