Acute Liver Failure in Childhood and Neonates

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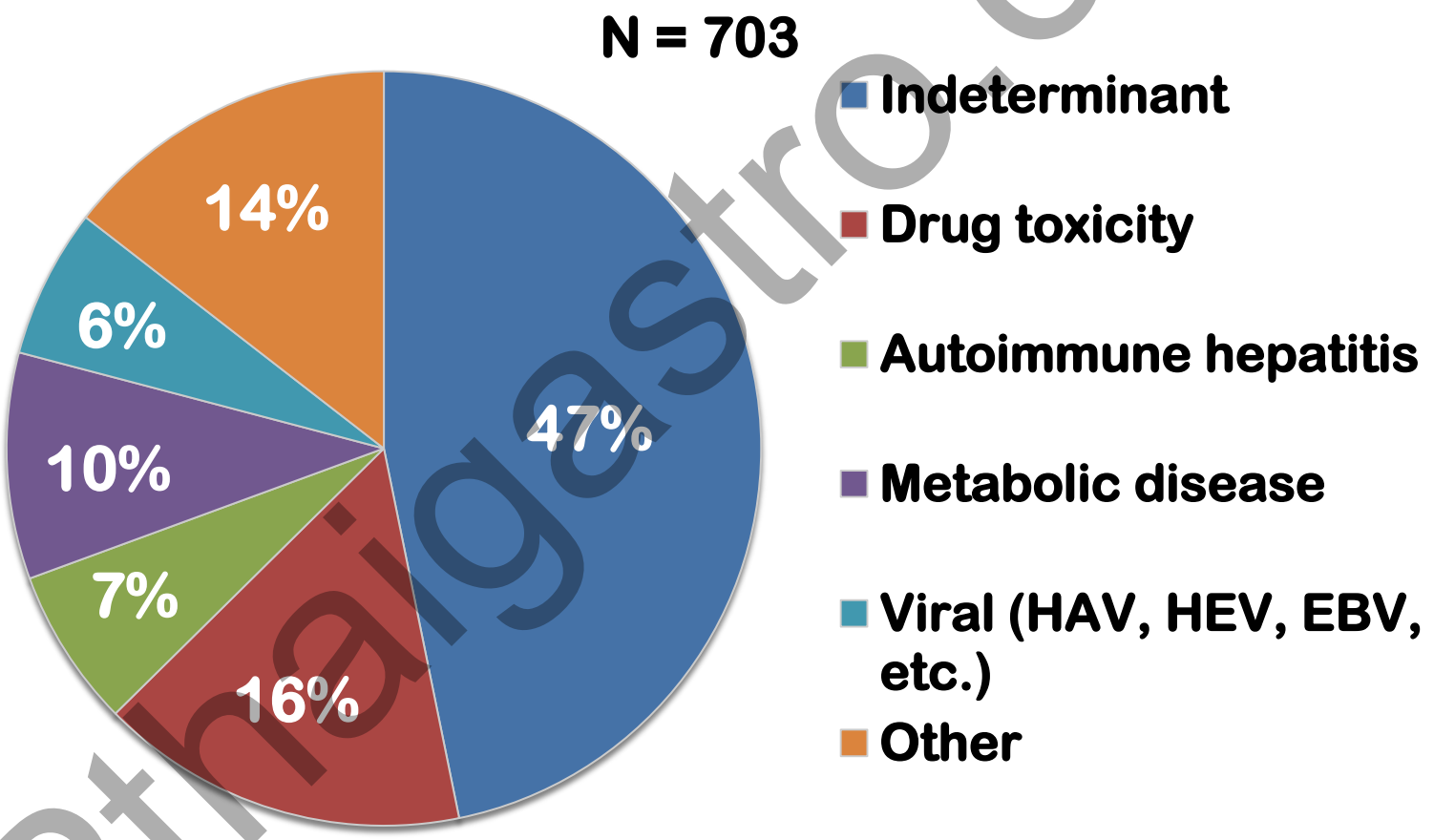
Definition

A rare multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in patient with no recognized underlying chronic liver disease…

