Hyperbilirubinemia

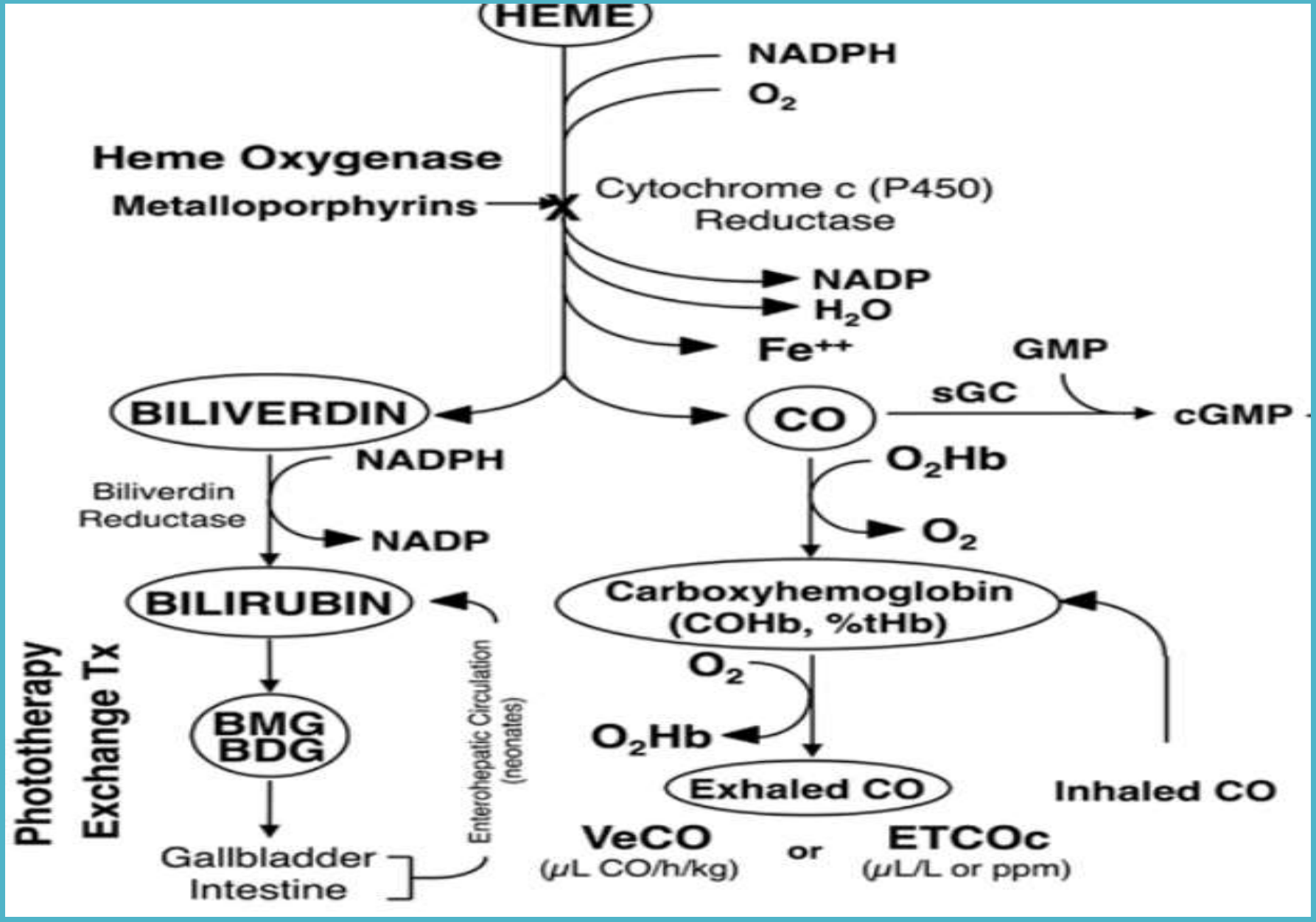
Dr. Salma Burayzat

Assistant Professor

Pediatric Gastroenterology, Hepatology and Nutrition

Hyperbilirubinemia

- Definition
- Types


HEME
NADPH
O_2
Heme Oxygenase
Metalloporphyrins
Cytochrome c (P450) Reductase
NADP
H_2O
Fe^{++}
GMP
sGC
cGMP
BILIVERDIN
CO
NADPH
O_2Hb
Biliverdin Reductase
NADP
O_2
BILIRUBIN
Carboxyhemoglobin (COHb, %tHb)
Phototherapy
Exchange Tx
BMG
BDG
Enterohepatic Circulation (neonates)
O_2
O_2Hb
Exhaled CO
Inhaled CO
Gallbladder
Intestine
VeCO
(µL CO/h/kg)
or
ETCOc
(µL/L or ppm)

