A Generalist's Approach to Inborn Errors of Metabolism

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Alberta Children's Hospital

Objectives (Junior Residents)

By the end of this session, residents will be able to:

1. Categorize the various Inborn Errors of Metabolism
2. Describe several ways in which Inborn Errors of Metabolism can present
3. Name some initial screening labs when an Inborn Error of Metabolism is suspected

Objectives (Senior Residents)

By the end of this session, residents will be able to:

1. Categorize the various Inborn Errors of Metabolism
2. Describe the acute, and chronic ways that Inborn Errors of Metabolism can present
3. Know when to clinically suspect an Inborn Error of Metabolism
4. Order appropriate investigations, and interpret them to make a diagnosis of an Inborn Error of Metabolism
5. Begin management for a patient with a newly diagnosed metabolic disorder, and patient with a known metabolic disorder with acute deterioration

What is an Inborn Error of Metabolism?

A large group of rare genetic diseases that generally result from a defect in an enzyme or transport protein which results in a block in a metabolic pathway.

Remember…pattern recognition is key

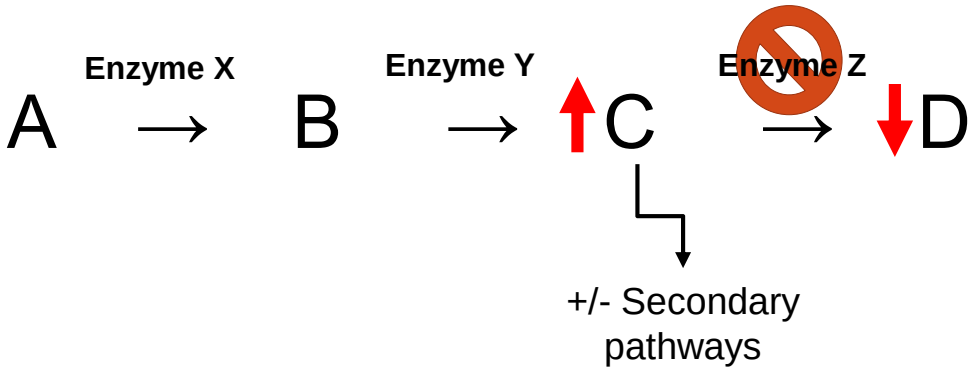
Metabolic Principles

Clinical features and phenotypic spectrum of IEMs are widely variable

- Genetic variation
- Age
- Acuity
- Severity
- Systems affected

However, you can find common patterns in presentation by understanding biochemistry

Metabolic Principles



Clinical features of IEMs can result from direct and indirect effects of:

- Accumulated substrates proximal to the block (eg. Galactosemia)
- Effects on secondary pathways (eg. Hyperammonemia in OAs)
- Deficient products distal to the block (eg. Hypoglycemia in GSD type1a)
- Accumulation of unusual intermediates (eg. Secondary carnitine deficiency)

INBORN ERROR OF METABOLISM

SMALL MOLECULE

PROTEIN

Aminoacidopathy

- Phenylalanine (PKU)
- Tyrosine (Tyrosinemia, Albinism)
- Methonine (Homocysteinuria)
- Cysteine (Sulfite oxidase deficiency)
- Trypotophan (Hartnup)
- Branched chain amino acids (MSUD
- Glycine (Hyperglincinemia)

Urea Cycle Defects

- CPS
- NAGS
- OTC
- Arginosuccinate sythetase/lyase
- Arginase

Organinc Acidemia

- Methylmalonic
- Propionic
- Isovaleric
- multiple carboxylase biotinidase deficiency
- Glutaric acidemia

CARBOHYDRATE

Glycogen Storage disease

- GSD 1 – Von Gierke
- GSD II – Pompe
- GSD IV – Debrancher enzyme deficiency
- Phosphorylase kinase deficiency
- Glycogen synthetase deficiency
- Fackoni Bickel
- McArdle
- Lactate dehydrogenase deficiency

Fructose

- Fructosuria
- Herediatry Fructose Intolerance

Galactose

- Galactosemia
- Galactokinase deficiency

Disorders of Gluconeogenesis

- Fructose 1,6 dipohsphatse deficiency
- Phosphoenolpyruvate carboxykinase deficiency

Disorders of Pyruvate Metabolism

- Pyruvate dehydrogenase complex defect
- Pyruvate carboxylase deficiency
- Respiratory chain defects (oxidative phosphorylation problems)

Disorders of Pentose Metabolism

- Pentosuria
- Transaldolase deficiency

LIPIDS

B oxidation defects

- SCAD
- MCAD
- LCAD
- VLCAD

Carnitine Disorders

- Primary carnitide deficiency
- Carnitine palmitoyltranferase I (CPTI)
- CPT II

Oxidative Phosphorylation

- Glutaric aciduria II
- Multiple Acyl CA Dehydrogenase deficiency

Ketogenesis

- HMG CoA Synthetase
- HMG CoA Lyase

Hyperlipoproteinemia

- Hypercholesterolemia
- Hypertriglyceridemia
- Disorders of HDL metabolism
- Low cholesterol (Abetalipoproteinemai, Smith Lemli Opitz)
- Disorders of Intracellular Cholesterol metabolsim

COMPLEX MOLECULE/ORGANELLE

PEROXISOMAL (VLCFA Breakdown)

Disorder of Peroxisomal Import

- Zellweger
  - Neonatal Adrenoleukodystrophy
  - Infantile Refsum disease
  - Rhizomelic chondrodysplasia punctate

Defect of Single Peroxisomal Enzymes

- X linked Adrenoleukodystrophy
  - Childhood cerebral form
  - Adolsecent
  - Adrenomyeloneuropathy
  - Addisons
- Acyle CoA Lyase deficiency
- Classic Refsum disease

LYSOSOMES

Mucopolysaccharidoses

- I – Hurler/Shiae
- II – Hunter
- III – San Fillipo
- IV – Morquio
- VI – Maroteaux Lamy
- VII – Sly
- IX

Sphingolipidoses

- Fabry
- Farber
- Gaucher
- GM1 gangliosidoses
- GM2 gangliosidoses (Tay sach, Sandhoff)
- Niemann Pick
- Krabbe
- Metachromic leukodystrophy

Oligosaccharidoses

- Aspartylglucosaminuria
- Fucosidosis
- Mannosidosis
- Sialidosis
- Schindler disease

Lipid Storage Disorders

- Nieman Pick
- Wolman
- Ceroid Lipofuscinosis

Mucolipidoses

- II – I cell disease
- III – Pseudo Hurler
- IV

MITOCHONDRIA

- Kearns Sayre
- Earson
- Chronic progressive external opthalmoplegia
- MELAS
- MERRF
- NARP
- MILS – Maternally inherited Leigh Syndrome
- Mitochondrial myopathy
- SNHL – Non syndromeic aminoglycoside induced sensoryneural hearing loss

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Porphyria
Disorders of Metal Metabolism
Purine and Pyrimadine Metabolism

Disorders of protein metabolism

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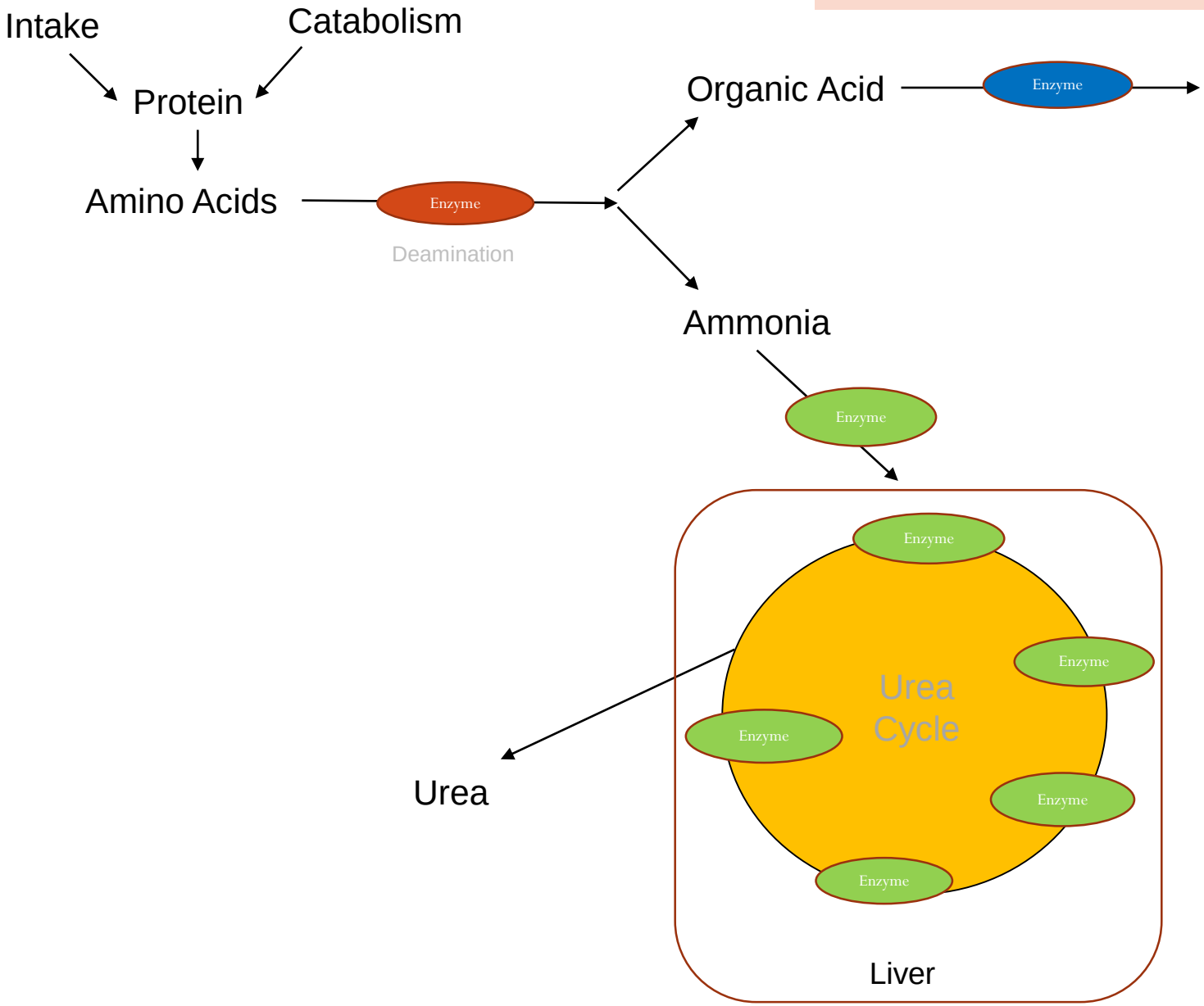

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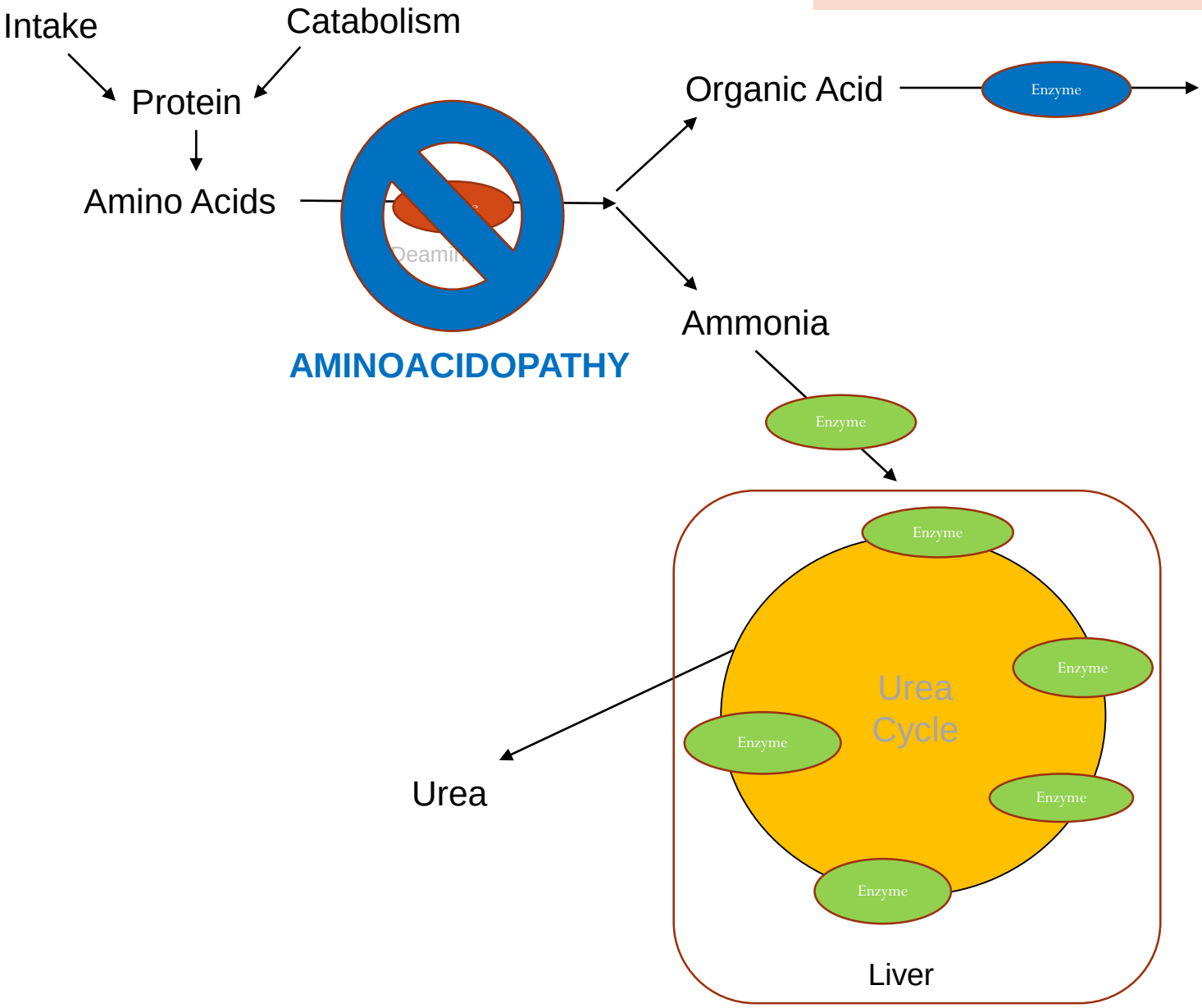

