LACTIC ACIDOSIS, PYRUVATE DEHYDROGENASE, INVESTIGATIONAL NEW DRUGS

AND YOU!

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OVERARCHING AGENDA

- Lactic acidosis and its relationship to mitochondrial disease
- Emergency Investigational New Drug Applications
  - How do they work?
  - Can they help me or my child?
  - When can I use them?
  - What are the drawbacks?
- How do eINDs work with clinical trials?
  - The phases of clinical trials
  - How to find endpoints for clinical trials
  - Natural history importance

CASE

- First VBG: *pH* 7.11/CO_2 22/HCO_3 6.8/*BE* -20.4
- Anion Gap is 28
- Lactate is 17.9

Key Question 1: How to manage his severe acidosis?

Key Question 2: Does the lactate fully account for the acidosis?

WHAT IS METABOLIC ACIDOSIS?

- Metabolic acidosis is defined by

  - **low pH** (<7.35 venous)
  - In the presence of **low bicarbonate** (<22)
  - May or may not have compensatory low CO2
    - Kussmaul respirations

WHY IS ACIDOSIS BAD (SHORT TERM)

- Compensatory respiration is fatiguing and not sustainable
- Prolonged, untreated metabolic acidosis may cause
  - Bradyarrhythmia
  - Systemic hypotension
  - Pulmonary hypertension
- Major cause of fatality in neonates with mitochondrial disease

WHY IS ACIDOSIS BAD (LONG TERM)

- Carbon wasting can cause failure to thrive & growth delay

- Carbon wasting may result in delayed myelination and/or developmental delay

- Acidosis triggers central emesis center and can cause low appetite/vomiting

CAUSES OF METABOLIC ACIDOSIS

Keto-acidosis

- Mitochondrial patients may not be able to oxidize betahydroxybutyrate
- UA strips check for acetone, which requires betahydroxybutyrate oxidation
  - If UA negative, but unaccounted for acid, check BOHB!

Lactic acidosis

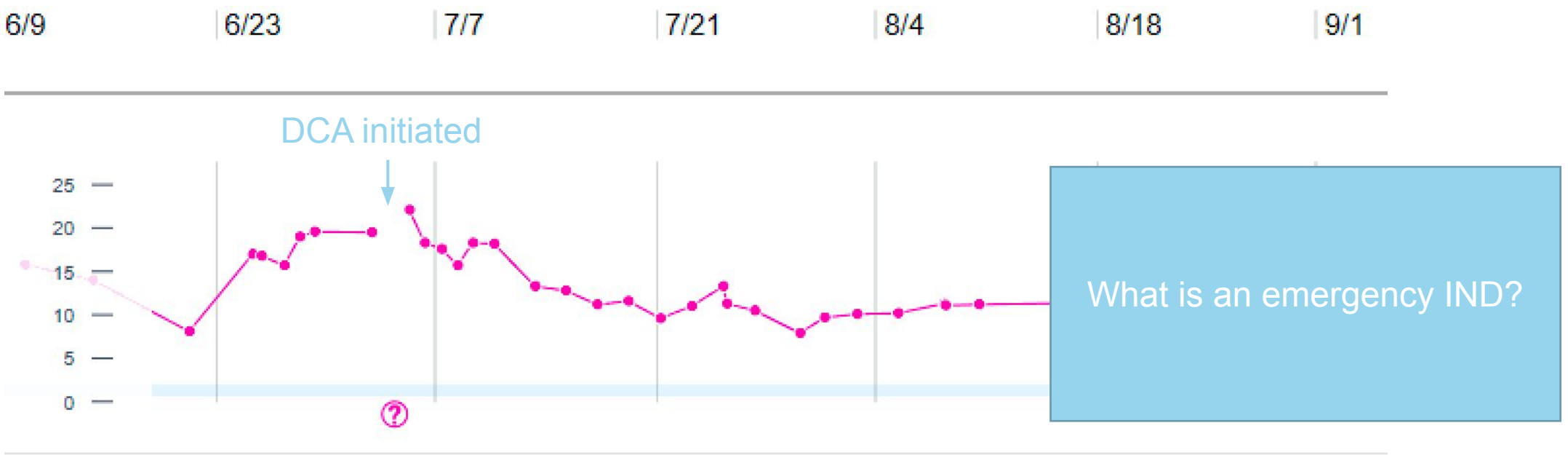
- Lactate pKa is ~4
- Bicarbonate pKa is ~10
  - So they are roughly “equal strength”

Renal tubular acidosis

- Renal Fanconi is common in mitochondrial disease
- Primary or secondary cause of acidosis
  - Wasting of supplemental bicarb
  - May increase needed supplementation

BACK TO OUR CASE

- Infant has persistent lactic acidosis
- Rapid exome + mtDNA is sent and diagnoses Pearson Syndrome
- We ask for emergency IND to use dichloroacetate



What is an emergency IND?