Bhudari and Vergani

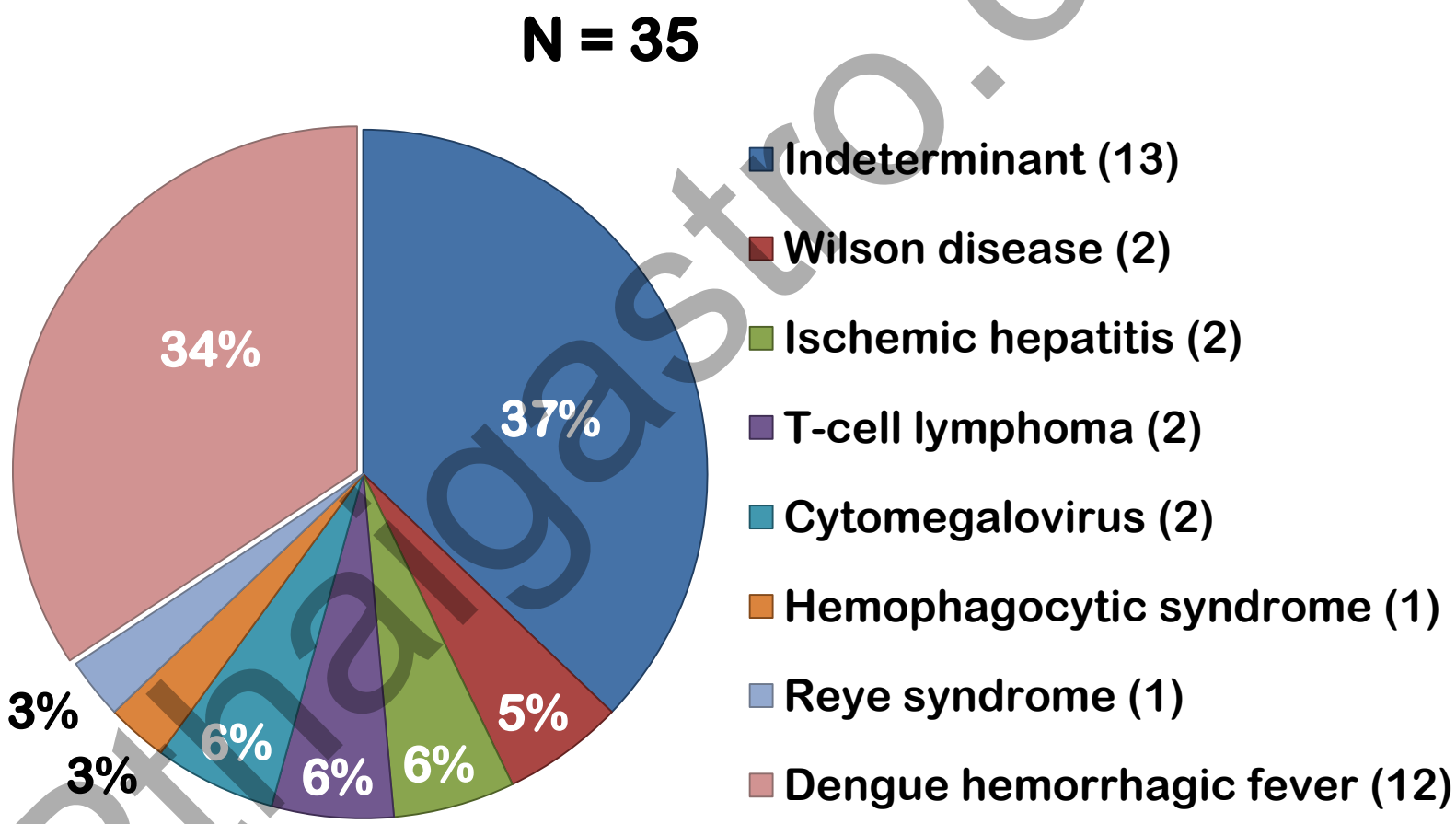
- **Biochemical evidence of liver injury**
- **No history of chronic liver disease**
- **Hepatic-based coagulopathy (not corrected by vitamin K administration)**
  - **PT > 15 seconds or INR > 1.5 (with HE)**
  - **PT > 20 seconds or INR > 2.0 (regardless of HE)**

Etiology: PALF Study Group Database



Narkewics et al. J pediatr 2009;155:801-6

Etiology of ALF in Thai Children



Poovorawan Y et al. Ann Trop Paediatr 2006;26:17-23.

Clinical manifestations

- **Neonates**
- Non specific: lethargy, poor feeding, vomiting

- **Infants and older children**

(most patients are previously healthy !!!)

Prodromic phase: malaise, myalgia, nausea, vomiting, fever

Subsequent jaundice may be minimal in some causes; toxin, metabolic disease, Reye syndrome

Clinical manifestations (2)

Sign & Symptoms of Liver Dysfunction

Hypoglycemia

- Decreased gluconeogenesis
- Impaired glycogen storage
- Hyperinsulinism
- Increased glucose use

Coagulopathy

- Reduction in coagulation factor synthesis
- Reduction in platelet numbers and function
- Intravascular coagulation