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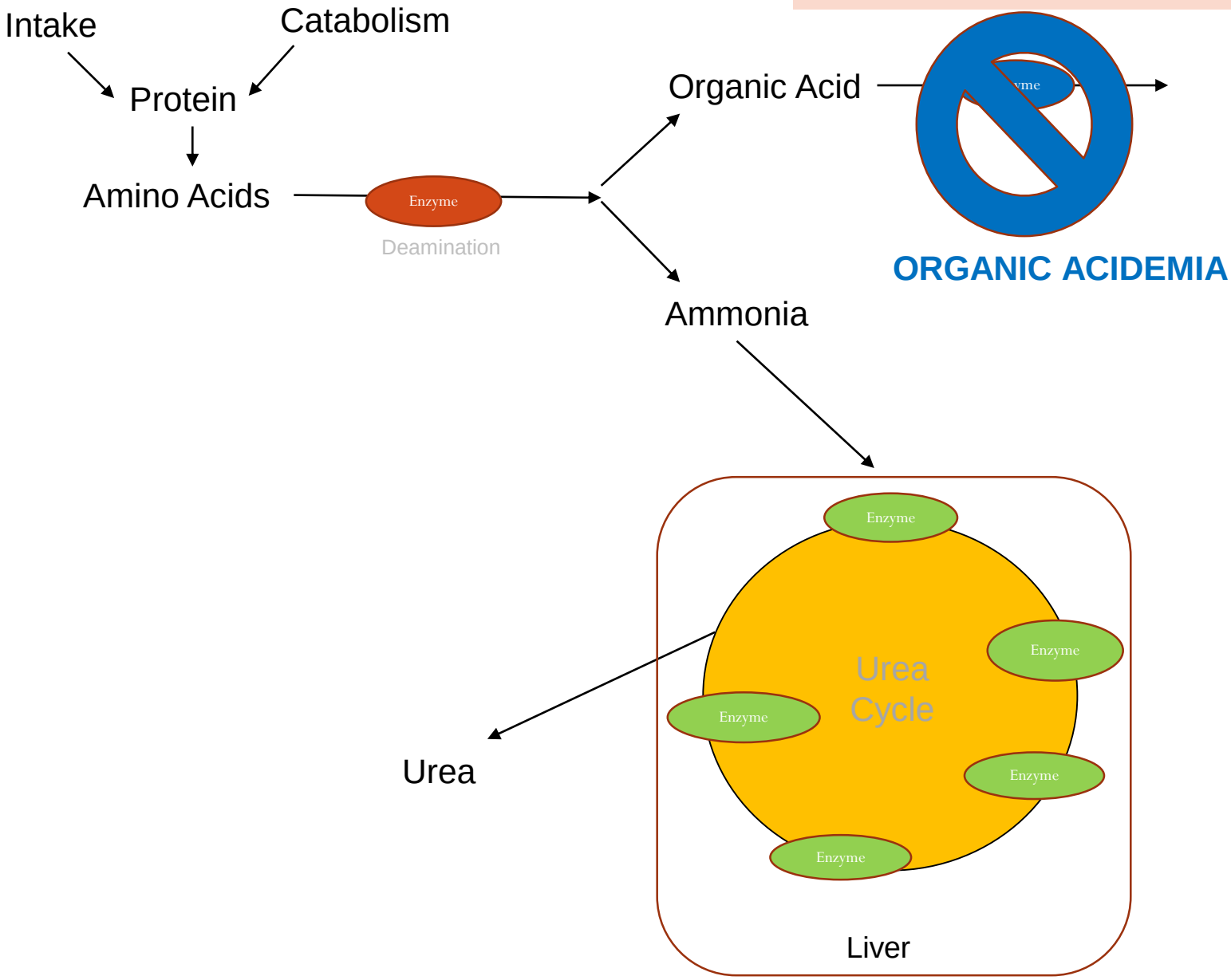

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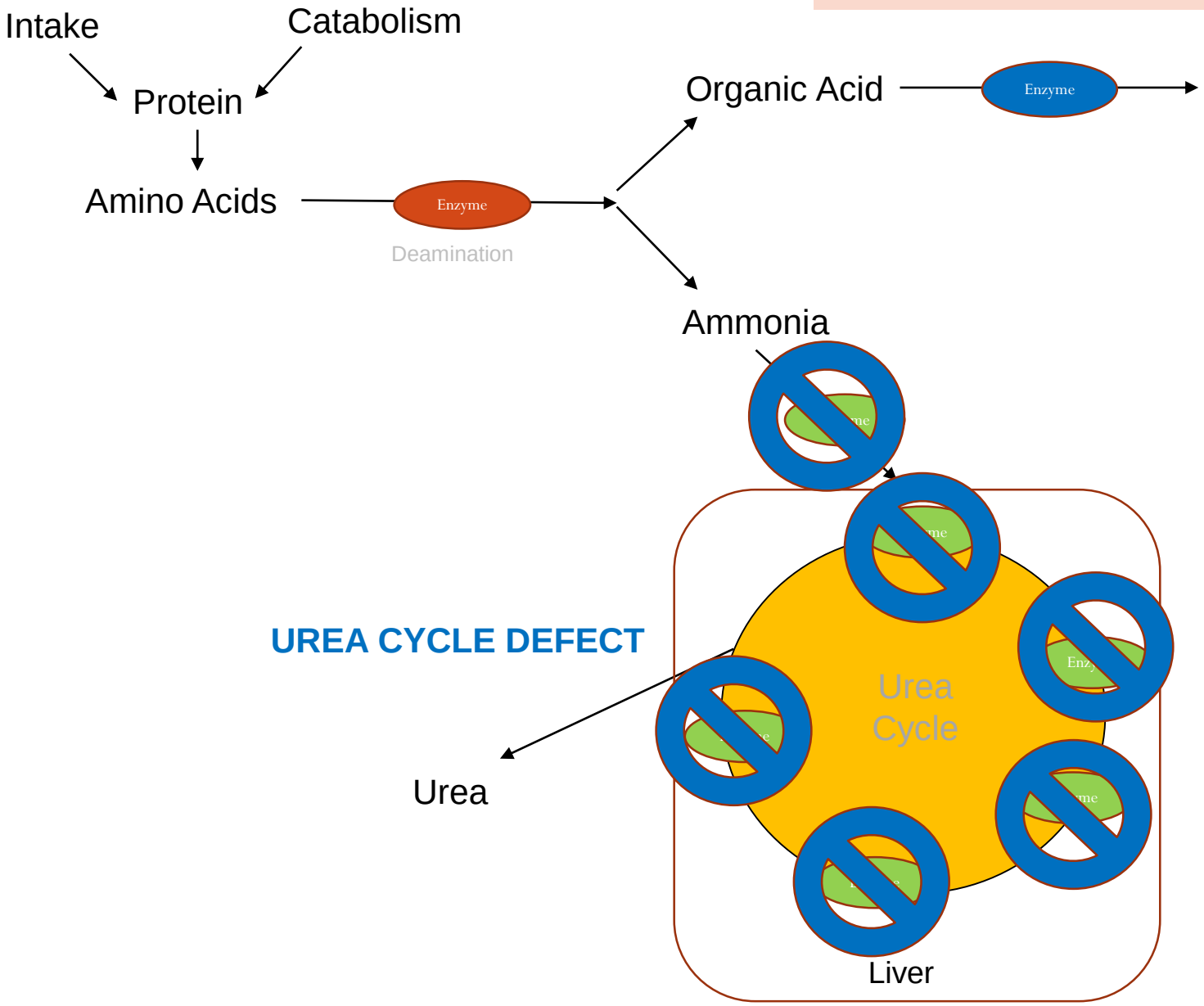
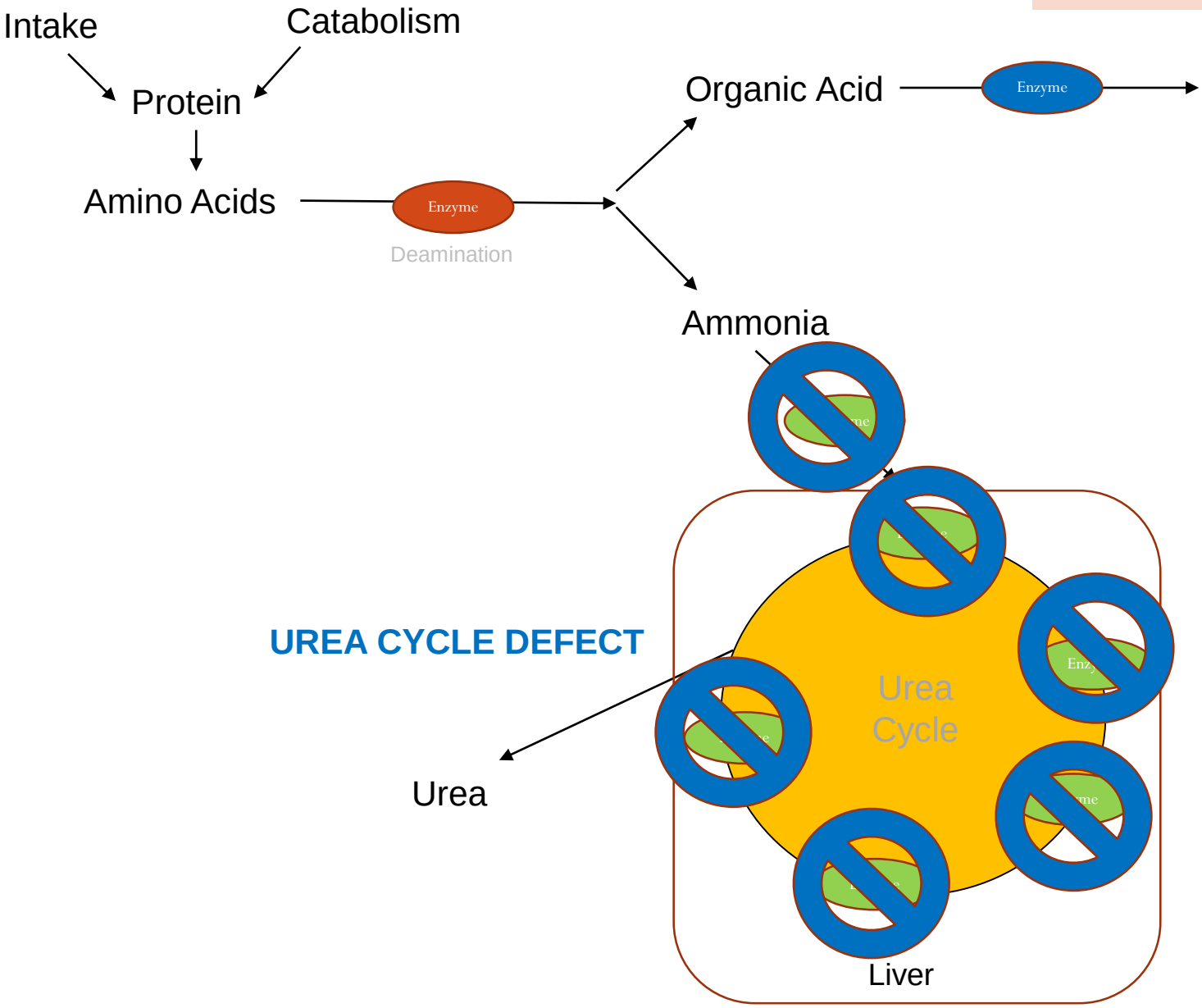


Urea Cycle Defects

UREA CYCLE DEFECTS



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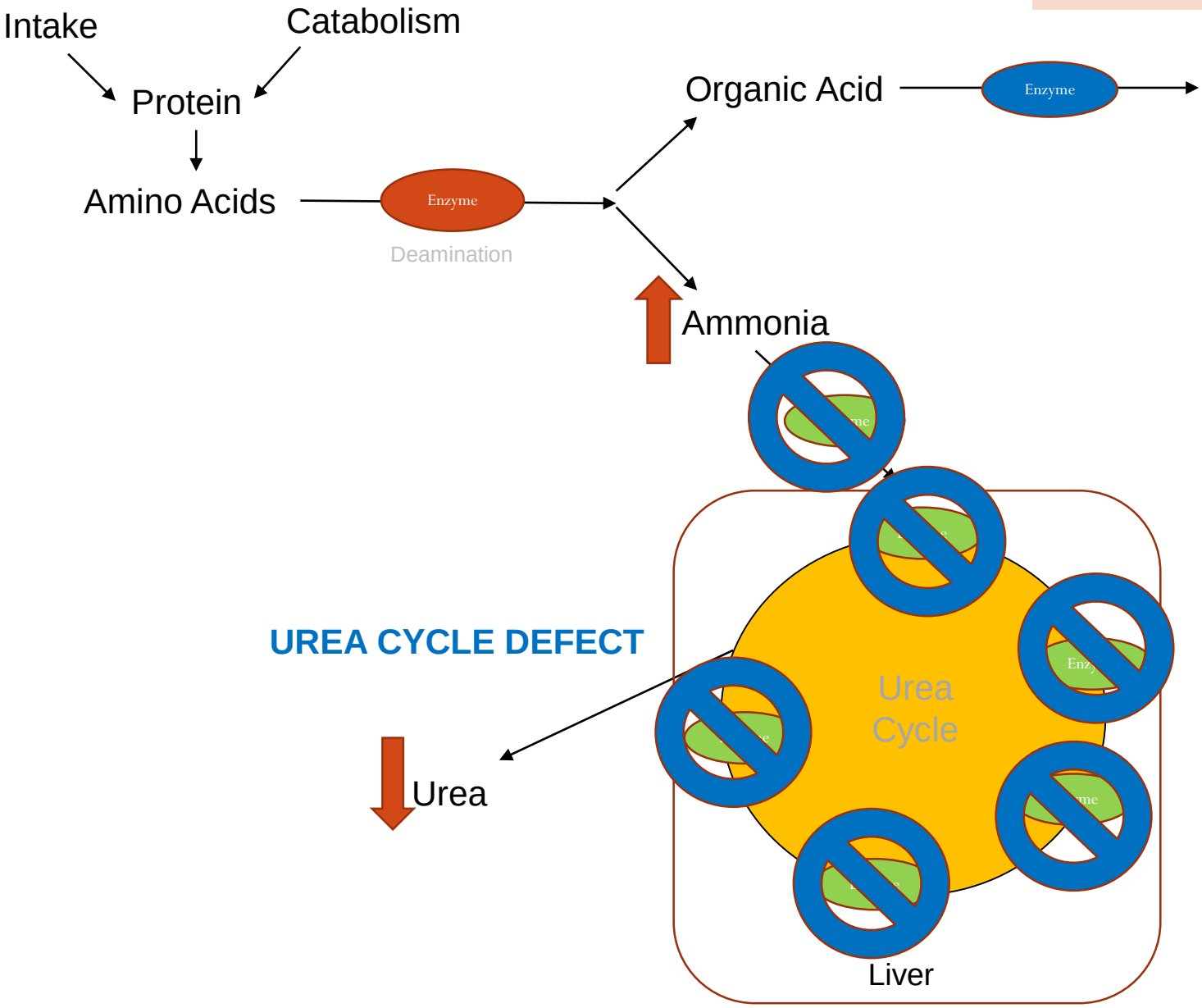


Urea Cycle defects

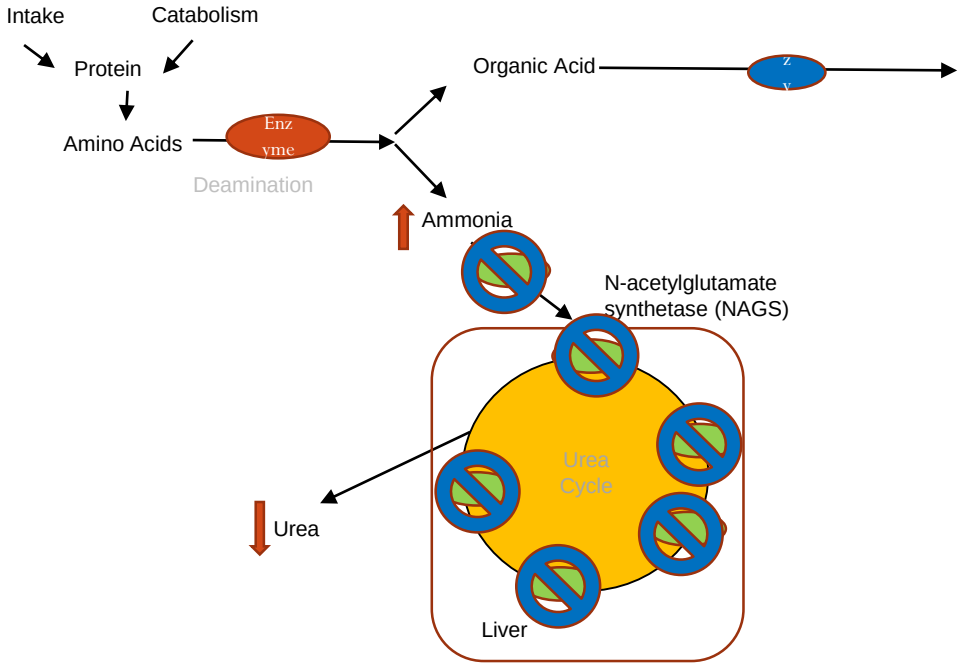
- Clinical Presentation?
- Physical Exam?
- Labs?

