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Early Cholestasis and Vitamin K Deficiency Secondary to Biliary Atresia presenting as Coagulopathy and Thymic Hemorrhage

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GME Research Days

May 17, 2024

Objectives

- Describe a case of late-onset vitamin K deficiency and cholestasis presenting as jaundice and coagulopathy with associated bleeding into thymic structures

- Disclosures: None

Case Presentation

- 4-week-old term male brought to ED with chief complaint of bruising

HPI:

- 1 day history of increased fussiness, decreased oral intake, and bruising
- Initial bruises were noted on his scalp and lower back without known trauma

PMH:

- Born at 39 week gestation without significant complications during pregnancy/delivery
- Received Vitamin K injection and Hepatitis B vaccination in newborn nursery
- Circumcision performed in newborn nursery with minor associated bleeding
- Followed regularly with PCP for jaundice below phototherapy threshold
- Newborn screen WNL

Case Presentation

FH:

- Noncontributory

SH:

- Lives with mother and father; no known sick exposures

ROS:

- Positive for fatigue, fussiness, jaundice, bruising, and increased work of breathing; otherwise negative

Physical Examination

- **General:** Responsive during examination. Fussy but consolable. In moderate respiratory distress
- **Head:** Normocephalic, anterior fontanelle soft and flat. Circular nodular bruise along left temporal scalp approximately 1cm in diameter
- **Eyes:** Extraocular movements intact; conjunctivae non-erythematous without discharge. Scleral icterus present
- **ENT:** Palate with overlying bruising/petechiae
- **Neck:** Supple without lymphadenopathy
- **Respiratory:** Tachypneic. Breath sounds clear and equal with symmetrical lung expansion, good aeration. Visible grunting, subcostal and intercostal retractions present
- **CV:** Tachycardic without rubs, murmurs, or gallops; normal peripheral perfusion without edema; 2+ brachial pulse bilaterally
- **GI:** Soft, non-distended, hepatomegaly present
- **GU:** Normal genitalia for age and sex. Circumcised
- **Musculoskeletal:** Normal range of motion for all extremities, normal strength with no swelling, tenderness, or visible deformity
- **Neuro:** No focal deficits, normal tone
- **Skin:** Diffusely jaundiced. 1 cm diameter bruise to left shoulder. 1 cm diameter nodular bruise along midline thoracic spine

Laboratory Evaluation

Hematology	
WBC	19.68 H
Hgb	10.8
Hct	31.9
Platelet	487 H

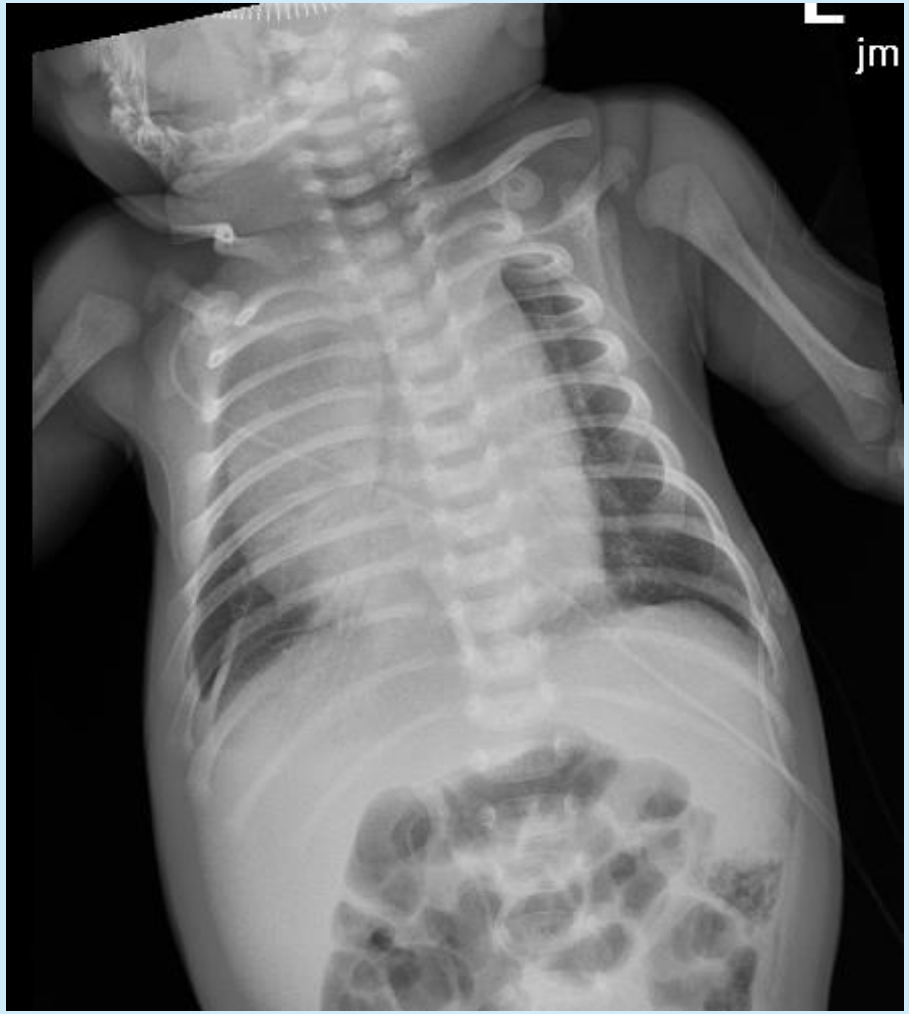
Coagulation		
PT	>125.0 H	>125.0 H
INR	TNP *	>20.00 * !
INR Interp	INR Interp *	INR Interp *
aPTT	>250.0 H	>250.0 H
Heparin Neutralized		>250.0 * H
Fibrinogen	406 H	

