LFTs and Hepatitis ABCs

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Yale PA Online Program

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Objectives

- Discuss the physiology behind the bilirubin pathway and the pathophysiology resulting from disruptions in the normal pathway.
- Interpret hepatic function tests and their significance in common forms of hepatic disease.
- Evaluate the etiologic factors, pathophysiology and laboratory findings in viral hepatitis.

Overview

- Hepatic Function Tests
- Bilirubin Pathway
- Disruptions in the Bilirubin Pathway
  - Pre-hepatic, hepatic, post-hepatic jaundice
- Relationships of Hepatic Function Tests
- Viral Hepatitis Testing
- Case Studies

Hepatic Function Tests

- Tests for Hepatocellular Damage
  - Bilirubin -Total Bilirubin - (TBil)
    - Conjugated Bilirubin (Direct Bili)
      - Measured
    - Unconjugated Bilirubin (Indirect Bili)
      - Calculated
  - Transaminases
    - AST = aspartate aminotransferase (SGOT)
    - ALT = alanine aminotransferase (SGPT)

Hepatic Function Tests

- Tests for Obstructive Disease
  - Bilirubin -Total Bilirubin - (TBil)
    - Conjugated Bilirubin (Direct Bili)
      - Measured
    - Unconjugated Bilirubin (Indirect Bili)
      - Calculated
  - Enzyme Tests
    - Alkaline phosphatase (ALP)
    - Gamma-glutamyl transferase (GGT)

Other Laboratory Tests to Evaluate Hepatic Function

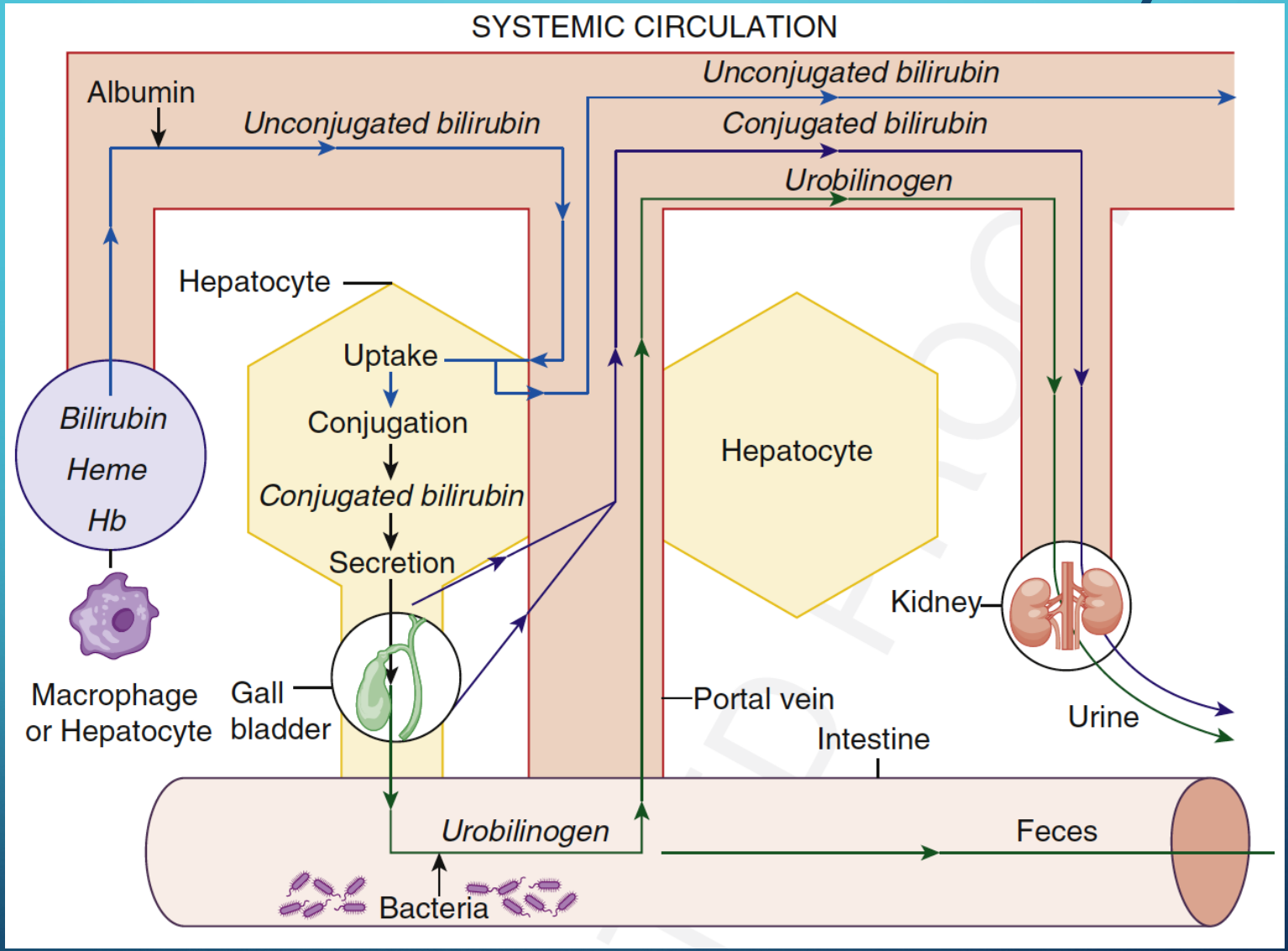
- Normal Synthesis
  - Proteins
    - Albumin
    - Pre-albumin
  - Coagulation Factors
    - Prothrombin Time (PT)
    - Partial Thromboplastin Time (PTT)
  - Cholesterol
- Metabolic Function
  - Blood Urea Nitrogen (BUN)
  - Glucose
  - Ammonia
- Hepatitis Panel Tests

Question #1

A patient presents with elevated urobilinogen in urine and feces, elevated serum indirect bilirubin and a normal serum direct bilirubin. Which one of the following conditions would you suspect?