Inherited disorders of bilirubin conjugation

Crigler-Najjar syndrome type 1

Autosomal recessive

Glucuronyl transferase deficiency

Severe unconjugated hyperbilirubinemia develops in in the first 3 days of life

Kernicterus is almost universal complication

Stools are pale yellow.

Crigler-Najjar syndrome type 1

Diagnosis

- Decreased bilirubin concentration in the bile
- Measuring hepatic glucuronyl transferase activity in a liver biopsy
- DNA diagnosis

Treatment

- Serum unconjugated bilirubin concentration should be kept to <20 mg/dL
- Exchange transfusions and phototherapy.
- liver transplantation cures the disease

Crigler-Najjar syndrome type II

- Autosomal recessive
- Partial deficiency of enzymes activity
- Development of kernicterus is unusual.
- Stool color is normal
- Significant response to phenobarbital in type 2

Gilbert syndrome

Common, affecting up to 5-10% of the white population

Decrease normal gene activity but only to ~30%.

Usually presents after puberty

Total serum bilirubin concentrations fluctuate from 1 to 6 mg/dl, mainly unconjugated

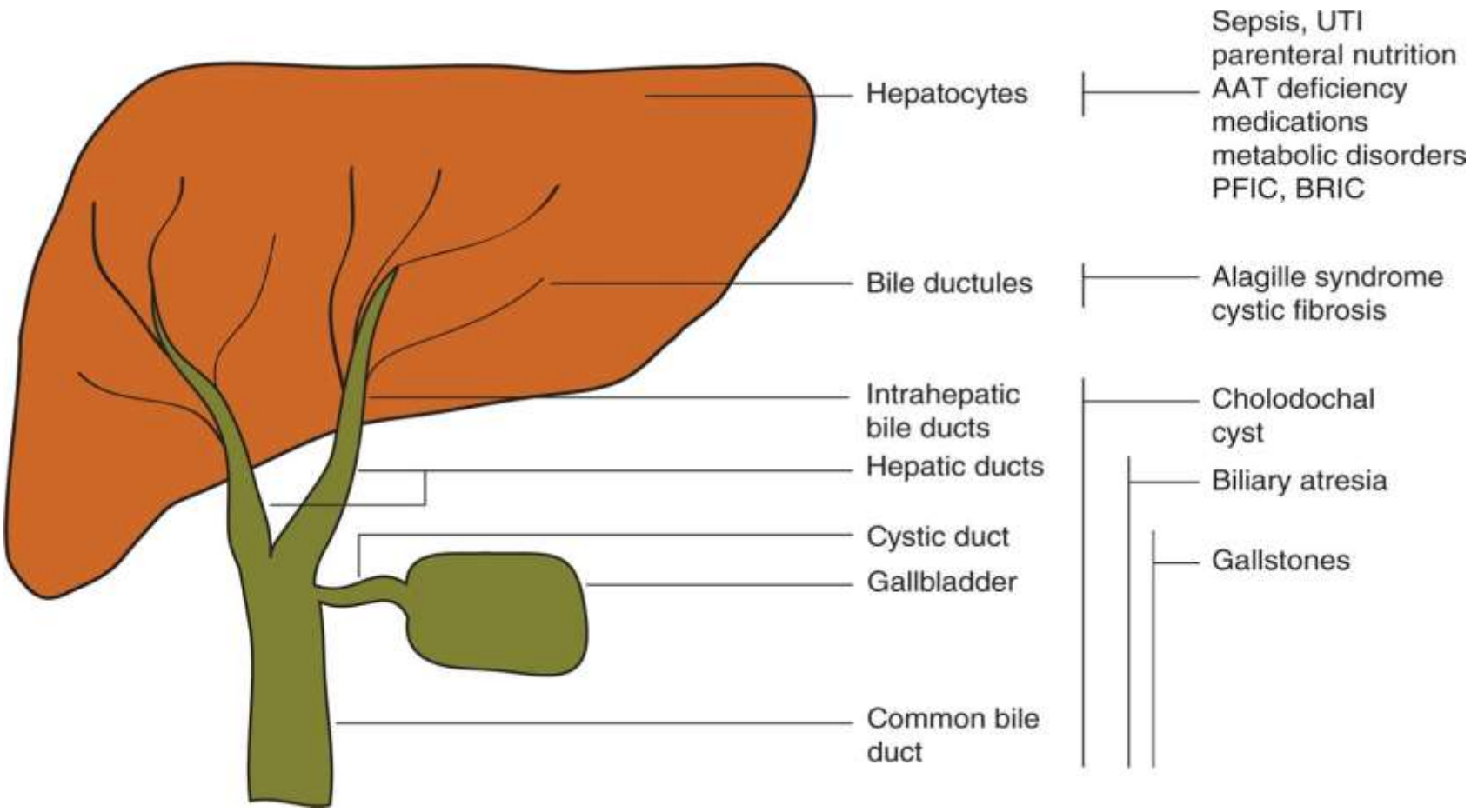
Cholestasis

Cholestasis

The first step in evaluating a jaundiced infant is to measure the serum concentrations of both total and conjugated bilirubin.

An elevated conjugated bilirubin is an abnormal finding and requires additional evaluation

Cholestasis



Cholestasis-History

Vomiting

Stooling pattern

Stool color

Urine

Excessive bleeding

Consanguinity

Congenital infections

Prenatal ultrasonography and

Neonatal infection

Dietary history

Weight gain

Cholestasis-Physical examination

- Assessment of general health
- Measurement of vital signs
