

## **Michelle Marshall, MSN, APRN, NNP-BC**

Michelle Marshall is a Neonatal Nurse Practitioner working at Children's Mercy Hospital in Kansas City, MO. She lives in Leawood, KS, with her husband, two daughters, and a very noisy dog. She enjoys all aspects of NICU care but is particularly interested in the care of infants with congenital cardiac differences.



# A Mystery Case

Michelle Marshall, DNP, APRN, NNP-BC



I have no financial or commercial interests to disclose



# A consultation from Well Baby Nursery ...

A term female infant presents with "unusual breathing" at 18 hours of life

Infant is undressed on radiant warmer for observation

RN has just finished feeding infant who took 20 mL of term infant formula by bottle

On portable monitor:

Heart rate 130-140

Respiratory rate 30

SpO<sub>2</sub> 100%



# Initial Examination

- General
- Neuro
- Respiratory
- Cardiovascular

# Initial Examination

- General
- Neuro
- Respiratory
- Cardiovascular
- Anterior fontanelle soft and flat
- Sutures overriding
- No apparent dysmorphic features
- Infant has been bottle feeding well since birth
- Voiding and stooling

# Initial Examination

- General
  - **Neuro**
  - Respiratory
  - Cardiovascular
- Alert, irritable
  - High-pitched cry
  - Mild generalized hypertonicity
  - Normal root, suck, grasp

# Initial Examination

- General
  - Neuro
  - Respiratory
  - Cardiovascular
- Clear and equal bilateral breath sounds
  - Deep breathing with low-normal respiratory rate
  - Moderate intercostal and subcostal retractions

# Initial Examination

- General
  - Neuro
  - Respiratory
  - Cardiovascular
- Grade III/VI cardiac murmur
  - Bounding pulses in lower extremities

# Initial Examination

- General
- Neuro
- Respiratory
- Cardiovascular
- Remainder of exam is within normal limits

# Next steps...?

- Admit to NICU for further workup of abnormal respiratory pattern
- Review maternal and birth history

## 18 hours ago ...

A healthy appearing term  
female infant delivered  
Let us review the history



# Histories

- Mother
- Labs
- Pregnancy
- Birth
- Infant

# Histories

- Mother
  - Labs
  - Pregnancy
  - Birth
  - Infant
- 30 years old
  - G2 P2
  - Diabetes
    - Well controlled
    - On Metformin
  - Medications
    - Prenatal Vitamin
    - Vitamin D
    - Famotidine
    - Metformin

# Histories

- Mother
  - Labs
  - Pregnancy
  - Birth
  - Infant
- Blood type O+
  - Antibody negative
  - Gonorrhea and Chlamydia negative
  - Hepatitis B negative
  - HIV negative
  - Rubella immune
  - RPR nonreactive
  - GBS positive (adequately treated)

# Histories

- Mother
  - Labs
  - Pregnancy
  - Birth
  - Infant
- Polyhydramnios
  - Possible enlarged ventricles on fetal US
  - Otherwise uncomplicated

# Histories

- Mother
  - Labs
  - Pregnancy
  - Birth
  - Infant
- Spontaneous vaginal delivery
  - Cephalic presentation
  - Precipitous delivery
  - ROM 2 hours
  - Apgars 8, 9
  - Routine delivery room care

# Histories

- Mother
  - Labs
  - Pregnancy
  - Birth
  - **Infant**
- Birthweight 3015
    - (26%)
  - Head circumference 33.5 cm
    - (26%)
  - Length 51 cm
    - (68%)