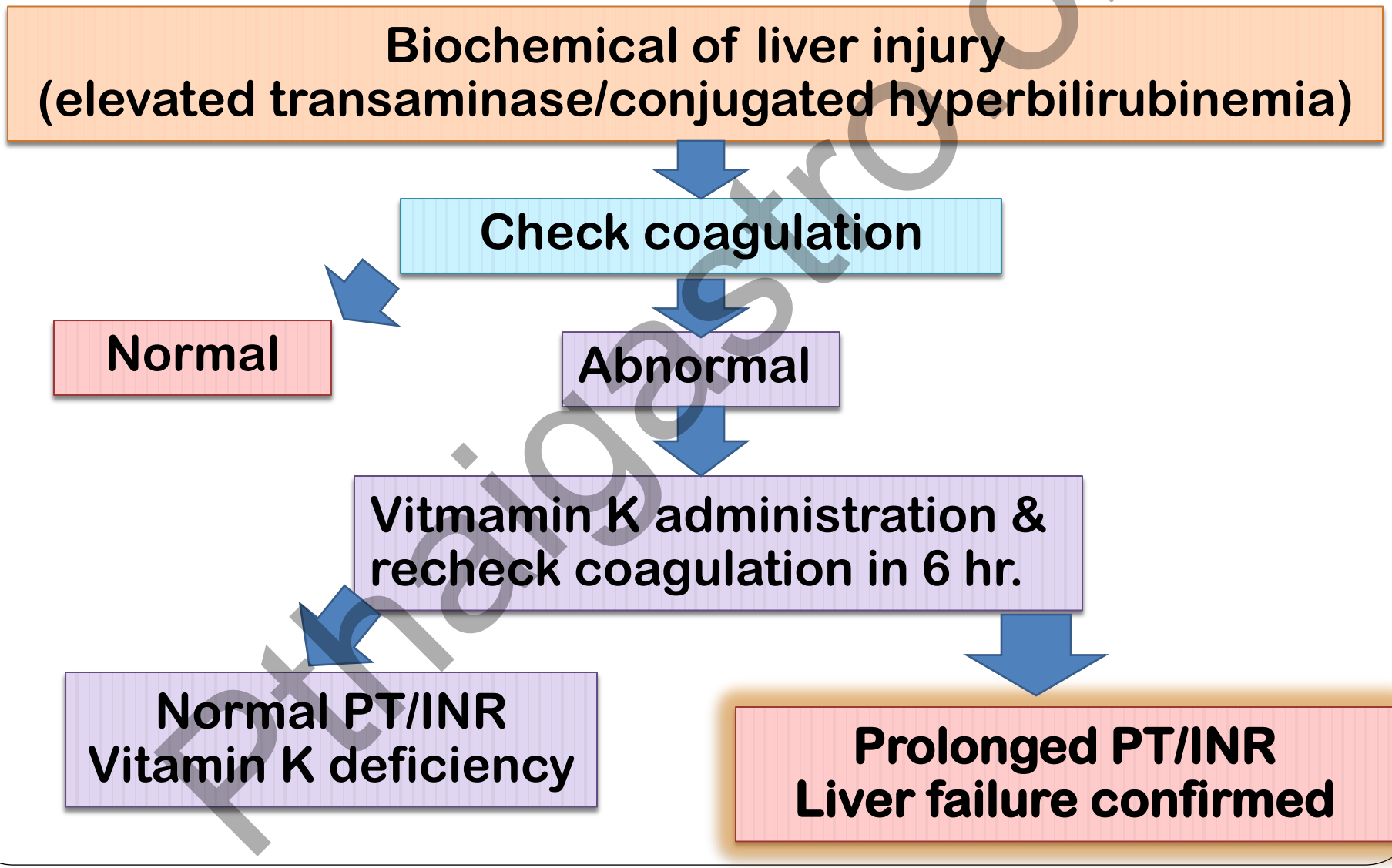
Encephalopathy

- Inappropriate amounts of neuroregulartory substances
- Fail to eliminate neurotoxins

Stage of Hepatic Encephalopathy

Stage	อาการ	Asterexis/Reflexes	Neurological Signs
I	เริ่มมีการเปลี่ยนแปลงของพฤติกรรมการนอนหลับ อารมณ์	ไม่พบ / ปกติ	Tremor, ลายมือเปลี่ยนแปลง
II	ซึม แต่ปลุกตื่นได้ สับสน	พบ / hyperreflexive	Dysarthria, ataxia
III	ซึมมากขึ้น ตอบสนองต่อ painful stimuli	พบ / hyperreflexive ตรวจพบ Barbinski sign	muscle rigidity, decerebrate
IV	ไม่รู้สึกตัว ไม่ตอบสนอง	ไม่พบ	decerebrate หรือ decorticate

Diagnosis of ALF



Do we need to identify cause of ALF ?

