In the name of GOD

Liver Emergencies in children: Cholestasis ALF

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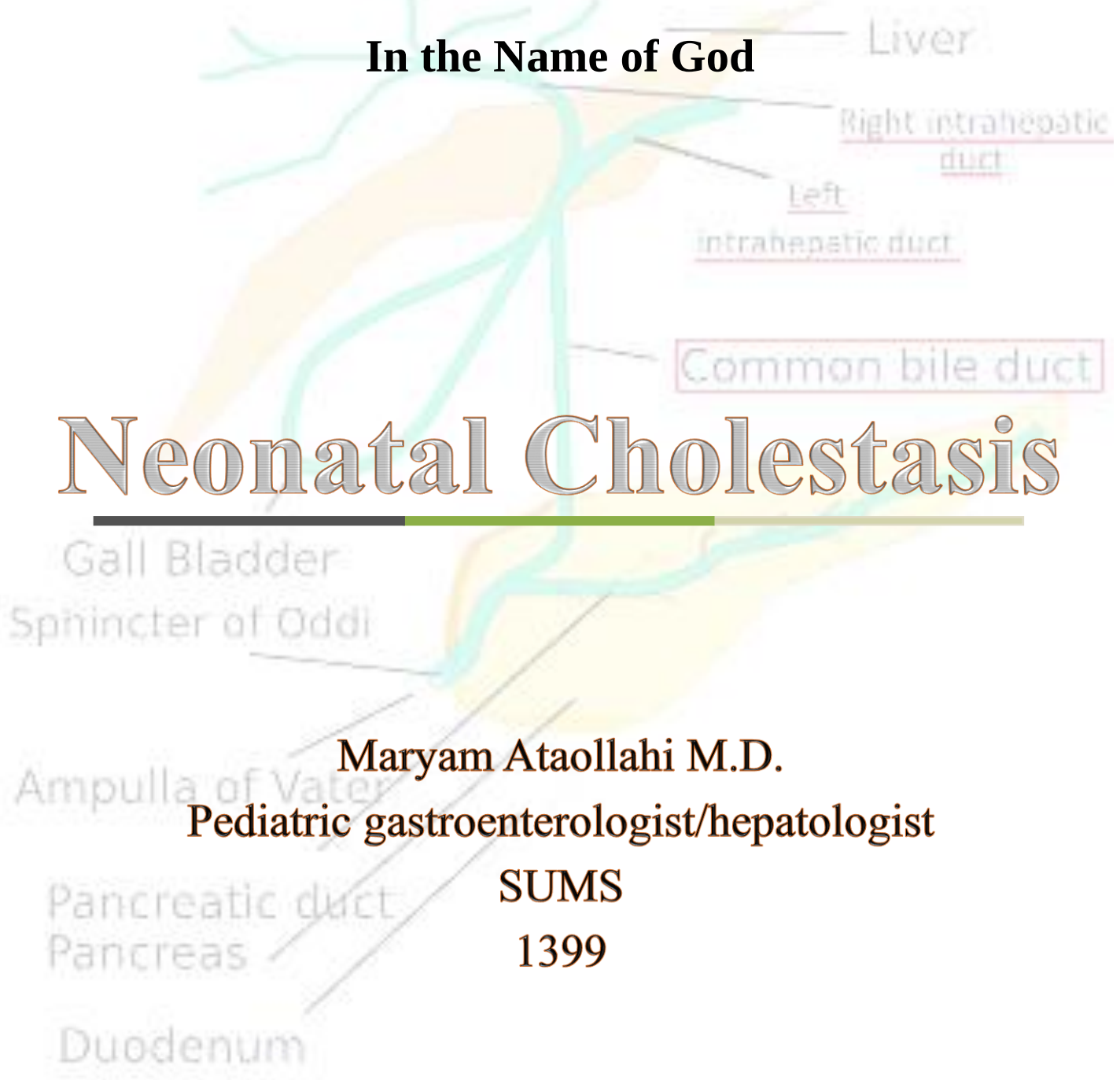
SUMS
1398

In the Name of God



Neonatal Cholestasis

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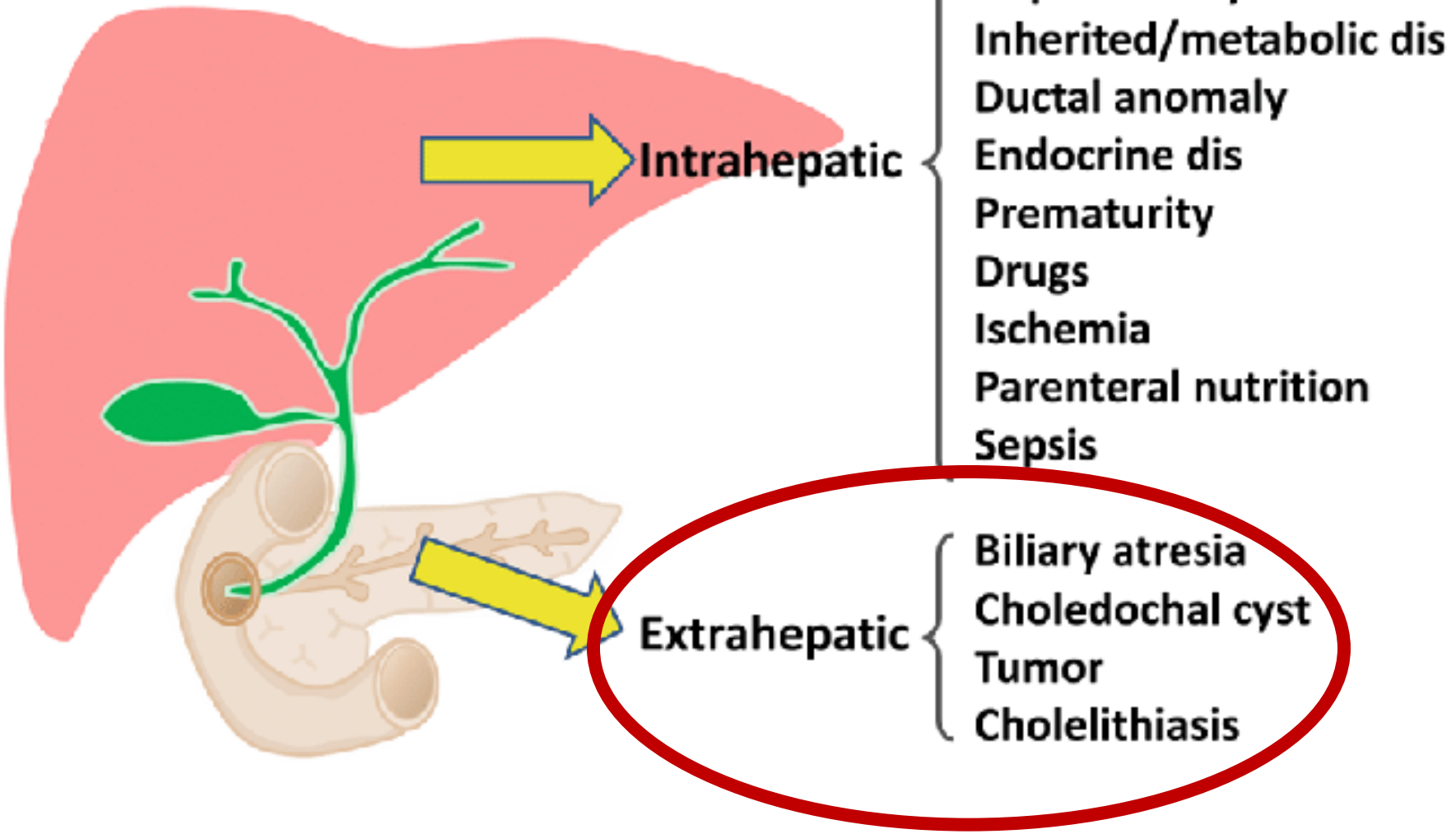
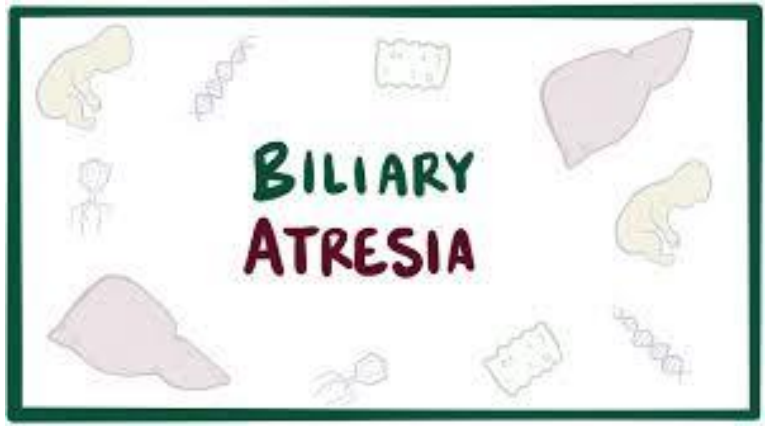
1399

- Neonatal cholestasis: prolonged conj. hyperbili
- Cause: diminished bile flow and/or excretion
  - Obstruction
  - Infection
  - Metabolic/genetic
  - Idiopathic
- Serum conj. Bili:
  - > 1 mg/dL if the total Bili is <5
  - >20 % of the total serum bili. if the total Bili. is >5