- Growth parameters
- Abnormal/ characteristic facial features
- Cardiac examination
- Abdominal examination
- Inspection of the urine and stool
- Bruising or petechial rash
- Fundoscopic examination

Cholestasis-evaluation

Evaluation should be undertaken in a staged approach :

The initial step is rapid diagnosis and early initiation of therapy of treatable disorders

Additional testing is directed at the diagnosis of specific conditions

Cholestasis-Laboratory evaluation

- Complete blood count with platelet count
- Urinalysis & culture
- Testing for reducing substances
- Thyroid function tests
- Blood cultures
- Acid-base status
- Total and conjugated bilirubin
- Serum ALT, AST, & GGT
- Prothrombin and partial thromboplastin times
- Serum albumin and glucose concentrations.
- Blood ammonia concentration
- Alpha-1 antitrypsin level
- Screening for cystic fibrosis

Cholestasis-Radiological evaluation

Ultrasonography

Hepatobiliary scintigraphy

MRCP

Liver biopsy

Cholangiogram

Biliary Atresia

Biliary atresia (BA) is a progressive, idiopathic, fibro-obliterative disease of the extrahepatic biliary tree that presents with biliary obstruction exclusively in the neonatal period

BA is the most common indication for liver transplantation in children.

BA has 3 types……

Pathogenesis is unknown

Biliary atresia

CLINICAL FEATURES

Biliary atresia

DIAGNOSIS

- Abdominal ultrasound: the gallbladder is usually either absent or irregular in shape
- Hepatobiliary scintigraphy: failure of tracer excretion suggests BA
- Liver biopsy

Biliary atresia

Management

Kasai procedure (hepatoportoenterostomy)

Alagille syndrome

Mutations in human Jagged1 gene (*JAG1*)