EMERGENCY INVESTIGATIONAL NEW DRUG (EIND) APPLICATION

AGENDA

WHAT IS AN EIND?

WHO IS INVOLVED?

IDEAL PROCESS

WHAT DOES THIS MEAN TO ME/MY CHILD?

SUMMARY

WHAT IS AN EMERGENCY IND?

Emergency use use of an investigational drug or biological product in **a single** human subject in a life-threatening/severely debilitating situation **without** standard acceptable

Life-threatening means the likelihood of death over time is high without treatment.

Severely debilitating means conditions that if untreated can cause major **irreversible** morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Source:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-investigational-dr

WHO IS INVOLVED?






PHYSICIAN

Physician initiates the process by contacting the manufacturer, sending paperwork to FDA, obtaining IRB approval, notifying Pharmacy, and obtaining informed consent from the family/patient.

MANUFACTURER

Drug manufacturer agrees to provide investigational drug, provides a sponsor letter, and ships drug at no charge to hospital pharmacy.

FDA

FDA approves the application for emergency use, provides physician with an eIND number, and obtains follow-up data from physician.

FAMILY/PATIENT

Family agrees to investigational drug and signs informed consent form.

PHARMACY

Pharmacy receives investigational drug, reviews paperwork , prepares for administration and provides to physician.

IRB

The hospital's institutional review board (IRB) must be notified of the physician's administration of the investigational drug.

IDEAL PROCESS

DAY 1

- **Physician** calls FDA to obtain authorization.
- **Physician** contacts manufacturer to obtain agreement to provide investigational drug.
- **Physician** obtains informed consent.

DAY 2

- **Manufacturer** arranges for shipment of investigational drug.
- **Physician** notifies pharmacy investigational drug is coming.

DAY 3-4

- **Manufacturer** writes sponsor letter .
- **Pharmacy** receives drug
- **Pharmacy** prepares for administration.
- **Physician** administers to patient.

DAY 5-ONWARD

- **Physician** notifies IRB of emergency expanded access use.
- **Physician** sends FDA completed application for emergency authorization and sponsor letter from manufacturer.
- **Physician** sends safety reports to FDA.
- **Physician** sends results summary to FDA.

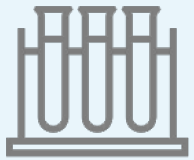
WHAT DOES THIS MEAN TO ME/MY CHILD?

WEIGHING THE RISK VERSUS BENEFIT

Your physician discusses the risks of the investigational drug and the potential benefits to help you determine if it is an appropriate option for you/your child.

You sign an informed consent form allowing administration of drug to you/your child even though the drug is not FDA approved.

ACCESS TO INVESTIGATIONAL DRUG PRIOR TO FDA APPROVAL



You have access to an investigational drug that has been shown to have some benefit in your/your child's condition but has not gone through the rigorous FDA approval process at this time.

The investigational drug is given to you/your child at no cost.

EVERYONE WANTS A SUCCESSFUL OUTCOME

Your physician has committed to the many steps required to submit the request, administer the drug and follow-up with the FDA.

The FDA has committed to rapidly responding to the request.

The drug manufacturer has committed to supplying and shipping the investigational drug and all required paperwork in an expedited manner free of charge.