Urea Cycle defects

- Clinical presentation
  - Generally presents first days of life
  - Altered LOC, lethargy, vomiting, cerebral edema
  - Tachypnea
  - Shock-like picture
  - Can present later – recurrent under-recognized episodes leading to developmental delay, protein aversion

Urea Cycle Defects

- Labs
  - Hyperammonemia
  - Respiratory alkalosis
  - No, or little urea – out of keeping of clinical state
  - May have hypoglycemia
  - Labs suggestive of multiorgan failure
  - Prolonged metabolic stress leads to pancytopenia



Urea Cycle Defects

Problem	Labs	Clinical Presentation
Enzymatic deficiency	Hyperammonemia Respiratory alkalosis	Lethargy Obtundation Seizures Tachypnea
Progressive worsened feeding	Metabolic acidosis (mild)	Tachypnea Poor perfusion/shock
Hypermetabolic/catabolic state	Hypoglycemia	Lethargy Obtundation
Shock	End organ labs abnormal	Poor perfusion End organ damage

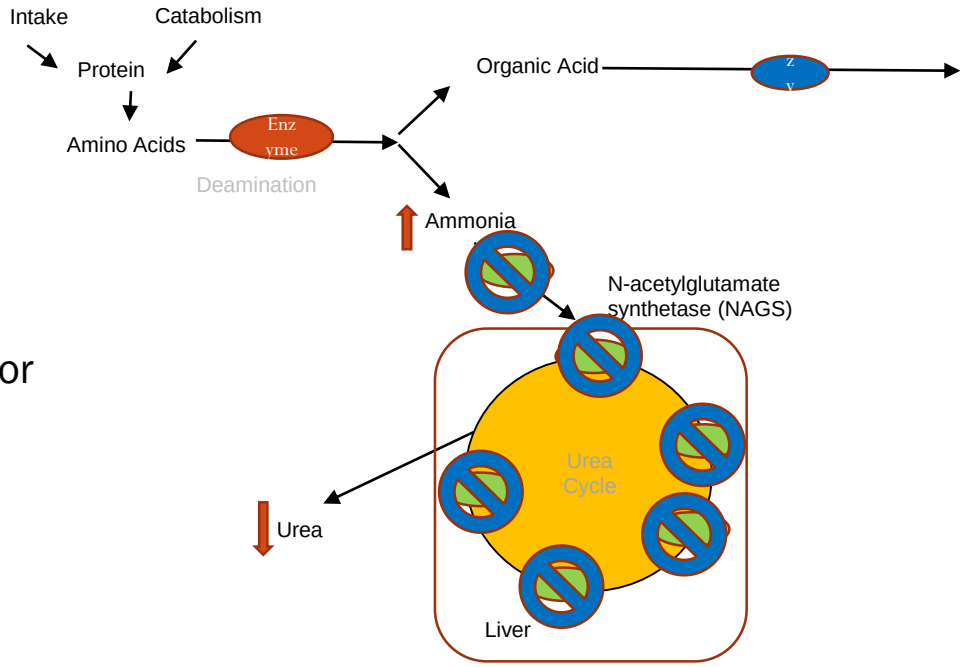
Urea Cycle Defects

- Diagnosis
  - Serum amino acids, organic acids
  - Urine organic acids (urine orotic acid)
  - Genetics

Urea Cycle Defects

MANAGEMENT PRINCIPLES:

1. ABCs
2. Stop protein/amino acid source
   - Stop protein intake
   - Stop catabolic process
   - Treatment of the precipitating factor
3. Eliminate toxic metabolites
4. Prevent and monitor for sequelae



Urea Cycle Defects

Stop protein/aa source and stop catabolism

- Halt any PO/GT intake until discussed with metabolics – they need specialized formula
- Aim for anabolism
  - IV fluids – high rate and high dextrose (D10). Maintain IV until PO is fully tolerated
  - High caloric supplementation in consultation with metabolics. (carbs and lipids)
  - Consider insulin
- Treat the precipitant – infection, injury, surgery, puberty, dietary change

Urea Cycle Defects

Eliminate toxic metabolites

- Dialysis: Indicated if severe hyperammonemia, coma, severe electrolyte disturbances
- Sodium benzoate, sodium phenylbutarate
- L-carnitine (PO or IV): restores free carnitine levels (, where carnitine levels are often low anyways)

Urea Cycle Defects

Prevent and monitor for sequelae

- Cerebral edema: Neurological monitoring. Maintain osmolality
- Other organ involvement

Urea Cycle Defects

Chronic/Long term management

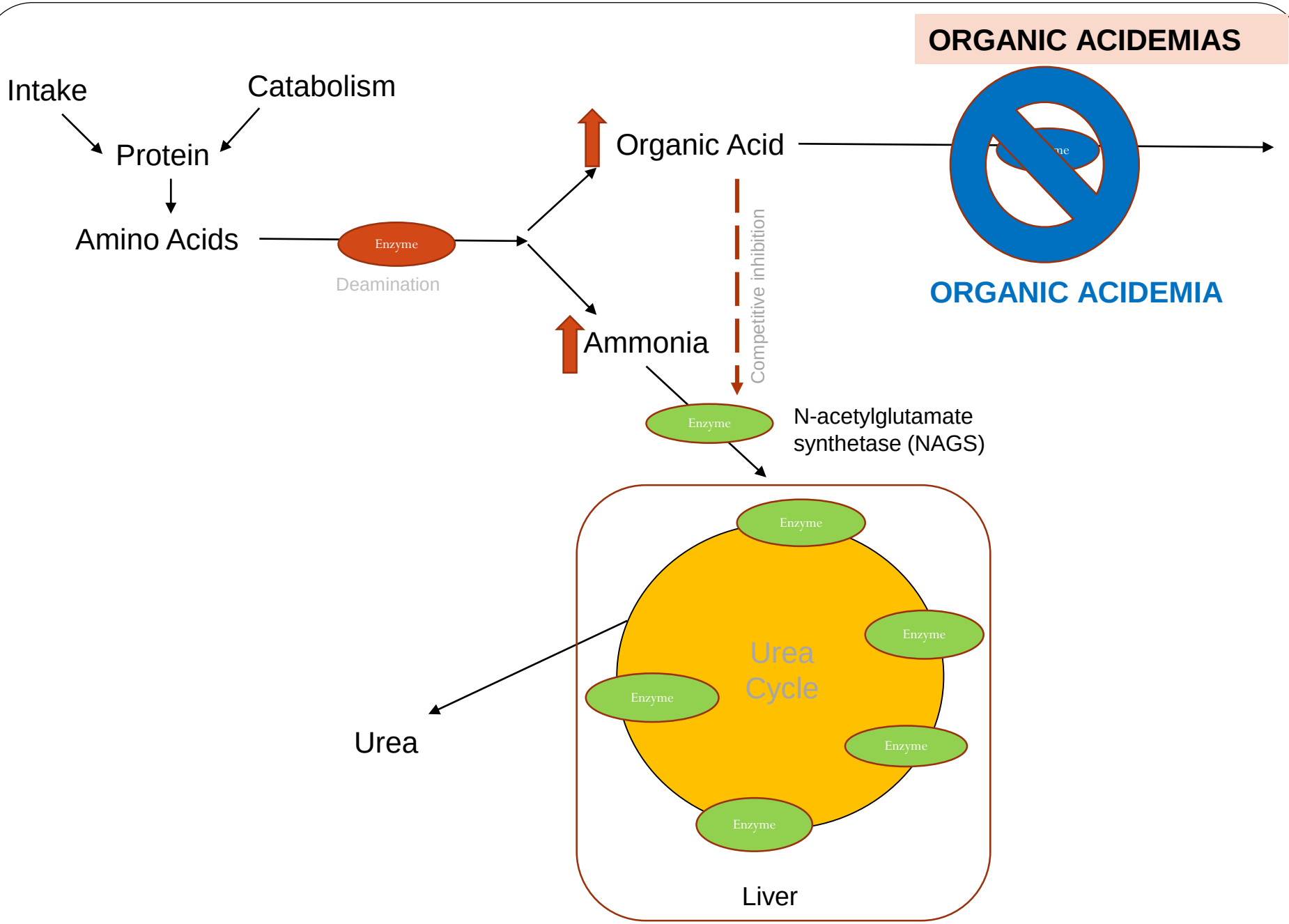
- Protein restriction
- Arginine or citrulline supplementation
- Sodium or glycerol phenylbutyrate
- Sick day management
- Liver transplant

Urea Cycle Defects

Specific Urea Cycle Defects

- Ornithine Transcarbamylase Deficiency (OTC)
- CPS
- NAGS
- Arginosuccinate sythetase/lyase
- Arginase

Organic Acidemia


ORGANIC ACIDEMIAS
Intake
Catabolism
Protein
Amino Acids
Enzyme
Deamination
Organic Acid
Ammonia
Competitive inhibition
ORGANIC ACIDEMIA
Enzyme
N-acetylglutamate synthetase (NAGS)
Urea
Enzyme
Enzyme
Enzyme
Enzyme
Enzyme
Urea Cycle
Liver

Organic Acidemias

- Clinical Presentation?
- Physical Exam?
- Labs?

Organic Acidemias

- Clinical presentation
  - Infancy
  - Progressively worse feeding
  - Vomiting and lethargy
  - Tachypnea
  - Shock
  - Multiorgan failure
  - Stroke
  - Late onset cardiomyopathy and cardiac dysrhythmia

Organic Acidemias

- Labs and diagnosis
  - Hyperammonemia
  - Anion gap metabolic acidosis
  - Marked ketonuria
  - May have hypoglycemia
  - Labs suggestive of multiorgan failure (hepatitis, renal failure, pancreatitis)
  - Prolonged metabolic stress leads to pancytopenia

Organic Acidemias

Biochemical problem	Labs	Clinical Presentation
Increased organic acid production	Hyperammonemia (NAG synthase inhibition)	Lethargy Obtundation Tachypnea Seizures
	AG Metabolic acidosis (ketone and organic acid production)	Tachypnea Poor perfusion/shock
Increased glucose utilization/hypermetabolic state	Hypoglycemia	Lethargy Obtundation
	Ketosis and ketogenesis	Vomiting Fatty liver/hepatomegaly (mobilized FFA stores)

Organic Acidemias

- Diagnosis
  - Urine organic acids
  - Acyl carnitine and carnitine profile

Organic Acidemias

MANAGEMENT PRINCIPLES:

1. ABCs
2. Stop protein/amino acid source
   - Stop protein intake
   - Stop catabolic process
   - Treatment of the precipitating factor
3. Eliminate toxic metabolites
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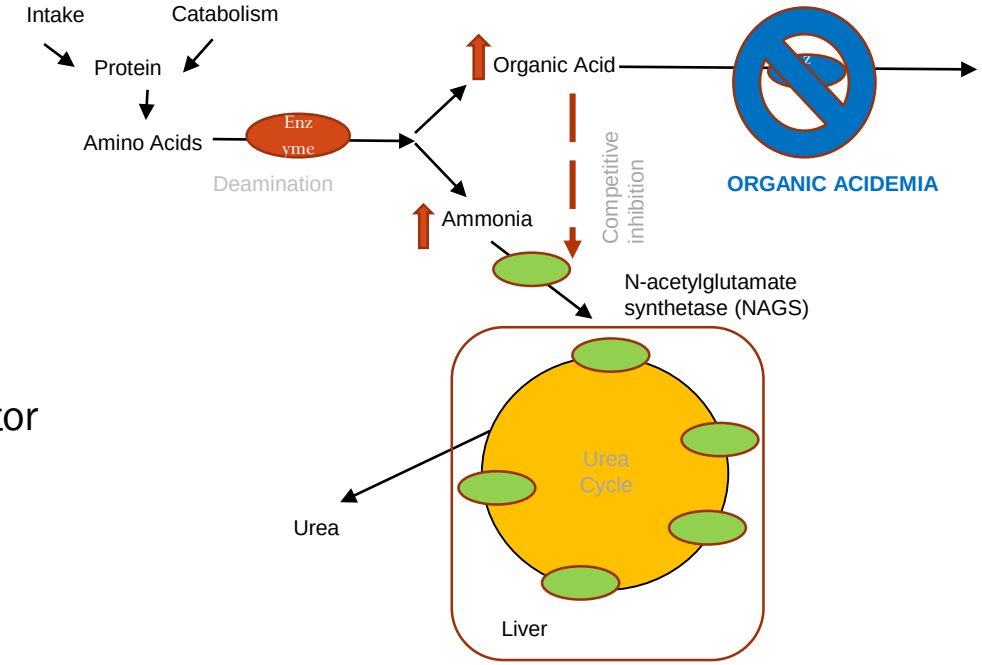