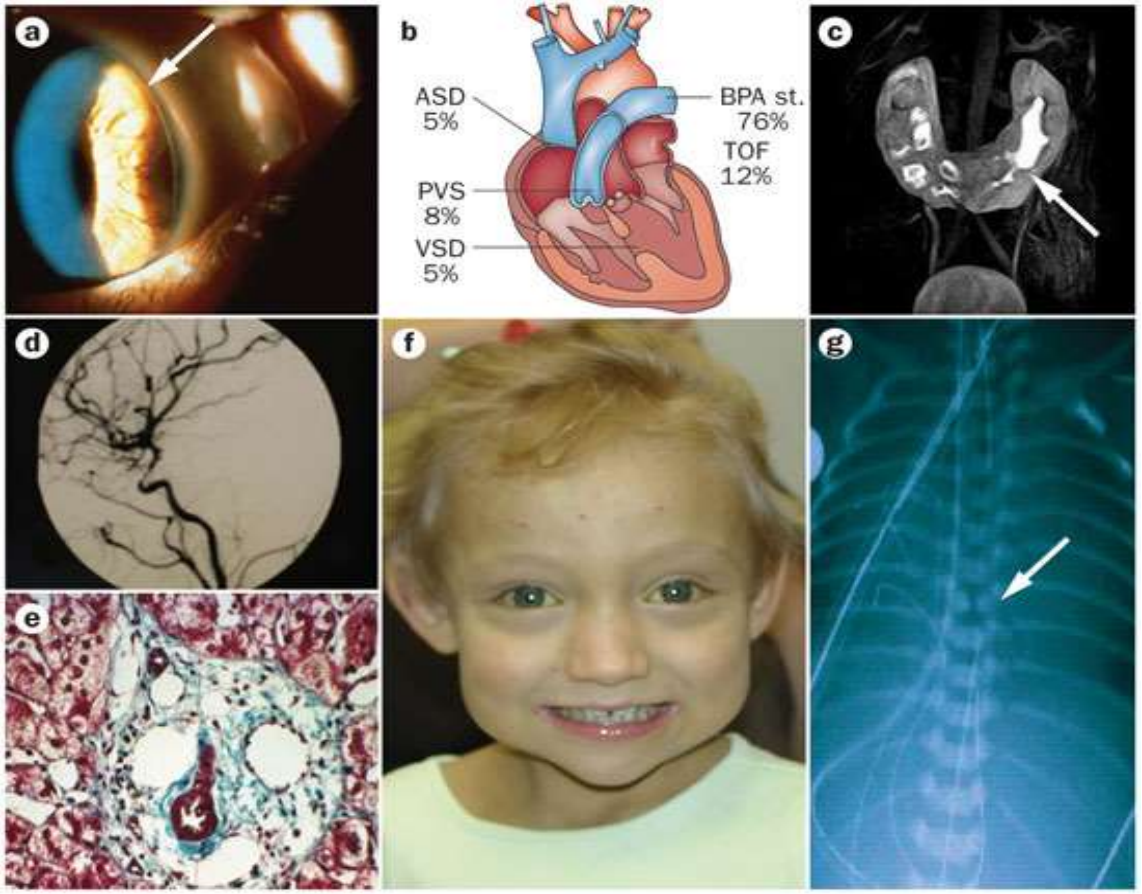
Autosomal dominant……..

Arteriohepatic dysplasia is the most common syndrome with intrahepatic bile duct paucity.

Absence or marked reduction in the number of interlobular bile ducts in the portal triads

Alagille syndrome

Clinical manifestations



Alagille syndrome

The prognosis for prolonged survival is good, but patients are likely to have pruritus, xanthomas with markedly elevated serum cholesterol levels

Some cases require transplantation

Idiopathic neonatal hepatitis

Can occur in either sporadic or familial form

Neonate appears ill, failure to thrive

HIDA scan: failure of uptake

Liver biopsy: giant cell hepatitis

Treatment: supportive, majority recover

Progressive familial intrahepatic cholestasis (PFIC)

