1. **Acidosis vs. Alkalosis**

- Acidosis: process of acidification
  - Acidemia: pH of BLOOD below 7.35
    - severe acidemia depresses nervous system, coma, death

- Alkalosis: process of alkalization of body fluids
  - Alkalemia: pH of BLOOD above 7.45
    - severe alkalemia → overexcitability of nervous system, muscle spasm, convulsions, death

2. **Amino Acid Disorders (Characteristics)**

- defects in catabolism of amino acids (and sometimes in their synthesis)

  - Amino Acidurias:
    - increase of specific amino acids in urine
      - eg. Phenylketonuria, Maple Syrup Urine Disease, Argininosuccinate Aciduria

  - Organic Acidurias:
    - increased non-amino organic acids in urine
      - eg. Isovaleric acidemia

  - Urea cycle disorders:
    - some steps involving amino acids
      - eg. Argininosuccinic aciduria (aka amino aciduria)

3. **Arginosuccinic Acidemia**

   - Urea Cycle Disorder
   - Accumulation of argininosuccinic acid

4. **Biotinidase deficiency**

   - biotin is a coenzyme in carboxylation reactions in gluconeogenesis and in fatty acid synthesis
   - Biotinase is an enzyme that releases dietary biotin from protein

   - Screening in newborns: indicated by low biotinase activity in blood samples
   - Sx: neurologic abnormalities like seizures, hypotonia, ataxia, developmental delay, hearing loss, cutaneous abnormalities (eg. skin rash)

   - Treatment: oral biotin

5. **Bone Marrow Transplantation**

   - Hematopoietic stem cell transplantation (HSCT) treats lysosomal storage disease like Hunter and Hurler

   - HSCT can retard neurological degeneration in lysosomal storage diseases whereas ERT cannot

   - Bone marrow gives rise to microglial cells that act as macrophages in the CNS

   - microglial cells can secrete some of the lysosomal enzymes that can be taken up by other cells (cross-correction)

6. **Case Summary 1:**

   - 7 day old male born normal

   - lost interest in feeding and was irritable

   - lethargic and pale, hypotonic and poorly responsive

   - Labs:
     - normal CBC
     - Gases: high pH, low pCO2, low HCO3-
     - normal electrolytes
     - blood glucose normal
     - Ammonia high

   - alkalosis → not respiratory because HCO3- is low → metabolic alkalosis

   - high NH3 → urea cycle defect

   - not hyperglycemic
7. Case Summary 2
9 month old girl
lethargy and unresponsive
diarrhea, fever, vomiting
lost interest in feeding
dehydrated
deep and rapid breathing
enlarged liver
hypotonic and hyporflexic
seizure
labs:
low pH, low pCO2, HCO3 low
increased anion gap
normal electrolytes
slightly elevated ammonia
urinalysis: 3+ ketones
plasma amino acids: increased
glycine
Urine organic acids:
methylmalonic acid
MRI: bilateral infarcts thalamus

9. Congenital Adrenal Hyperplasia (CAH)
metabolic acidosis bc low HCO3 but low pH too
high methylmalonic acid → methylmalonic aciduria

10. Congenital Hypothyroidism
Endocrine Disorder
-deficiency in thyroid hormone (thyroxine)
or-elevated levels of thyroid stimulating hormone (TSH)
Sx: in newborn can’t really tell, but maybe dull look and puffy face, untreated → mental and growth retardation
Treatment: oral thyroxine supplement

11. Cystic Fibrosis (CF)
Endocrine Disorders
-mutations in the CFTR gene that encodes a chloride channel
-cannot get Cl- out of cell, so more Na+ comes in to even the ion balance
-more Na+ on inside → more H2O uptake by cell → dehydration of extracellular mucus → patient cannot clear mucus (and bacteria in it) from lungs → infection
Screening:
-immunoreactive trypsinogen (IRT) which is secreted at high levels by a stressed pancreas like in cases of CF
-elevated Na+ and Cl- in sweat
-genetic tests for defect in common mutations in CFTR gene