Organic Acidemias

Stop protein/aa source and stop catabolism

- Halt any PO/GT intake until discussed with metabolics – they need specialized formula
- Aim for anabolism
  - IV fluids – high rate and high dextrose (D10). Maintain IV until PO is fully tolerated
  - High caloric supplementation in consultation with metabolics. (carbs and lipids)
  - Consider insulin
- Treat the precipitant – infection, injury, surgery, puberty, dietary change

Organic Acidemias

Eliminate toxic metabolites

- Dialysis: Indicated if intractable acidosis, severe hyperammonemia, coma, severe electrolyte disturbances
- L-carnitine (PO or IV): Conjugates and detoxifies organic acids, and restores free carnitine levels (, where carnitine levels are often low anyways)
- Carglumic acid: NAG analogue

Organic Acidemias

Prevent and monitor for sequelae

- Acute pancreatitis: Check amylase and lipase, monitor clinically
- Strokes: Neurologic monitoring. Consider CT/MRI if neuro symptoms
- Cerebral edema: Neurological monitoring. Maintain osmolality
- Other organ involvement

Organic Acidemias

Chronic/Long term management

- Dietary restriction
- Vitamin supplementation
- Carnitine supplementation
- Sick day management
- Transplantation

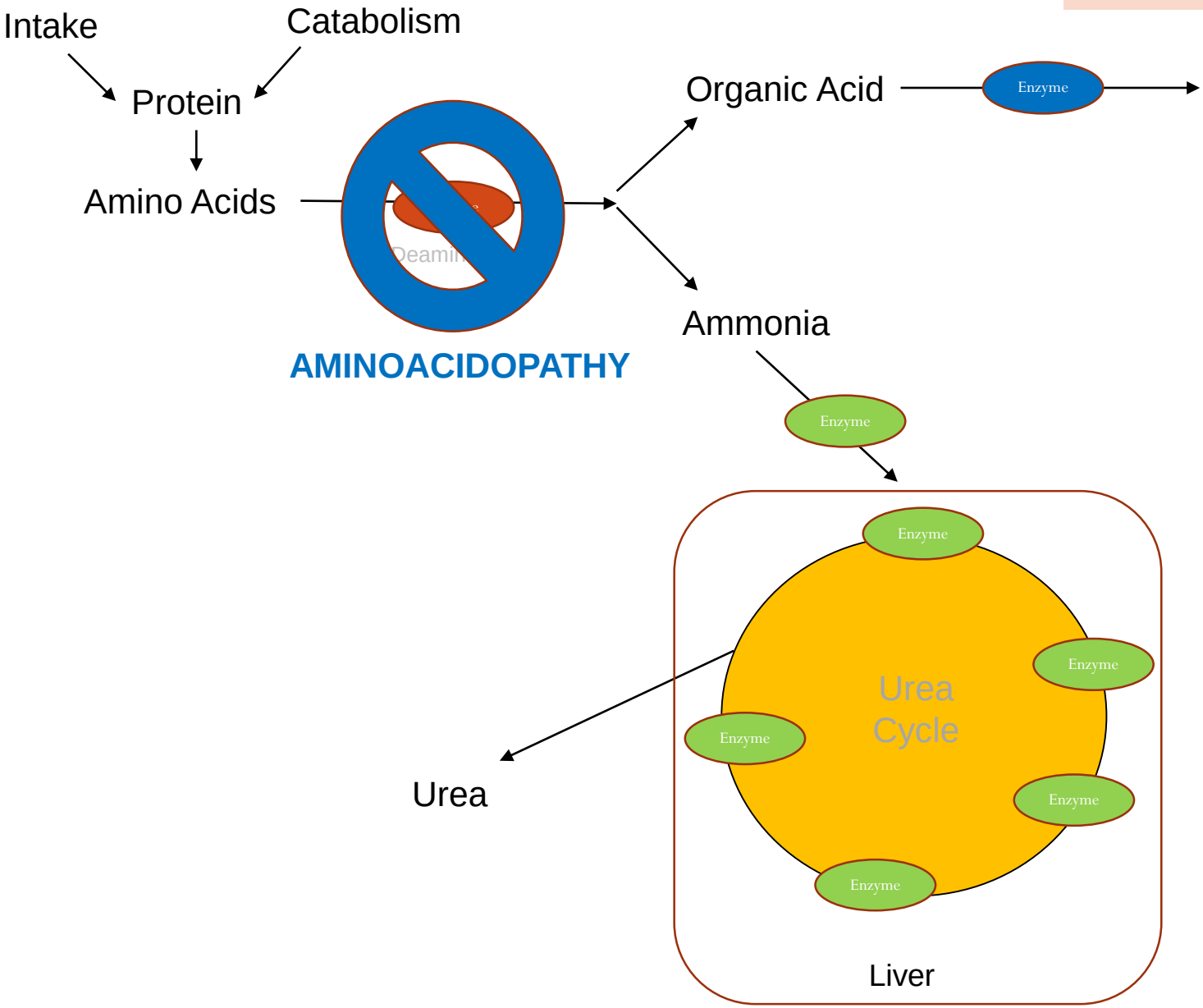
Organic Acidemias

Specific Organic Acidemias

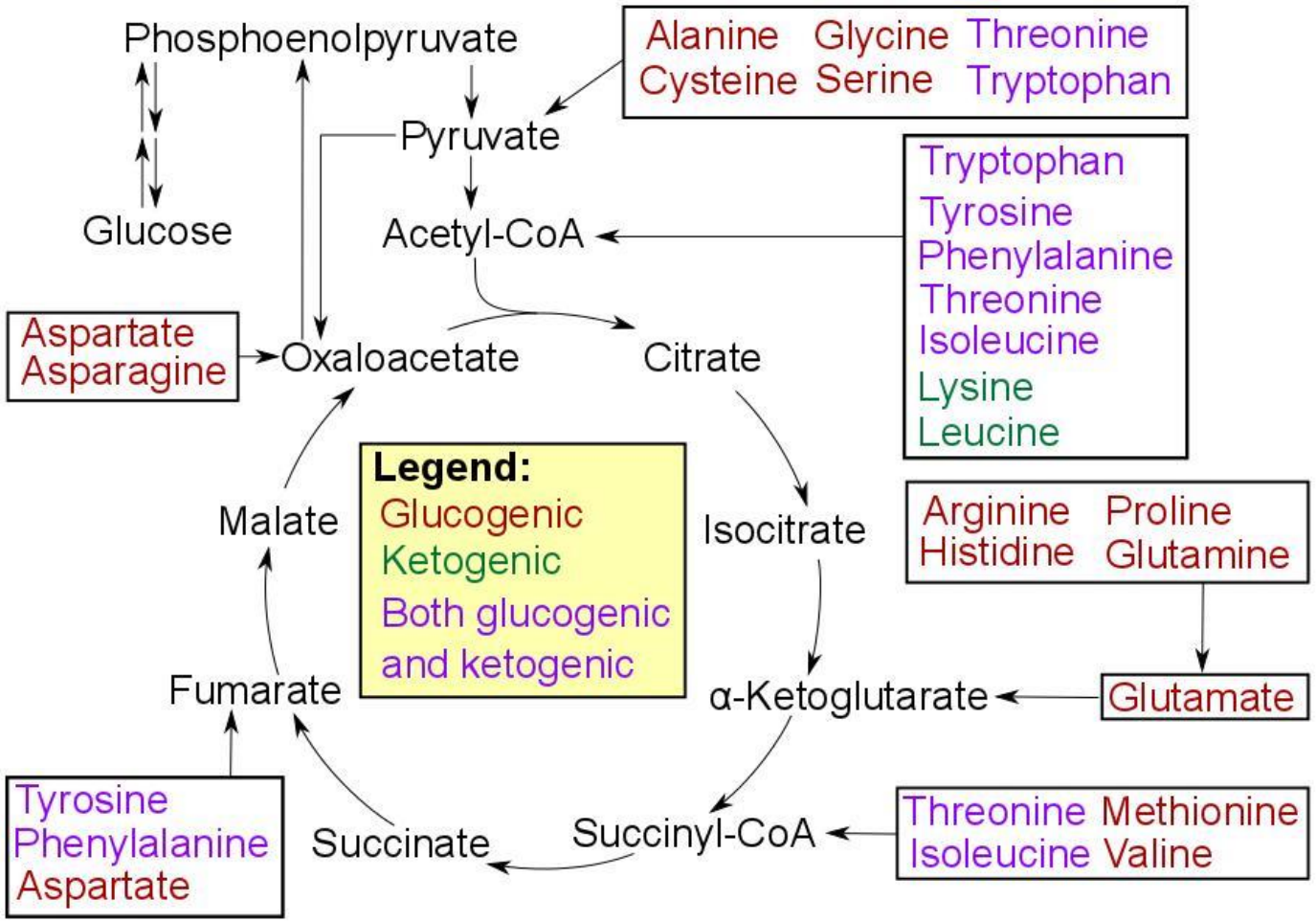
- Propionic Acidemia
- Methylmalonic Acidemia
- Glutaric Acidemia

Aminoacidopathy

AMINOACIDOPATHIES



Why is the clinical presentation so heterogeneous? Because of THIS



Reference: https://step1.medbullets.com/biochemistry/102091/amino-acid-catabolism

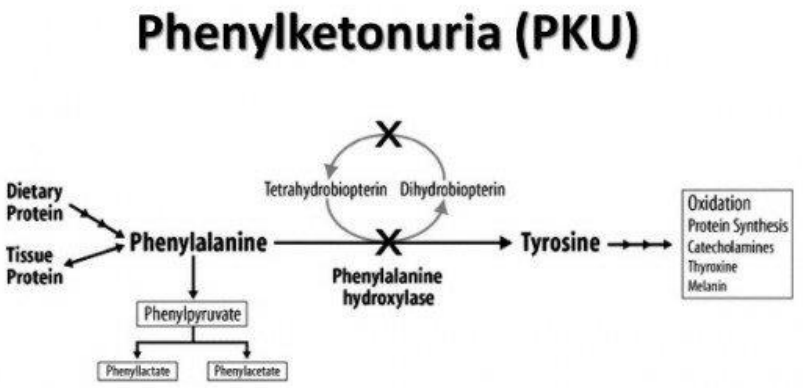
Aminoacidopathies

- Enzymatic block prevents metabolism of CERTAIN amino acids (, not all)
- Clinical presentation depends on which block occurs, and what the toxic metabolites are. Presentation in this group is highly variable
- Examples:
    - Phenylalanine (PKU)
    - Branched chain amino acids (MSUD)

Aminoacidopathies

Phenylketonuria - Deficiency of Phenylalanine hydroxylase (occasionally, due to a BH4 metabolism defect)

- Clinical presentation
  - Microcephaly
  - GDD
  - Eczematous rash
  - Mood and cognitive disorders
  - Teratogenic – infants would be dysmorphic, microcephalic, IUGR, CHD
- Diagnosis
  - Newborn screen
  - Plasma amino acids, urine organic acids
- Treatment
  - Dietary restriction of phe, monitor blood phe levels
  - BH4 supplementation

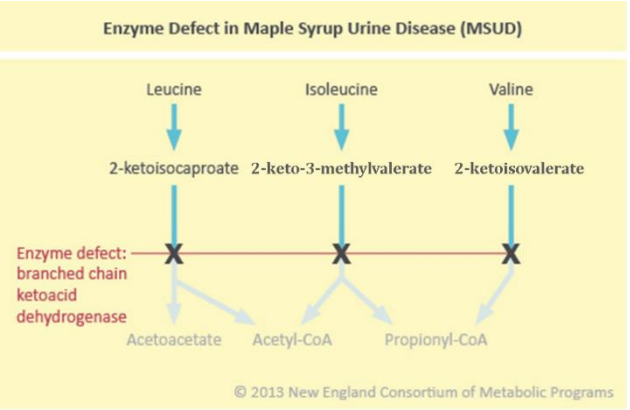


Reference: https://www.semanticscholar.org/paper/Food-products-made-with-glycomacropeptide%2C-a-whey-a-Calcar-Ney/f57c2c3d09518bd03c144db43f1857bdd98823d6/figure/0

Aminoacidopathies

Maple Syrup Urine Disease - Deficiency in branched chain a-ketoacid dehydrogenase

- Clinical presentation
  - Acute decompensations (high leucine intake, or catabolic stress)
  - Headache, confusion, hallucinations, lethargy, vomiting
- Diagnosis
  - Plasma amino acids, urine organic acids
- Treatment
  - Acute
    - Stop leucine intake
    - Stop catabolic stress (High dextrose, IV fluids, lipids, NG feeds)
    - Monitor for cerebral edema
    - Dialysis
  - Chronic
    - Life long leucine restriction