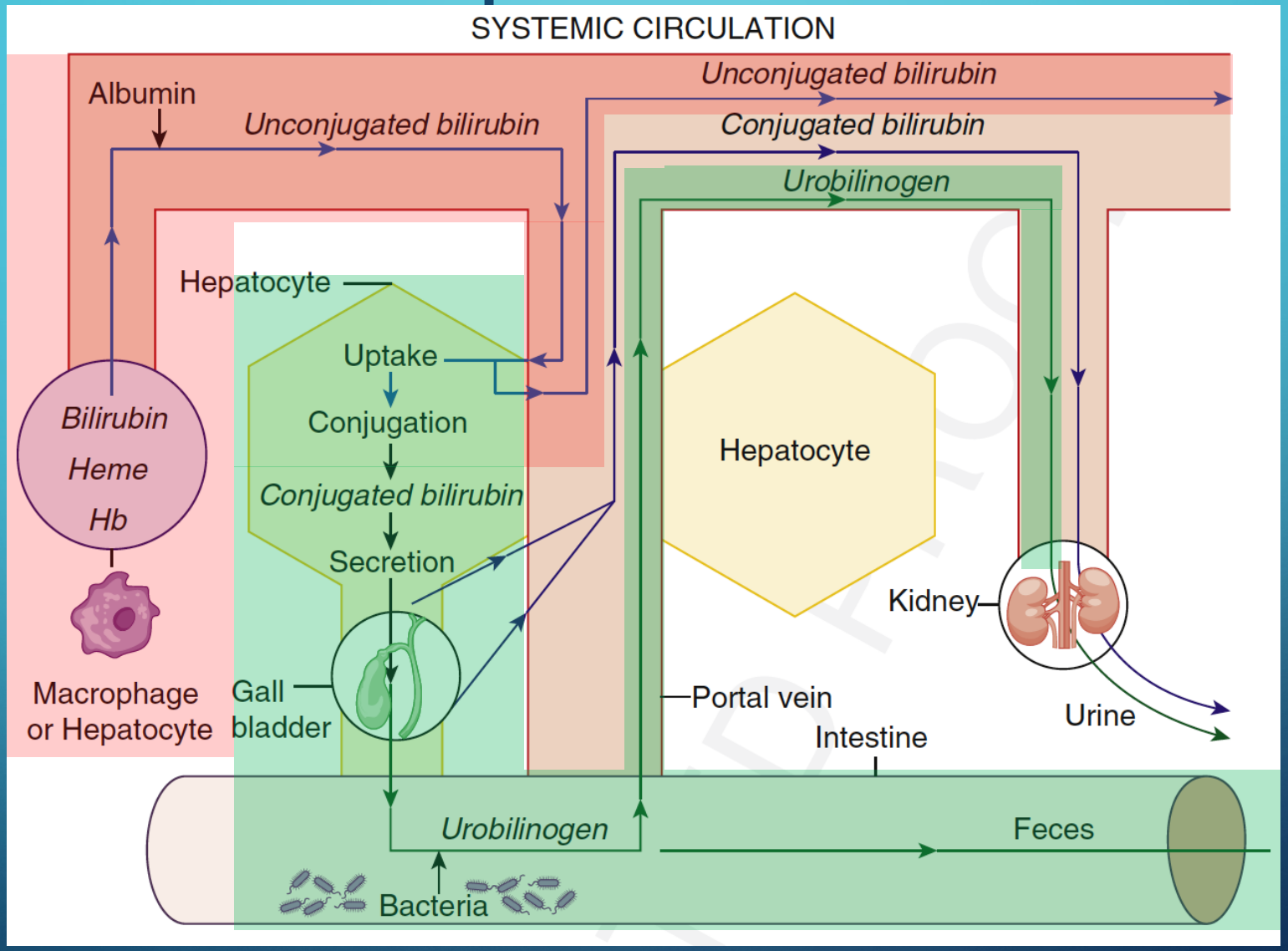
A. Pre-hepatic jaundice
B. Hepatic jaundice
C. Post-hepatic jaundice
D. No jaundice present

Normal Bilirubin Pathway



McDaniel, MJ. Hepatic Function Testing: The ABCs of the Liver Function Tests. Physician Assistant Clinics. 2019; 4(3), 541-550.