Overview

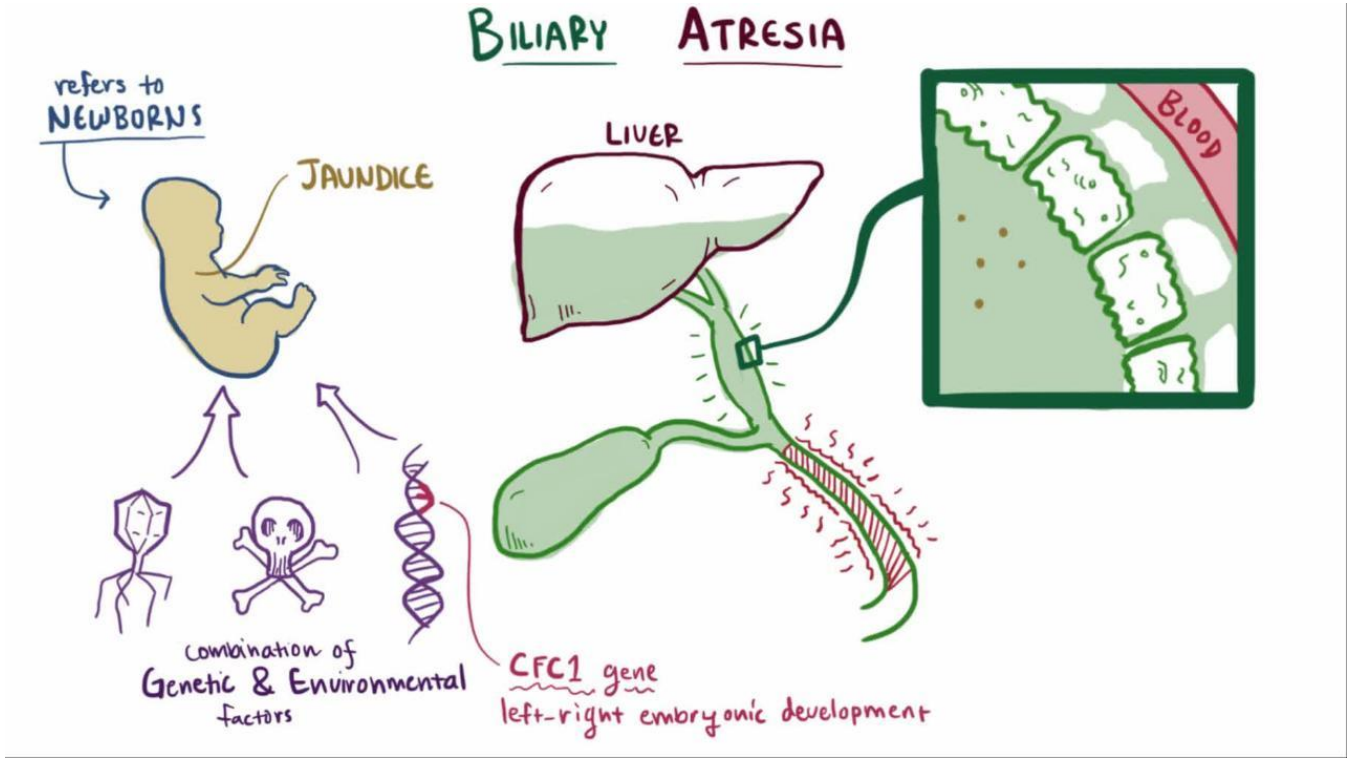
- Physiologic jaundice (unconj. hyperbili): resolves by 14 d of age
- 2 - 15 % of newborns: jaundiced at 2 wks of age .
- Most: benign breast milk jaundice
- A few: biliary atresia: prompt Dx & Rx
- Any infant jaundiced at the 2-week: should be evaluated for cholestasis (T. & D. Bili)


Intrahepatic
Hepatobiliary infections
Inherited/metabolic dis
Ductal anomaly
Endocrine dis
Prematurity
Drugs
Ischemia
Parenteral nutrition
Sepsis
Extrahepatic
Biliary atresia
Choledochal cyst
Tumor
Cholelithiasis

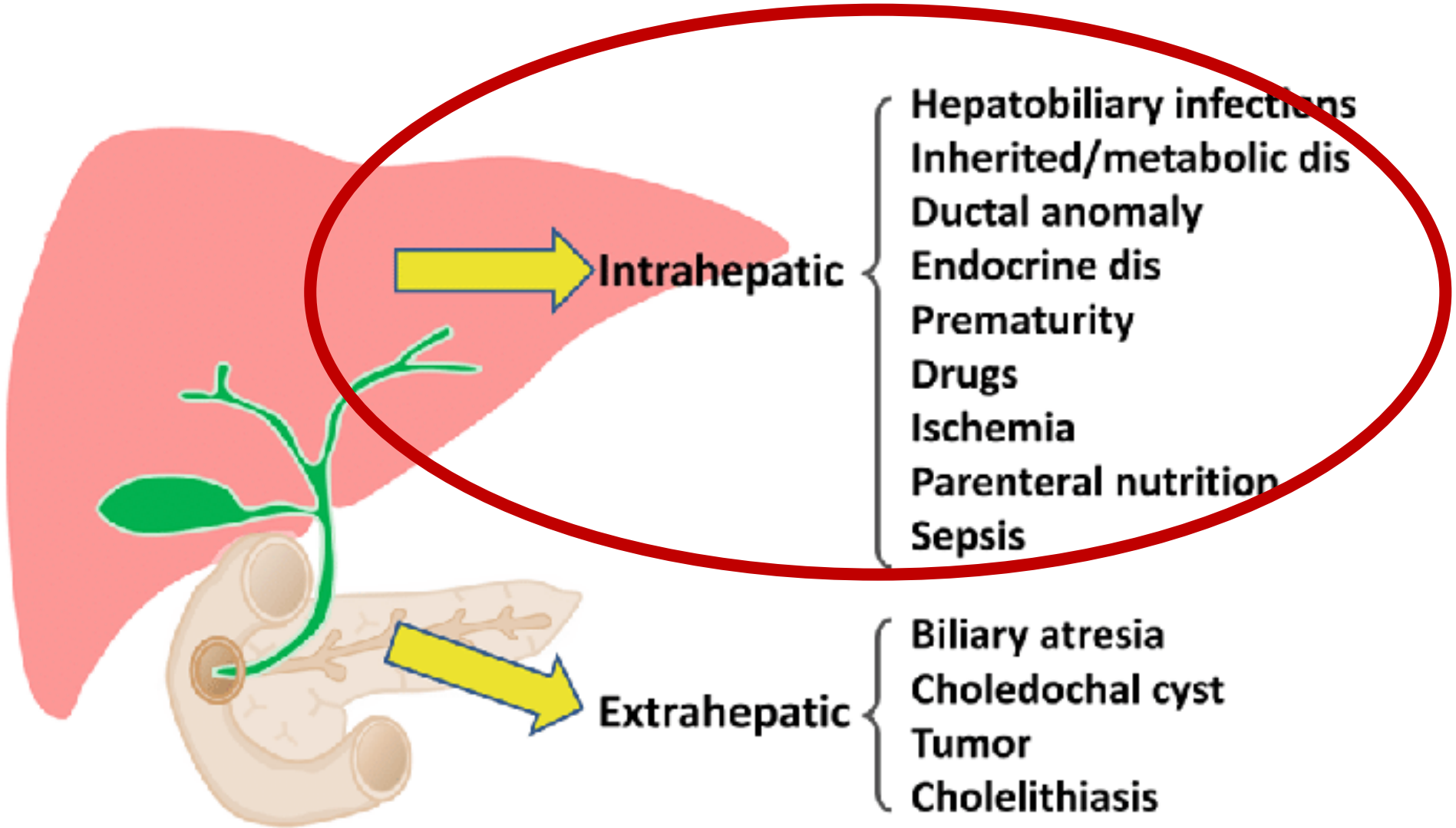


- Must be recognized promptly: ? improves outcome
- Most require liver transplantation.
- healthy at birth: progressive jaundice within the 1st 8 weeks of life.
- acholic (pale-colored) stools, firm liver and splenomegaly.

- Syndromic BA with laterality defects & splenic anomalies



- Choledochal cyst
- Inspissated bile/plug Sx:
  - severe jaundice associated hemolysis due to Rh or ABO incompatibility
  - patients with CF
- Gallstones or biliary sludge
- Tumors
- Neonatal sclerosing cholangitis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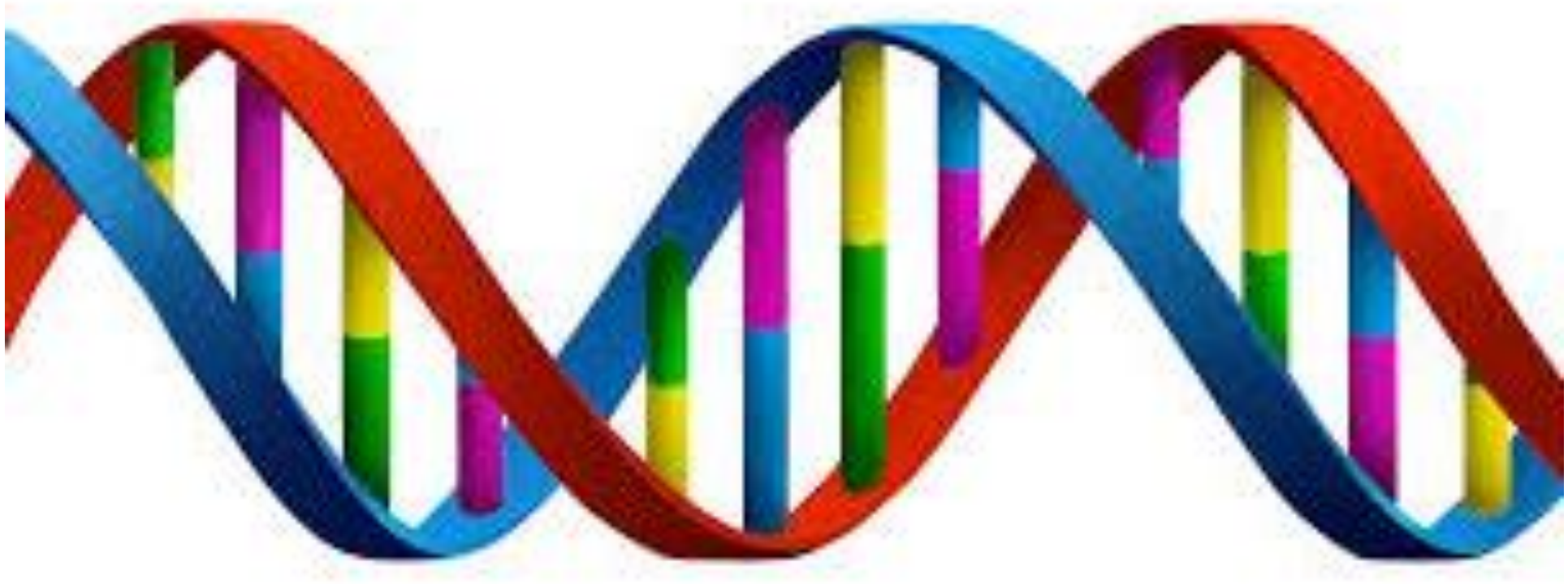
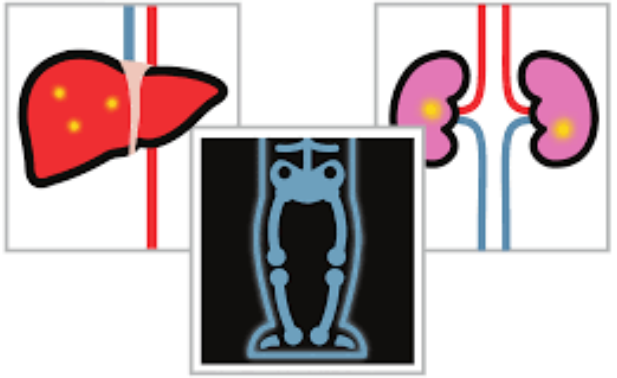
METABOLIC/GENETIC DISORDERS



Galactosemia

- GALT deficiency.
- Conj. & unconj hyperbili after the onset of galactose-containing feedings (human or cow's milk)
- Sepsis: common
- Vomiting, diarrhea, FTT, RTA , cataracts, and coagulopathy.
- + reducing substances in the urine, GALT
- Newborn screening
- Treatment: elimination of galactose: start soy based formula