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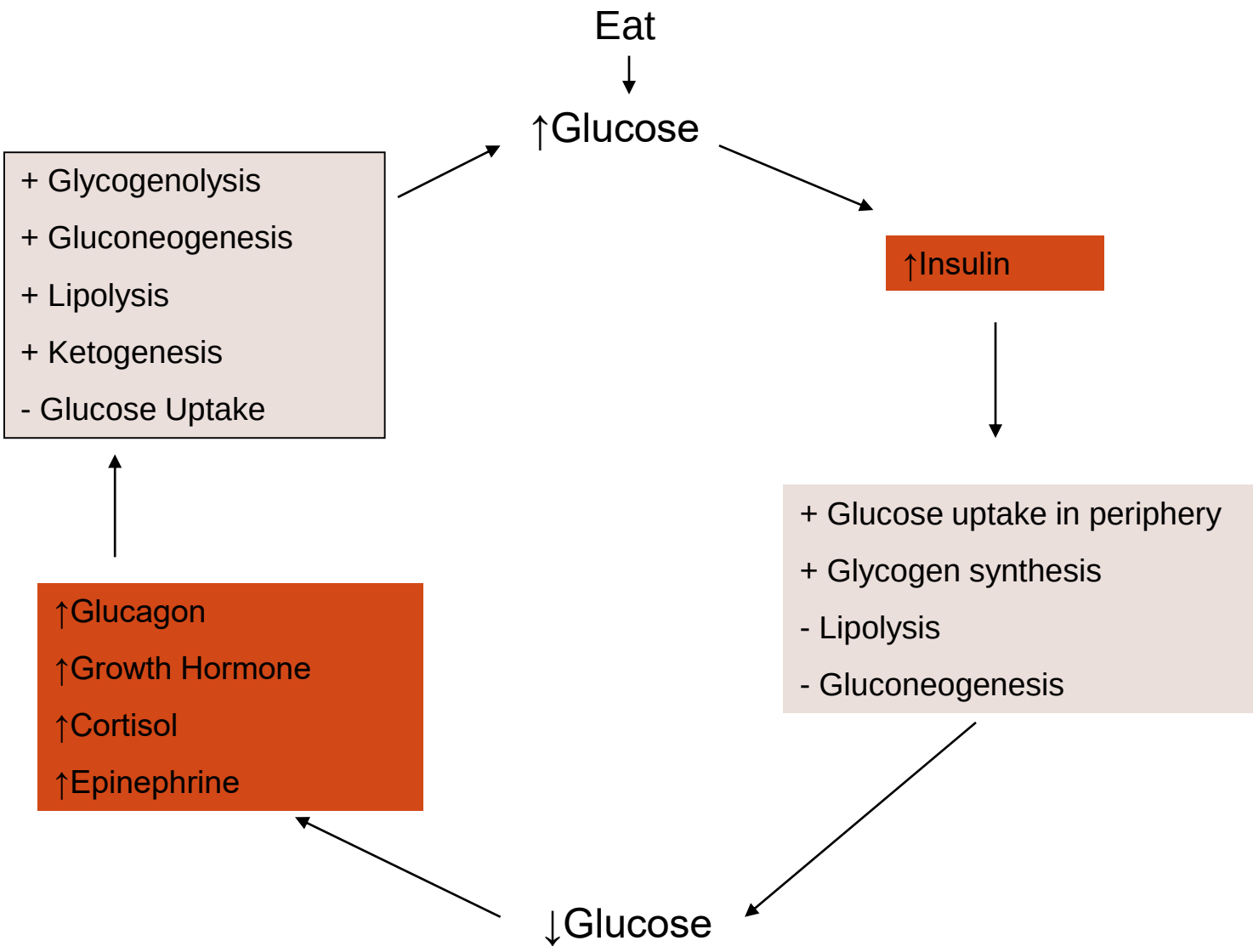
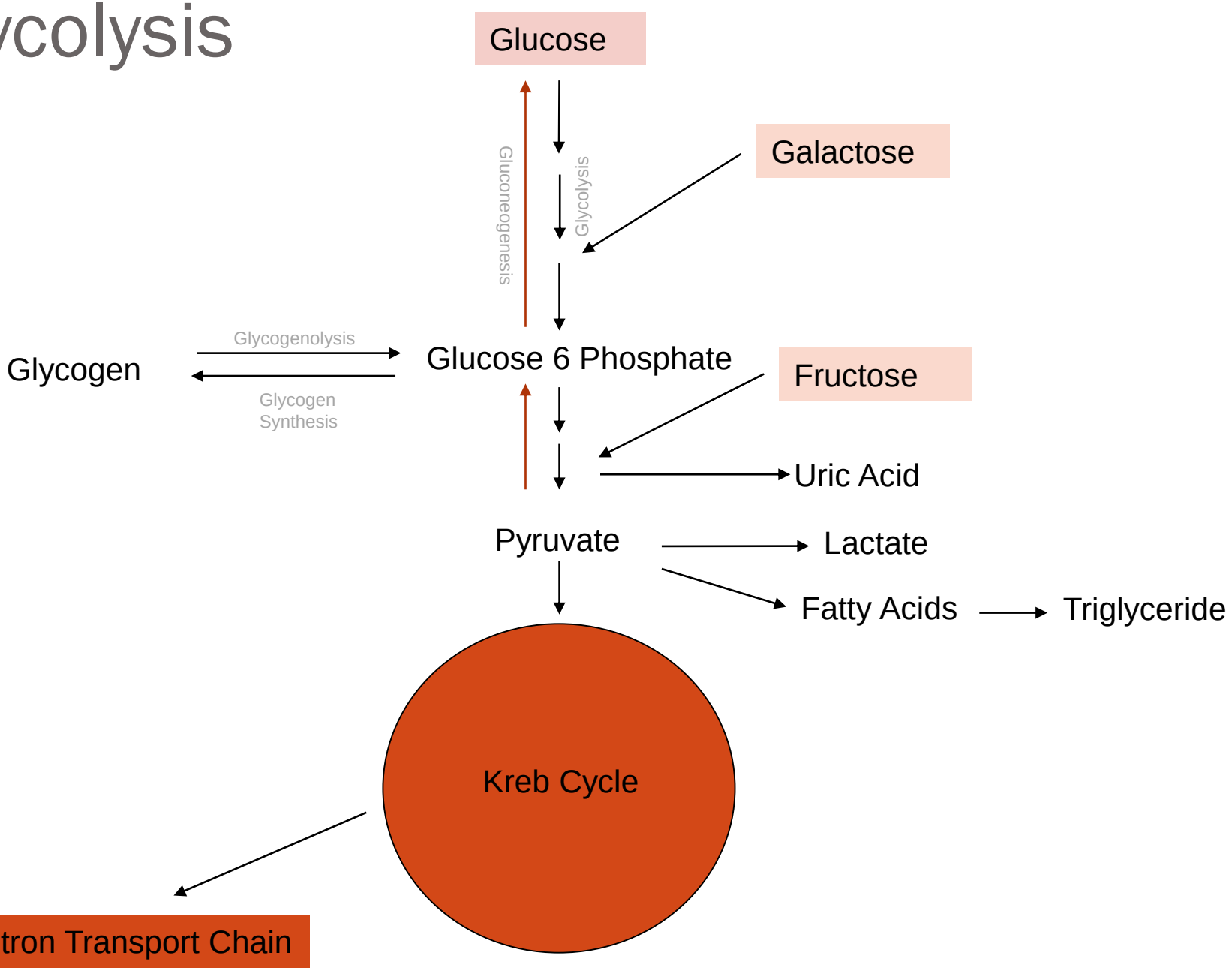
Purine and Pyrimadine Metabolism

Glucose Regulation



Glycolysis

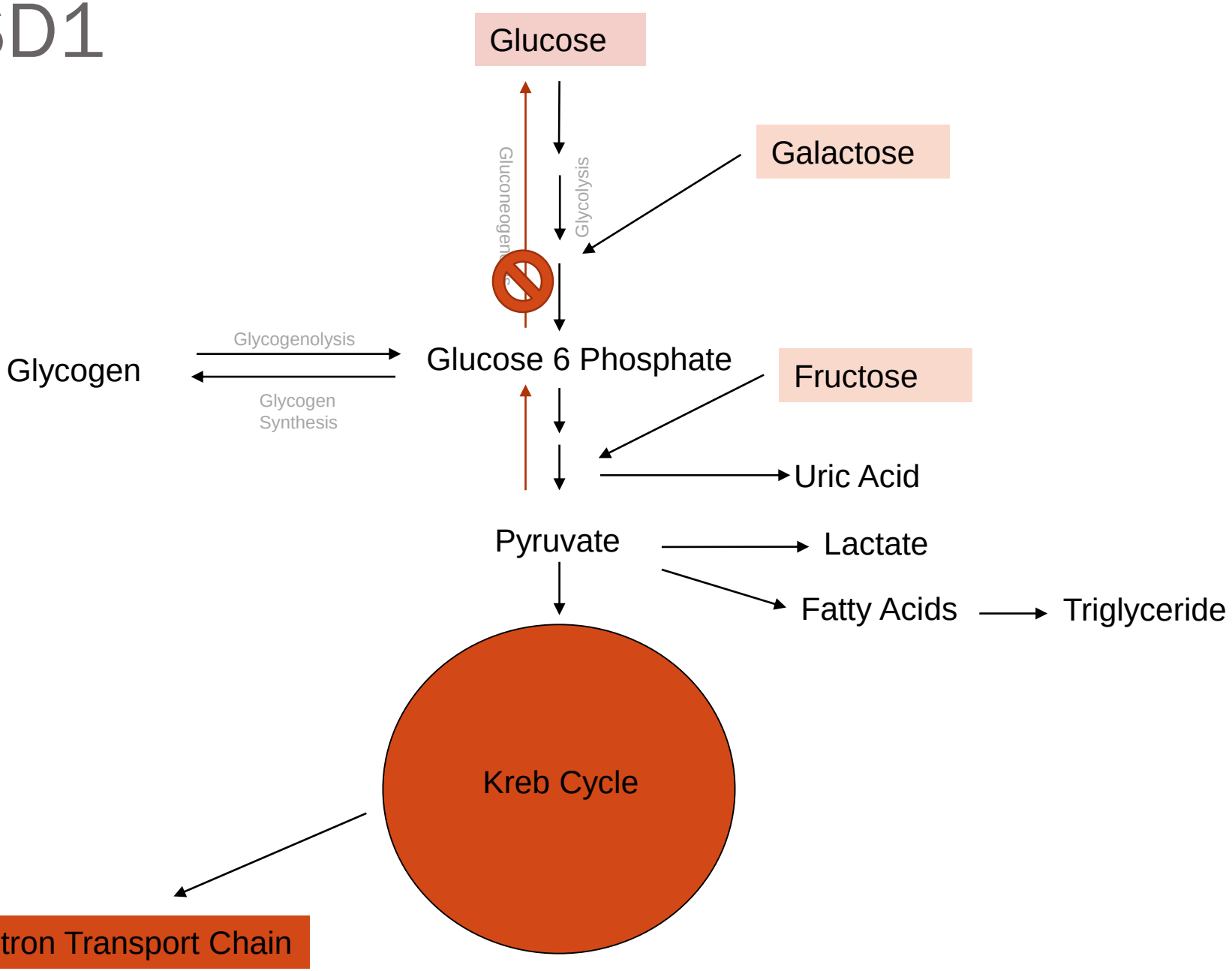

Glucose
Galactose
Gluconeogenesis
Glycolysis
Glycogen
Glycogenolysis
Glycogen Synthesis
Glucose 6 Phosphate
Fructose
Uric Acid
Pyruvate
Lactate
Fatty Acids
Triglyceride
Kreb Cycle
Electron Transport Chain

Glycogen Storage Diseases

Glycogen Storage Disease

- Inability to degrade stored glycogen
- Extremely heterogeneous clinical presentations

GSD1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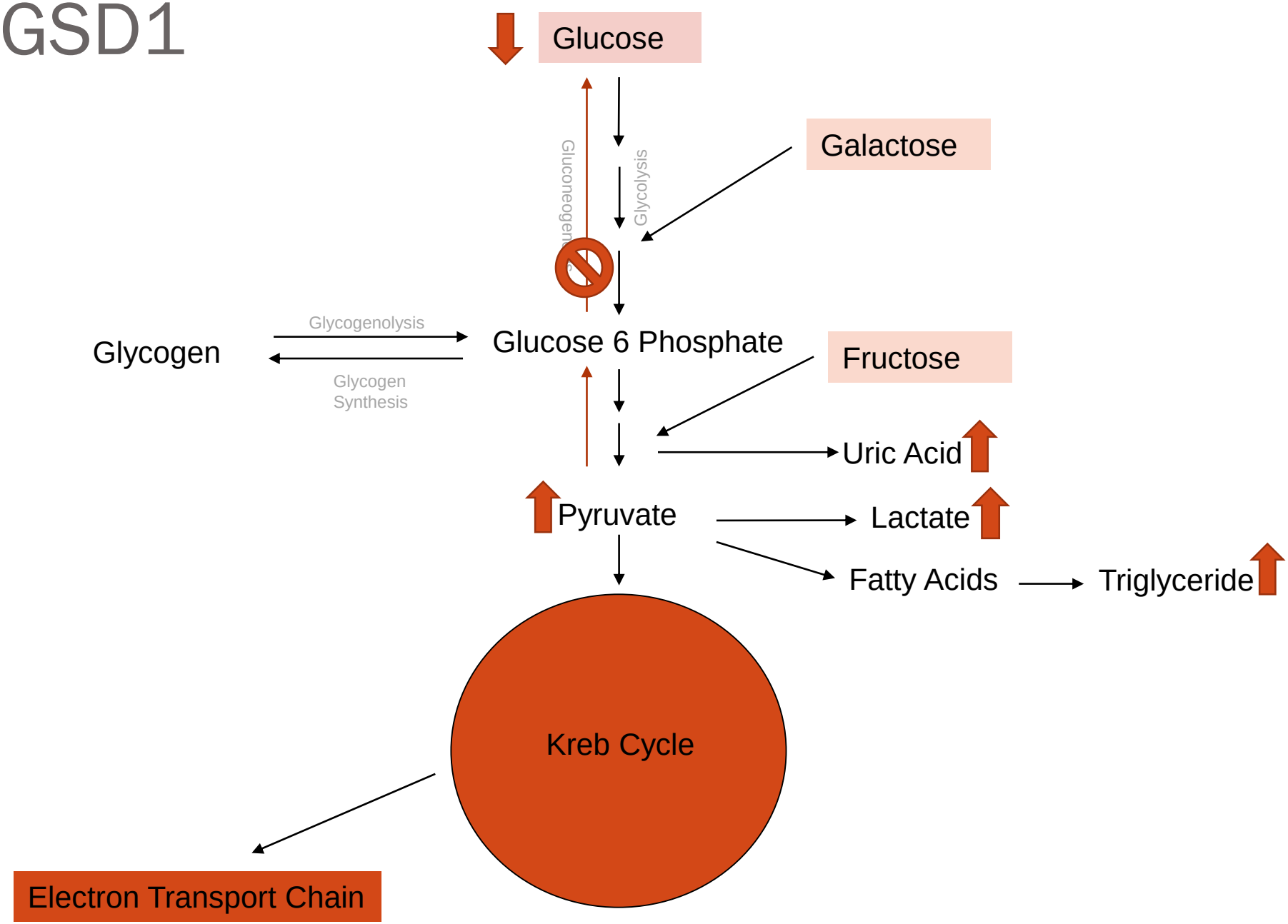
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GSD 1

- Clinical Presentation?
- Physical Exam?
- Labs?