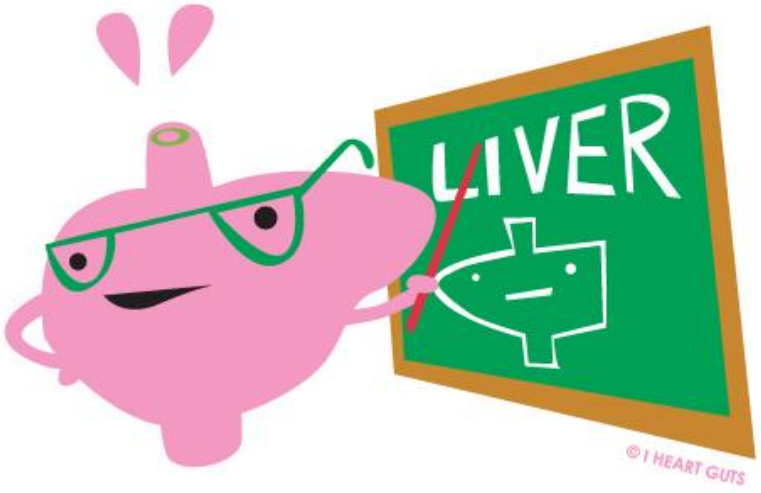
YES

- Some etiologies have specific treatment
- Different prognosis in different etiology

- **Limitation!!!...**blood volume required for many tests, lack of time interval after presentation, lack of proper tests, etc.
- **Liver biopsy** for histology is not critical and may be harmful

Diagnostic Approach

- Age group
- History
- Physical examination
- Laboratory investigations



Etiology of ALF (by Age Group)

	Neonates and infants	Older children
Infection	Herpesvirus, echovirus, adenovirus, HBV	HAV, HEV, HBV, EBV, dengue ,parvovirus, etc.
Metabolic disease	Galactosemia, tyrosinemia, fructose intolerance, mitochondrial disease	Wilson's disease, mitochondrial disease
Ischemia	Congenital heart disease, severe asphyxia	Shock (ischemic hepatitis)
Immune disorders	Hemophagocytic lymphohistiocytosis	Autoimmune hepatitis, hemophagocytic syndrome (secondary)
Drugs/ Toxins	Valproate, acetaminophen	Same as infant, *Aminita phalloides*
Others	Neonatal hemochromatosis(NH), Reye syndrome, malignancy	Reye syndrome, malignancy

History

- History of fetal loss, IUGR, oligohydramnios: **NH**
- History of gram negative (*E.Coli*) septicemia: **galactosemia**
- Recurrent liver failure/ recurrent Reye syndrome, consanguinity, occur after acute illness: **inborn error of metabolism**
- History of neurological manifestations (seizure, hypotonia): **mitochondrial disorder**
- History of viral infection (within 3weeks) and salicylic acid use: **Reye syndrome**
- History of liver disease in family: **Wilson's disease**
- Prodrome symptoms: **viral hepatitis**
- Drugs or toxins: **Toxic hepatitis**

NH, neonatal hemochromatosis

Physical examination

- **Neurologic status and level of encephalopathy**
- **Sign of chronic liver disease: Wilson's disease, autoimmune hepatitis**
- **Liver size:**
  - **Decreasing liver size with worsen liver functions: fulminant liver failure**
  - **Hepatomegaly with massive ascites: Budd-Chiari syndrome**
- **Jaundice: not always present → Reye syndrome, toxin**
- **Eye examination:**
  - **Cataract: galactosemia**
  - **Kayser-Fleischer ring: Wilson's disease**

Warning Signs of Progressive Disease

- Prolonged PT that is unresponsive to vitamin K
- Persistent jaundice (rapid increased of bilirubin, progressive decline of serum aminotransferase)
- Decreasing liver size
- Increasing lethargy or occasional hallucination
- Hemorrhagic diathesis and systemic collapse

Whitington PF, Alonso EM, Squires RH. Acute liver failure. In: Kelly Deirdre A, editor. Diseases of Liver and Biliary System in Children. 3rd ed. 2008;p. 106-25.

Laboratory Investigations

Initial laboratory evaluation

Biochemical tests

- Liver function tests, blood sugar
- Serum electrolytes, BUN, creatinine
- Arterial blood gas, lactate, blood ammonia