Pre-hepatic Jaundice



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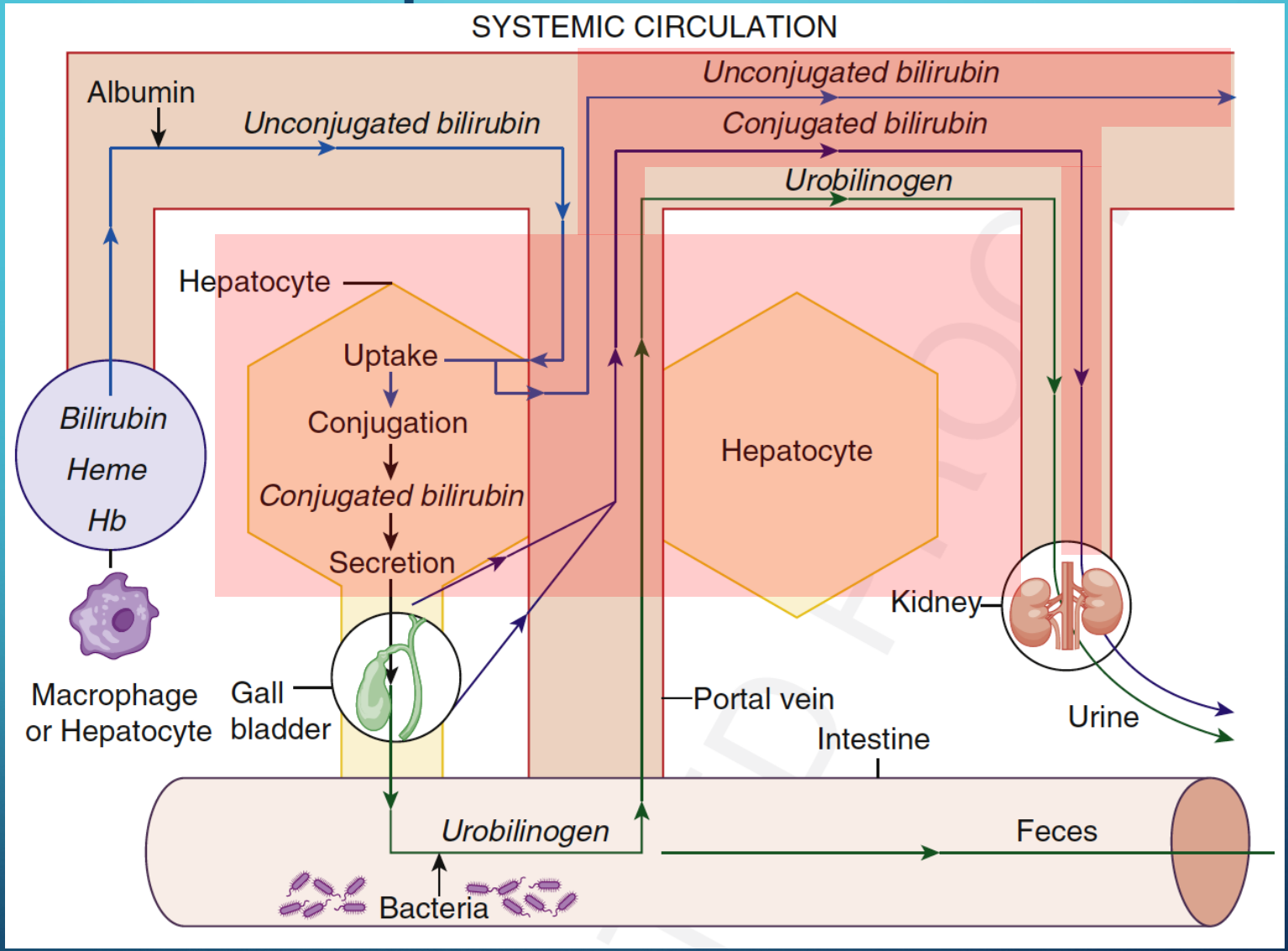
Abnormal Bilirubin Pathway

- Pre-hepatic jaundice
  - ↑ indirect (unconjugated) bilirubin in serum due to increased heme breakdown
  - ↔ direct (conjugated) bilirubin in serum
  - ↑ direct (conjugated) bilirubin in gut
    ↑ urobilinogen in urine and feces