## NICU Admission ...

Family is updated and infant is admitted for workup of labored breathing

Mother reports her older child is a healthy 13 year old girl

Family history is unremarkable



# Evaluation

- Arterial Blood Gas
- Chest Xray
- CBC
- Blood Culture
- Blood glucose

# Evaluation

- Arterial Blood Gas
- Chest Xray
- CBC
- Blood Culture
- Blood glucose

pH 7.27

CO<sub>2</sub> 8

PaO<sub>2</sub> 126

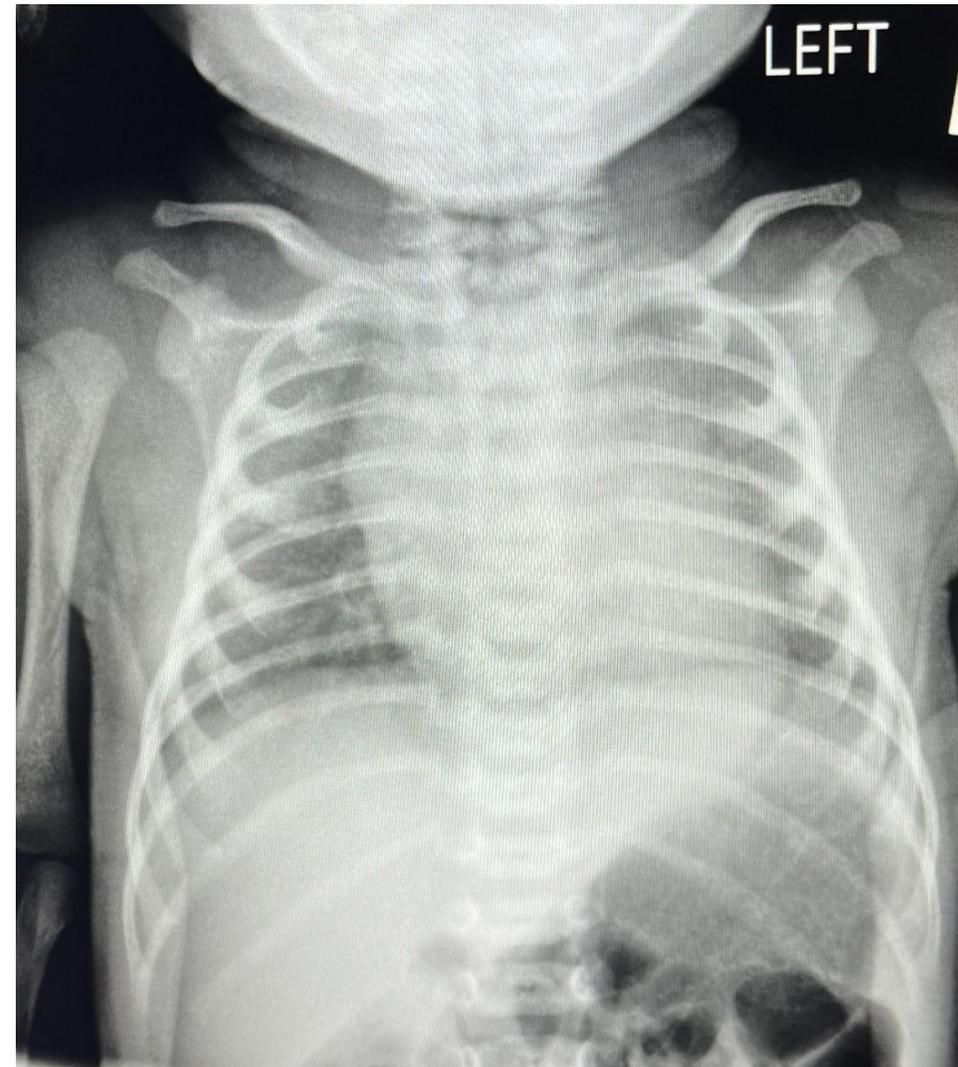
HCO<sub>3</sub> 3.8

Base -19.7

\*Confirmatory second sample was obtained with similar result

# Evaluation

- Arterial Blood Gas
- Chest Xray
- CBC
- Blood Culture
- Blood glucose



# Evaluation

- Arterial Blood Gas
- Chest Xray
- CBC
- Blood Culture
- Blood glucose

WBC 16.4

Seg 54%

Band 2%

Lymph 32%

Hgb 15.2

Hct 44

Plt 277

# Evaluation

- Arterial Blood Gas
- Chest Xray
- CBC
- Blood Culture
- Blood glucose

Point of Care Sample: 26

Repeat: 29

# DIFFERENTIAL DIAGNOSIS: What type of problem do you suspect?

Congenital Cardiac Difference

Metabolic Disorder

Primary Respiratory Problem

Infection

None of the above

# Management

- Neuro
- Respiratory
- Cardiovascular
- FEN, GI
- Metabolic
- ID
- Heme

# Management

- **Neuro**
  - Respiratory
  - Cardiovascular
  - FEN, GI
  - Metabolic
  - ID
  - Heme
- Prenatal US with possible ventriculomegaly
  - Head circumference 26%
  - Irritable with high-pitched cry
  - Head US is ordered, pending

# Management

- Neuro
  - Respiratory
  - Cardiovascular
  - FEN, GI
  - Metabolic
  - ID
  - Heme
- Labored breathing
  - Chest X-ray poorly expanded but within normal limits
  - SpO<sub>2</sub> 100%
  - ABG shows compensated metabolic acidosis
  - Infant is electively intubated
  - Post-intubation X-ray and ABG are unchanged

# Management

- Neuro
  - Respiratory
  - **Cardiovascular**
  - FEN, GI
  - Metabolic
  - ID
  - Heme
- Cardiac murmur Gr III/VI
  - Four extremity BP within normal limits, no gradient
  - SpO<sub>2</sub> 100% pre- and post-ductal
  - ABG shows compensated metabolic acidosis
    - NS bolus given
  - Echocardiogram is ordered
    - Mild persistent pulmonary hypertension