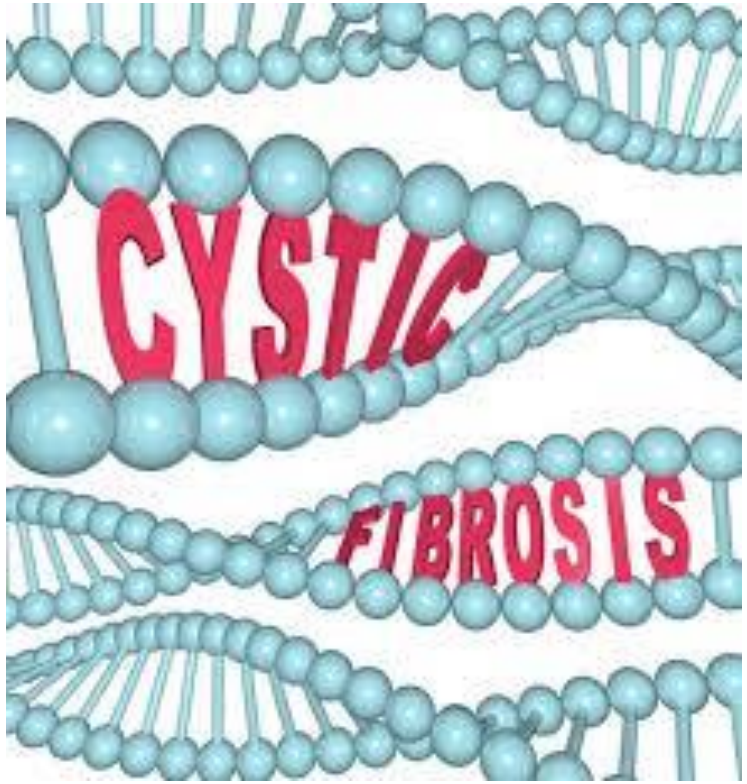
TYROSINEMIA



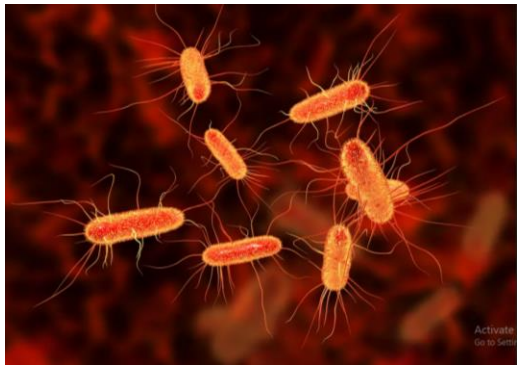
- Progressive liver dx , RTA, and neurologic impairment.
- coagulopathy
- ↑urinary excretion of succinylacetone
- Newborn screening

- PFIC is classified into 3 types.
- The most common type presenting in infancy: PFIC2

CF



- Jaundice and hepatomegaly slowly resolve.
- Infants with CF: meconium ileus or steatorrhea with FTT

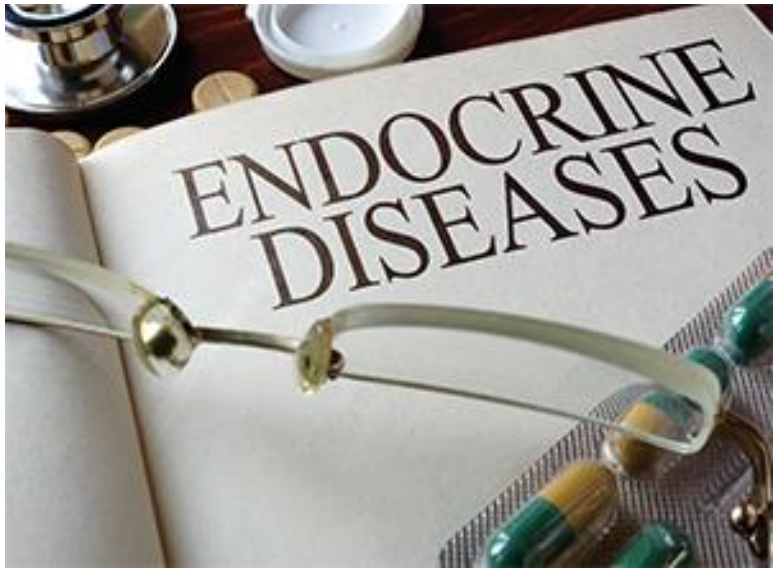


- TORCH and parvovirus B19
- Bacterial infections: gram+ and gram-: sepsis/UTI
- Jaundice may be the only presenting sign in patients with a UTI caused by E.coli

Alagille Syndrome

Paucity of interlobular bile ducts and the following associated features :

- Chronic cholestasis
- Cardiac anomalies: peripheral pulmonic stenosis
- Butterfly vertebrae
- Eye: posterior embryotoxon
- Dysmorphic facies: broad nasal bridge, triangular facies, deep set eyes
- Renal involvement: renal dysplasia
- Short stature
- Autosomal dominant

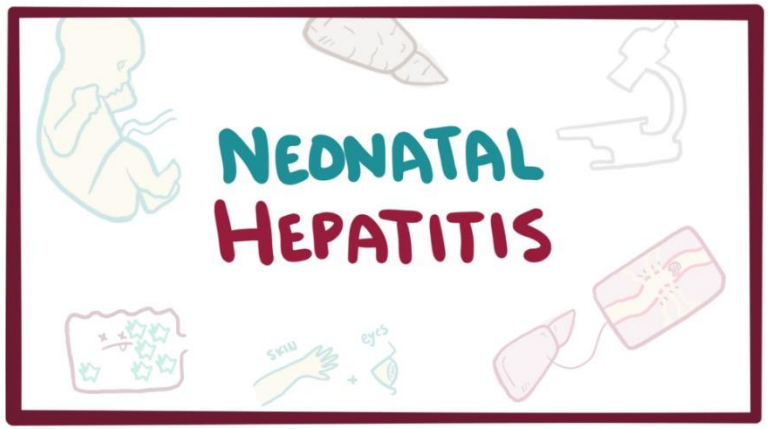


- Thyroid Disorders: TSH, free T4
- Panhypopituitarism:
  - Hypoglycemia
  - shock from adrenal insufficiency
  - microphalus in male infant

OTHER

- Gestational alloimmune liver dx
- Alpha-1-Antitrypsin Deficiency
- Bile Acid Synthesis Disorders

IDIOPATHIC



- Without an obvious etiology after a complete evaluation
- Liver biopsy: multinucleated giant cells

NEONATAL HEPATITIS AND BILIARY ATRESIA, WHICH TYPICALLY OCCUR IN TERM INFANTS, ACCOUNT FOR 70 - 80 % OF CASES

in evaluating a jaundiced infant:

measure total & conjugated bilirubin.

- The initial step: rapid diagnosis and early initiation of therapy of treatable disorders:
- Biliary atresia:
  - surgical intervention (before 2 months of age): better outcome.
  - Important steps in diagnosis: ultrasonography and liver biopsy.
- Sepsis/UTI, hypothyroidism, panhypopituitarism, galactosemia, tyrosinemia: promptly

Helpful in differential diagnosis of neonatal cholestasis:

- Consanguinity (autosomal recessive disorder)
- Congenital infections
- Prenatal ultrasonography (choledochal cyst or bowel anomalies)
- Neonatal infection: UTI
- Dietary Hx (breast milk or galactose-containing formula)
- Wt gain (neonatal hepatitis and metabolic disease: FTT
- Vomiting: metabolic dx
- Stooling pattern:
  - delayed stooling in CF, hypothyroidism
  - diarrhea in infection, metabolic disease, PFIC

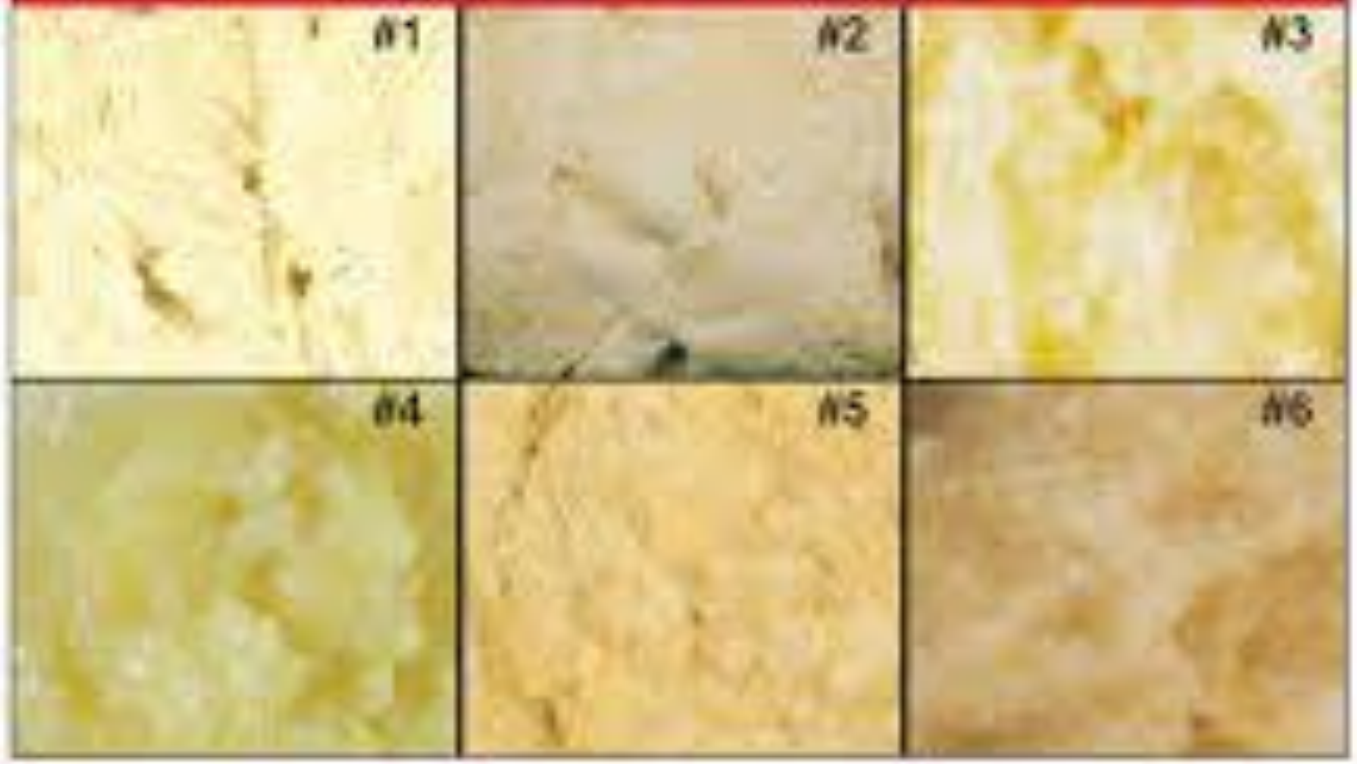
- Stool color
- Urine color
- Excessive bleeding: coagulopathy: vit. K def.
- Irritability: metabolic dx or sepsis
- Lethargy: metabolic dx, sepsis, ↓thyroidism, pan↓pituitarism
- FHx of similar problems: (CF, alpha-1 ATD, PFIC, Alagille syndrome)