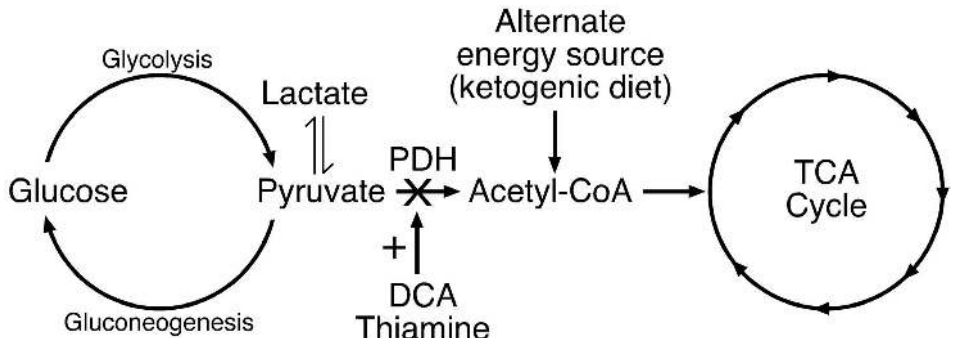
POTENTIAL OBSTACLES

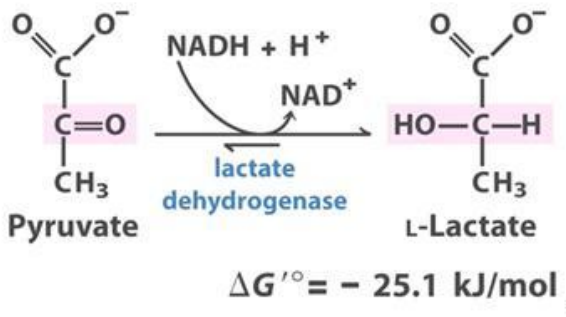
- The process may take longer than anticipated due to many steps and many different people involved in the request, resulting in delayed investigational drug administration.
- The manufacturer may not be set up to provide investigational drug.
- The drug has to be **actively being made** with a manufacturer sponsor

DICHLOROACETATE

HOW CAN WE TREAT ACIDOSIS?

- Limited tools in our toolbox:
  - Sodium bicarbonate (direct buffer)
  - Other buffers
- Emerging therapies
  - Dichloroacetate (DCA)
  - Niacin/niacinamide





Taylor, et al. PNAS 200

DICHLOROACETATE, BEYOND EIND

- Dichloroacetate is currently available via eIND only

- Following phase 3 clinical trial (currently closed to enrollment) in pyruvate dehydrogenase

- Understanding the story of DCA in PDCD is an important story for family advocacy

HOW TO MAKE A SUCCESSFUL CLINICAL TRIAL

- We need to understand the natural history of the disease
  - Including the full range of patients
- We need to understand how biomarkers relate to disease severity
  - E.g. is lowering lactate alone enough to be successful?
- We need to know how common the disease is
- Bigger clinical trials can build on individual treatments

MEDICINE & SCIENCE TAKE TIME

Clinical recognition		Syndrome named	Disease is a spectrum		Multiple genetic diseases		
Diagnostics	Biomarker discovery		Gene discovery	Gene sequencing available		Exome major diagnostic strategy	
Treatment		Diet treatment proposed (1 case)	DCA treatment proposed (1 case)		Animal models for treatment & DCA trial with other diseases		Phase 3 clinical trial

RETROSPECTIVE NATURAL HISTORY IS LIMITED

Things I thought I knew about PDCD in 2010

- Pyruvate/lactate is high. This is a good biomarker
- PDCD causes Leigh syndrome and that's the same as other Leigh syndromes
- We should always treat them with diet.
- Everyone has intellectual disability
- Everyone dies in childhood
- Symptoms are always epilepsy

2010

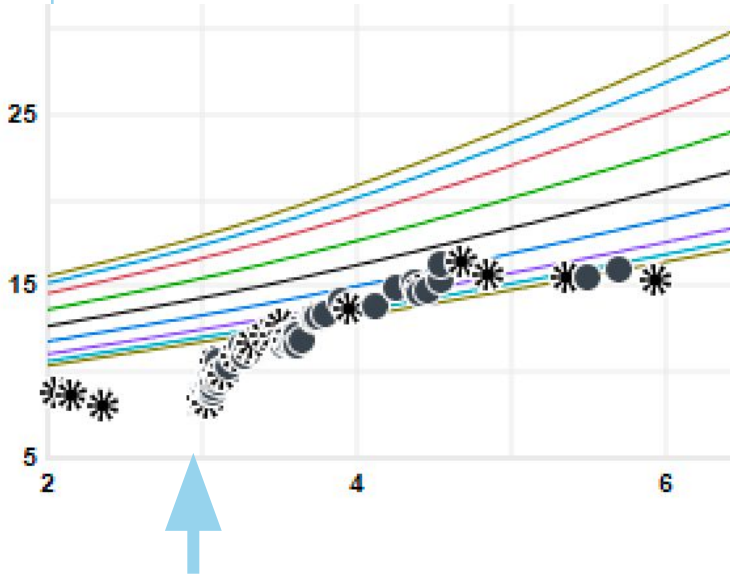
Dear Rebecca,
We are putting together a case series of patients with PDCD deficiency. Can you please contribute some cases?