# Management

- Neuro
  - Respiratory
  - Cardiovascular
  - FEN, GI
  - Metabolic
  - ID
  - Heme
- IDM
  - Breast and bottle feeding well with normal glucoses in newborn nursery
  - Hypoglycemia on admit to NICU
    - D10W bolus given
    - Starter TPN at 60 mL/kg/day
  - Umbilical lines placed

# Management

- Neuro
  - Respiratory
  - Cardiovascular
  - FEN, GI
  - Metabolic
  - ID
  - Heme
- Basic Metabolic panel ordered:
    - Na 148
    - K 4.1
    - Cl 110
    - CO<sub>2</sub> 4
    - BUN 12
    - Creatinine 0.8
    - Glucose 69
    - Ca 10.4

# Management

- Neuro
  - Respiratory
  - Cardiovascular
  - FEN, GI
  - Metabolic
  - ID
  - Heme
- Recurrent hypoglycemia 3 hours later
    - Point of care glucose 34
    - Second D10W bolus given
    - IV rate increased to 80 mL/kg/day

# Management

- Neuro
  - Respiratory
  - Cardiovascular
  - FEN, GI
  - **Metabolic**
  - ID
  - Heme
- Profound metabolic acidosis on ABG
  - Lactate: 16.1
  - Ammonia: 98
  - State metabolic screen is sent
  - Sodium bicarbonate infusion started
  - IV fluids changed from Starter TPN to D10W

# Management

- Neuro
  - Respiratory
  - Cardiovascular
  - FEN, GI
  - Metabolic
  - ID
  - Heme
- Labs are repeated after NS bolus and bicarbonate infusion:
    - Lactate 12.6
    - ABG
      - pH 7.38
      - CO<sub>2</sub> 15
      - PaO<sub>2</sub> 115
      - HCO<sub>3</sub> 8.7
      - Base -13.9
      - Now intubated, on FiO<sub>2</sub> 0.21

# Management

- Neuro
  - Respiratory
  - Cardiovascular
  - FEN, GI
  - Metabolic
  - ID
  - Heme
- GBS positive mother
    - adequate antibiotic treatment
    - ROM 2 hours
  - CBC benign
  - Blood culture pending
  - Infant placed on ampicillin and gentamicin

# Management

- Neuro
  - Respiratory
  - Cardiovascular
  - FEN, GI
  - Metabolic
  - ID
  - Heme
- Mother O+
  - Infant B+, DAT negative
  - Hgb and Hct before NICU admit: 18.9/54
  - Hgb and Hct on admit: 15.2/44
  - No petechiae or bruising
  - Bilirubin level 5.1 at 12 hours of age

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# DIFFERENTIAL DIAGNOSIS: Now what type of problem do you suspect?