Additional labs: Negative DAT

Chemistry	
Specimen Integrity	
Sodium	132
Potassium	5.4
Chloride	103
Carbon Dioxide	26
Anion Gap	3 L
Calcium	9.1
Glucose	116 H
BUN	12
Creatinine	0.22
Phosphorus	
Magnesium	
C Reactive Protein	2.7 H
Protein Total	5.9
Albumin	3.4
Bilirubin, Total	11.1 H
Bilirubin, Direct	5.6 H
Bilirubin, Indirect	5.5 H
AST	109 H
ALT	82 H
Alk Phos	524 H

Imaging

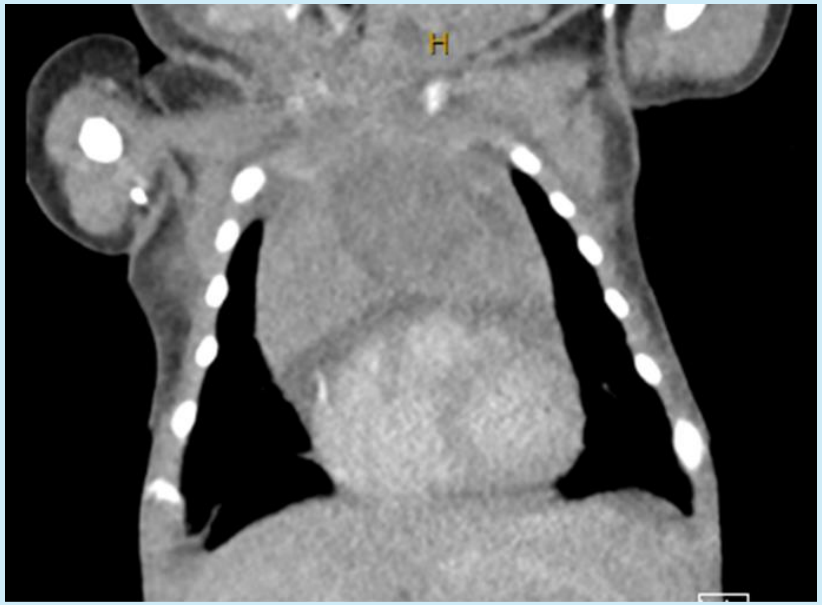
- **CXR:** Patchy right basilar opacity with generous mediastinum
- **Abdominal US:** Bilateral pleural effusions with adjacent atelectasis, questionable mild hepatomegaly
- **CT Head:** No acute intracranial process