Hepatic Jaundice

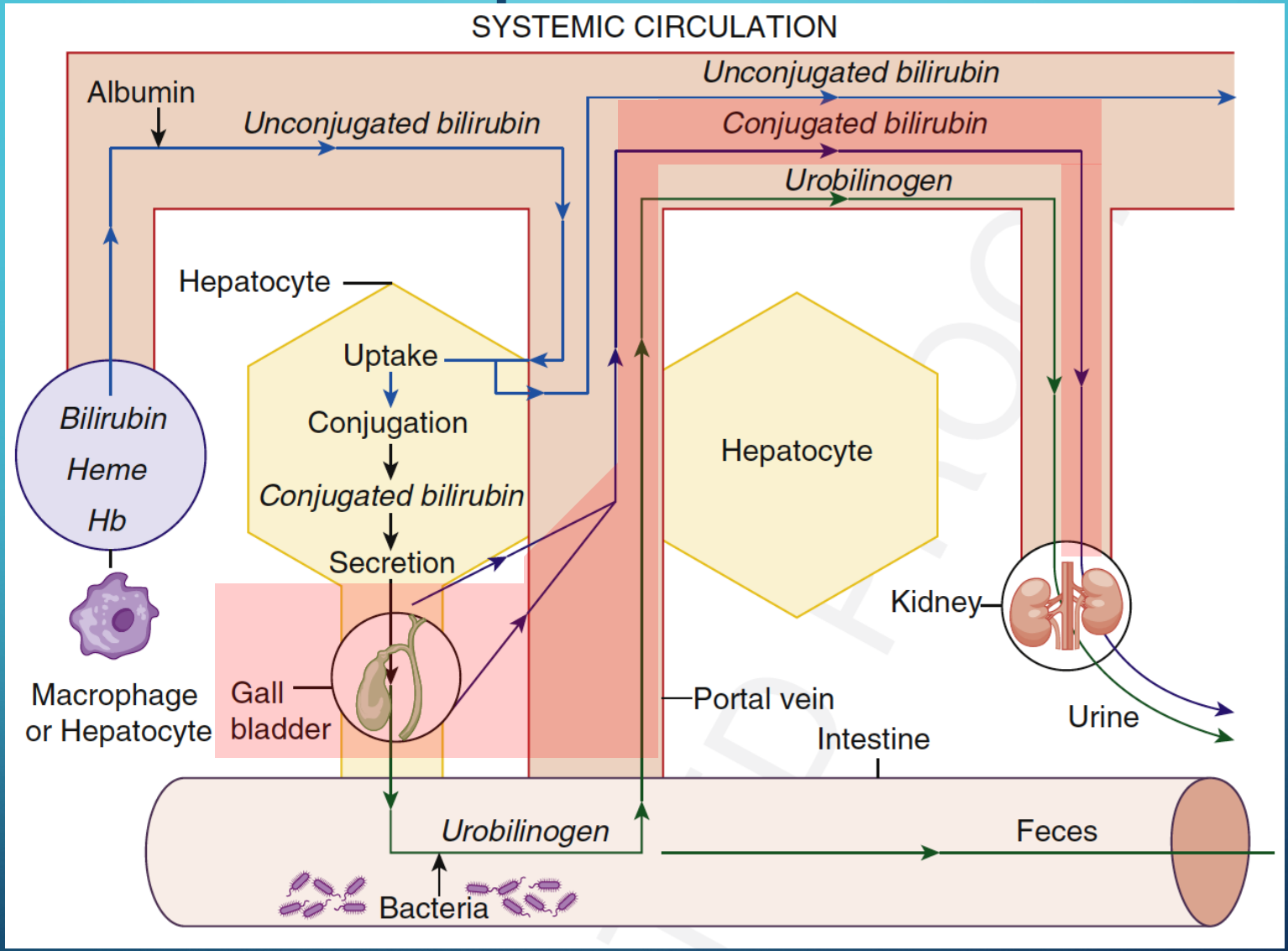


McDaniel, MJ. Hepatic Function Testing: The ABCs of the Liver Function Tests. Physician Assistant Clinics. 2019; 4(3), 541-550.

Abnormal Bilirubin Pathway

- Hepatic jaundice
  - ↑ indirect (unconjugated) bilirubin in serum due to impaired function of hepatocytes
  - ↑ direct (conjugated) bilirubin in serum due to swollen hepatic ducts blocking excretion
  - ↓ direct (conjugated) bilirubin in gut
    - pale stools
    - no urobilinogen in urine
    - bilirubin in urine

Post-hepatic Jaundice



McDaniel, MJ. Hepatic Function Testing: The ABCs of the Liver Function Tests. Physician Assistant Clinics. 2019; 4(3), 541-550.

Abnormal Bilirubin Pathway

- Post-hepatic jaundice
  - ↔ indirect (unconjugated) bilirubin in serum
  - ↑ direct (conjugated) bilirubin in serum due to obstruction blocking excretion
  - ↓ direct (conjugated) bilirubin in gut
    - pale stools
    - no urobilinogen in urine
    - bilirubin in urine

Summary

- ↑ indirect bilirubin
  - Hemolysis of RBC
  - Impaired cellular function of liver
- ↑ direct bilirubin
  - Obstruction to bilirubin excretion
- REMEMBER:
  - Bilirubin in the urine is never normal
    - But trace urobilinogen is normal

Question #2

Which liver function test is the most specific for hepatocellular damage?

A. Direct bilirubin (DBIL)
B. Alkaline phosphatase (ALP)
C. Aspartate aminotransferase (AST)
D. Gamma glutamyl transferase (GGT)

Hepatic Function Tests

- Alkaline Phosphatase (ALP)
  - Found in bone, liver, intestine, kidney, leukocytes, and placenta
  - One of first enzymes elevated in bile duct obstruction
  - GGT and 5'Nucleotidase can help differentiate elevated nonspecific ALP as hepatic in origin

Hepatic Function Tests

- Gamma-Glutamyltransferase (GGT)
  - Specific for liver
  - Particularly sensitive to alcohol ingestion
    - Alcohol induces GGT synthesis

- Increased GGT and ALP = hepatobiliary obstruction

Hepatic Function Tests

- Aminotransferases
  - Most often associated with hepatocellular damage
    - Aspartate Aminotransferase (AST)
      - Found in heart, liver, skeletal muscle, kidney
      - Old name:
        SGOT (serum glutamic-oxaloacetic transaminase)
    - Alanine Aminotransferase (ALT)
      - Found primarily in liver
      - Old name:
        SGPT (serum glutamic-pyruvic transaminase)

Question #3

A De Ritis Ratio (AST/ALT) of 6.0 would be indicative of which hepatic condition?

A. Acute viral hepatitis
B. Chronic viral hepatitis
C. Alcoholic hepatitis
D. Extrahepatic cholestasis
E. Intrahepatic cholestasis

De Ritis Ratio

- The numerical result obtained when AST activity is divided by ALT activity in the same serum sample.
- Used to distinguish clinical conditions where AST and ALT can be elevated to varying degrees
  - ALT = acute conditions
  - AST = chronic conditions