Important physical examination:

- Growth parameters: HC, Wt
- General health:
  - ill-appearance: infection or metabolic disease
  - infants with biliary atresia typically appear well
- General appearance (Alagille, Down,…)
- Funduscopic exam
- Cardiac murmur
- Abdominal examination (ascites; liver size, position, and consistency; spleen size and consistency; umbilical hernia)
- Direct examination of the urine and stool color: stool pigment is a key aspect
- Bruising or petechiae

BC INFANT STOOL COLOUR CARD©
SCREENING PROGRAM FOR BILIARY ATRESIA

Abnormal Stool Colours



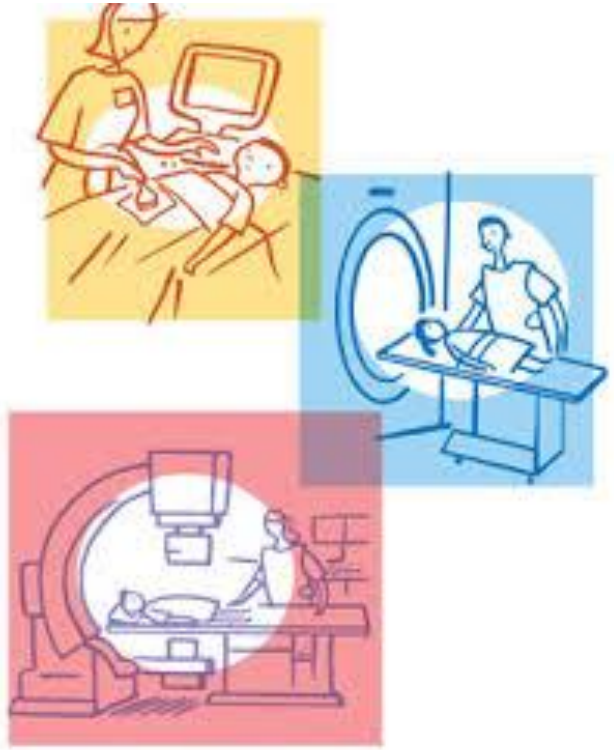
Normal Stool Colours

- CBC, INR, AST, ALT, ALP, GGT, TB/DB, albumin, glucose
  - GGT: primarily raises the concern for biliary atresia
  - higher in the 1st month of life compared with older children.
- TSH, T4
- U/A, U/C, reducing substances

- VBG, serum ammonia, lactate level, cholesterol
- RBC GALT
- Urine succinylacetone
- PCR for CMV, HSV, listeria
- Genetics - consider gene panels or exome sequencing
- Sweat chloride analysis (CFTR genetic testing)
- ZZ or SZ 1 phenotype
- Serum bile acids, cortisol
- Ferritin

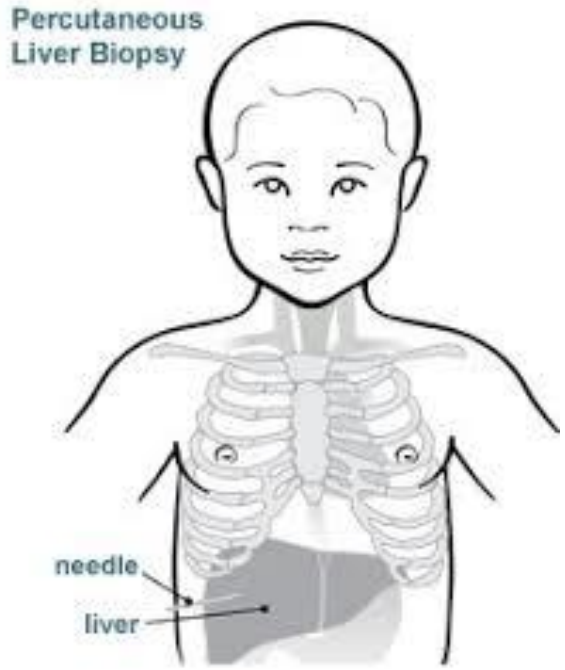
IMAGING STUDIES

- Ultrasonography: initial test:
  - gallbladder
  - triangular cord sign
- CXR: lung and heart disease
- Spine: spinal abnormalities (butterfly vertebrae)
- Echocardiogram



Liver biopsy

- Percutaneous liver biopsy: recommended for most infants with neonatal cholestasis



- Cholangiogram
  - Open cholangiogram: If the above steps in the evaluation support the diagnosis of biliary atresia: intraoperative cholangiogram, which is the gold standard in the diagnosis
- ERCP
- MRCP

- Ophthalmology
- Metabolic/genetics
- Cardiology
- General pediatric surgery
- Nutrition/dietician

TABLE 2. Parameters of clinical interest in the history of the cholestatic infant

Family history	
Consanguinity	Increased risk of autosomal recessive disorders
Neonatal cholestasis in the parents or siblings	Cystic fibrosis, α-1-antitrypsin deficiency, progressive familial intrahepatic cholestasis, Alagille syndrome are all genetic conditions causing neonatal cholestasis
History of repeated fetal loss or early demise	Gestational alloimmune liver disease
Spherocytosis and other hemolytic diseases	Known to aggravate conjugated hyperbilirubinemia
Prenatal history	
Prenatal ultrasonography findings	Presence of choledochal cyst, cholelithiasis, bowel anomalies or concern for syndrome
Cholestasis of pregnancy	May be seen in heterozygotes for *PFIC* gene mutations; mitochondrial disorder
Acute fatty liver of pregnancy	Neonatal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency
Maternal infections	TORCH infections
Infant history	
Gestational age	Prematurity as a risk factor for neonatal hepatitis
SGA	Increased risk of neonatal cholestasis, congenital infections
Alloimmune hemolysis; glucose-6-P-dehydrogenase deficiency; hydrops fetalis	Increased risk of neonatal cholestasis
Neonatal infection	Urinary tract infection, sepsis related cholestasis, CMV, HIV, syphilis, etc
Newborn screen	Panhypopituitarism galactosemia, fatty acid oxidation defects, cystic fibrosis
Source of nutrition: breast milk, formula, PN	Galactosemia, hereditary fructose intolerance, PN-associated liver disease
Growth	Genetic and metabolic disease
Vision	Septo-optic dysplasia
Hearing	PFIC1, TJP2
Vomiting	Metabolic disease, bowel obstruction, and pyloric stenosis
Stooling	Delayed stooling: CF, panhypopituitarism; diarrhea: infection, metabolic disease
Stool color	Acholic stools: cholestasis, biliary obstruction
Urine characteristics: smell and color	Dark urine (conjugated hyperbilirubinemia), metabolic disease
Excessive bleeding	May indicate coagulopathy, vitamin K deficiency
Disposition: irritability, lethargy	Metabolic disease or sepsis, panhypopituitarism
Abdominal surgery	Necrotizing enterocolitis, intestinal atresia

TABLE 3. Physical findings in children with neonatal cholestasis

Assessment of general health	Ill appearance may indicate infection or metabolic disease, infants with biliary atresia typically appear well
General appearance	Dysmorphic features: Alagille syndrome in the neonate rarely exhibits characteristic facial appearance with a broad nasal bridge, triangular facies, and deep-set eyes. Typical facial features may appear at around 6 months of age, but are often nonspecific (69)
Vision/slit lamp examination	
Hearing	Congenital infection, storage disease, septo-optic dysplasia, posterior embryotoxon, cataracts
Congenital infections, PFIC1, TJP2, mitochondrial	
Cardiac examination: murmur, signs of heart failure	Congenital heart disease: Alagille syndrome, biliary atresia splenic malformation syndrome
Abdominal examination	Presence of ascites; abdominal wall veins, liver size and consistency, spleen size and consistency (or absence thereof), abdominal masses, umbilical hernia
Stool examination (crucial—the primary physician should make every effort to view stool pigment)	Acholic or hypopigmented stools suggest cholestasis or biliary obstruction
Neurologic	Note overall vigor and tone

PFIC = progressive familial intrahepatic cholestasis; TJP = tight-junction protein.

Targeted investigations:

Tier 1.

Blood - CBC, INR, AST, ALT, ALP, GGT, TB DB (or conjugated), albumin, glucose, TSH, T4 if newborn screen unavailable

Urine - urinalysis, culture, reducing substances (rule out galactosemia)

Consider additional bacterial cultures of blood or other fluids, especially if infant clinically ill.

Tier 2.

General - serum bile acids, cortisol

Consideration of specific etiologies

Metabolic - serum ammonia, lactate level, cholesterol, red blood cell galactose-1-phosphate uridyltransferase, urine for succinylacetone and organic acids. Consider urine for bile salt species profiling

ID - PCR for CMV, HSV, listeria

Genetics - consider gene panels or exome sequencing

Sweat chloride analysis (CFTR genetic testing) as appropriate

Imaging:

CXR - lung and heart disease

Spine - spinal abnormalities (butterfly vertebrae)

Echocardiogram

Cholangiogram

Liver biopsy

Considerations for consultations:

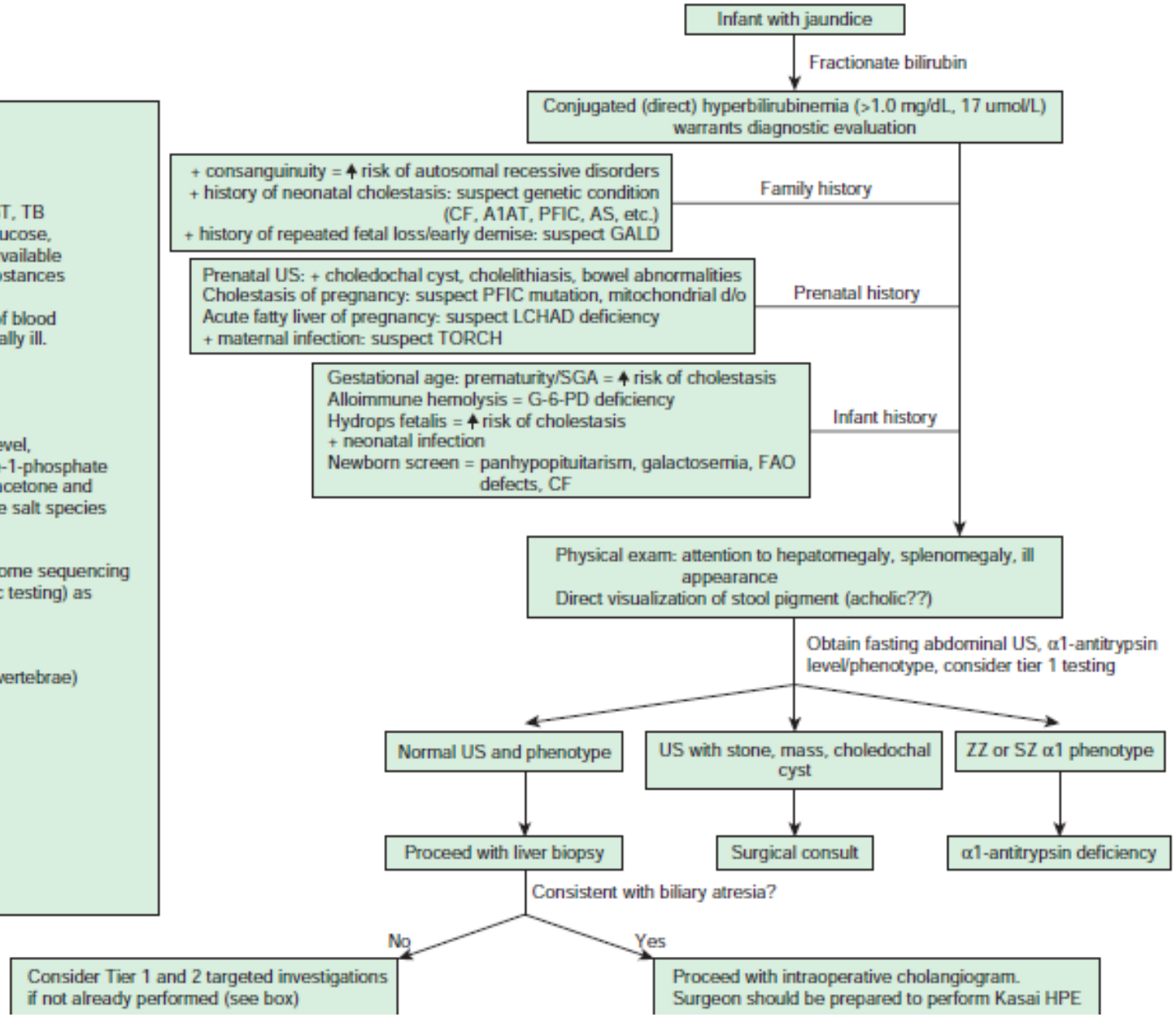
Ophthalmology

Metabolic/genetics

Cardiology

General pediatric surgery

Nutrition/dietician



TREATMENT

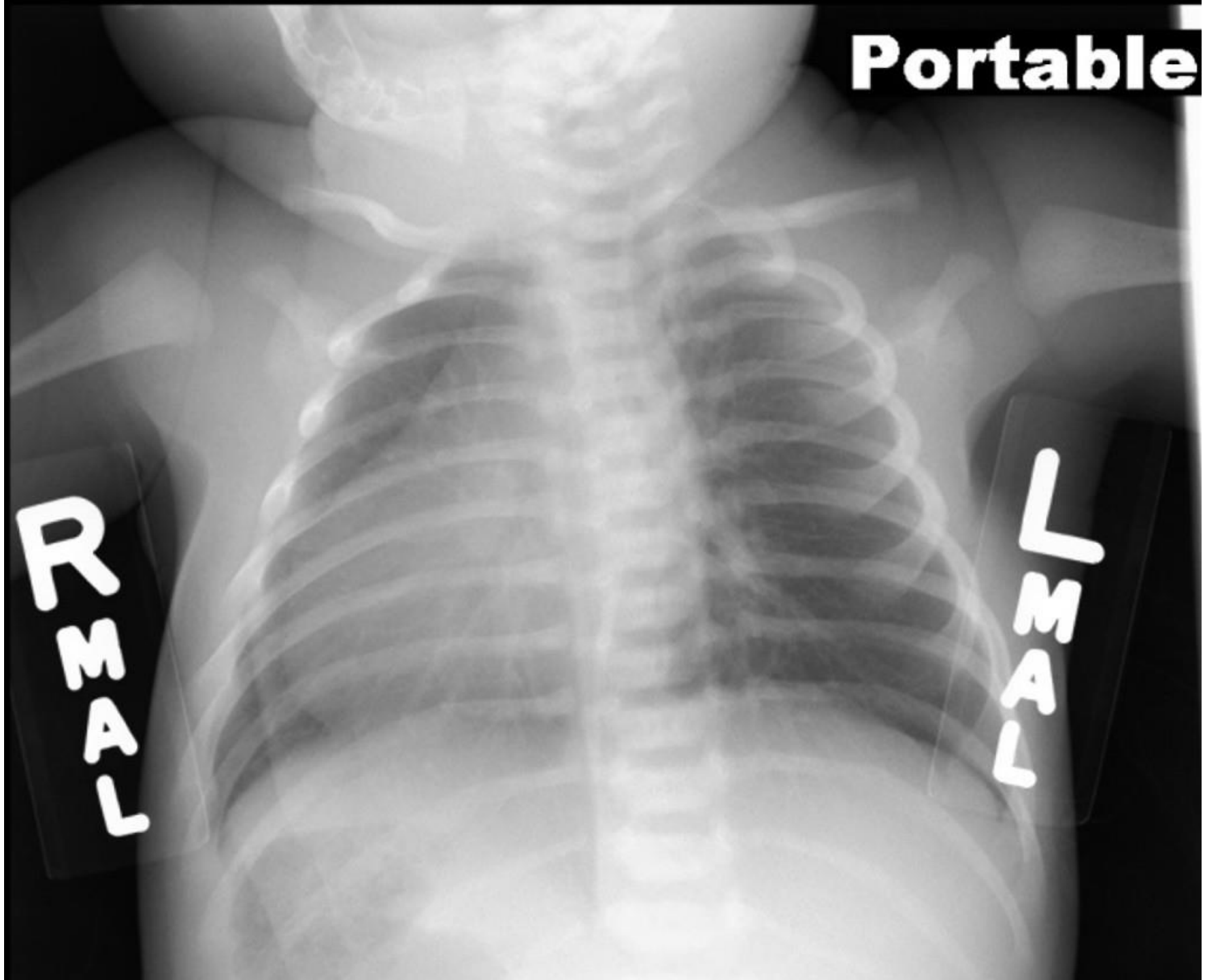
- Treat the etiology
- Supplementation
- Treat complication

Nutritional factor	Index of assessment	Treatment options	Toxicity
Energy	Anthropometrics, triceps and subscapular skinfold thickness, serial measurements of weight/height, indirect calorimetry, fat malabsorption	Caloric goal: 125% of RDA based on weight for height at 50th percentile Glucose polymers (Polycose powder or solution) to ↑ to 24–27 cal/oz formula Supplemental night-time nasogastric drip feedings MCT infant formulae (Pregestimil, Alimentum) MCT oil supplements: 1–2 mL/kg daily in 2–4 doses	Financial burden, essential fatty acid deficiency Aspiration pneumonia
Essential fatty acids	Deficiency: triene:tetraene ratio >0.3, ↓ linoleic acid	Corn oil or oral lipid emulsions IV lipid emulsions	
Protein	Mid-arm muscle circumference, serum albumin, prealbumin, RBP, transferrin	Infants: protein intake 2–3 g/kg per day Hepatic encephalopathy: protein intake 0.5–1.0 g/kg per day Branched-chain amino acid supplements	Unknown
Fat-soluble vitamins			
Vitamin A	Deficiency: retinol:RBP molar ratio <0.8 or serum retinol < 20 mg/dL; relative dose response; conjunctival impression cytology; xerosis, Bitot spots, etc.	5000–25 000 U/day orally of water-miscible preparation of vit. A	Hepatotoxicity, pseudotumor cerebri, bone lesions, hypercalcemia
Vitamin D	Deficiency: calcifidiol <14 ng/mL	Vit. D (Drisdol), 3–10× RDA for age Rickets: calcifidiol (Calderol), 3–5 mg/kg per day Osteomalacia: calcitriol (Rocaltrol), 0.05–0.2 mg/kg per day	Hypercalcemia Hypercalcemia, nephrocalcinosis
Vitamin E	Deficiency: vit. E:total lipid ratio <0.6 mg/g (age <1 year), <0.8 mg/g (age >1 year)	α-Tocopherol (acetate) 25–200 IU/kg per day TPGS (Liqui E), 15–25 IU/kg per day	Potentiation of vit. K deficiency coagulopathy, diarrhea, hyperosmolality (TPGS)
Vitamin K	Deficiency: prolonged prothrombin time, Elevated PIVKA-II	Mephyton, 2.5 mg twice/wk to 5.0 mg/d AquaMEPHYTON (IM) 2–5 mg every 4 wk	

Water-soluble vitamins		Prevent deficiency of water-soluble vitamins dose: 1–2× RDA	Fat-soluble vitamin toxicity
Minerals and trace elements			
Calcium	Deficiency in steatorrhea despite corrected vit. D status	25–100 mg/kg per day up to 800–1200 mg/day	Hypercalcemia, hypercalciuria
Phosphorus	Low serum phosphorus despite corrected vit. D and calcium status	25–50 mg/kg per day up to 500 mg/day	Gastrointestinal intolerance
Magnesium	Deficiency: serum Mg <1.4 mEq/L	Magnesium oxide, 1–2 mEq/kg daily orally or 50% solution of magnesium sulfate, 0.3–0.5 mEq/kg IV over 3 hours (max. 3–6 mEq)	Respiratory depression, lethargy, coma
Zinc	Deficiency: plasma zinc <60 µg/dL	Zinc sulfate solution (10 mg/mL elemental zinc) 1 mg/kg/d orally for 2–3 mo	↓ Intestinal absorption of copper and iron
Selenium	Deficiency: plasma Se <40 µg/L	1–2 µg/kg per day oral sodium selenite or 1–2 µg/kg per day Se in TPN	Dermatologic changes (skin eruptions, pathologic nails, hair loss), dyspepsia, diarrhea, anorexia
Iron	Deficiency: ↓ serum iron, ↑ total iron-binding capacity, iron saturation index <16%	5–6 mg/kg per day elemental iron	Teeth staining, hemorrhagic gastroenteritis, metabolic acidosis, coma, liver failure

↑, increased; ↓, decreased; IM, intramuscularly; IV, intravenous; MCT, medium-chain triglyceride; PIVKA-II, protein induced in vitamin K absence; RBP, retinol-binding protein; RDA, recommended daily allowance; TPGS, tocopherol polyethylene glycol-1000 succinate; TPN, total parenteral nutrition.