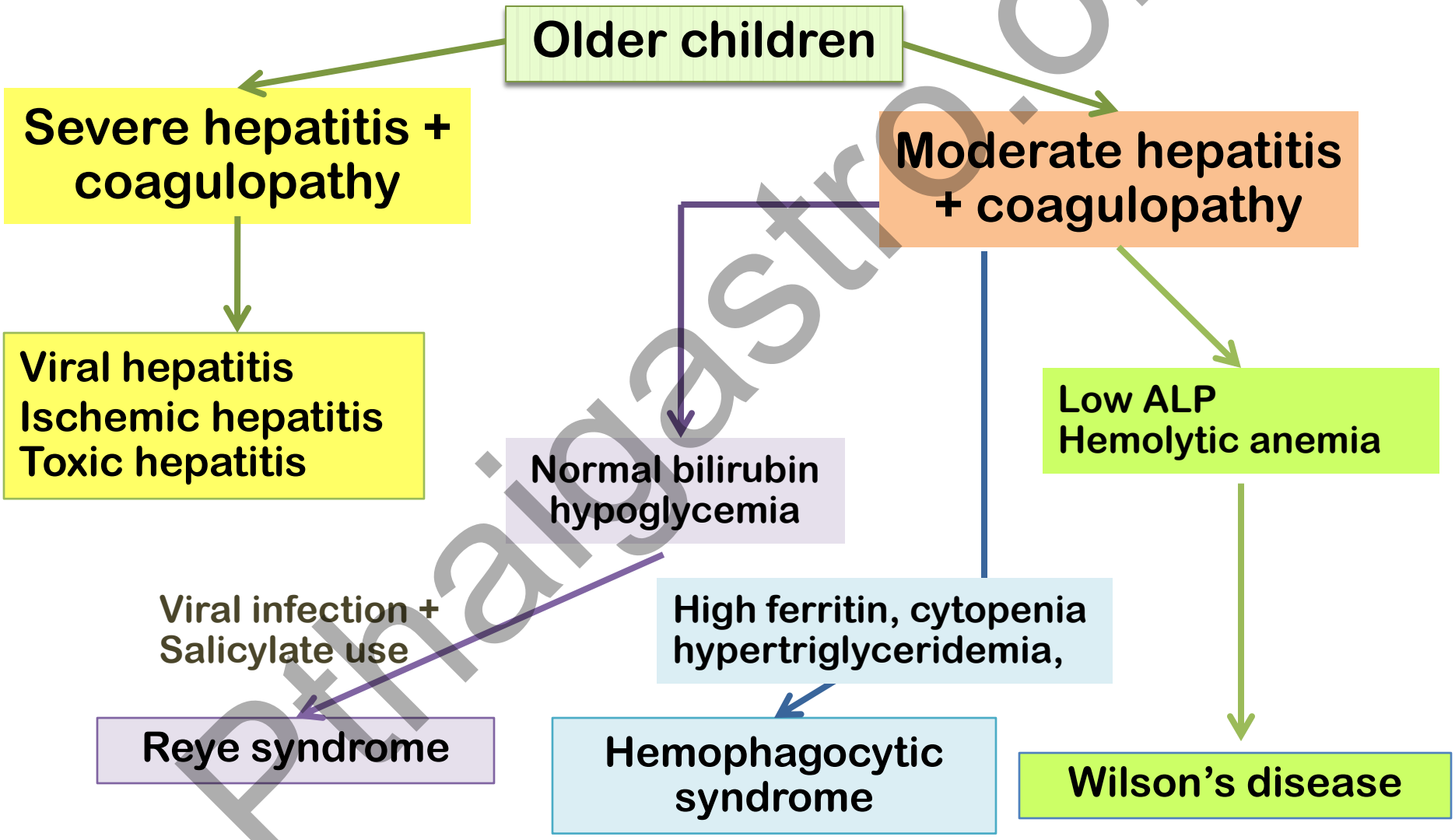
Hematological tests

- Complete blood count & peripheral blood smear
- Prothrombin time / INR
- Reticulocyte count

More investigations in neonates

- Herpes simplex virus PCR
- α-fetoprotein, serum ferritin
- Urine reducing substance