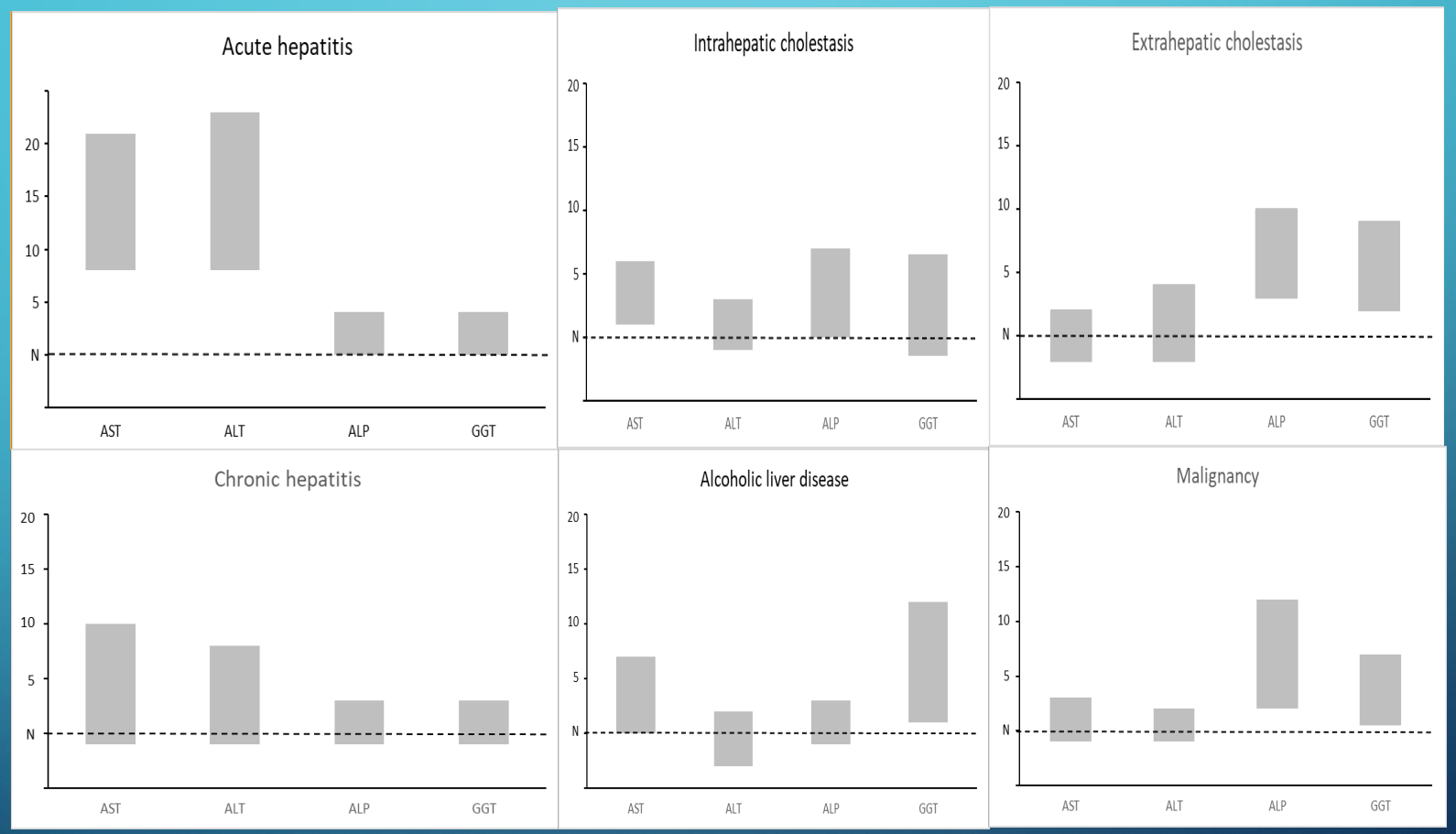
AST/ALT = De Ritis Ratio

- In Hepatocellular Damage
  - ALT > AST = acute viral hepatitis
    - de Ritis ratio < 1.0
  - AST > ALT = chronic or alcoholic hepatitis
    - de Ritis ratio >1.0, but <2.0 in chronic
    - often > 5.0 in alcoholic hepatitis

AST/ALT = De Ritis Ratio

- In Obstructive Disease (Cholestasis)
  - AST/ALT = de Ritis ratio < 1.5
    - Extrahepatic (acute process)
  - AST/ALT = de Ritis ratio > 1.5
    - Intrahepatic (chronic process)

Relationship of AST and ALT to ALP and GGT in Hepatic Diseases



Adapted from McClatchey, K.D. Clinical Laboratory Medicine. Williams & Wilkins, 1994, p. 268.

Question #4

An *R* Ratio of 1.5 would be indicative of which hepatic condition?

A. Hepatocellular liver injury
B. Cholestatic injury
C. Mixed pattern

R Ratio

- 2017 ACG Clinical Guidelines
- *R* ratio assesses pattern of liver injury

$$R = (\text{ALT}/\text{ALT ULN})/(\text{ALP}/\text{ALP ULN})$$

- *R* ratio > 5 identifies hepatocellular liver injury
- *R* ratio < 2 identifies cholestatic injury
- *R* ratio 2 - 5 indicates a mixed pattern

ULN = upper limit of normal

Relationship of AST and ALT to ALP and GGT in Hepatic Diseases

Liver Disease	AST	ALT	AST/ALT	*R* ratio	ALP	GGT
Acute Hepatitis	↑ 10-20x	↑ 10-30x	< 1.0	> 5	N to ↑ 3x	N to ↑ 3x
Chronic Hepatitis	N to ↑ 10x	N to ↑ 8x	> 1.0	> 5	N to ↑ 3x	N to ↑ 3x
Alcoholic Liver Disease	N to ↑ 7x	N to ↑ 2x	>5.0	> 5	N to ↑ 2x	↑ 1-10x
Intrahepatic Cholestasis	N to ↑ 5x	N to ↑ 3x	>1.5	< 2	N to ↑ 7x	N to ↑ 7x
Extrahepatic Cholestasis	N to ↑ 3x	N to ↑ 5x	<1.5	< 2	↑ 2-10x	↑ 2-10x
Malignancy	N to ↑ 5x	N to ↑ 3x	>1.5		↑ 2-10x	↑ 1-7x

Evaluating Hepatic Function Tests

- Liver Disease Present?
  - Measure hepatic function tests
- Cell Damage?
  - Measure aminotransferase levels (de Ritis ratio, R ratio)
- Obstruction?
  - Measure ALP, GGT
- Liver metabolism compromised?
  - Prothrombin time and serum albumin
- Acute or chronic?
  - Measure serum globulins

Hepatitis

Viral Causes of Hepatitis

- Hepatitis viruses
- Herpes viruses
  - CMV
  - EBV
- Coxsackie viruses

Toxic Hepatitis

- Due to drugs, toxic metal exposures, metabolic disorders, metastasis

Question #5

Which of the following hepatitis viruses is typically transmitted via a fecal-oral route?