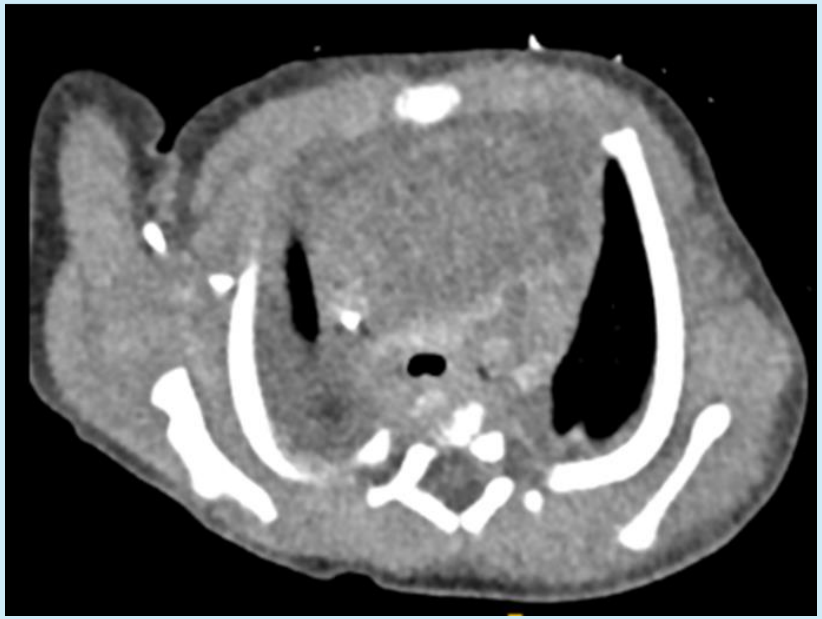


Imaging

- **CT Chest:** Heterogenous mass bifurcating the thymus with mass effect, displacement of the great vessels, narrowing of the trachea
- **MRI Chest:** Suggestive of hemorrhage given relative T2 hypointensity with an intermediate intensity rim; non-enhancing on T1

- Additionally obtained echocardiogram, US chest with similar findings
  - Ultrasound demonstrating solid appearance of mass





(4.3 cm transverse, 3.2 cm AP, 3.9 cm CC)

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Clinical Course

- Additional coagulation studies were obtained including VWF testing, factor levels, ROTEM
  - Factor levels for VII, IX were low, suggestive of Vitamin K Deficiency

Factor V Activity	83
Factor VII Activity	<7 L
Factor VIII Activity (Clot-based)	186 H
Factor IX Activity	1 L

- Infant received 2 mg injectable Vitamin K for three days, 50 IU/kg Kcentra, and 15 mg/kg FFP with normalization of coagulation studies

PT	>125.0 H
INR	>20.00 * !
INR Interp	INR Interp *
aPTT	>250.0 H
Heparin Neutralized aPTT	>250.0 * H

PT	13.4
INR	0.98
INR Interp	INR Interp *
aPTT	34.3
Heparin Neutralized aPTT	

Clinical Course

- Biopsy of mass identified normal thymic tissue
- Coagulation studies remained within normal limits with no further bleeding symptoms observed.
- Infant was able to be transferred out of the ICU on hospital day 8

Clinical Course

- HIDA scan, cholangiogram, and liver biopsy were completed prior to discharge
  - **HIDA Scan:** Absence of radiotracer within the gallbladder or intestinal loops at 24 hours, findings consistence with cholestasis. Biliary atresia is not excluded.
  - **Cholangiogram:** Flow from the biliary tree into the bowel
  - **Liver Biopsy:** Cholestatic liver disease, portal fibrosis with bridging fibrosis (Stage 4/4), negative for CMV
- Readmitted and underwent intraoperative cholangiogram and Kasai procedure at 8 weeks of age with confirmed diagnosis of biliary atresia

Discussion

Biliary atresia, cholestasis, vitamin K deficiency: how do they relate?