Defect in the canalicuar membrane transporters

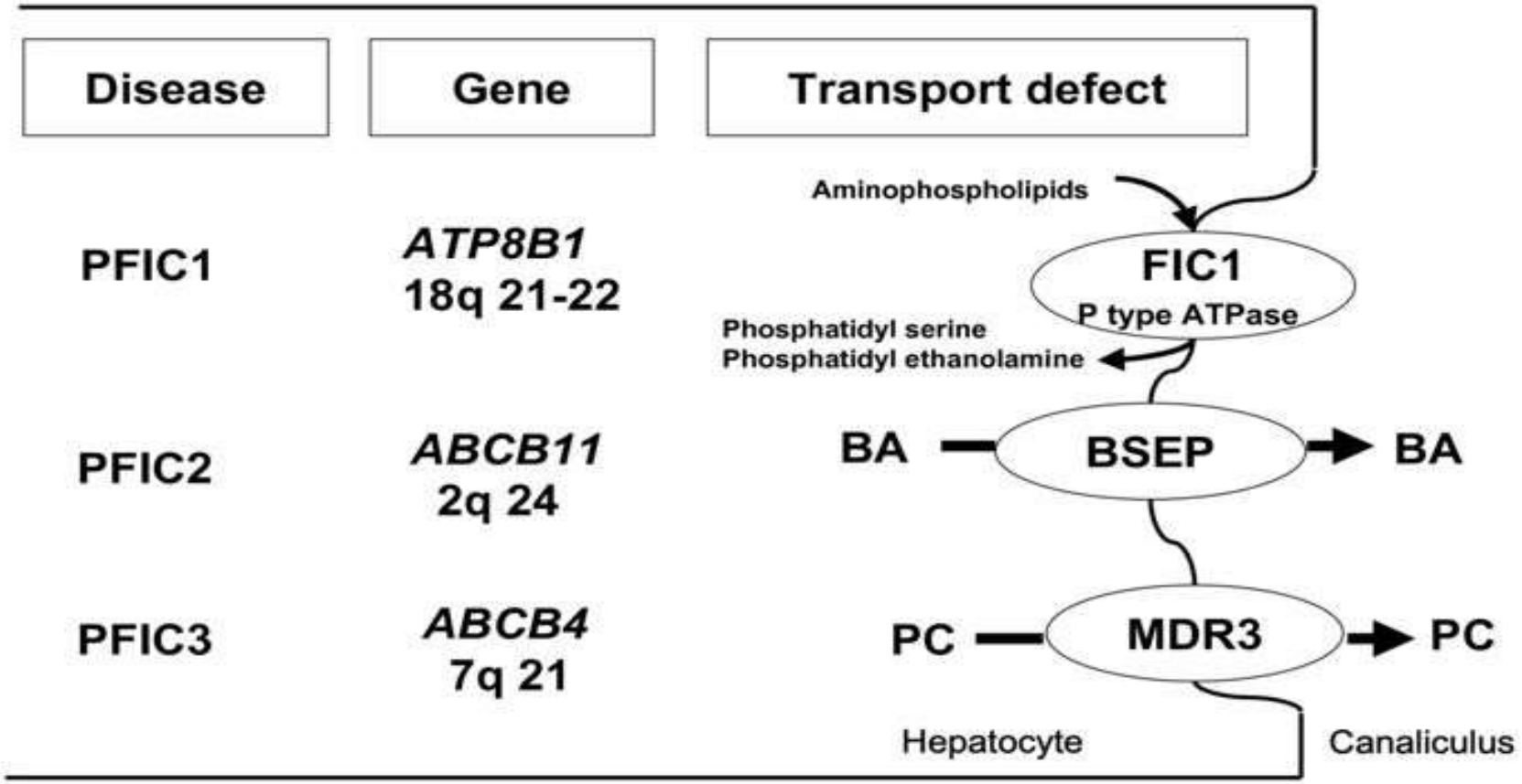
PFIC type 1 (Byler disease) is a severe form of intrahepatic cholestasis.

PFIC type 2 (BSEP deficiency)

PFIC type 3 (MDR3 disease)

Affected patients present with steatorrhea, pruritus, vitamin D–deficient rickets, gradually developing cirrhosis

Progressive familial intrahepatic cholestasis (PFIC)



Progressive familial intrahepatic cholestasis (PFIC)

	PFIC 1	PFIC 2	PFIC 3
Onset	First few mo	First few mo	Late infancy (~30%)/ Childhood/ adults
ESLD	First decade	rapid, first few years	I-II decade
Extra hepatic	Pancreatitis, diarrhea, hearing loss, short stature, Abn sweat chloride	**none**	**none**
γGT	**N/ low**	**N / low**	**Raised**
Liver biopsy	Bland cholestasis	Giant cell hepatitis, Hepatocellular necrosis, portal fibrosis	Bile ductular proli-feration Inflammatory infiltrate, fibrosis
E microscopy	Granular bile	Amorphous bile	-
AFP	N	increased	N
Serum bile acids	Raised ++	Raised ++	Raised +
Bile: Primary BS Biliary phospho-lipids	Reduced Normal	Severely reduced Normal	Normal Reduced

Zellweger (cerebrohepatorenal) syndrome

Autosomal recessive disorder marked by progressive degeneration of the liver and kidneys

The disease is usually fatal in 6-12 mo.