Congenital Cardiac Difference

Metabolic Disorder

Primary Respiratory Problem

Infection

Something else altogether

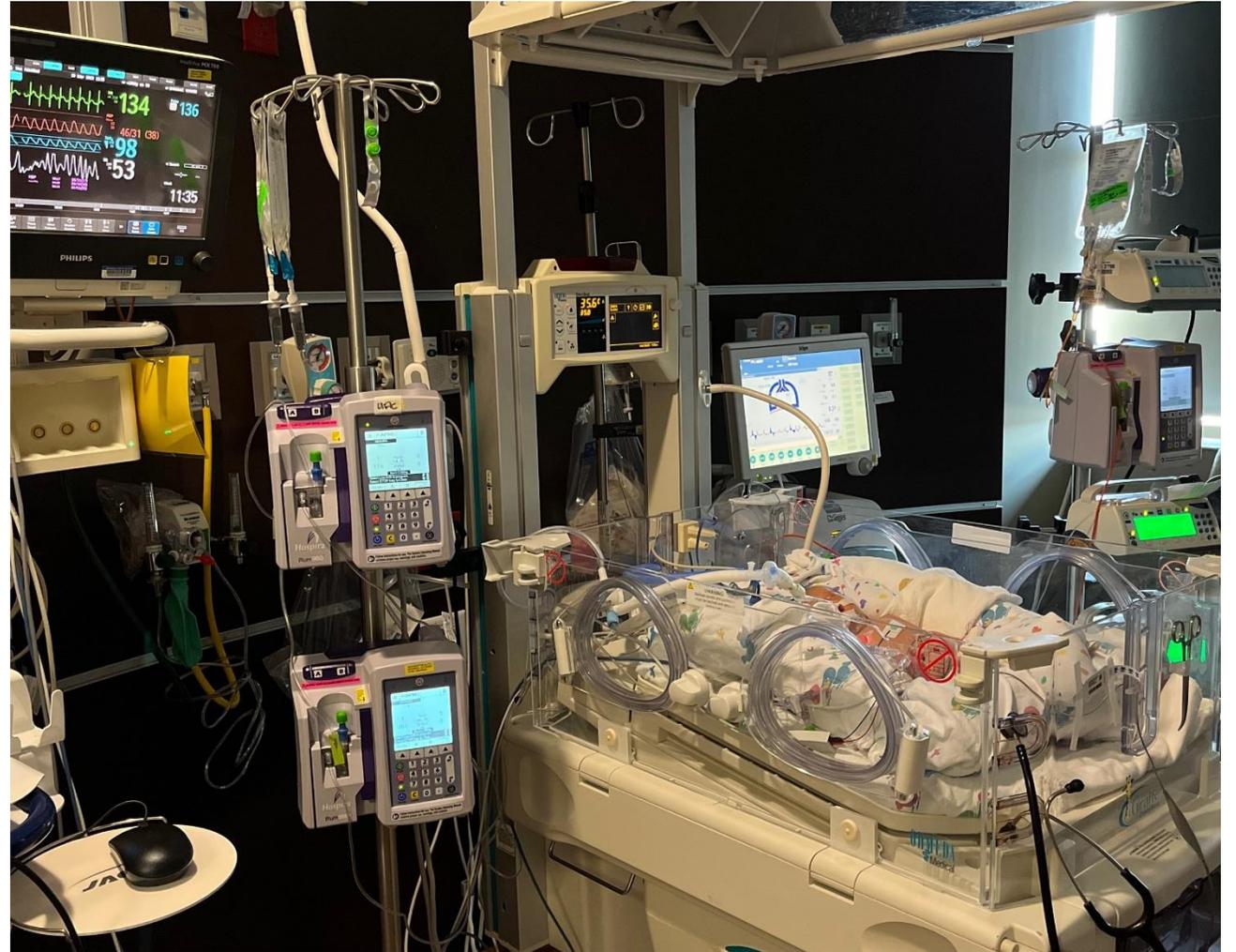
# Transport

- Transport team has arrived to take infant to higher level of care

# Further Workup and Diagnosis ...

Infant safely transfers to regional referral center

Specialty consults are ordered



# Specialty Evaluations

- Neurology
- Metabolic Genetics

# Specialty Evaluations

- Neurology
- Metabolic Genetics
- Head US
  - Grade III IVH
  - Signs of liquefactive necrosis
  - Suggestive of prenatal cerebral insult
- MRI brain
  - Confirms Gr III IVH
  - Periventricular hemorrhage with cystic changes
- Risk of developmental delay

# Specialty Evaluations

- Neurology
- Metabolic Genetics
- Head imaging findings coupled with lactic acidosis and perinatal history raise suspicion for infectious etiology
- Continue broad antibiotic coverage

# Specialty Evaluations

- Neurology
- Metabolic Genetics
- Metabolic and lactic acidosis raises suspicion for inborn error of metabolism
- State screens:
  - Admission screen is normal for age
  - Serial repeat screens are normal

# Specialty Evaluations

- Neurology
- Metabolic Genetics
- Plasma amino acids: mild non-specific changes
- Ketonuria
- Acylcarnitine profile: essentially normal
- Beta Hydroxybutyrate: 344.6 (high)
- Creatine kinase: 1352 (high)

# Specialty Evaluations

- Neurology
- Metabolic Genetics
- Preliminary testing not suggestive of overt metabolic disease
- However, lactic acidosis persists
- Targeted genetic testing is sent
- Infant experiences recurrence of severe lactic acidosis when enteral feeds are attempted
- Continues to require sodium bicarbonate drip

# Specialty Evaluations

- Neurology
- Metabolic Genetics