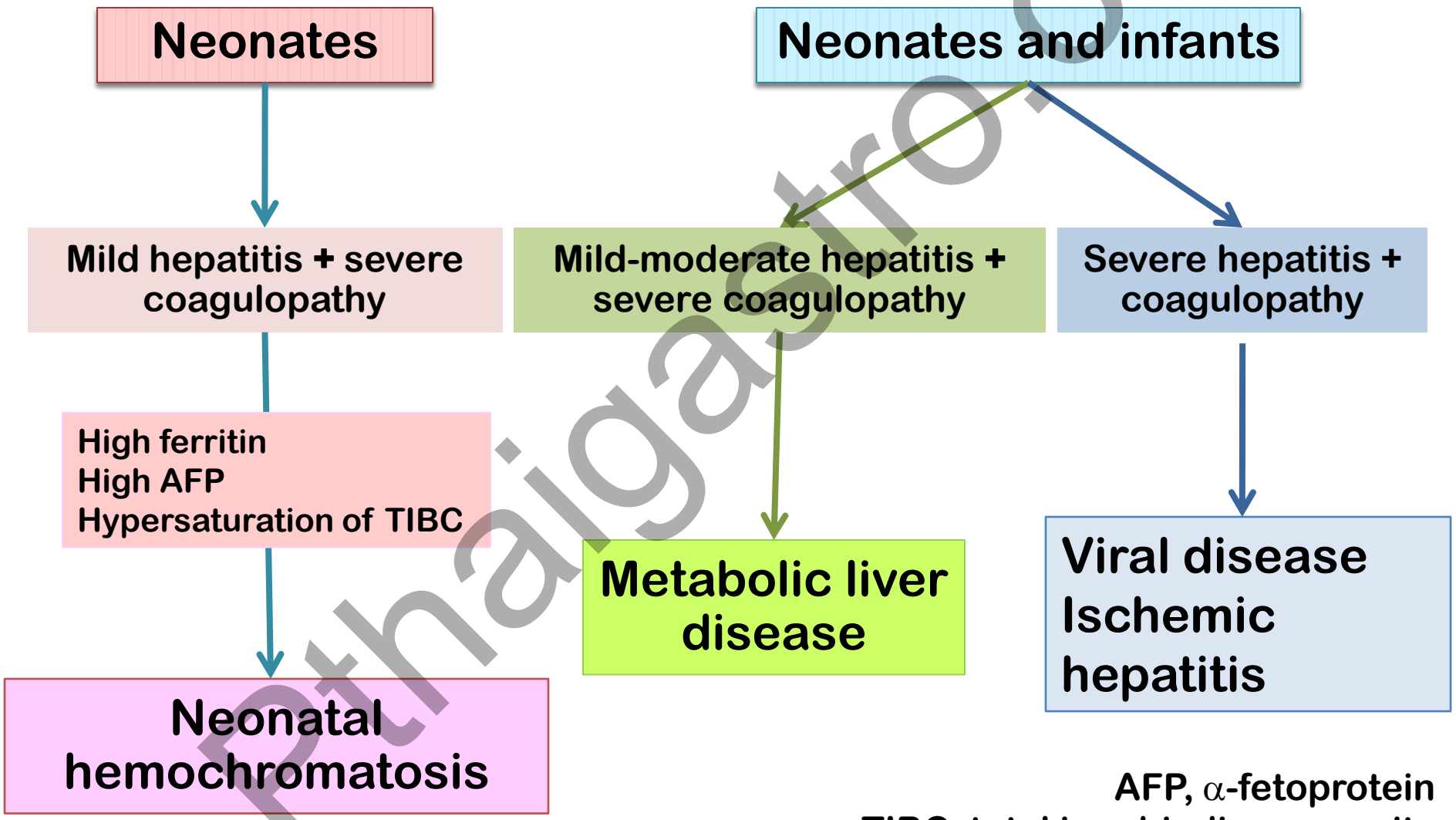
Laboratory Investigations



Disease-specific Investigations

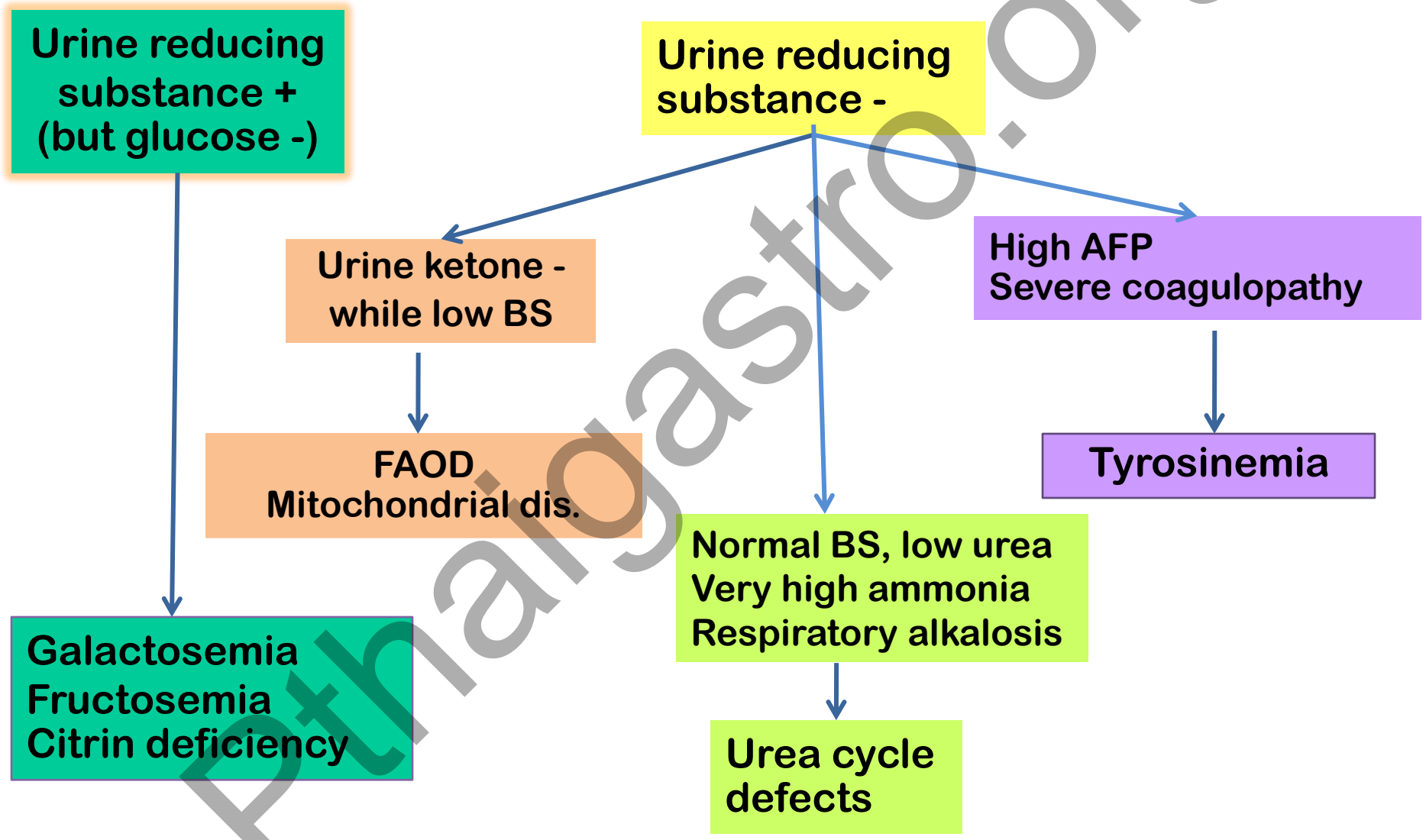
Disease/Condition	Investigation
Wilson's disease	Serum celuroplasmin 24-hr urine copper Eye examination (Kayser-Fleischer rings)
Autoimmune hepatitis	Autoantibodies (ANA, ASMA, anti-LKM)
Hemophagocytic lymphohistiocytosis (familial & secondary)	Serum triglyceride, serum ferritin Bone marrow examination
Toxic/drugs	Acetaminophen level Urine toxic screening
Viral infection	Anti-HAV IgM HBsAg, HBc IgM, HBc Ag Anti-HCV, HCV PCR Anti-HEV IgM EBV IgM, IgG, CMV IgM, IgG PCR for HSV, EBV, CMV, HHV-6, enterovirus, adenovirus, parvovirus