GSD 1

- Clinical Presentation
  - Young (~3 month, when they start to stretch out their feeds)
  - Progressively poor feeding
  - Lethargy, seizures
  - Growth failure

- Physical Exam
  - Course facies? Cherubic
  - General – Lethargic, pale
  - CVS/Resp – Normal
  - Abdo – May have hepatomegaly

- Labs
  - Ketotic hypoglycemia
  - Lactic acidosis
  - Hyperuricemia
  - Hypertriglyceridemia
  - Type 1b has neutropenia

GSD 1

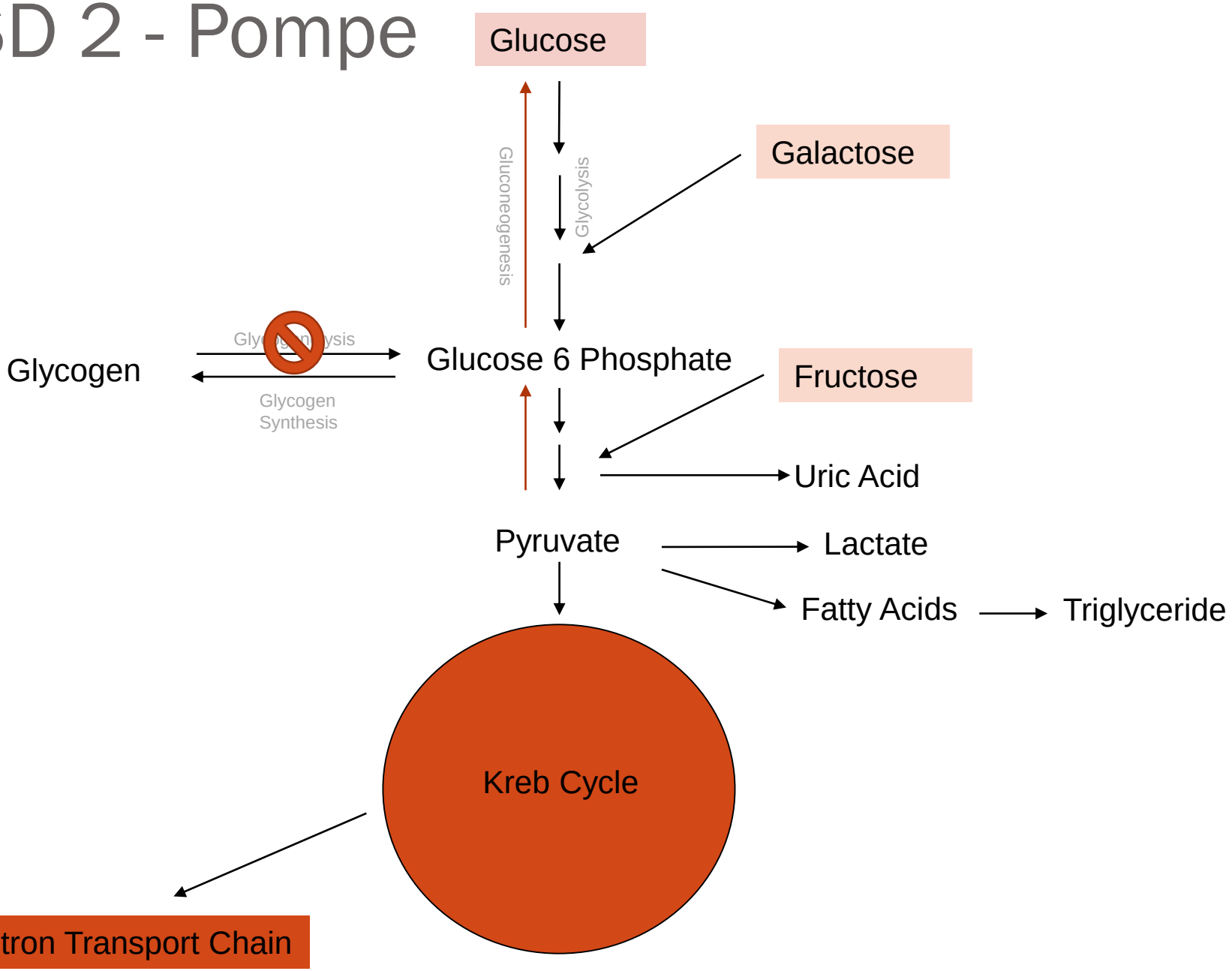
- Acute decompensation management principles
  1. ABCs
  2. Provide glucose
  3. Treat inciting factor
  4. Monitor for acute complications/sequelae

GSD 1

- Long term complications
  - Neutropenia and frequent infections
  - Hepatic adenomas
  - Renal insufficiency
  - IBD

- Long term treatment
  - Cornstarch
  - Continuous feeds
  - Sick day monitoring

GSD 2 - Pompe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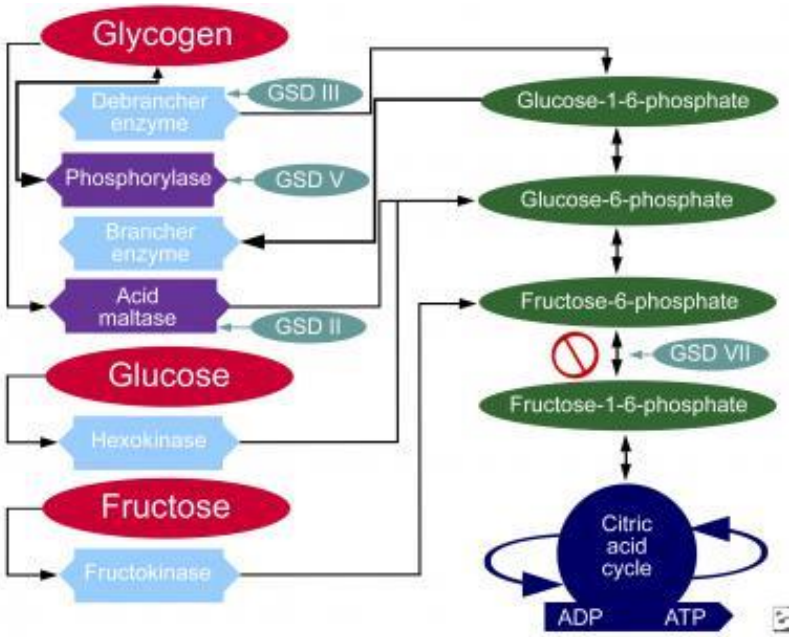
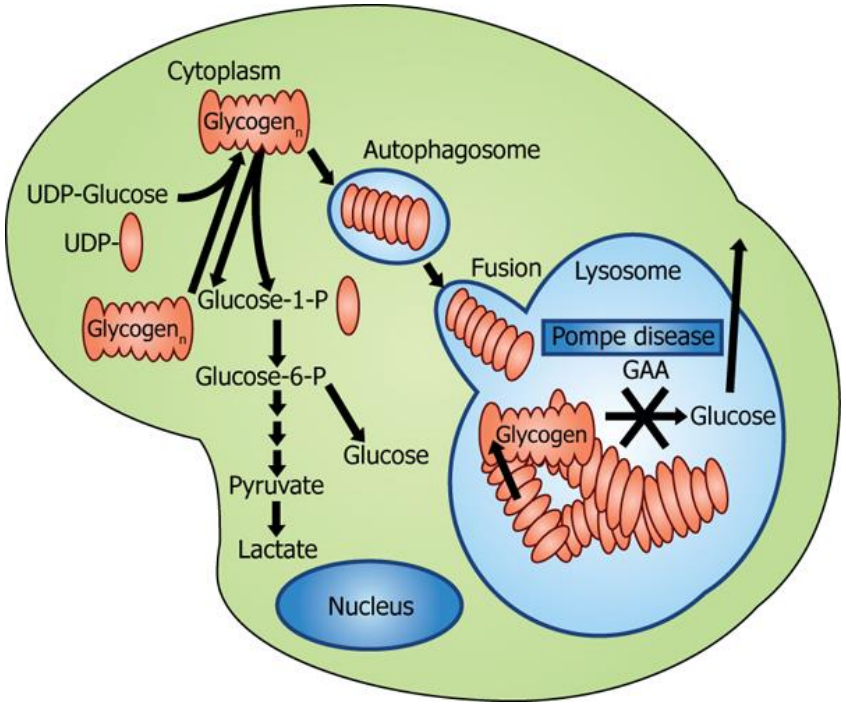
GSD2:

- Pompe disease (glycogen storage disease II, Acid alpha glucosidase (GAA)/acid maltase deficiency)
- More accurately classified as a lysosomal storage disease



Reference: https://emedicine.medscape.com/article/119506-overview

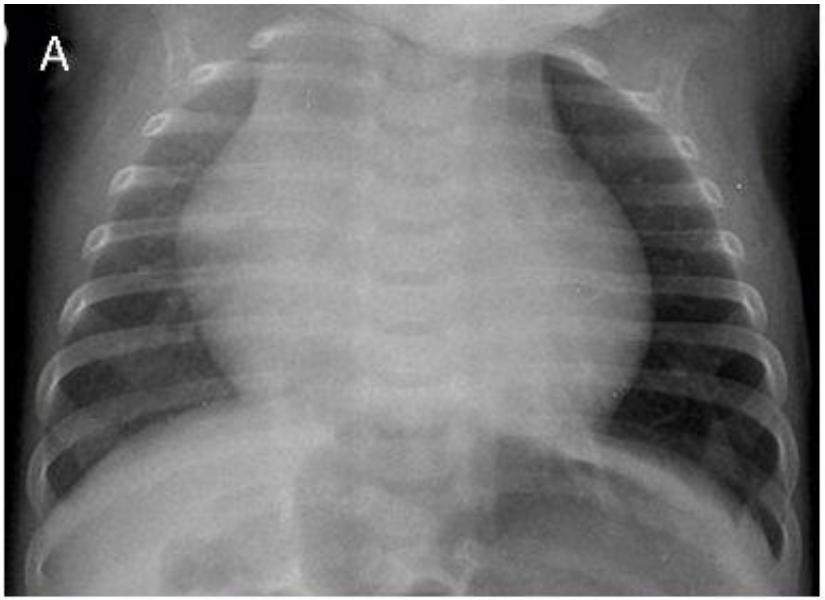


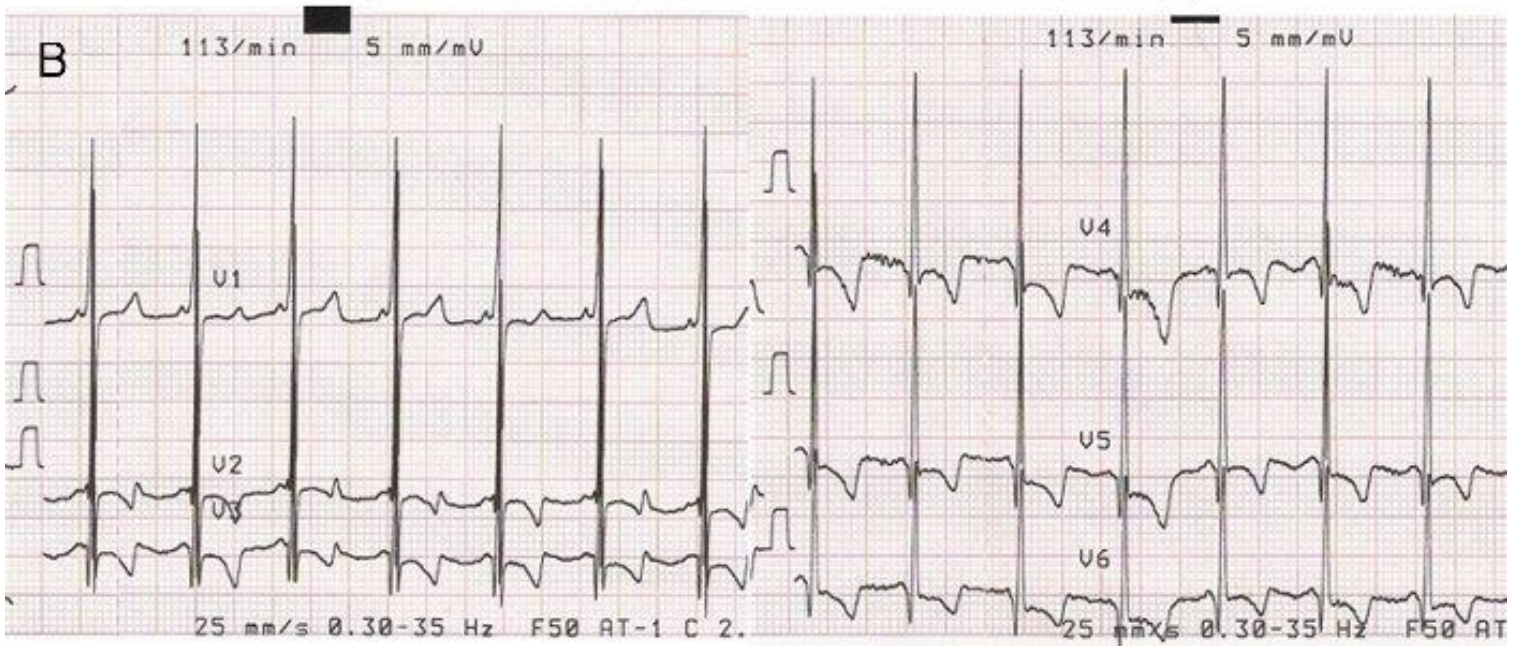
Reference: https://hubpages.com/education/Genetic-Disorders-Pompe

Pompe Disease

- Pathophysiology: Deficiency of enzymes in lysosomes, leads to accumulation of glycogen (skeletal, cardiac, smooth muscle)

- Clinical Presentation:
  - Classic infantile-onset:
    - Pompe disease often presents in the first two months of life
    - Hypotonia, generalized muscle weakness, cardiomegaly and hypertrophic cardiomyopathy, feeding difficulties, failure to thrive, respiratory distress, and hearing loss.
    - Death in the first year of life from progressive left ventricular outflow obstruction
  - Juvenile onset
    - Less cardiomyopathy than above
  - Adult onset
    - Progressive myopathy
    - Can present as late as 60s





Reference: https://www.revespcardiol.org/en-when-should-we-start-enzyme-articulo-S1885585711003306