- DOL 7 lactate and pyruvate are drawn simultaneously
  - Lactate 12
  - Pyruvate 0.51
  - Ratio 23.5
- Elevated lactate:pyruvate ratio
- Leaving mitochondrial disorders, specifically pyruvate carboxylase deficiency at top of differential

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# DIFFERENTIAL DIAGNOSIS: Now what type of problem do you suspect?

Congenital Cardiac Difference

Metabolic Disorder

Primary Respiratory Problem

Infection

Something else altogether

# Differential Diagnosis

- Now what type of problem do you suspect?
  - Congenital Cardiac Difference
  - Metabolic Disorder
  - Primary Respiratory Problem
  - Infection
  - Something else altogether
- Blood culture is negative, serial CBCs are normal
- Genetic testing results in homozygous variant in pyruvate carboxylase

# Pyruvate Carboxylase Deficiency

A very rare neurometabolic disorder



# Pyruvate Carboxylase Deficiency

- Overview
- Inheritance
- Pathophysiology
- Presentation
- Treatment

# Pyruvate Carboxylase Deficiency

- Overview
- Inheritance
- Pathophysiology
- Presentation
- Treatment
- Disorder of mitochondrial metabolism
- Incidence 1:250,000 live births
- Equally affects males and females
- Three identified types

# Pyruvate Carboxylase Deficiency

- Overview
- Inheritance
- Pathophysiology
- Presentation
- Treatment
- Type A
  - Infantile Form
  - Occurs more often in native tribes of North America
- Type B
  - Severe Neonatal Form
  - Occurs more often in Europe, especially in France
- Type C
  - Intermittent or Benign Form

# Pyruvate Carboxylase Deficiency

- Overview
  - **Inheritance**
  - Pathophysiology
  - Presentation
  - Treatment
- Autosomal recessive
  - Inherited mutation in pyruvate carboxylase (PC) gene
  - Resultant decrease in or absence of pyruvate carboxylase enzyme