12. Diagnosis of Acid-Base Imbalances
Arterial blood gas measurements:
1. Note pH high (alkalosis) or low (acidosis)
2. Decide whether CO2 or HCO3- is in abnormal range
3. If cause is change in CO2, problem is respiratory
4. If cause is change in HCO3-, problem is metabolic
13. **Enzyme Replacement Therapy (ERT)**

- Enzyme replacement therapy doesn’t work for majority of lysosomal storage diseases w/ neurological degeneration since the proteins can’t be delivered to the CNS

Works for:
- Gaucher’s disease
- Lysosomal storage disease → defect in glucocerebrosidase (GCR)

Treatment: IV delivery of recombinant GCR modified with oligosaccharide chains with terminal mannose residues which direct protein for uptake into macrophages and then into lysosomes

14. **Explain how mass spectrometry is used in newborn screening**

Used to detect overabundance of specific compounds in:
- Amino acidemias
- Organic acidemias
- Fatty acid oxidation disorders

Tandem Mass Spectrometry (2 successive separations)
- Separate by mass/charge ratio (m/z)

Sample is ionized → m/z separation (MS1 precursor ion) → fragment → m/z separation (MS2 product ion) → detection

15. **Fatty Acid Oxidation Disorders (Characteristics)**

- Inability to derive energy from fatty acids
- Hypoketotic hypoglycemia
- Fasting intolerance
- Acute symptoms: vomiting, lethargy, coma
- Treatment: high carb diet, avoid fasting
- Abnormal organic acid levels in urine

16. **Galactosemia**

Carbohydrate Metabolism Disorder (inherited)

- Deficiency in galactose-1-phosphate uridylyltransferase (GALT)
- Inability to metabolize galactose (a product of lactose digestion)

Lab tests:
- Urinalysis: positive for reducing sugar
- Chromatography: total RBC analysis positive for Gal-1-P and galactose concentrations
- Biochemical testing: deficiency of galactose-1-phosphate uridylyltransferase (GALT) enzyme activity

Sx: no appetite, vomit after breast feeding, diarrhea, weight loss, jaundice (enlarged liver) after 5 days, cataracts after 2 weeks

Treatment: low lactose diet (low milk diet) → cured everything but cataracts

17. **Glycogen Storage Diseases (GSD) (Characteristics)**

- Excessive storage of glycogen (except for GSD IV that results in abnormal glycogen that damages liver)

GSD I, III, V, and VIII manifest as hypoglycemia and hepatomegaly

GSD II, V, VII manifest as muscle weakness

GSD IV and IX manifest as hepatic cirrhosis

Diagnosis requires many metabolic and biochemical tests

GSD I (glucose 6-phosphatase deficiency) → high lactic and uric acid levels

18. **Homocystinuria**

Deficiency in Cystathionine B-Synthase (uses B6 and B12 as cofactors)

Treatment:
- Dietary restriction of methionine
- Supplement with vitamins Pyridoxine (Vit B6), folic acid, and Vit B12
19. **Hyperphenylalaninemia**

Amino Acid Disorder

Refer to genetic mutations that block metabolic pathways (usually due to a single enzyme deficiency)

Symptoms usually from absence of required metabolic product or accumulation of a toxic intermediate

Detection usually involves assaying for abnormal metabolite concentrations

Enzymopathies are usually recessive and can cause loss of multiple enzyme activities - eg. loss of common cofactor like Vit B12

Phenotypic homology: similar phenotypes induced by deficiencies in different enzymes in same or related pathways (eg. fatty acid oxidation pathway deficiency)

Partial defects produce symptoms that are subset of those produced by complete loss - eg. partial HGPRT deficiency causes hyperuricemia but complete loss causes Lesch-Nyhan syndrome

20. **Inborn Errors of Metabolism (IEM)**

refer to genetic mutations that block metabolic pathways (usually due to a single enzyme deficiency)