Overview of Cholestasis & Hyperbilirubinemia

- Bile is synthesized by hepatocytes, flows through bile ducts, is stored in the gall bladder, and eventually drains into the duodenum
  - Composed of water, bile acids, phospholipids, cholesterol, bilirubin, protein
- Cholestasis represents impaired bile flow from intrahepatic or extrahepatic causes
- Bilirubin = the end catabolite of hemoglobin and heme-containing proteins
  - Unconjugated bilirubin is conjugated by uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) in the intestines/liver
- Indirect (unconjugated) can be physiologic in neonates
- Direct (conjugated) is **never** physiologic

Image: :healthmd.net/neonatal-jaundice-causes-symptoms-tests-treatment/

Overview of Biliary Atresia

- Biliary atresia is a progressive, obliterative process involving a segment or all the extrahepatic biliary tree in the neonatal period
- Disease progression -> disruption or obliteration of the extrahepatic bile duct limen
  - Leads to cholestasis and chronic liver damage
- Most common cause of neonatal jaundice requiring surgery, and most common indication for liver transplantation in children

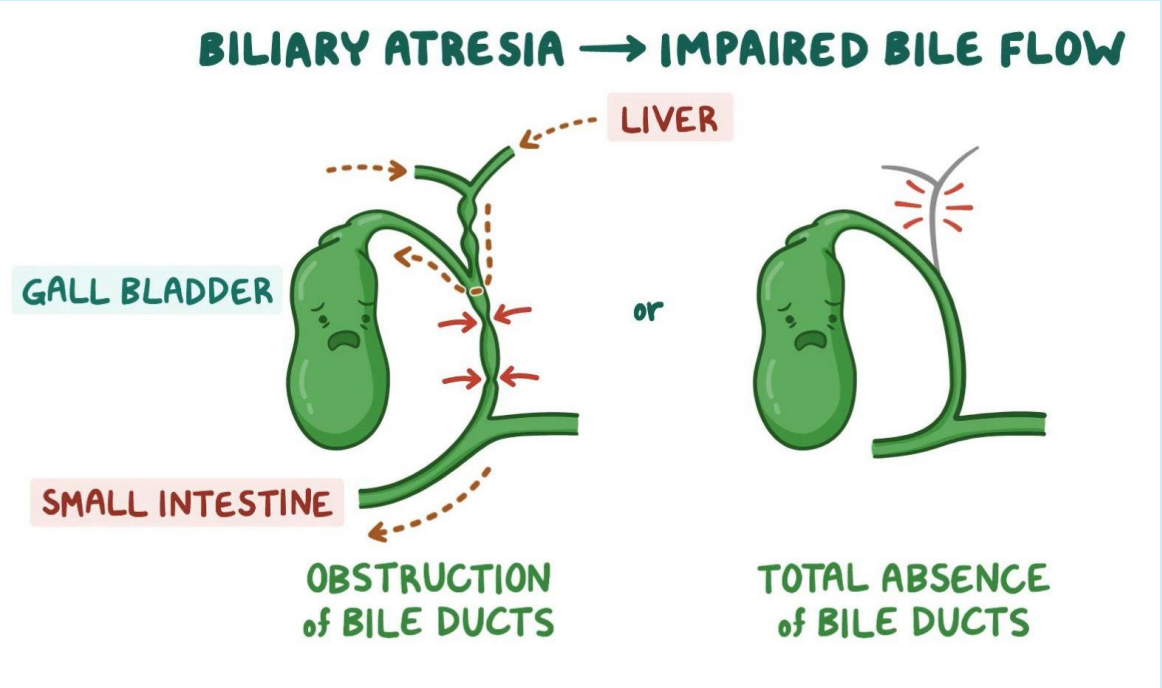
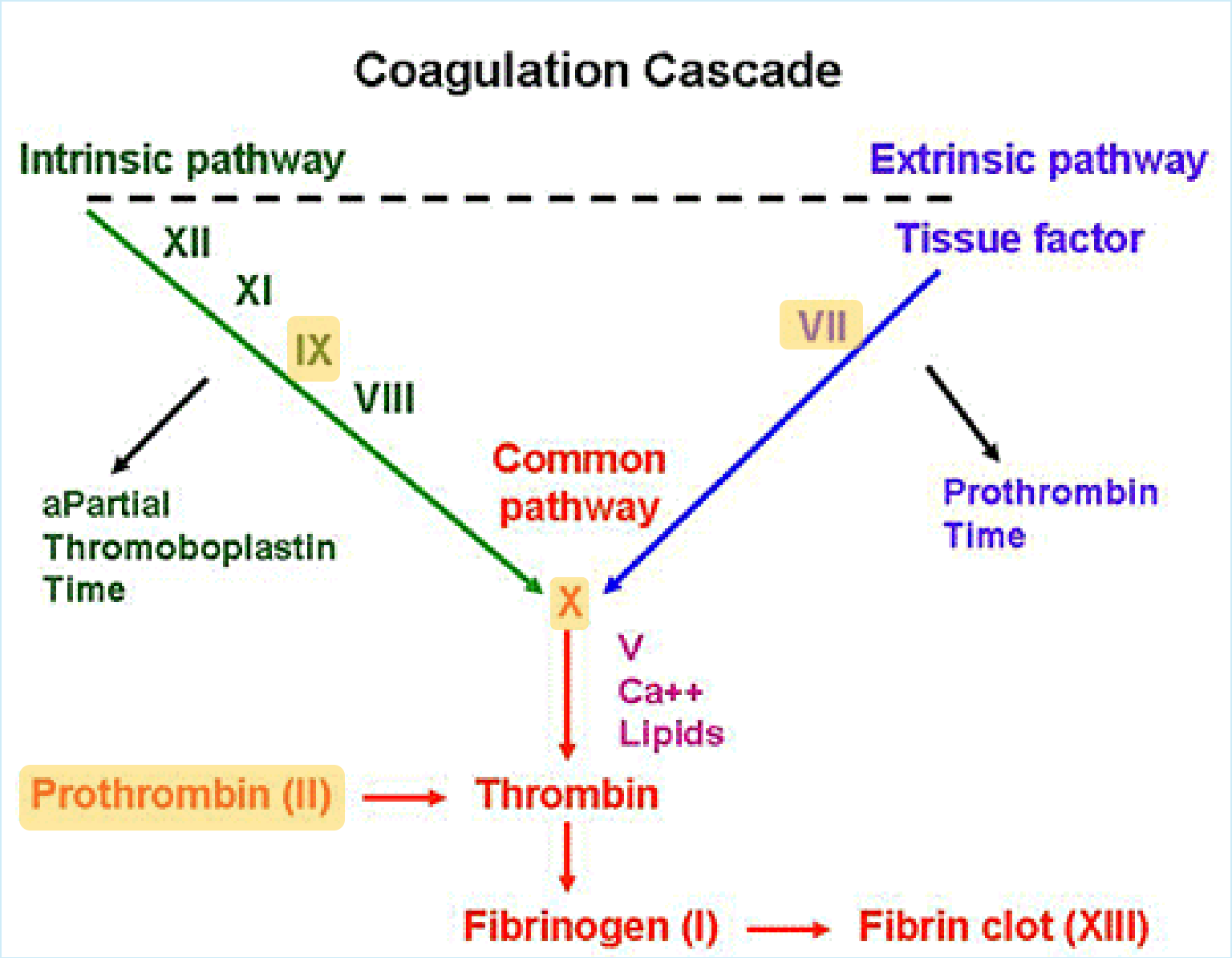