Pompe Disease

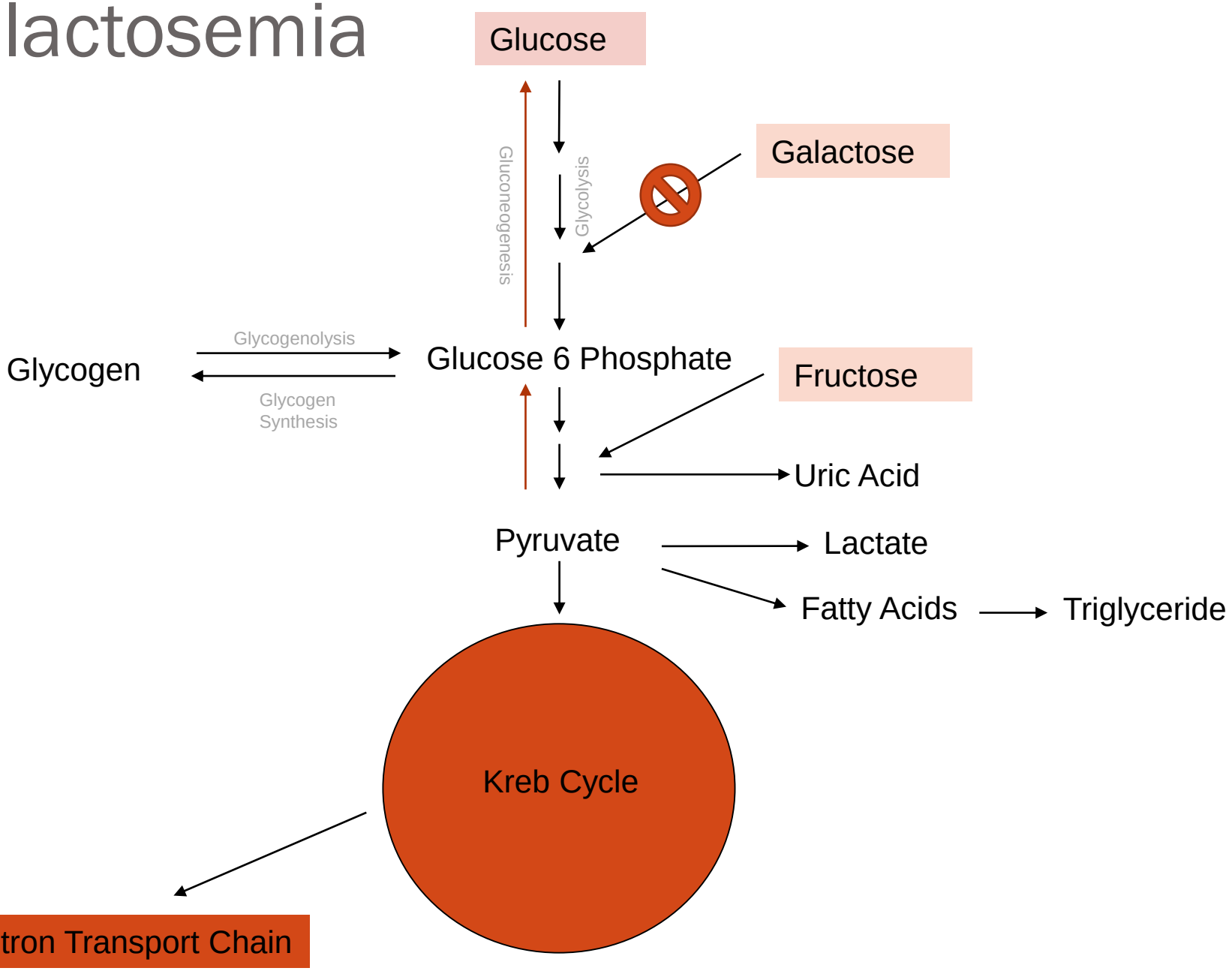
Management

- Supportive
  - Cardiac (CM, arrhythmias)
  - Resp (Respiratory insufficiency, frequent infections, sleep disordered breathing)
  - GI (Poor feeding, aspiration, poor growth)
  - Neuro (Poor tone, motor delays, hearing impairment)
  - MSK (Weakness, contractures)

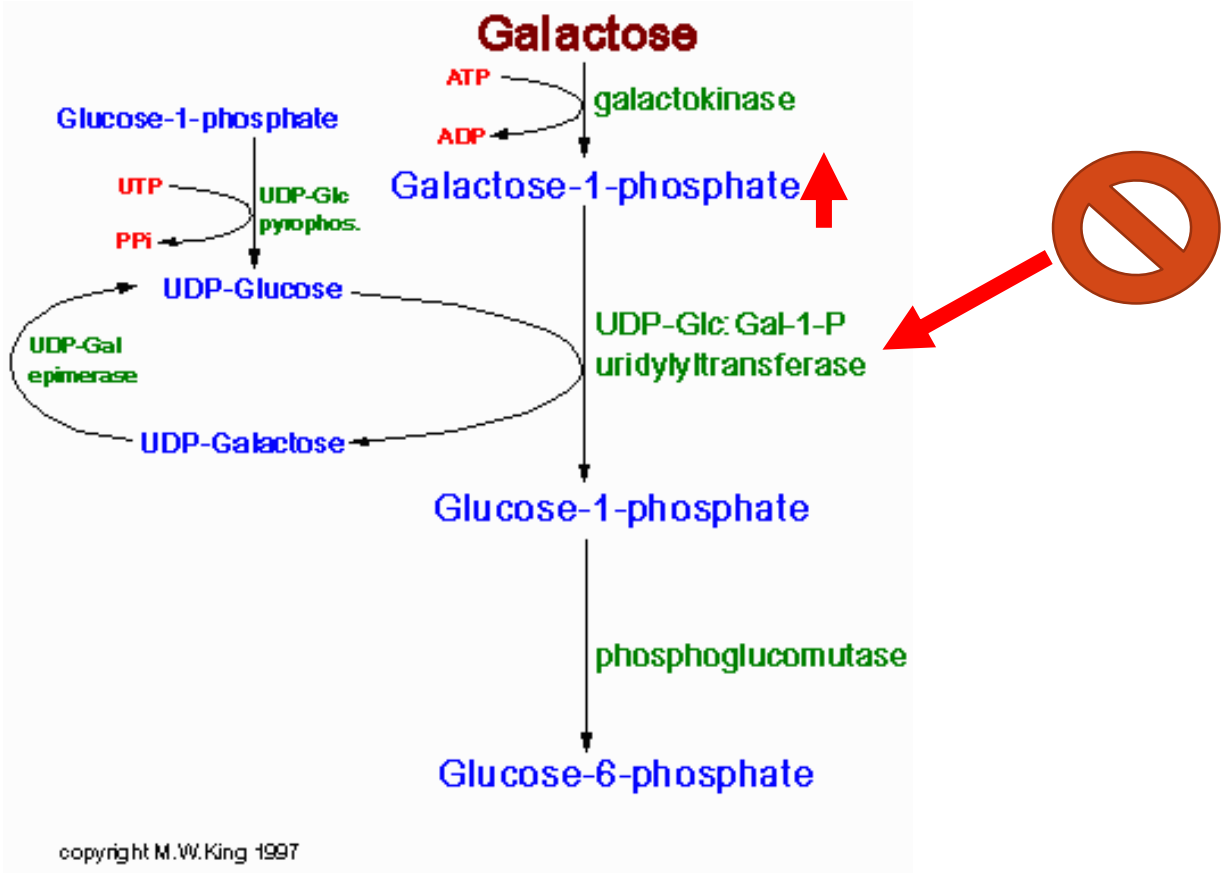
- Definitive Treatment: enzyme replacement therapy (ERT) within 1st 6 months of life

Galactosemia

Galactosemia

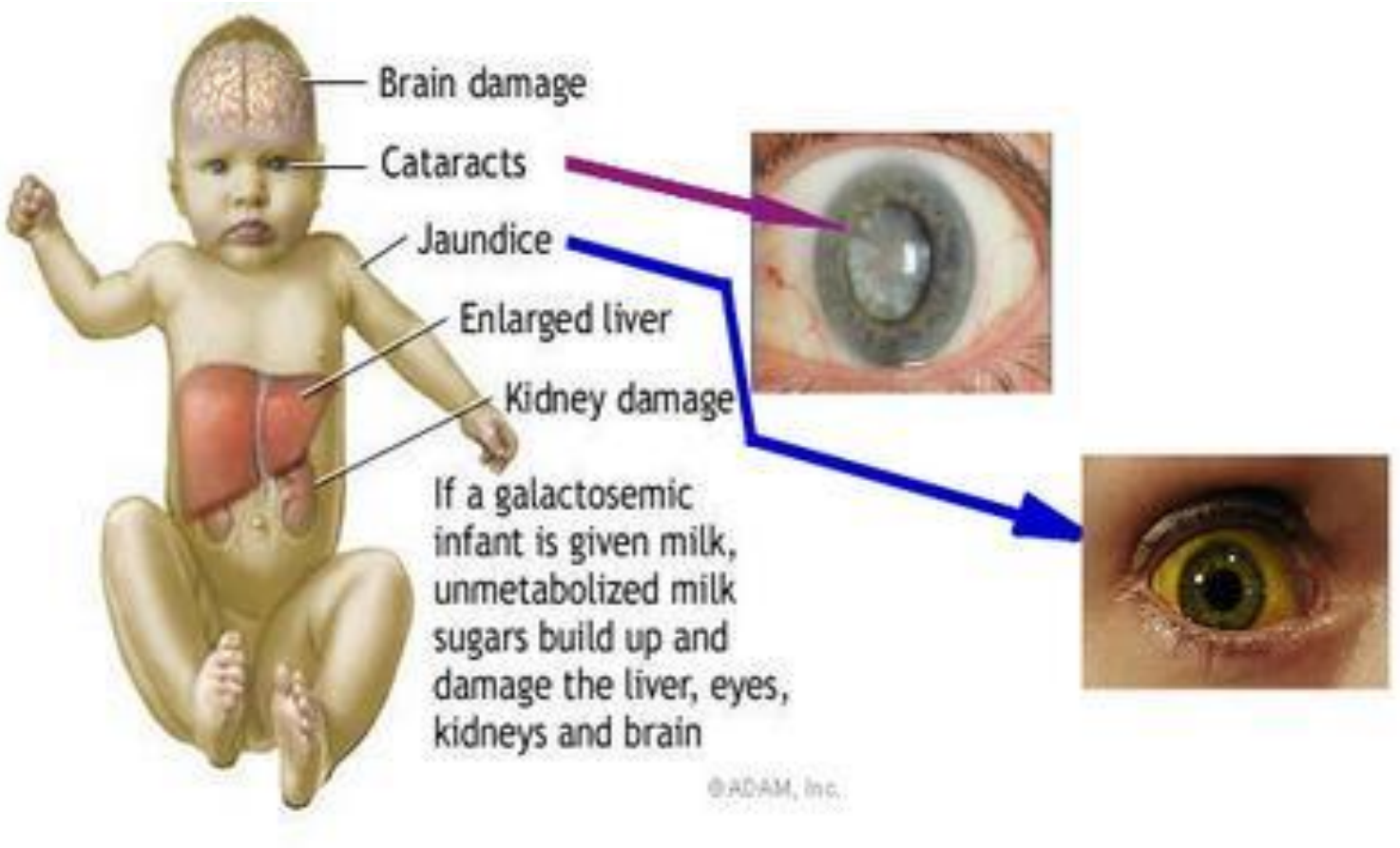


→ Lactose → Glucose + Galactose



Reference: https://www.medicalhomeportal.org/diagnoses-and-conditions/galactosemia

Clinical Presentation



Reference: https://www.mountsinai.org/health-library/diseases-conditions/galactosemia

Galactosemia

- CNS: Developmental delay/low IQ, speech problems (vocabulary and articulation), abnormal motor function, ataxia
- HEENT: Cataracts
- CVS:
- GI: Hepatitis, hyperbilirubinemia, liver failure, cirrhosis
- GU: Renal impairment
- MSK: Decreased bone mineral density
- Heme: Bleeding and coagulopathy (secondary to liver failure)
- Endo: Growth delay, primary ammenorrhea, premature ovarian failure
- ID: Sepsis (*Escherichia coli*, *Klebsiella*, *Enterobacter*, *Staphylococcus, Beta-streptococcus*, *Streptococcus faecalis*)

Galactosemia

- The diagnosis of classic galactosemia
  - elevated erythrocyte galactose-1-phosphate concentration
  - reduced erythrocyte galactose-1-phosphate uridylyltranserase (GALT) enzyme activity
  - Genetics (*GALT*)
  - Newborn screen – GALT enzyme activity

Galactosemia - treatment

Acute decompensation management principles

1. ABCs
2. Provide glucose
3. Treat/eliminate inciting factor (galactose)
4. Monitor for acute complications/sequelae
    - Hypoglycemia
    - Hyperbilirubinemia
    - Liver failure
    - Sepsis
    - Hyperammonemia

Treatment

- Galactose-free diet
  - Soy-based formulas
  - Elemental formula

- Experimental: inhibitors of the GALK enzyme

Disorders of lipid metabolism

RN ERROR OF METABOLISM

SMALL MOLECULE

PROTEIN

Aminoacidopathy
- Phenylalanine (PKU)
- Tyrosine (Tyrosinemia, Albinism)
- Methonine (Homocysteinuria)
- Cysteine (Sulfite oxidase deficiency)
- Trypotophan (Hartnup)
- Branched chain amino acids (MSUD
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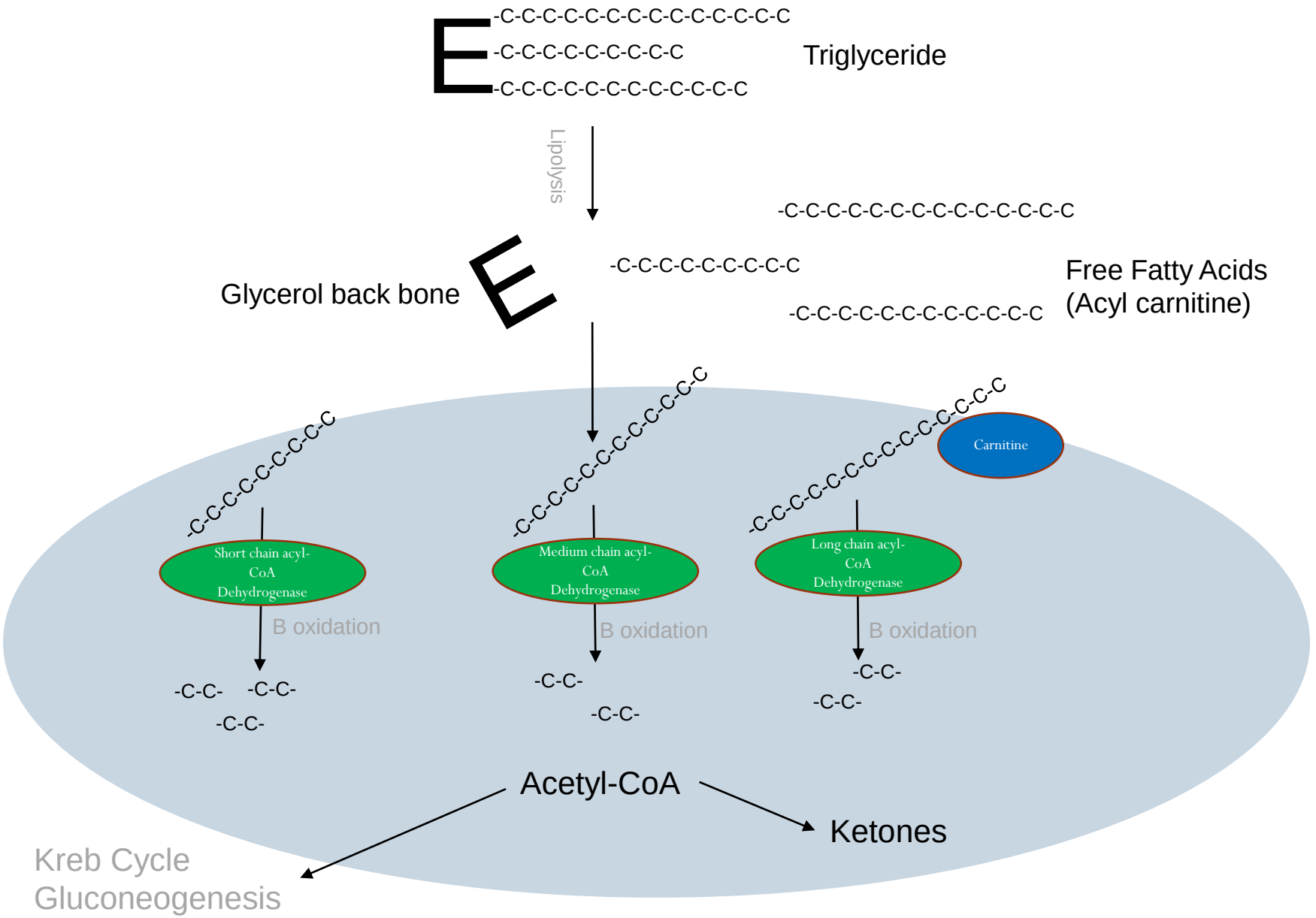
Lipid Metabolism