# Pyruvate Carboxylase Deficiency

- Overview
  - Inheritance
  - Pathophysiology
  - Presentation
  - Treatment
- Decrease or absence of pyruvate carboxylase (PC) enzyme
  - PC enzyme functions in mitochondria in oxaloacetate production
  - Oxaloacetate is critical to glutamine-glutamate cycle
  - Glutamate (excitatory neurotransmitter) is essential in normal neurologic function and development
  - Important role in gluconeogenesis and energy metabolism

# Pyruvate Carboxylase Deficiency

- Overview
  - Inheritance
  - Pathophysiology
  - **Presentation**
  - Treatment
- Type A (Infantile)
    - Onset in infancy
    - Metabolic acidosis
      - Mild-moderate lactic acidosis and ketoacidosis
    - Developmental delay
    - Hypotonia
    - Failure to grow
    - Episodes of vomiting and tachypnea with exacerbations of acidosis
    - Death in infancy or childhood, some survive to adulthood

# Pyruvate Carboxylase Deficiency

- Overview
  - Inheritance
  - Pathophysiology
  - **Presentation**
  - Treatment
- Type B (Severe Neonatal)
    - Onset shortly after birth
    - Metabolic acidosis
      - Lactic acidosis
      - Ketoacidosis
      - Hyperammonemia
    - Hypoglycemia, hyponatremia
    - Severe developmental disability
    - Hypotonia, abnormal reflexes and ocular movements, seizures
    - Hepatomegaly, liver failure
    - Death usually in first 3 months

# Pyruvate Carboxylase Deficiency

- Overview
  - Inheritance
  - Pathophysiology
  - **Presentation**
  - Treatment
- Type C (Intermittent or Benign)
    - Metabolic acidosis
      - Mild
      - Usually episodic
    - Normal or mildly delayed development
    - Normal life expectancy

# Pyruvate Carboxylase Deficiency

- Overview
  - Inheritance
  - Pathophysiology
  - **Presentation**
  - Treatment
- Brain MRI findings
    - Type A
      - May have symmetric cystic lesions in cortex, basal ganglia, cerebellum, brain stem
      - Generalized hypomyelination
    - Type B
      - May have ventricular dilation and periventricular white matter cysts

# Pyruvate Carboxylase Deficiency

- Overview
  - Inheritance
  - Pathophysiology
  - Presentation
  - **Treatment**
- Hydration
  - Correction of metabolic acidosis
  - Alternative energy
    - IV nutrition
    - Enteral diet high in carbohydrate and protein, low in fat

# Pyruvate Carboxylase Deficiency

- Overview
  - Inheritance
  - Pathophysiology
  - Presentation
  - **Treatment**
- Medications
    - Citrate supplementation
      - reduces acidosis
      - provides substrate for citric acid cycle
    - Aspartic acid supplementation
      - Supports urea cycle
      - Decreases hyperammonemia
      - Little neurologic benefit
    - Biotin supplementation
      - Optimizes remaining PC enzyme activity
      - Little efficacy demonstrated