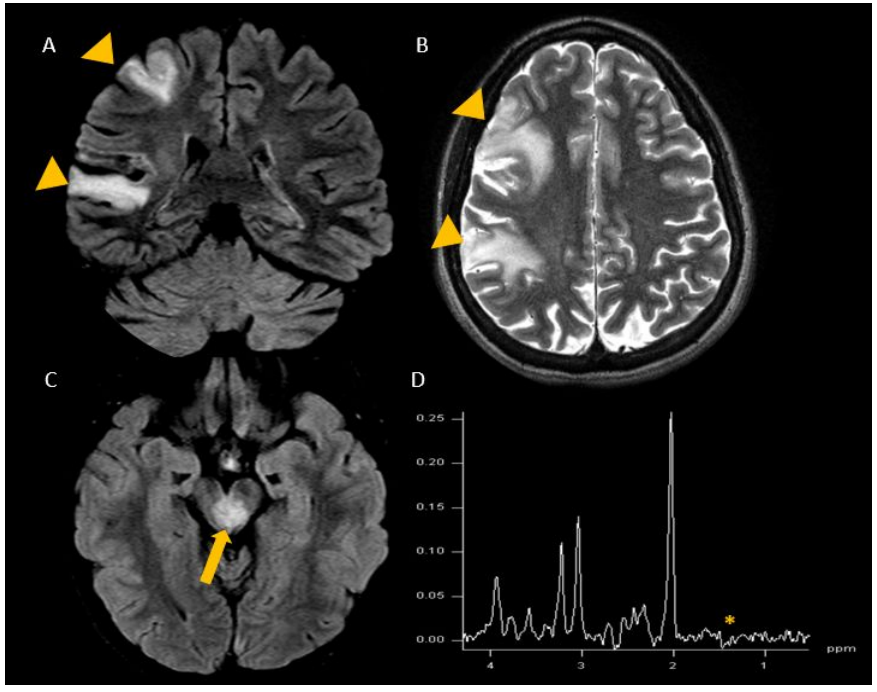
WE HAVE TO CONFESS HUMILITY

Case 1:
3 yo boy with failure to thrive

Leigh syndrome

Now not breathing well





The levels of pyruvate and lactate and the ratio of lactate to pyruvate are essentially normal.
This test was developed and its performance characteristics determined by the
Palmieri Metabolic Lab at the Children's Hospital of Philadelphia. not
been cleared nor approved by the FDA. This laboratory is certified under the
Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing.