Symptoms usually from absence of required metabolic product or accumulation of a toxic intermediate

Detection usually involves assaying for abnormal metabolite concentrations

Enzymopathies are usually recessive and can cause loss of multiple enzyme activities - eg. loss of common cofactor like Vit B12

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Partial defects produce symptoms that are subset of those produced by complete loss - eg. partial HGPRT deficiency causes hyperuricemia but complete loss causes Lesch-Nyhan syndrome

21. **Isovaleric Acidemia**

Organic Acid Disorder

Relevant acylcarnitine metabolites

Organic acidemias (eg. Isovaleric acidemia) - note: organic acidemias sometimes accompanied by hyperammonemia (→ alkalosis)

But ammonia concentration usually less than in urea cycle disorder, so net metabolic affect is metabolic acidosis - increase anion gap by replacing bicarbonate ion

22. **Know the classes of IEM routinely screened in newborns**

Early onset (acute crisis): acidosis, hyperammonemia, hypoglycemia eg. urea cycle defects

Late onset (3 years old) often result in neurological deterioration (eg. lysosomal storage diseases)

Types of IEM screened:

- Congenital Hearing loss (very prevalent)
- Sickle Cell Disease
- Hypothyroidism
- Amino Acid Disorder
- Organic Acid Disorder
- Fatty Acid Oxidation Disorder
- Urea Cycle Disorder
- Carbohydrate Metabolism Disorder
- Lysosomal Storage Disorder

23. **Know the criteria for newborn screening (state-governed)**

Screen newborns if:

- Treatable disorder
- Early treatment is critical
- Sufficiently high incidence/prevalence rate
- Low false positive/false negative
- Low cost of screening method
24. **Lysosomal Storage Disorders**

Deficiencies in enzymes that degrade complex molecules in lysosomes.

3 substrate groups depend on lysosomes:

1. **Mucopolysaccharidoses**
   - Glycosaminoglycan (complex polysaccharide)
   - Eg. Hurler syndrome, Hunter syndrome

2. **Oligosaccharidoses**
   - Less complex polysaccharides
   - Eg. mannosidosis, sialidosis and fucosidoses

3. **Sphingolipidoses**
   - Sphingolipids
   - Eg. Tay-Sachs, Gauchers, Niemann-Pick Disease A

Usually patients normal at birth but Sx progress in childhood due to accumulation of degradation intermediates in lysosomes, cellular damage and death.

Sx: developmental regression, hepatosplenomegaly, neurodengeneration, cherry red spot in retina.

Treatment: difficult, but enzyme replacement therapy and bone marrow transplantation could be effective for some.

25. **Maple Syrup Urine Disease**

Amino Acid Disorder

Accumulation of leucine and isoleucine

Treatment:
- Dietary restriction of methionine, threonine, valine and isoleucine

26. **Medium-chain acyl-CoA DHD deficiency**

MCADD

Fatty Acid Oxidation Disorder

- Often causes hypoglycemia (can’t break down FA to Acetyl-CoA so can’t use Acetyl-CoA to make glucose)

Look for increased medium chain acylcarnitines and decreased long chain acylcarnitines on mass spec.

27. **Metabolic acidosis vs. alkalosis**

Metabolic acidosis:
- Decreased HCO3-
- Decreased pH
- Due to loss of bicarbonate ions (diarrhea), accumulation of acids (ketosis)
- Respiratory compensation:
  - Hyperventilation (increase loss of CO2)

Metabolic alkalosis:
- Increased HCO3-
- Increased pH
- Due to vomiting, excessive intake of alkaline drugs
- Respiratory compensation:
  - Hypoventilation (slows loss of CO2)

28. **Organic Acidemias (Characteristics)**

- Disorders of fatty acid metabolism
- Nonarnino organic acids accumulate in serum and urine eg. isovaleric acidemia
- Metabolic acidosis, high anion gap
- Symptoms of encephalopathy, vomiting, lethargy several days after birth

Treatment: dietary restriction of amino or fatty acids that cannot be metabolized.