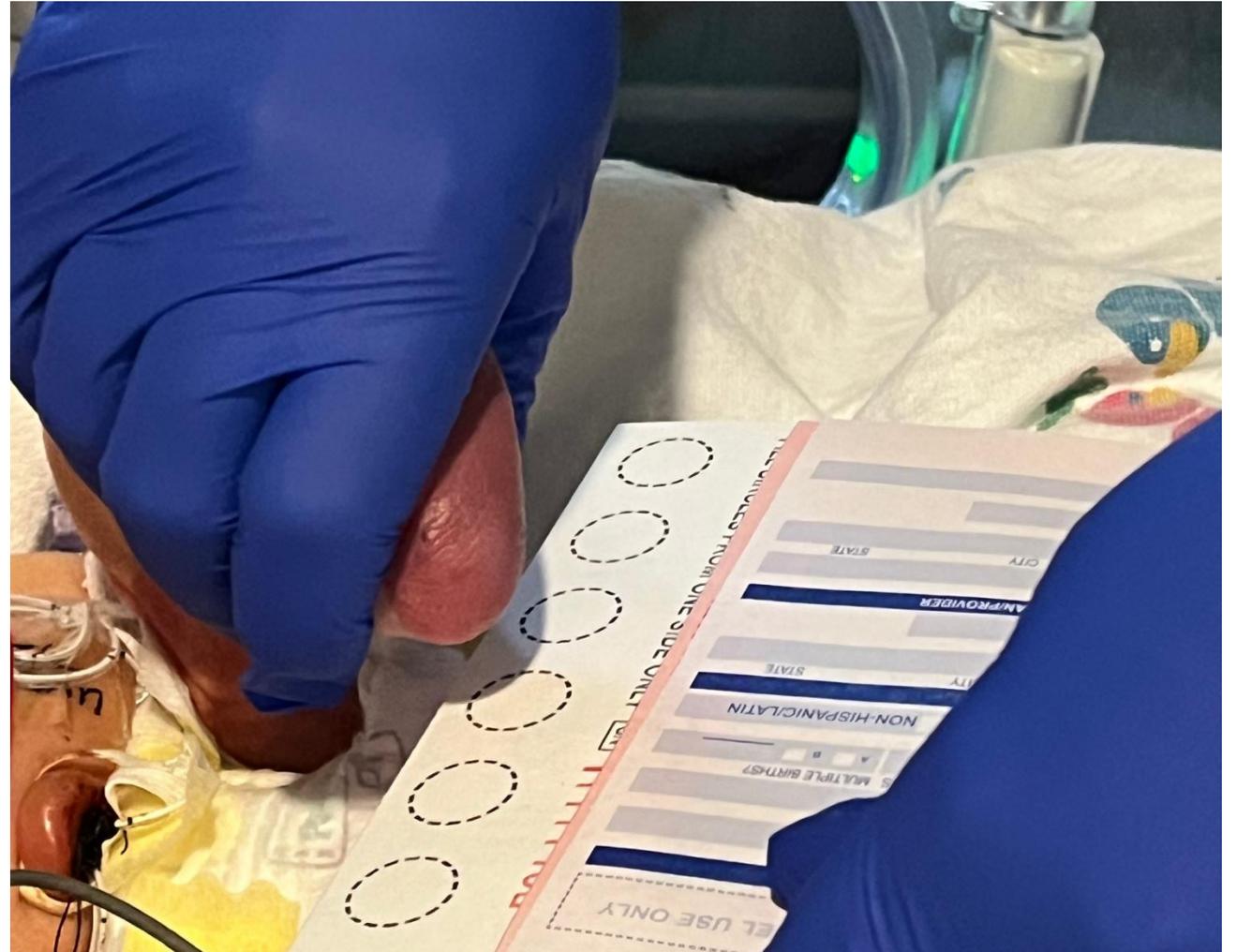
# Outcome

- This infant was found to be homozygous for a PC gene mutation which has been reported in individuals with Type A
- This infant was presumed to have Type B based on presentation and clinical course
- Infant was unable to tolerate full enteral feeds without recurrence of severe acidosis
- Multiple attempts to wean from sodium bicarbonate drip were unsuccessful
- Infant died just after 3 months of age

# Newborn Metabolic Screens

Started with the blood spot testing for PKU in 1960s

Has evolved to encompass more diseases over time



# Newborn Metabolic Screens

- What?
- When?
- Why?
- Who?