C/P: severe, generalized hypotonia and markedly impaired neurologic function with psychomotor retardation.

Patients have an abnormal head shape and unusual facial features, hepatomegaly, renal cortical cysts, calcifications of the patellas and greater trochanter, and ocular abnormalities.

Hepatic cells on ultrastructural examination show an absence of peroxisomes.

characteristic facial features such as a high forehead, underdeveloped eyebrow ridges, and wide-set eyes; and neurological abnormalities such as mental retardation and seizures

Aagenaes syndrome

Idiopathic familial intrahepatic cholestasis associated with lymphedema of the lower extremities.

Affected patients usually present with episodic cholestasis with elevation of serum aminotransferases, alkaline phosphatase, and bile acids.

Good prognosis, >50% have normal life span.

The locus for Aagenaes syndrome is on chromosome 15q.

Metabolic liver disease
When should we consider of metabolic liver disease?

Sick neonate not responding to usual treatment

Cholestasis , hepatomegaly

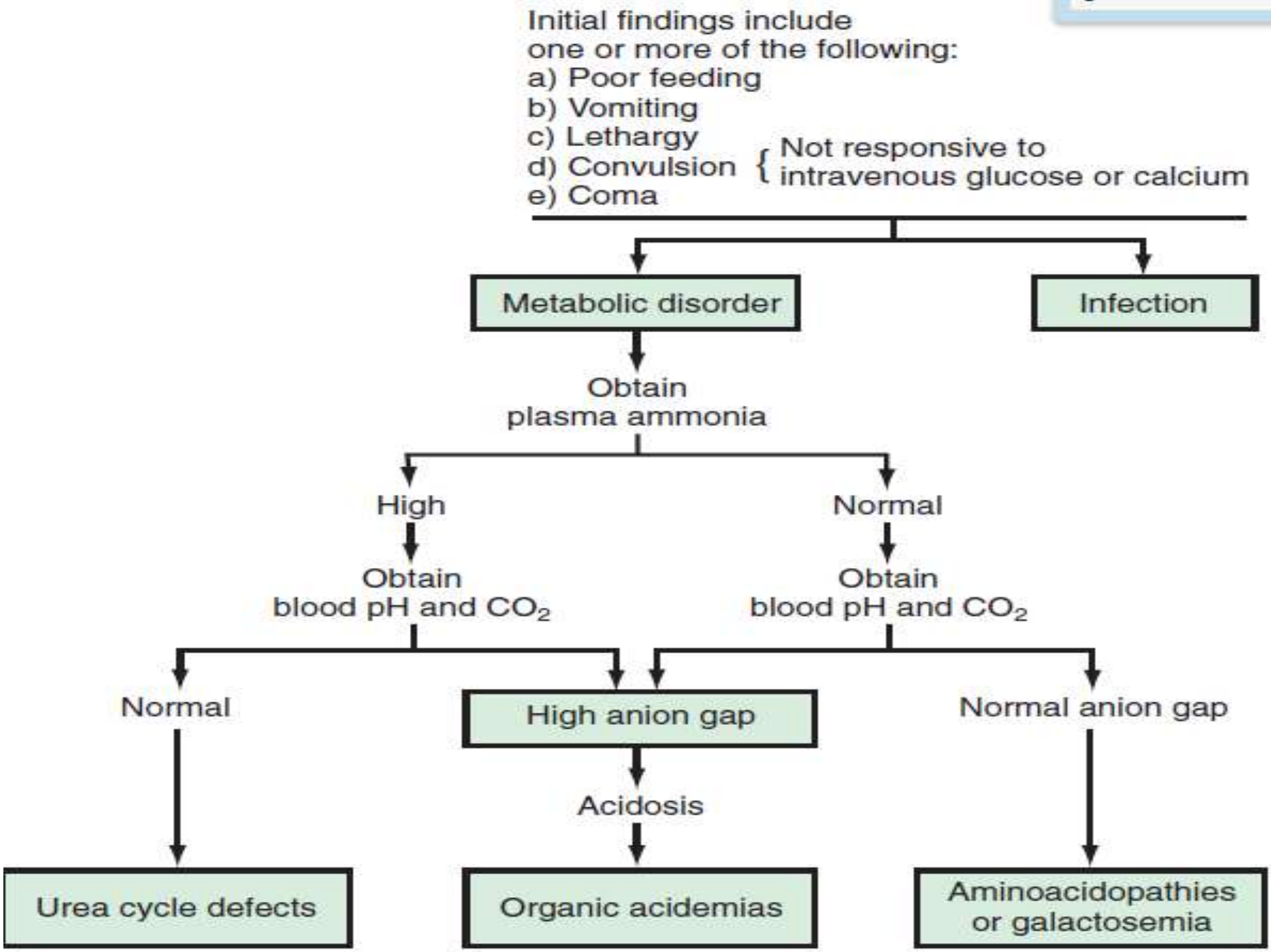
Seizure

Failure to thrive

Dysmorphic features

Metabolic acidosis

Persistent vomiting


Initial findings include
one or more of the following:
a) Poor feeding
b) Vomiting
c) Lethargy
d) Convulsion
e) Coma
Not responsive to intravenous glucose or calcium
Metabolic disorder
Infection
Obtain plasma ammonia
High
Normal
Obtain blood pH and CO_2
Obtain blood pH and CO_2
Normal
High anion gap
Normal anion gap
Acidosis
Urea cycle defects
Organic acidemias
Aminoacidopathies or galactosemia

Galactosemia

Galactosemia is the most common metabolic cause of liver disease

deficiency of the galactose-1-phosphate uridyltransferase (GALT)

Manifestations

Symptoms of classic galactosemia occur in neonates within days of ingestion of lactose