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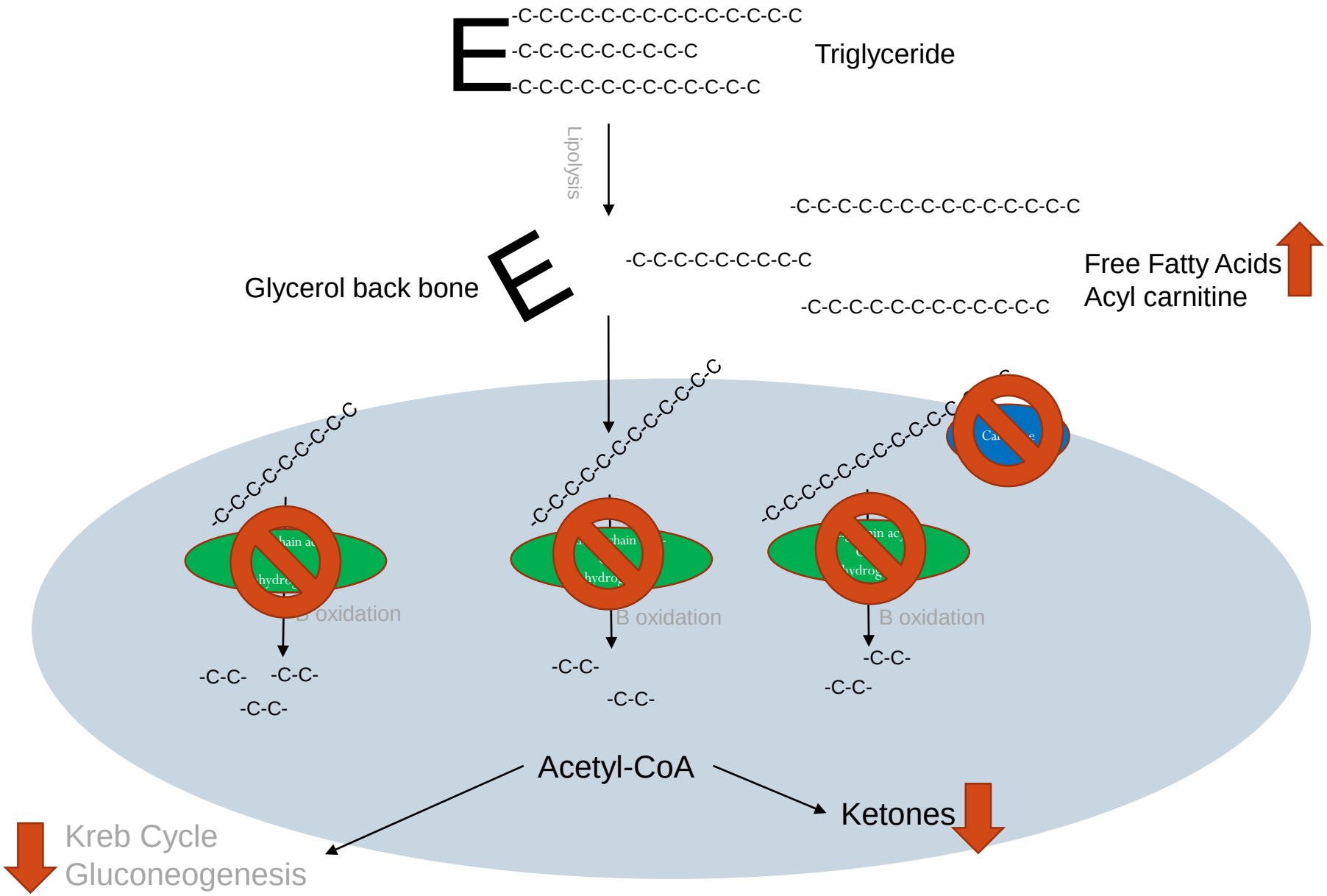

Fatty Acid Oxidation Defects

- Basic Science: Deficiency in SCAD, MCAD, LCAD, or carnitine
- Clinical presentation
  - Normal at birth, developmentally appropriate
  - Presents in infancy or early childhood during prolonged fast
  - Hypoketotic hypoglycemia – lethargy, seizure, coma
  - Can present with sudden death
  - LCFAOD can also have rhabdomyolysis, cardiomyopathy, liver dysfunction

Fatty Acid Oxidation Defects

- Labs:
  - Hypoketotic hypoglycemia during acute episode
  - Hepatitis

- Diagnosis
  - Plasma Acylcarnitine profile
  - Urine organic acids
  - Carnitine (free and total)

Fatty Acid Oxidation Defects

- Acute Treatment:
  - When sick, high dextrose
  - NO lipids
  - Avoid prolonged fasting

- Long term treatment
  - Dietary fat restriction – can use MCT oil in LCFAOD
  - Carnitine supplementation

Complex Molecule/Organelle Disorders

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Complex Molecule/Organelle Disorders

In general, presentation is different from "small molecules"

- Present more insidiously, less acute deteriorations
- "Storage" issues – organomegaly, course facies
- Neurological/developmental issues and regression
- Bony deformities
- Sensory issues

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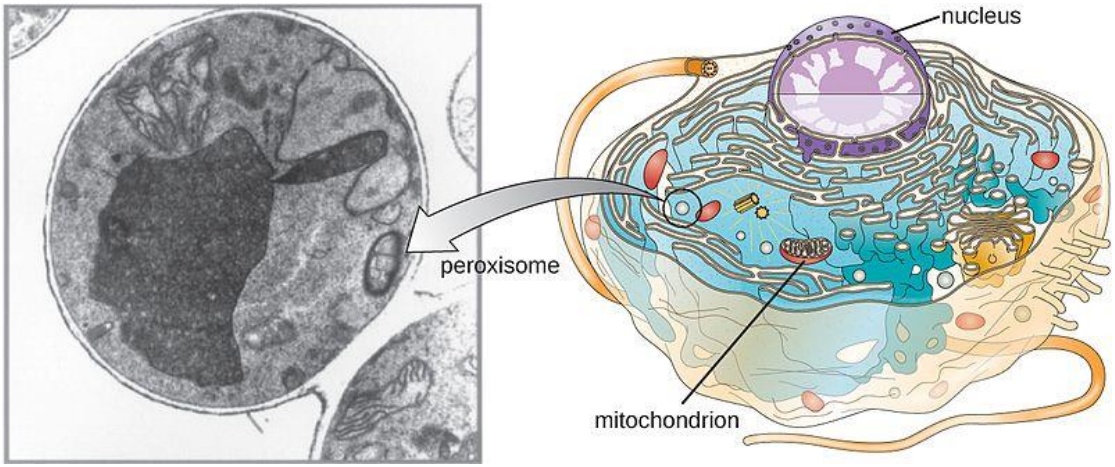

Reference: https://pediaa.com/difference-between-lysosome-and-peroxisome/

- Involved in beta oxidation of VLCFAs
- Defects lead to accumulation of VLCFA
- Examples: Zellweger, adrenoleukodystrophy

Peroxismal Disorders

Zellweger

- Absent peroxisomes
- Dysmorphic
- Hypotonia
- Hearing and vision defects
- Seizures
- Liver disease
- MRI shows leukodystrophy

- Work up: MRI head, VLCFAs

Adrenoleukodystrophy

- X linked
- Deficiency is VLCFA oxidation
- School aged onset
- Developmental regression
- New spasticity
- Adrenal failure

- Work up: MRI head, VLCFAs

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LYSOSOMES

Mucopolysaccharidoses
- I – Hurler/Shiae
- II – Hunter
- III – San Fillipo
- IV – Morquio
- VI – Maroteaux Lamy
- VII – Sly
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- Fabry
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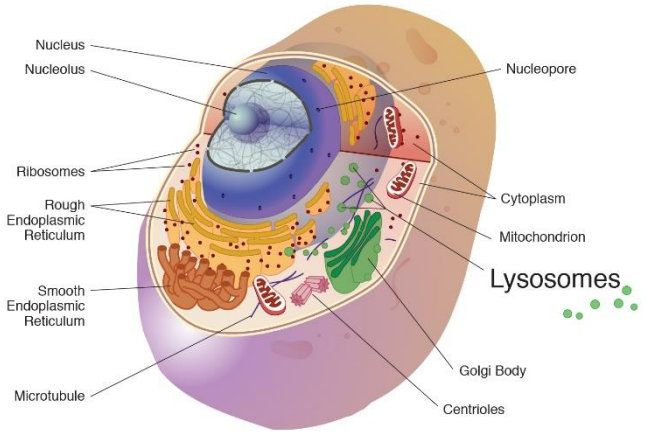
OTHER

Porphyria

Disorders of Metal Metabolism

Purine and Pyrimadine Metabolism

Lysosomal Storage Disorders



Reference: https://www.genome.gov/genetics-glossary/Lysosome

- Lysosomes – an organelle that digests large molecules for recycling or degradation
- Lysosomal storage disorders are due to inability to break these down, and progressive accumulation in tissues
    1. Mucopolysaccharides
    2. Sphingolipids
    3. Oligosaccharides

Mucopolysaccharidoses

- Clinical features
  - Progressive symptoms, wide spectrum of severity
  - Normal at birth
  - Coarse facial features
  - Corneal clouding
  - Bony deformities, short stature
  - Developmental regression, or cognitively normal
  - Visceromegaly
  - Tendency for hernias
  - Xray – dysostosis multiplex
- Treatment
  - Enzyme Replacement Therapy
  - Stem cell transplant

Reference: https://en.wikipedia.org/wiki/Mucopolysaccharidosis

Mucopolysaccharidoses

- Work up
  - Urine glycosaminoglycan (GAG)
  - Urine oligosaccharides
  - Lymphocyte or fibroblast enzymatic activity
  - Genetic testing

INBORN ERROR OF METABOLISM

SMALL MOLECULE

PROTEIN

Aminoacidopathy
- Phenylalanine (PKU)
- Tyrosine (Tyrosinemia, Albinism)
- Methonine (Homocysteinuria)
- Cysteine (Sulfite oxidase deficiency)
- Trypotophan (Hartnup)
- Branched chain amino acids (MSUD
- Glycine (Hyperglincinemia)

Urea Cycle Defects
- CPS
- NAGS
- OTC
- Arginosuccinate sythetase/lyase
- Arginase

Organinc Acidemia
- Methylmalonic
- Propionic
- Isovaleric
- multiple carboxylase biotinidase deficiency
- Glutaric acidemia

CARBOHYDRATE

Glycogen Storage disease
- GSD 1 – Von Gierke
- GSD II – Pompe
- GSD IV – Debrancher enzyme deficiency
- Phosphorylase kinase deficiency
- Glycogen synthetase deficiency
- Fackoni Bickel
- McArdle
- Lactate dehydrogenase deficiency

Fructose
- Fructosuria
- Herediatry Fructose Intolerance

Galactose
- Galactosemia
- Galactokinase deficiency

Disorders of Gluconeogenesis
- Fructose 1,6 dipohsphatse deficiency
- Phosphoenolpyruvate carboxykinase deficiency

Disorders of Pyruvate Metabolism
- Pyruvate dehydrogenase complex defect
- Pyruvate carboxylase deficiency
- Respiratory chain defects (oxidative phosphorylation problems)

Disorders of Pentose Metabolism
- Pentosuria
- Transaldolase deficiency

LIPIDS

B oxidation defects
- SCAD
- MCAD
- LCAD
- VLCAD

Carnitine Disorders
- Primary carnitide deficiency
- Carnitine palmitoyltranferase I (CPTI)
- CPT II

Oxidative Phosphorylation
- Glutaric aciduria II
- Multiple Acyl CA Dehydrogenase deficiency

Ketogenesis
- HMG CoA Synthetase
- HMG CoA Lyase

Hyperlipoproteinemia
- Hypercholesterolemia
- Hypertriglyceridemia
- Disorders of HDL metabolism
- Low cholesterol (Abetalipoproteinemai, Smith Lemli Opitz)
- Disorders of Intracellular Cholesterol metabolsim

COMPLEX MOLECULE/ORGANELLE

PEROXISOMAL (VLCFA Breakdown)

Disorder of Peroxisomal Import
- Zellweger
  - Neonatal Adrenoleukodystrophy
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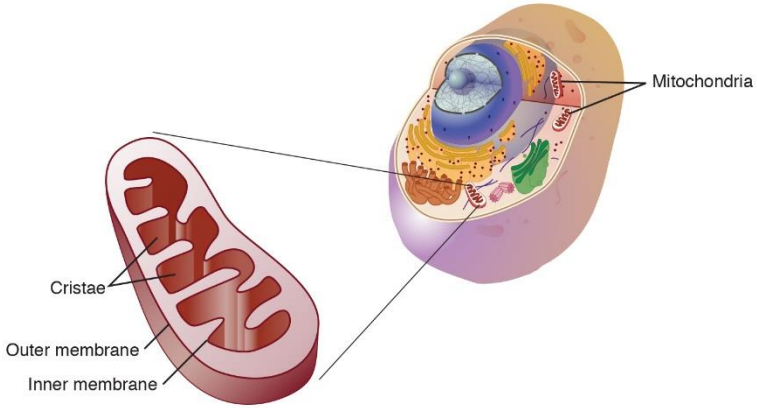
Mitochondrial Disorders



Reference: https://www.genome.gov/genetics-glossary/Mitochondria

- Responsible for energy production (Remember that Kreb cycle?)
- Defects in mitochondria affect tissues with the highest energy demand (brain, cardiac muscle, skeletal muscle)
- Inheritance:
  - If defect in mitrochondrial genome – maternal
  - If defect in nuclear genes required for mitochonidria to function, - mendelian

Mitochondrial Disorders

- Work up
  - Lactate may be elevated
  - MRI
  - Muscle biopsy (ragged red fibres
  - Specialised DNA testing
  - Assays for respiratory chain activity

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Resources

- **Paul A. Levy. Inborn Errors of Metabolism. Pediatrics in Review. April 2009, VOLUME 30 / ISSUE 4**

- Gregory M. Rice, Robert D. Steiner. Inborn Errors of Metabolism (Metabolic Disorders). Pediatrics in Review. January 2016, VOLUME 37 / ISSUE 1

- https://newenglandconsortium.org/

- **Gene reviews**

Questions

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