# Newborn Metabolic Screens

- What?
  - When?
  - Why?
  - Who?
- A blood spot test collected on special filter paper
  - Test is sent to state laboratory
    - Results returned to facility of collection or to ordering provider
  - Diseases included in screening vary by state
    - MO tests for 77 conditions
    - KS tests for 34 conditions
  - Opt-out
    - Both MO and KS allow families to opt-out of testing

# Newborn Metabolic Screens

- What?
- When?
- Why?
- Who?
- Sample is collected between 24-48 hours of age
- Too early:
  - Some results will not be accurate if test is drawn before 24 hours
  - Will require repeat test
- Too late:
  - May lead to delay in care for serious condition

# Newborn Metabolic Screens

- What?
  - When?
  - Why?
  - Who?
- Incidence
    - Most individual metabolic diseases are rare
    - Collective incidence of metabolic disease is 1:2000 live births
    - This may be an underestimate!
  - Infant may have no symptoms
    - Placenta is often protective for fetus
    - Most are born normally grown and well-appearing

# Newborn Metabolic Screens

- What?
  - When?
  - Why?
  - Who?
- Many conditions covered by state screens have known therapies
  - Many have good outcomes if detected and treated early
  - Detection allows for prenatal detection in subsequent pregnancies
  - Low false negative rate

# Newborn Metabolic Screens

- What?
- When?
- Why?
- Who?
- Ideally every infant should be screened!
- State laws require testing of all newborns
- MO and KS allow families to opt-out for religious regions

## What Should I do?

What should raise suspicion for and inborn error of metabolism?

What can I do to best manage this infant early in the course?



# Early Management Guidance

- Red Flags
- First Steps
- Considerations

# Early Management Guidance

- Red Flags
- First Steps
- Considerations
- History of parental consanguinity
- History of unexplained neonatal death in sibling
- Two common presentation patterns

# Early Management Guidance

- Red Flags
  - First Steps
  - Considerations
- Two common patterns:
    - Healthy at birth, later develops symptoms:
      - Poor feeding
      - Lethargy or irritability
      - Abnormal breathing
      - Vomiting
      - Metabolic acidosis
      - Hyperammonemia is variable
      - Ketonuria is highly suggestive as neonates do not commonly produce ketones

# Early Management Guidance

- Red Flags
  - First Steps
  - Considerations
- Two common patterns:
    - Profound neurologic symptoms:
      - Often present at birth
      - Decreased level of consciousness
      - Seizures, apnea
      - Hypotonia
      - Without significant acidosis or hyperammonemia

# Early Management Guidance

- Red Flags
  - First Steps
  - Considerations
- Metabolic acidosis
    - Unexplained
    - Persistent
    - Evaluation of anion gap may assist diagnosis
    - Lactic acidosis
      - Non-specific, may be other etiology
      - Persistent lactate  $> 3$  mmol/L without history of asphyxia or concern for organ failure is suspicious for metabolic disease

# Early Management Guidance

- Red Flags
- First Steps
- Considerations
- Hypoglycemia
  - Non-specific
  - Can be early presentation of:
    - Fat oxidation defect
    - Glycogen storage disease
    - Disorder of gluconeogenesis
  - Can be secondary symptom of inborn errors of metabolism with hepatic effects

# Early Management Guidance

- Red Flags
- First Steps
- Considerations
- Cardiac Differences
  - Cardiomyopathy
    - With or without pericardial effusion
    - Especially when accompanied by hypotonia
  - Arrhythmias

# Early Management Guidance

- Red Flags
  - First Steps
  - Considerations
- Other:
    - Liver dysfunction
    - Cataracts
    - Dysmorphic appearance
      - Facial
      - Skeletal
    - Jaundice
    - Abnormal body odor

# Early Management Guidance

- Red Flags
  - **First Steps**
  - Considerations
- Promptly obtain newborn metabolic screen (regardless of infant's age in hours)
  - Stop milk feeds
  - Ventilator support for respiratory depression

# Early Management Guidance

- Red Flags
  - **First Steps**
  - Considerations
- IV fluids D10W with electrolytes as needed
    - Avoidance of fat and protein while awaiting preliminary screenings and diagnosis
    - Careful attention to maintain glycemic control and normal electrolytes

# Early Management Guidance

- Red Flags
  - First Steps
  - Considerations
- Bicarbonate for acidosis as needed
    - May cause hypernatremia
    - Follow electrolytes closely
  - Sodium benzoate for hyperammonemia

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