X 7

“CHILDHOOD” DISEASES HAVE UNPREDICTABLE ADULT COURSES

Case 3:
~15 yo man longstanding diagnosis of *PDHA1* mutation

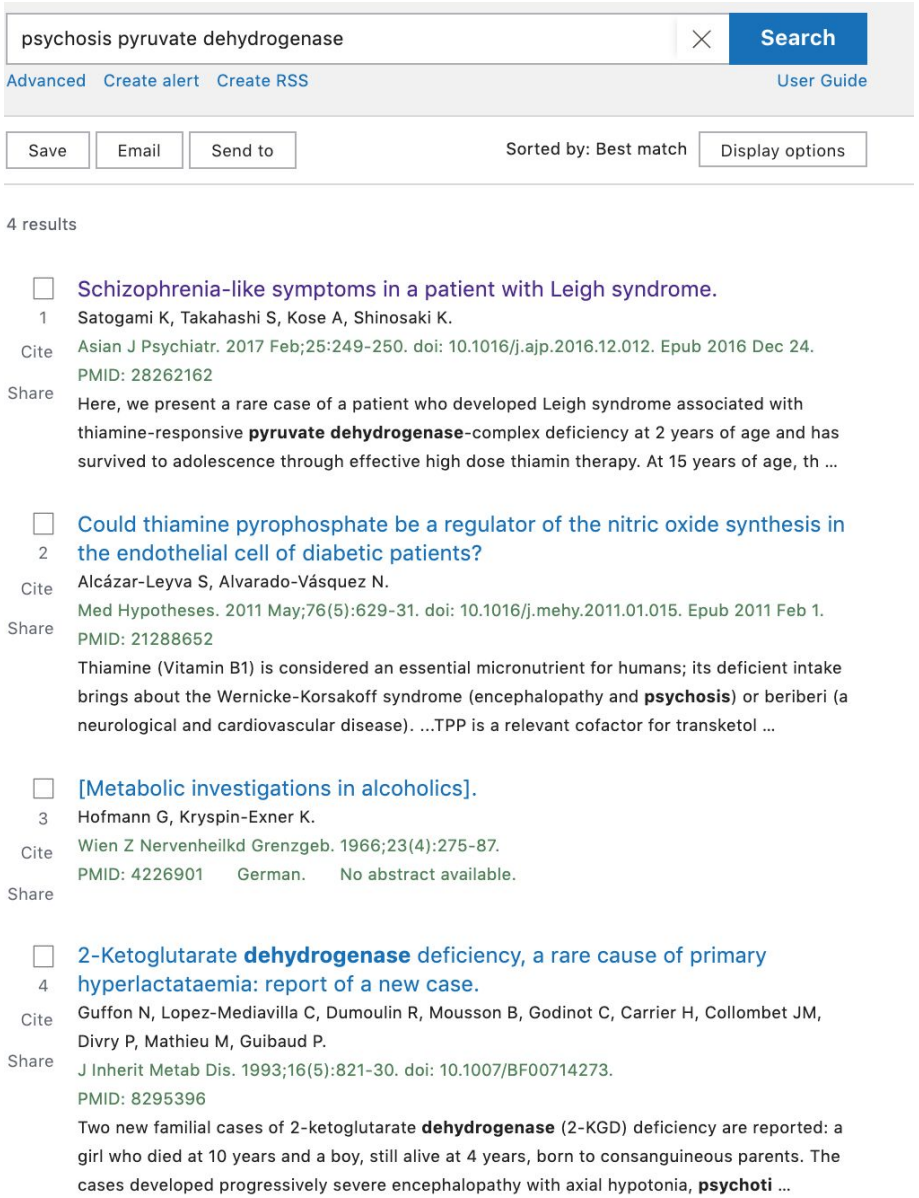
Participated in school, needed some extra help but can read, do math, write

Now having audio & visual hallucinations

Parents feel like he is disengaged

- He seems mild overall
- Are hallucinations related to his disease? To his meds? Seizures?
- Schizophrenia isn’t rare…

WE LEARN FROM EACH OTHER



Dear Mito listserv,
Is this an association?

Hi Rebecca,
We had an engineer with PDCD in his middle age. He was doing great, had an advanced degree and then developed schizophrenia symptoms.

PRECLINICAL TRIAL WORK

Component	**Rationale**	**Lesson**	**Strategy**
Natural history	How do we know if we're making it better?	We don't understand late symptoms/full spectrum	Longitudinal natural history studies
Quality of life	The patient gets to judge if they're "better"	This is highly individual	Patient-reported outcomes & surveys
Are there markers of response?	Quality of life might take a long time to improve	Biomarkers are hard and imperfect	Quantification of QOL

HOW CAN YOU BE A GOOD PATIENT ADVOCATE

- Physicians need to see ”a lot” of patients with the same rare disease
  - Form groups of patients
  - Don’t feel bad about a second opinion
- Find umbrella groups for advocacy & trials.
- But make sure to remind people that you’re an individual
- Be honest about your values & how you’re actually feeling
- Understand we’re on a journey with you & it takes time!

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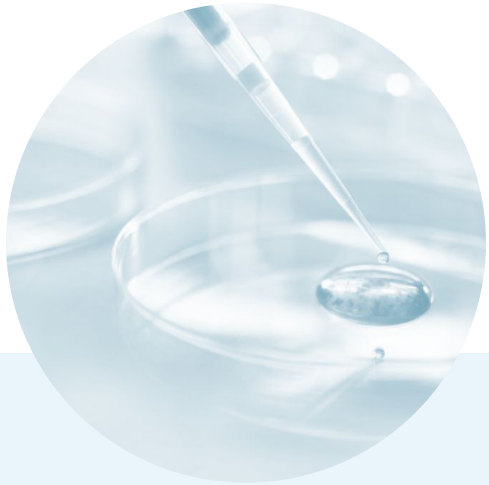

THANK YOU

QUESTIONS?