29. **Organic Acidemias (Characteristics)**

Organic acidemias (eg. Isovaleric acidemia)
- Note: organic acidemias sometimes accompanied by hyperammonemia (→ alkalosis) but ammonia concentration usually less than in urea cycle disorder, so net metabolic affect is metabolic acidosis
- Increase anion gap by replacing bicarbonate ion (eg. anion gap = [Na+] - ([Cl-] + [HCO3-]))

30. **Other disorders that aren't detected by mass spec but require specific tests in Ohio**

- Biotinidase deficiency
- Congenital adrenal hyperplasia
- Congenital hypothyroidism
- Cystic fibrosis
- Galactosemia
- Hemoglobinopathies (sickle cell anemia, and S/beta thalassemia) → screened by electrophoresis
<table>
<thead>
<tr>
<th>Phenylketonuria</th>
<th>Amino Acid Disorder</th>
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<tbody>
<tr>
<td>Phenylalanine hydroxylase (which uses a biopterin cofactor)</td>
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<tr>
<td>Accumulation of phenylalanine and tyrosine (remember F → Y)</td>
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<td>Treatment:</td>
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<tr>
<td>- dietai restriction of phenylalanine and aspartame</td>
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<tr>
<td>- supplement with Biopterin cofactor (can help overcome defect in residual enzyme activity)</td>
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<tr>
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<td>Acylcarnitine profile abnormalities</td>
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<td>High lactate/pyruvate ratio (normal: 10:1 to 20:1)</td>
<td>Pyruvate carboxylase deficiency</td>
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<th>Specific defects in amino acid metabolism have specific patterns</th>
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<td>Respiratory acidosis:</td>
<td>Excess CO2 in blood caused by hypoventilation (apnea), inadequate movement of CO2 from tissues to lungs</td>
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<td>- renal compensation: increased excretion of H+ and reabsorption of HCO3-</td>
<td>Respiratory alkalosis:</td>
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<tr>
<td>- drop in CO2 concentration in blood often caused by hyperventilation (tachypnea, panic attack)</td>
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<td>Disorders of ketogenesis</td>
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1. Ingestion of certain sugars
-disorders of carb intolerance (e.g. galactosemia and hereditary fructose intolerance)

2. Ingestion of protein
-urea cycle defects, organic acidemias, amino acid disorders, hyperinsulinism with hyperammonemia

3. Ingestion of carbs
-pyruvate DHD deficiency, mitochondrial respiratory chain disorders, hyperinsulinism

4. Introduction of complementary foods
-eg. infant cereals, fruit juice, vegetables, meats
-carb metabolism disorders, urea cycle defects, an organic acidemias

5. Infection, fever, fasting or catabolism
-amino acid disorders, organic acidemias, fatty acid oxidation disorders, urea cycle defects, disorders of gluconeogenesis and glycogenolysis

Tyrosinemia
Amino acid disorder
Treatment:
-dietary tyrosine, phenylalanine

Urea Cycle Disorders (Characteristics)
-defects in any enzymes in urea cycle
-high levels of ammonia in blood (hyperammonemia)
-problems begin after consumption of protein
-eg. vomiting, lethargy, brain damage (encephalopathy)
-enzyme defect identified by analyzing amino acids in blood and urine

Treatments:
-low protein, high carb diet (since NH₃ from protein breakdown can't be handled by urea cycle)
-benzoic acid or phenylacetic acid to help clear ammonia

Which IEMs → acidosis?
Organic acidemias (eg. Isovaleric acidemia)
-note: organic acidemias sometimes accompanied by hyperammonemia (→ alkalosis) but ammonia concentration usually less than in urea cycle disorder, so net metabolic affect is metabolic acidosis
-increase anion gap by replacing bicarbonate ion

Which IEMs → alkalosis?
Hyperammonemia → induces tachypnea and thus respiratory alkalosis → sign of urea cycle disorder