Laboratory Investigations



AFP, α-fetoprotein
TIBC, total iron binding capacity

Suspected metabolic liver diseases (after exclude infection, toxin)



FAOD, fatty acid oxidation defects

Courtesy: Prof. D Wattanasirichaigoon

Disease-specific Investigations

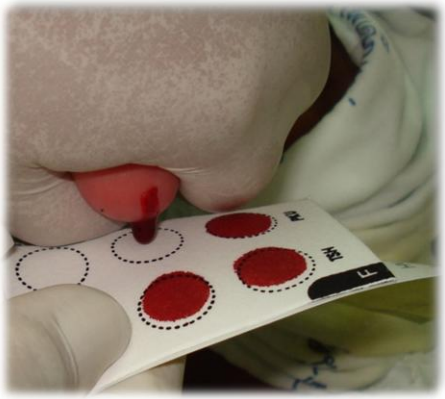
Disease/condition	Investigations
Neonatal hemochromatosis	MRI abdomen or buccal mucosa biopsy (for evidence of extrahepatic siderosis)
Tyrosinemia	Urine succinyl acetone
Galactosemia	Erythrocyte GALT activity
Fatty acid oxidation defects	Acylcarnitine profile (dry blood spot)
Urea cycle defect	Plasma amino acid and urine orotic acid
Mithochondrial disease	Mitochondrial DNA Blood lactate/pyruvate 3-OH-butyrate/acetoacetate muscle and liver biopsy for quantitative respiratory chain enzyme determination

GALT, galactose-1-phosphate uridyltransferase

Critical sample collection if suspected metabolic liver diseases

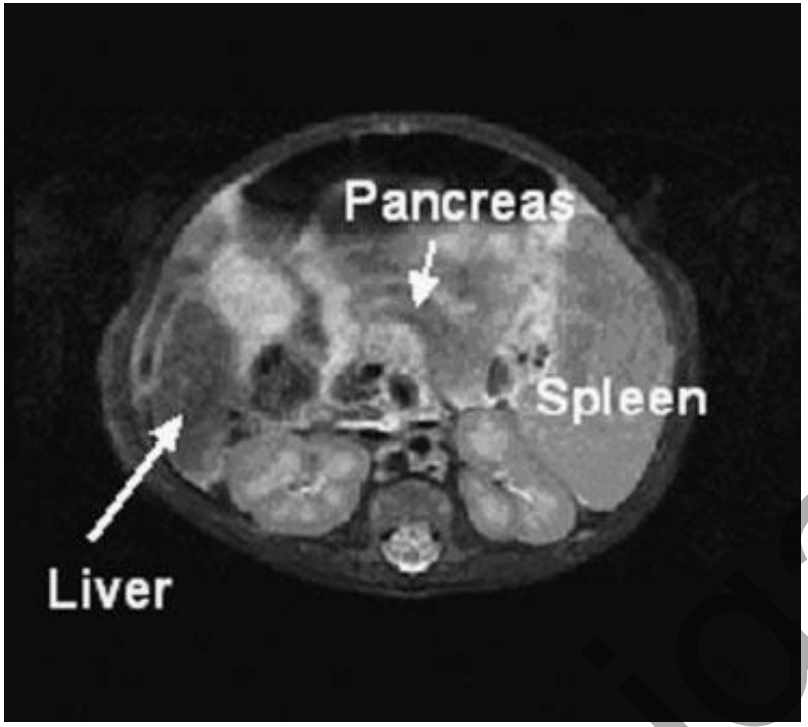
Caution !!!
blood sample should be collected before blood transfusion /exchange transfusion