A. Hepatitis A
B. Hepatitis B
C. Hepatitis C
D. Hepatitis D

	A	B	C	D	E
Source of virus	Feces	Blood/ blood-derived body fluids	Blood/ blood-derived body fluids	Blood/ blood-derived body fluids	feces
Route of transmission	Fecal-oral	Percutaneous permucosal	Percutaneous permucosal	Percutaneous permucosal	Fecal-oral
Chronic Infection	No	2-10% adults 30-90% < 5 yrs	60-85%	<5% coinfections ≤80% super-infections	No
Prevention	Pre/post-exposure immunization	Pre/post-exposure immunization	Blood donor screening; risk behavior modification	Pre/post-exposure immunization for HBV; risk behavior modification	Insure safe drinking water

Hepatitis A

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Hepatitis A

HAV shed in feces beginning 7-10 days after exposure.

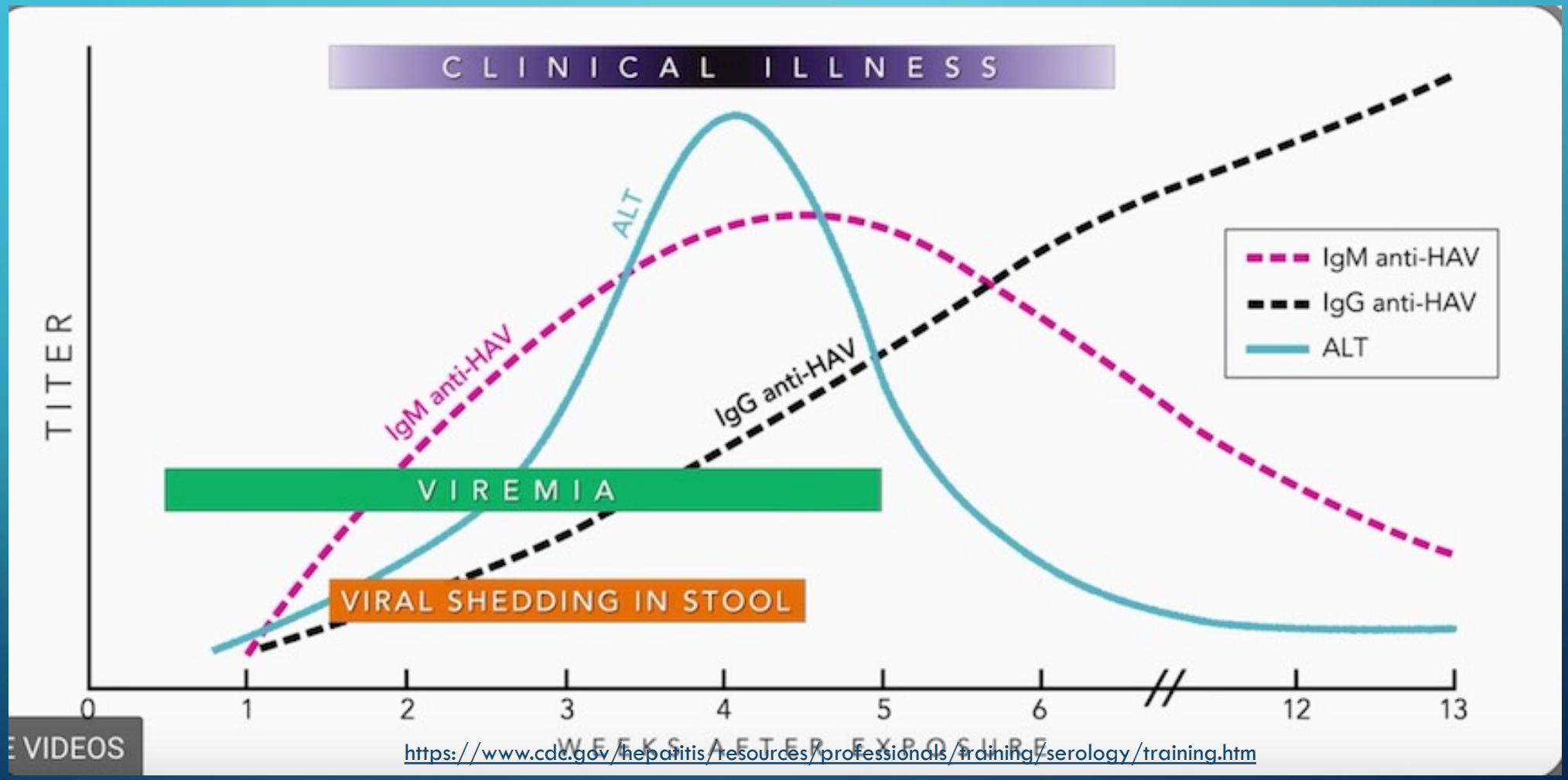
Detectable 14-21 days before onset of jaundice until 8 days after onset

Transmission

Close personal contact (household contact, sex contact, child day care)	Contaminated food, water (infected food handlers, raw shellfish)	Blood exposure (rare)

Mild, self-limiting, does not become chronic

Acute Hepatitis A Virus Infection



https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm

Lab Diagnosis of Hepatitis A

Non-specific abnormalities

- Increased ALT and AST, not correlated with outcome
  - ALP usually mildly elevated.
- Increased serum bilirubin; positive bilirubin in urine
- Elevated IgM, mild lymphocytosis, occ atypical lymphs on blood smear

Specific laboratory diagnosis

- HAV specific IgM antibodies (+ after infective stage)
- Virus or antigen detected in stool 1-2 weeks before symptoms
- Cell culture not used

Hepatitis B

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Question #6

Which of the following serologic markers signifies immunity to hepatitis B infection and is the only marker found as a result of Hepatitis B vaccination?