These manifestations include poor feeding, vomiting, diarrhea, failure to thrive, hypoglycemia, jaundice, hepatomegaly, elevated transaminases, coagulopathy, ascites, liver failure, renal tubulopathy, lethargy, irritability, seizures, cataracts, and Escherichia coli neonatal sepsis.

Galactosemia

Diagnosis

The biochemical profile of galactosemia includes elevated galactose in plasma, galactose-1-phosphate in erythrocytes, and galactitol (reducing substances) in urine.

Diagnosis is confirmed by measuring GALT enzyme activity in erythrocytes and sequencing the GALT gene.

Management

Lactose-free formula should be started during the first 3 to 10 days of life

Tyrosinemia Type I

Tyrosinemia type I occurs due to deficiency of fumarylacetoacetate hydrolase

Manifestations

Children with tyrosinemia type I can present during early infancy with vomiting, diarrhea, hepatomegaly, hypoglycemia, sepsis, liver failure with coagulopathy, ascites, jaundice, renal tubulopathy, and abnormal odor.

Tyrosinemia Type I

Diagnosis

Elevated urine succinylacetone and tyrosine metabolites

Elevated tyrosine and methionine in plasma.

Serum a-fetoprotein is markedly elevated.

Diagnosis can be confirmed by enzyme assay and molecular genetic testing for the FAH gene.

Management

Nitisinone (NTBC) (1–2 mg/kg/d divided in 2 doses)

Low tyrosine diet is also needed.

Hereditary Fructose Intolerance

It occurs due deficiency of fructose 1,6-biphosphate aldolase (aldolase B)

Manifestations

vomiting, hypoglycemia, jaundice, lethargy, irritability, seizures, coma, hepatomegaly, jaundice, elevated transaminases, coagulopathy, edema, ascites, liver failure, and renal tubulopathy.

Diagnosis

enzymatically by measuring the aldolase B activity in liver tissue and molecularly by sequencing the ALDOB gene.

Management

Management is based on eliminating sucrose, fructose, and sorbitol from diet.

General management of cholestasis

High calories for growth

Medium chain TG

ADEK vitamins

Ursodeoxycholic acid

Specific management for specific diagnosis