Image: osmosis.org/learn/Biliary_atresia:_Nursing

Overview of Vitamin K Deficiency

- Vitamin K is necessary for synthesis of clotting factors II, VII, IX, X in the liver
- Vitamin K is fat-soluble, requiring bile-salts for proper intestinal absorption
- Vitamin K deficiency is common in neonates
  - Placental transfer of Vitamin K is low – which is why we supplement at birth
  - Liver reserve levels in infants are lower than adult levels
  - Infant absorption of vitamin K is reduced in setting of immature gut flora
  - Vitamin K is low in breast milk


Coagulation Cascade
Intrinsic pathway
Extrinsic pathway
XII
XI
IX
VIII
Tissue factor
VII
aPartial
Thromoboplastin
Time
Common
pathway
Prothrombin
Time
X
V
Ca++
Lipids
Prothrombin (II)
Thrombin
Fibrinogen (I)
Fibrin clot (XIII)

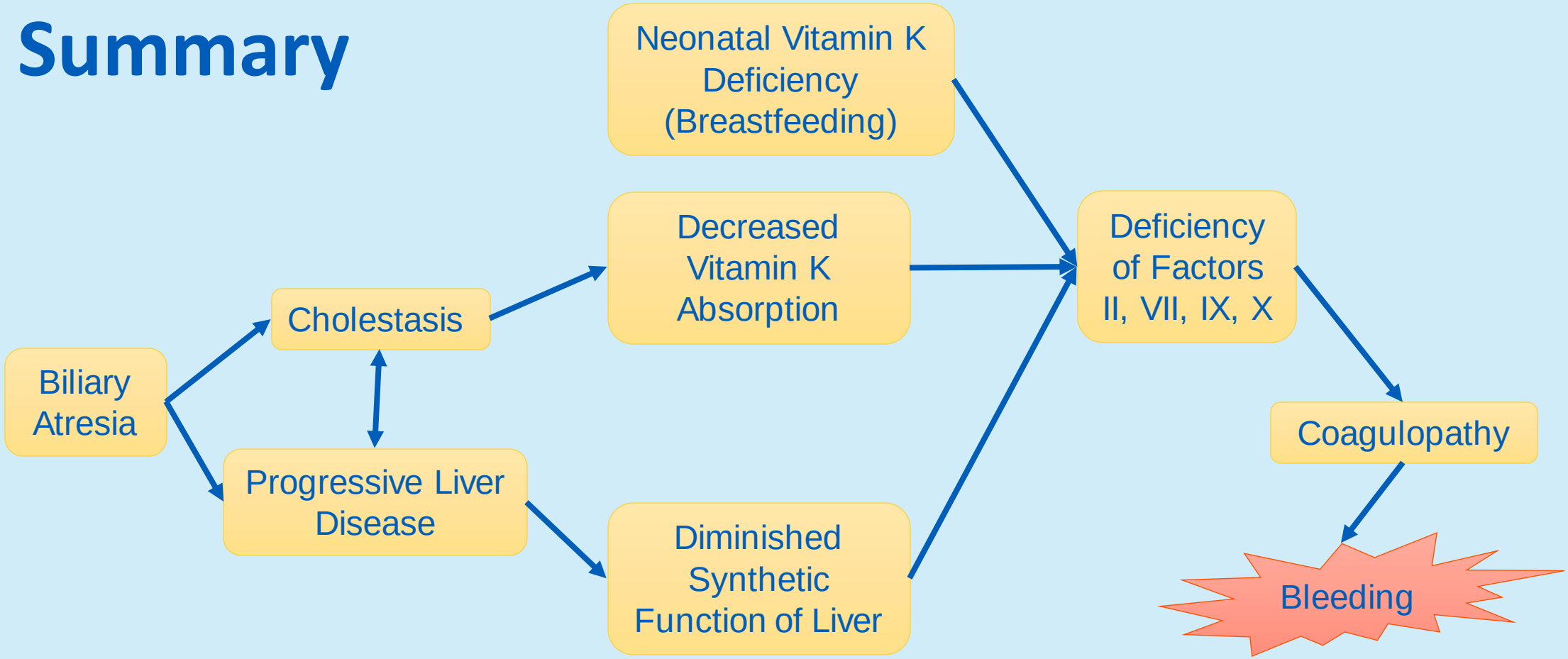
Vitamin K Deficiency Bleeding (VKDB)

- Early VKDB – in the first 24h of life
  - Typically only seen in mothers with medications that interfere with vitamin K metabolism – anticoagulants (warfarin), anticonvulsants
- Classic VKDB – Between 2-7 days of life
  - Associated with inadequate feeding
- Late VKDB – Between 8 days of life and 6 mos
  - Seen often in breastfed infants, and associated with hepatobiliary dysfunction/poor dietary absorption

Hematologic Manifestations

- There is wide variety in manifestations of bleeding
  - Cutaneous bruising
  - Post-circumcision bleeding, umbilical bleeding
  - Gastrointestinal bleeding
  - Intracranial hemorrhage (30-60% in late onset VKDB)
  - May additionally be associated with severe anemia
- Rare prior case reports of thymic hemorrhage have been previously identified in neonates
  - Associated with coagulopathy, abnormal imaging findings (widened mediastinum, appearance of cardiomegaly)
  - All case reports include respiratory distress as presenting symptom

Summary



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