A. HBsAg
B. HBeAg
C. Anti-HBsAg
D. Anti-HBcAg

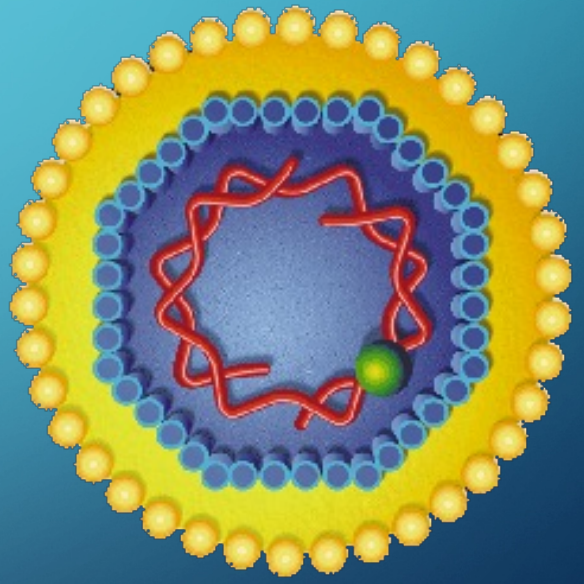
Transmission of HBV

- Humans serve as the viral reservoir
- HBsAg found in blood, blood products, feces, urine, bile, sweat, tears, saliva, semen, breast milk, vaginal secretions, CSF, synovial fluid and cord blood.
- Major routes of transmission are:
  - Percutaneous, mucous membrane exposure, sexual and perinatal

Course of HBV Infection

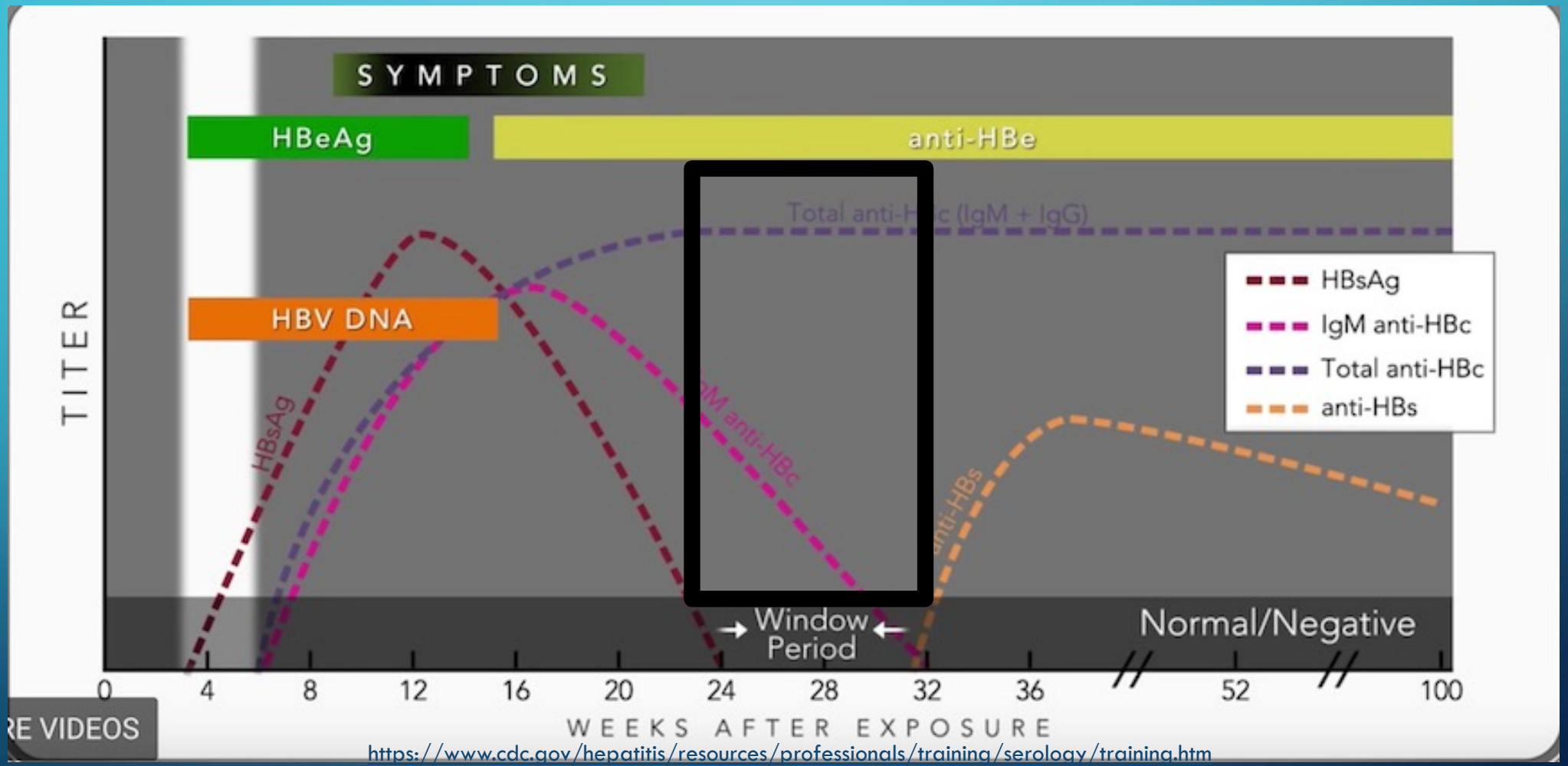
- In adults, most primary infections are self-limited, subclinical and resolve within 6 months of onset.