Treatment	Indications	Dosage	Toxicity
Bile acid-binding agents: cholestyramine, colestipol, aluminum hydroxide antacids, sucralfate (?)	Hypercholesterolemia, xanthoma, pruritus, hypercholemia(?)	250–500 mg/kg daily (cholestyramine and colestipol)	Constipation, hyperchloremic acidosis, binding of drugs, increased steatorrhea, intestinal obstruction
Naltrexone	Pruritus	50 mg/day (adults)	Nausea, headache, hepatotoxicity (?), opioid withdrawal reactions
Phenobarbital	Hypercholesterolemia, pruritus, hypercholemia(?)	3–10 mg/kg per day	Drowsiness, behavior changes, interference with vitamin d metabolism, risk for suicide and suicidal behavior
Rifampicin	Pruritus	10 mg/kg per day	Hepatotoxicity, drug interactions, hemolytic anemia, renal failure
Ursodeoxycholic acid	Pruritus, hypercholesterolemia, cholestasis, cystic fibrosis liver disease	10–30 mg/kg per day	Diarrhea, increased pruritus, hepatotoxicity(?)
Antihistamines	Pruritus	Diphenhydramine, 5–10 mg/kg daily or hydroxyzine, 2–5 mg/kg daily	Drowsiness
Ultraviolet B light	Pruritus		Skin burn
Carbamazepine	Pruritus	20–40 mg/kg/d	Hepatotoxicity, bone marrow suppression, fluid retention, behavioral changes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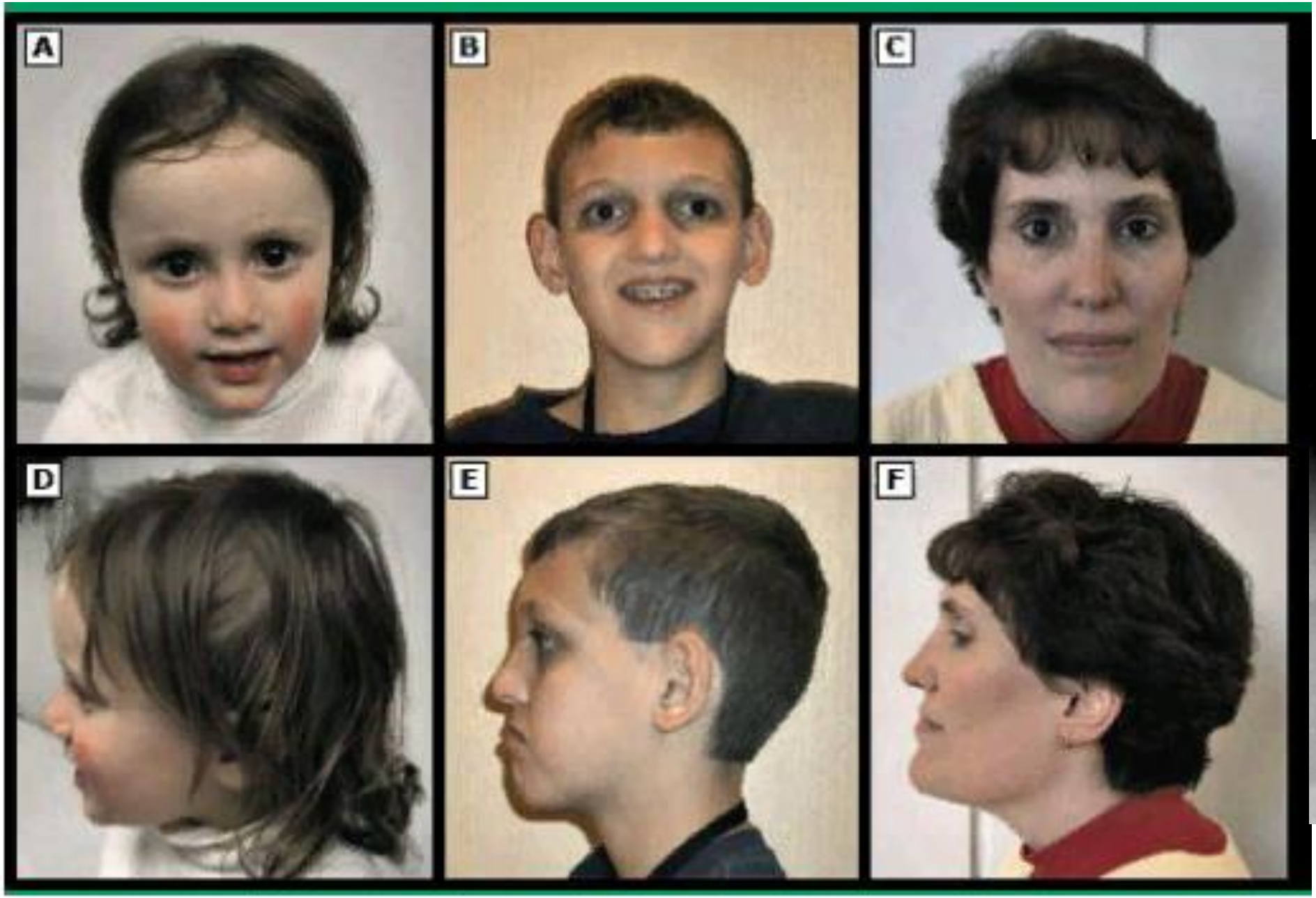
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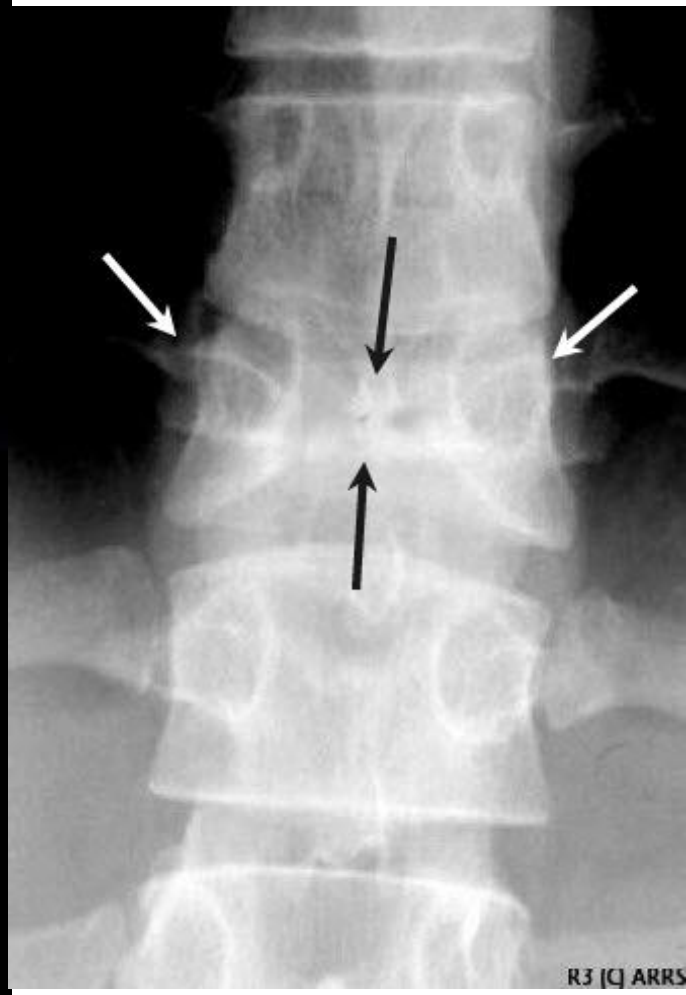
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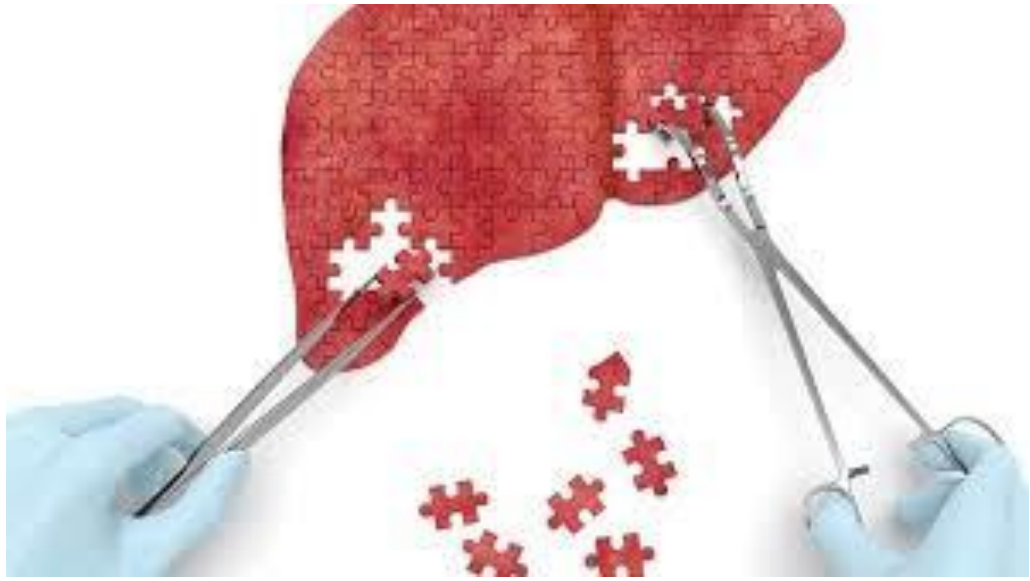
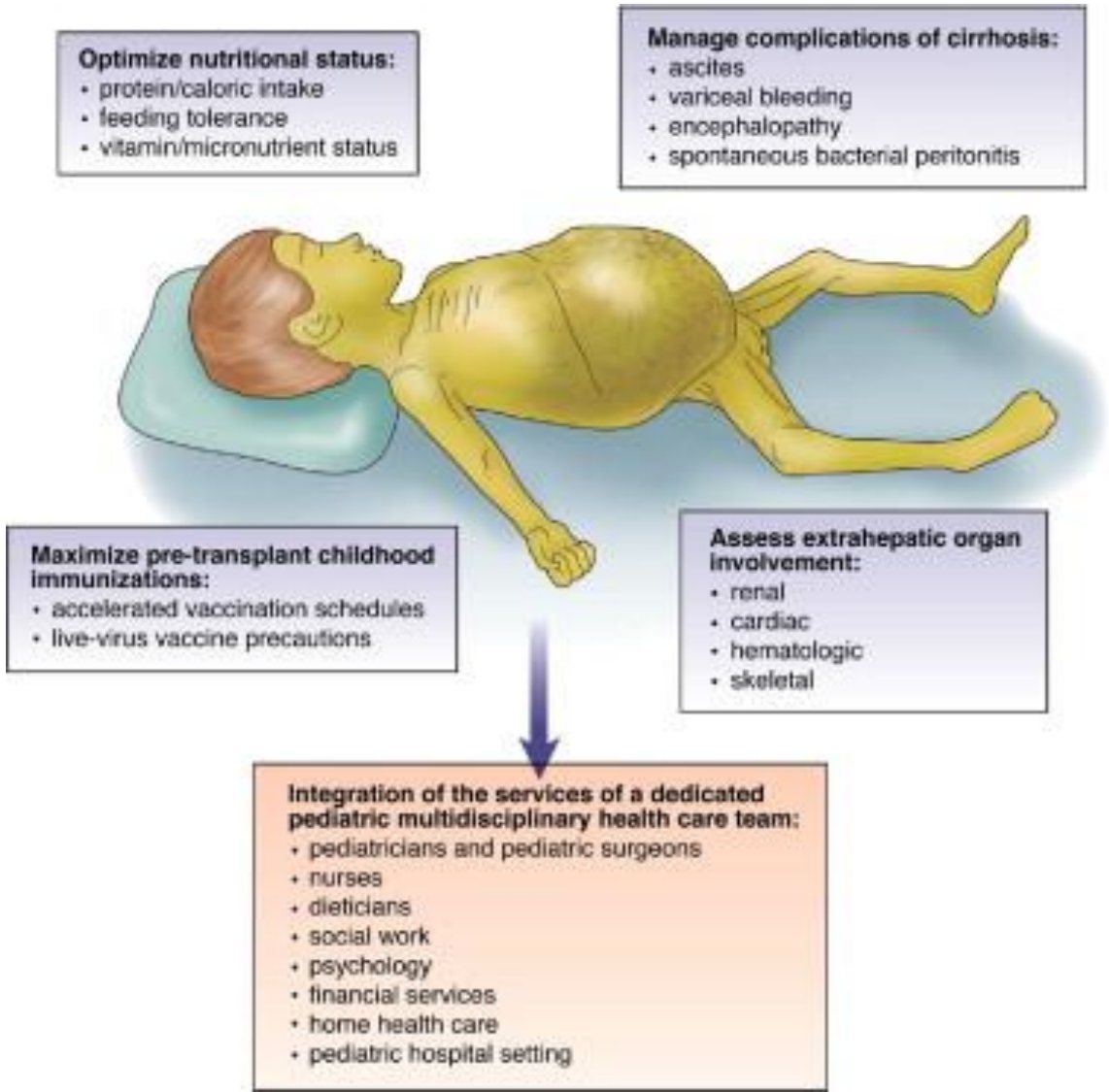
ALF:

(1) children with no known evidence of chronic liver disease
(2) biochemical evidence of acute liver injury
(3) coagulopathy not corrected by vitamin K.
PT:15 -19.9 or INR: 1.5 -1.9, with encephalopathy
PT: 20 or the INR 2.0 or more: with or without HE.



Liver cirrhosis with hepatic encepahlopathy

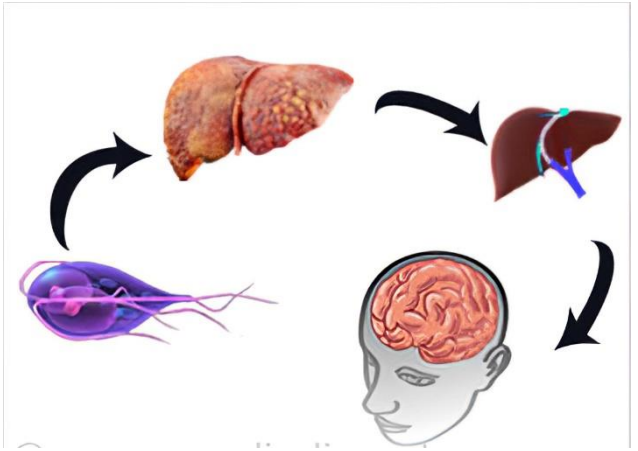


- Admission to PICU
- Frequent monitoring of mental status
- A cardiorespiratory and O2 saturation monitor
- Frequent bedside assessment by an experienced nurse or clinician.
- Check input and output
- Assess HE
- ↑respiratory effort, changing heart rate or changes in blood pressure: signs of infection, ↑cerebral edema, or elec. Imbalance
- In the absence of the need for volume resuscitation, total IVF: restricted to 85 - 95% of maintenance: avoid overhydration
- Sufficient glucose and phosphorus
- Some protein restriction: 1 g/kg/day

Laboratory monitoring

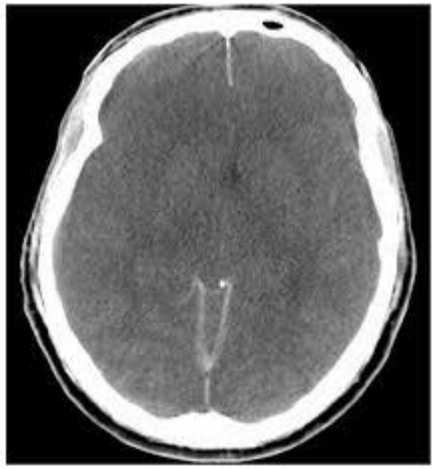
- CBC
- Electrolytes
- VBG
- Renal function tests
- Glucose, calcium, phosphorus
- Ammonia, coagulation profile, T.& D. bilirubin, and blood cultures.
- Diagnostic laboratory studies should be prioritized.

Central nervous system



- Hepatic Encephalopathy
- Changes in behavior, cognition, neurological examination, and EEG: stage 0-IV coma
- minimizing excess stimulation, ↓ protein intake, treating suspected sepsis
- removing sedative medications
- Lactulose: 1-3 cc/kg/day divided:adjust according to bowel movement
- Bowel “decontamination” with rifaximin/metronidazole
- Seizures: phenytoin, midazolam infusion, phenobarbital, levitaracetam, or topiramate.

Cerebral edema: (grade III or IV)



- Maintain oxygen saturation > 95%
- Fluid restriction between 85 and 90% of maintenance,
- Diastolic pressure >40mmHg,
- Adequate sedation, head elevation: 20° to 30° and neutral head position,
- Empiric broad spectrum antibiotics
- Hypertonic saline to maintain serum sodium: 145 – 150
- Mannitol keeping serum osmolarity <320 mOsm/L

Coagulopathy

- PT and INR
- both procoagulant proteins (factors V, VII, and X and fibrinogen) and anticoagulant proteins (antithrombin, protein C, and protein S) are reduced: balanced
- Efforts to “correct” the PT/ INR in the setting of active bleeding or in anticipation of an invasive surgical procedure.
- IV vitamin K

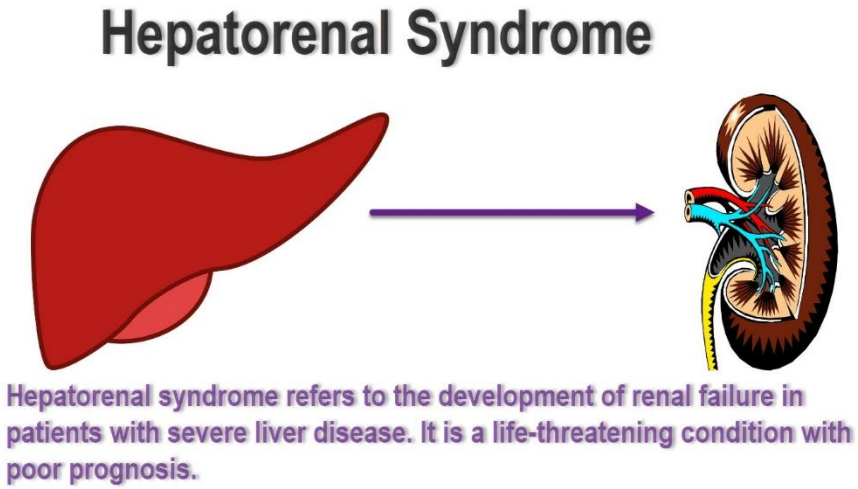
Ascites

- Hypoalbuminemia, excessive fluid administration, and infection.
- The primary treatment is fluid restriction.
- Diuretics should be reserved for patients with respiratory compromise or generalized fluid overload.
- Overly aggressive diuresis may precipitate hepatorenal syndrome.

Bleeding

- GI bleeding: surprisingly infrequently
- Prophylactic PPI or H2B
- Causes: gastric erosions or ulcers due to use of NSAIDs, or idiopathic gastroduodenal ulceration.
- Infection: culture and AB
- Platelets, blood, and plasma is necessary if bleeding is hemodynamically significant.

Renal system



- Prerenal azotemia can develop if fluid restriction is too excessive for the patient’s needs.
- Hepatorenal syndrome: Urine sodium is typically low.
- Simultaneously with both ALF and renal dysfunction: toxic injury (acetaminophen, drug) or Wilson disease.

Metabolic disorders

- Hypoglycemia: Glucose infusion rates as high as 10–15 mg/min/ kg via central venous catheter
- Hypokalemia
- Serum phosphorus
- Acid–base: respiratory alkalosis from hyperventilation, respiratory acidosis from respiratory failure, metabolic alkalosis from hypokalemia, and metabolic acidosis from hepatic necrosis, shock, and increased anaerobic metabolism.
- Keep the pt in relative acidosis

Infections

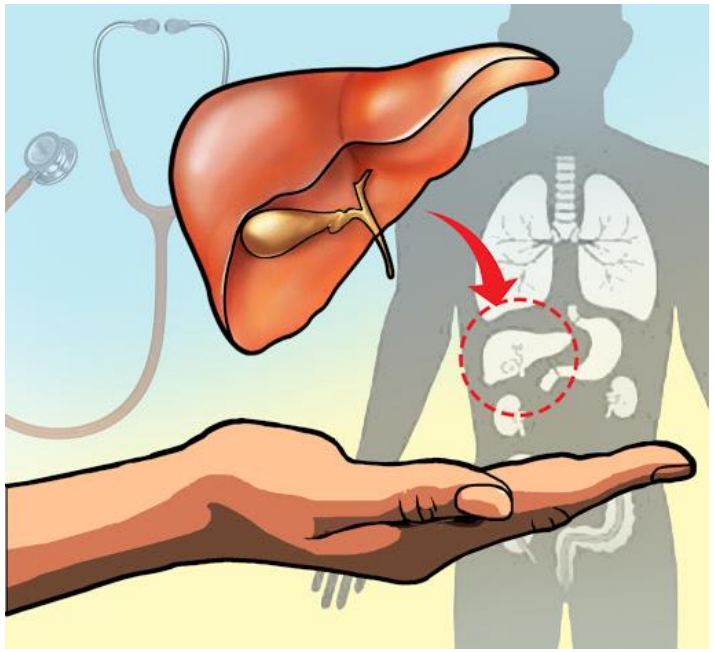
- ↑ susceptibility to bacterial infection and sepsis: immunedyf
- subtle evidence of infection: tachycardia, GI bleeding, ↓renal output, or changes in mental status.
- Fever may not be present.
- with any evidence of clinical deterioration: Blood cultures and antibiotics

Liver support

- Plasmapheresis/plasma exchange: removal of suspected toxins: in mushroom poisoning and Wilson: as a bridge for transplantation