- ✓ 1-2 mL of plasma/serum freeze at -20°C
  for amino acid analysis, carnitine analysis
- ✓ 5-30 mL of urine freeze at -20°C
  for organic acid analysis (include succinylacetone)
- ✓ Dry blood spot (www.neoscreen.go.th)
  for acylcarnitine proflie analysis
- ✓ 3-5 mL of EDTA blood at 4°C
  for DNA testing

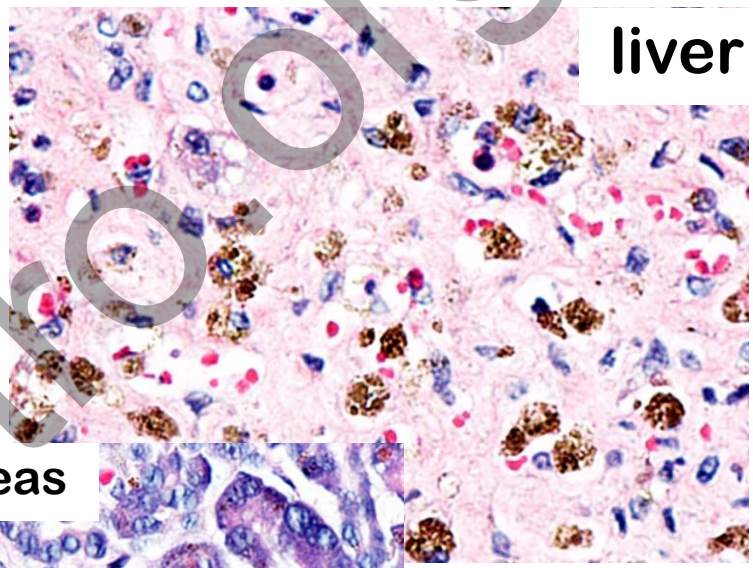


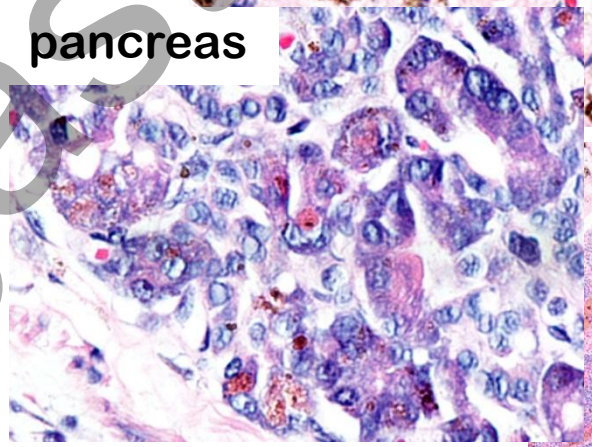
So… how can we treat a child with acute liver failure?

Neonatal hemochromatosis

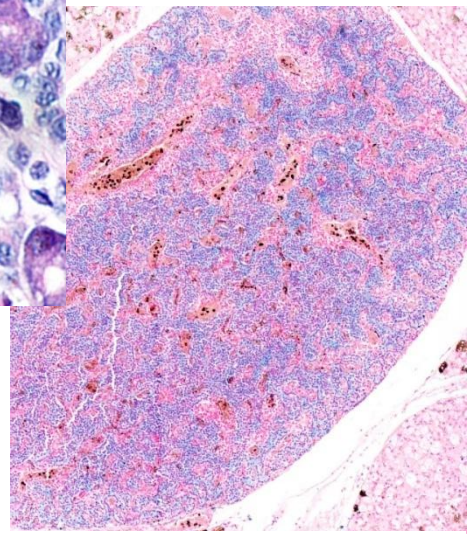


MRI abdomen demonstrates attenuated signal (dark) indicating increased iron storage in pancreas & liver, but typically absent in spleen





Intra and extrahepatic siderosis



Parathyroid gland

Whitington PF. Semin Liver Dis 2007;27:243-50.