Liver transplant

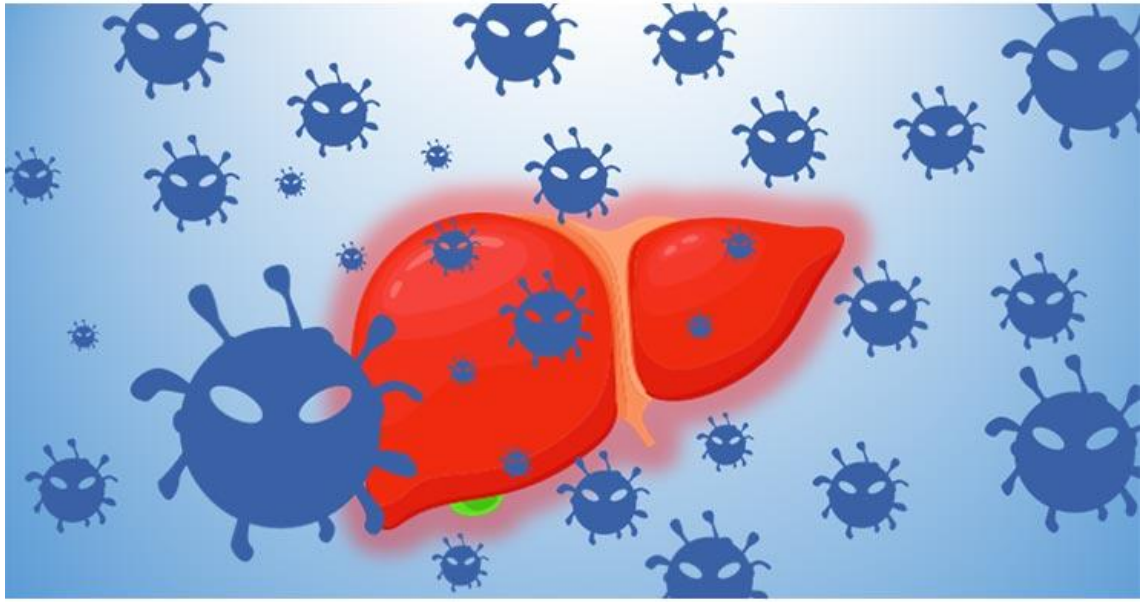
- life saving when a condition without specific therapy is irreversible or fails to respond to treatment. At the same time, liver transplant is also irreversible
- Long-term

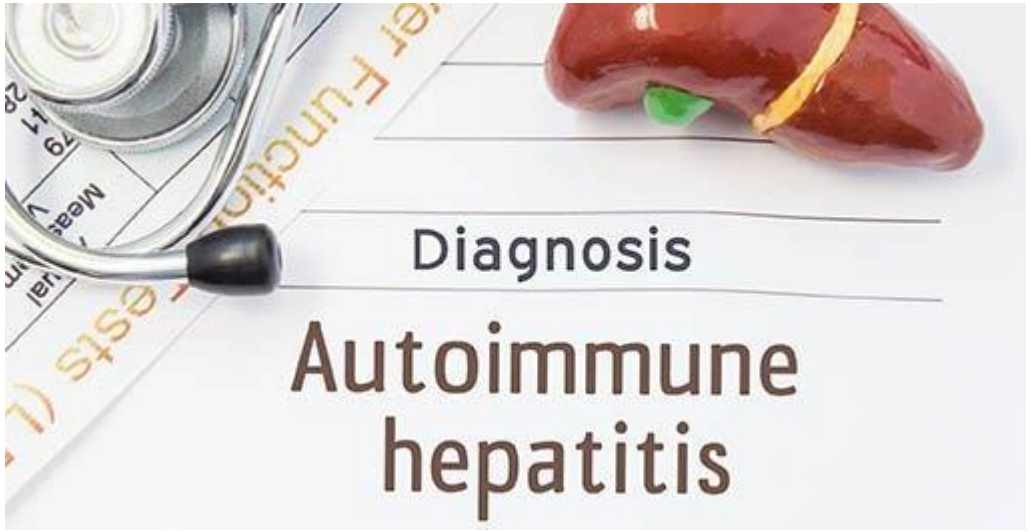


Etiology

Infection

- **Viral hepatitis:**
  - A, B, D, and rarely E
  - EBV, HSV, adenovirus, enterovirus, influenza A, CMV, parvovirus B19
- **Other infection**

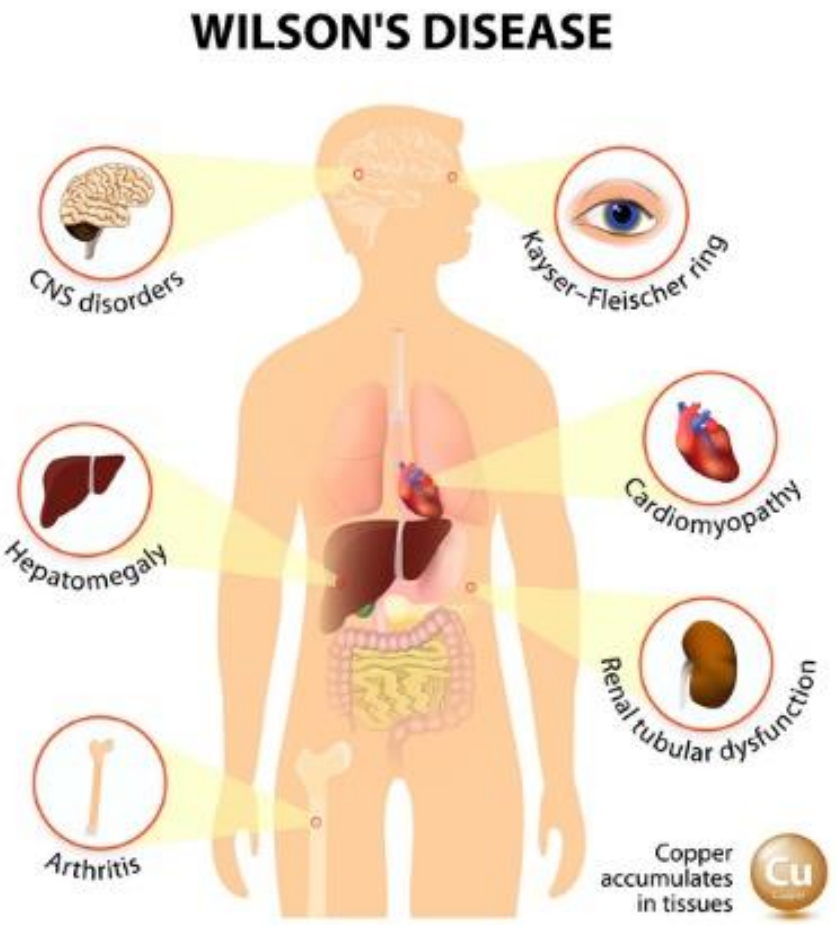




- 5% of cases
- Which component of LFT is rising?
- Autoimmune marker:
  - Antinuclear antibody: ANA
  - Anti–smooth muscle antibody: ASMA
  - liver-kidney microsomal antibody: LKM
  - elevated serum IgG level.

Metabolic Diseases

- Wilson, galactosemia, tyrosinemia, hereditary fructose intolerance, …
- Wilson with ALF:
  - high bilirubin levels
  - low alkaline phosphatase levels
  - low uric acid levels
  - AST levels >> ALT
  - Coombs-negative hemolytic anemia
  - Diagnosis



Neoplasm

- Leukemia, lymphoma, and familial HLH.
- HLH: fever, splenomegaly, cytopenias, high triglyceride levels, very high ferritin levels, low natural killer cell activity, high soluble CD25 levels, hemophagocytosis on bone marrow or liver biopsy

Gestational Alloimmune Liver Disease

- The most common cause of acute liver failure in the neonate.
- Maternal immunoglobulin (Ig) G antibodies
- With low/normal AST,ALT
- Significant hypoglycemia, jaundice, coagulopathy, and hypoalbuminemia.
- Alpha fetoprotein levels are typically high as are serum ferritin levels

Drug-Induced Liver Injury

- *Amanita phalloides* mushrooms
- Acetaminophen overdose.
  - the most common etiology of ALF in children and adolescents in US
- Idiosyncratic damage: halothane, isoniazid, ecstasy, sodium valproate.
- Herbal and weight loss supplements

- Accounts for 40–50% of acute hepatic failure cases in children.

Table 4.5 Age-specific diagnostic prioritization

Age	Tests
< 3 months of age	Herpes blood PCR (or other testing: HSV IgM, viral culture of blood or CSF, CSF PCR) Enterovirus blood PCR (or other testing) Lactate, pyruvate (mitochondrial screen) Plasma acylcarnitine profile (fatty acid oxidation defects) Ferritin (neonatal iron storage disease screen) Serum amino acid profile (urea cycle and metabolic) Echocardiography (cardiac dysfunction) Abdominal ultrasound with Doppler (vascular and anatomic dysfunction) Confirm newborn screen results (galactosemia) Confirm maternal hepatitis B serology
3 months to 4 years	HBsAg, HAV IgM, EBV (VCA IgM or EBV PCR) Lactate, pyruvate (mitochondrial screen) Autoimmune markers: ANA, ASMA, ALKM, IgG Drug history, acetaminophen level Plasma acylcarnitine profile (fatty acid oxidation defects) Serum amino acids Abdominal ultrasound with Doppler (vascular and anatomic)
5 years to 18 years	HBsAg, HAV IgM, EBV (EBV VCA IgM or PCR) Autoimmune markers: ANA, ASMA, ALKM, IgG Ceruloplasmin Drug history, acetaminophen level Lactate, pyruvate (mitochondrial screen) Plasma acylcarnitine profile (fatty acid oxidation defects) Serum amino acids Abdominal ultrasound with Doppler (vascular and anatomic)

Table 4.4 Metabolic disease presenting as acute liver failure

Age	Condition
<6 months	Galactosemia Niemann–Pick type C Tyrosinemia Glycosylation defect Mitochondrial disease[a]
7 months to 4 years	Mitochondrial disease[a] Tyrosinemia α_1-Antitrypsin deficiency Hereditary fructose intolerance Urea cycle defects
5 years to 18 years	Wilson disease Mitochondrial disease[a] Fatty liver of pregnancy

[a] Fatty acid oxidation defects, respiratory chain defects, mitochondrial DNA depletion.

Table 4.3 Medications and toxins associated with acute liver failure

Type	Xenobiotics
Anti-infective	Clavulanic acid/amoxicillin Trimethoprim–sulfamethoxazole Isoniazid Minocycline/doxycycline Quinolone (ciprofloxacin, norfloxacin) Voriconazole Macrolide (erythromycin, clarithromycin, azithromycin) Others
Anticonvulsants	Phenytoin Valproic acid Carbamazepine Others
Immunomodulators/ anti-inflammatory	Methotrexate Azathioprine Non-steroidal anti-inflammatory drugs Acetaminophen Biological (i.e. infliximab, basiliximab, etc.) Others


Thanks!
Any question?