- Antigens and Antibodies found in HBV (in order of appearance):
  - HBsAg – surface antigen
  - HBeAg – envelope antigen
  - HBcAb – antibody to core
  - HBeAb – antibody to envelope
  - HbsAb – antibody to surface antigen



Schematic of Hepatitis B Virus
(from CDC website)

Acute Hepatitis B Virus Infection With Recovery



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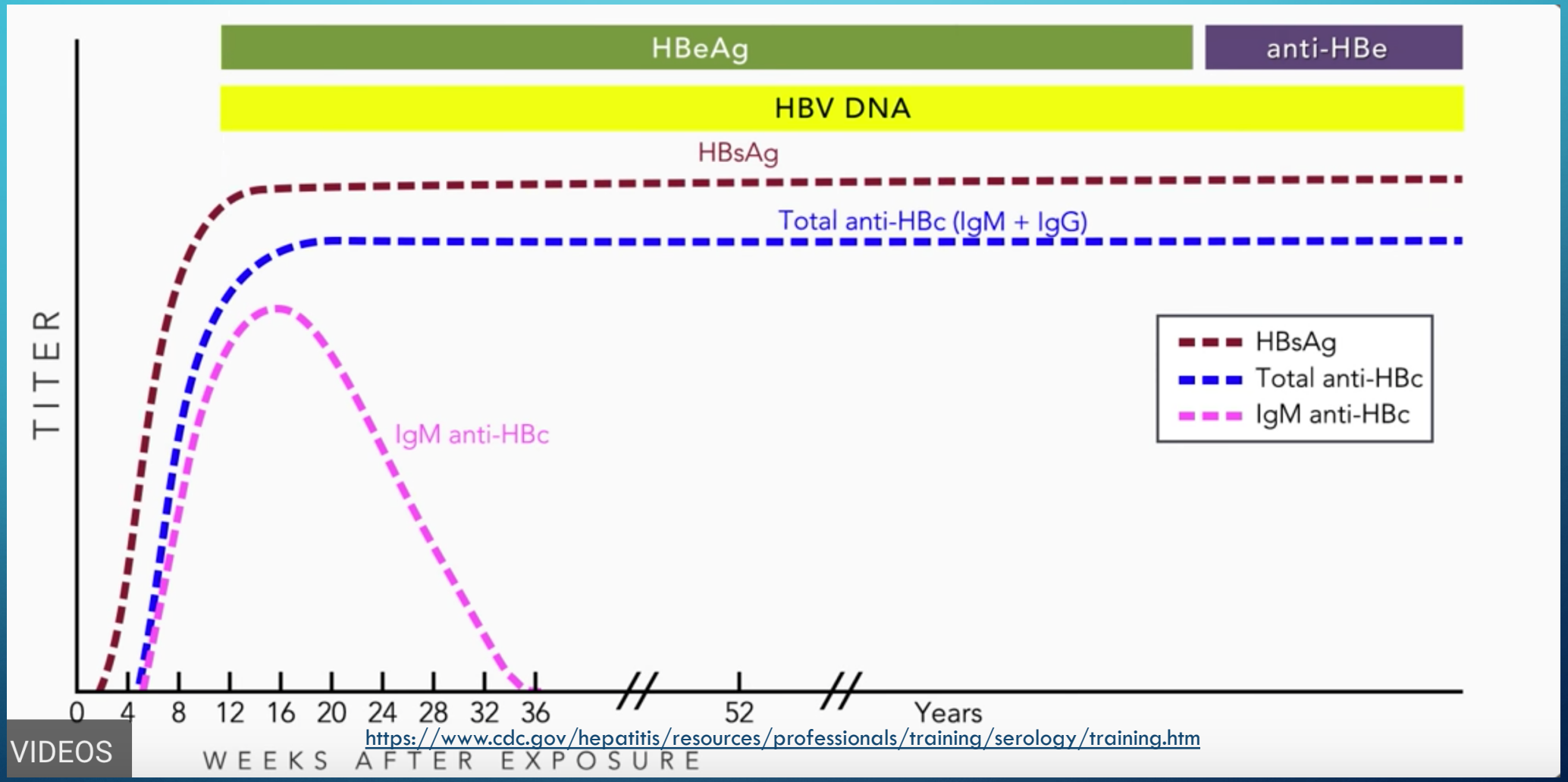
Chronic Hepatitis B Virus Infection



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https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm

Interpretation of Hepatitis B Markers

Phase of Infection	HBsAg	Anti-HBc	IgM Anti-HBc	Anti-HBs
Susceptible	Negative	Negative		Negative
Immune – Natural Infection	Negative	Positive		Positive
Immune – Hep B Vaccination	Negative	Negative		Positive
Acute Infection	Positive	Positive	Positive	Negative
Chronic Infection	Positive	Positive	Negative	Negative

Hepatitis C

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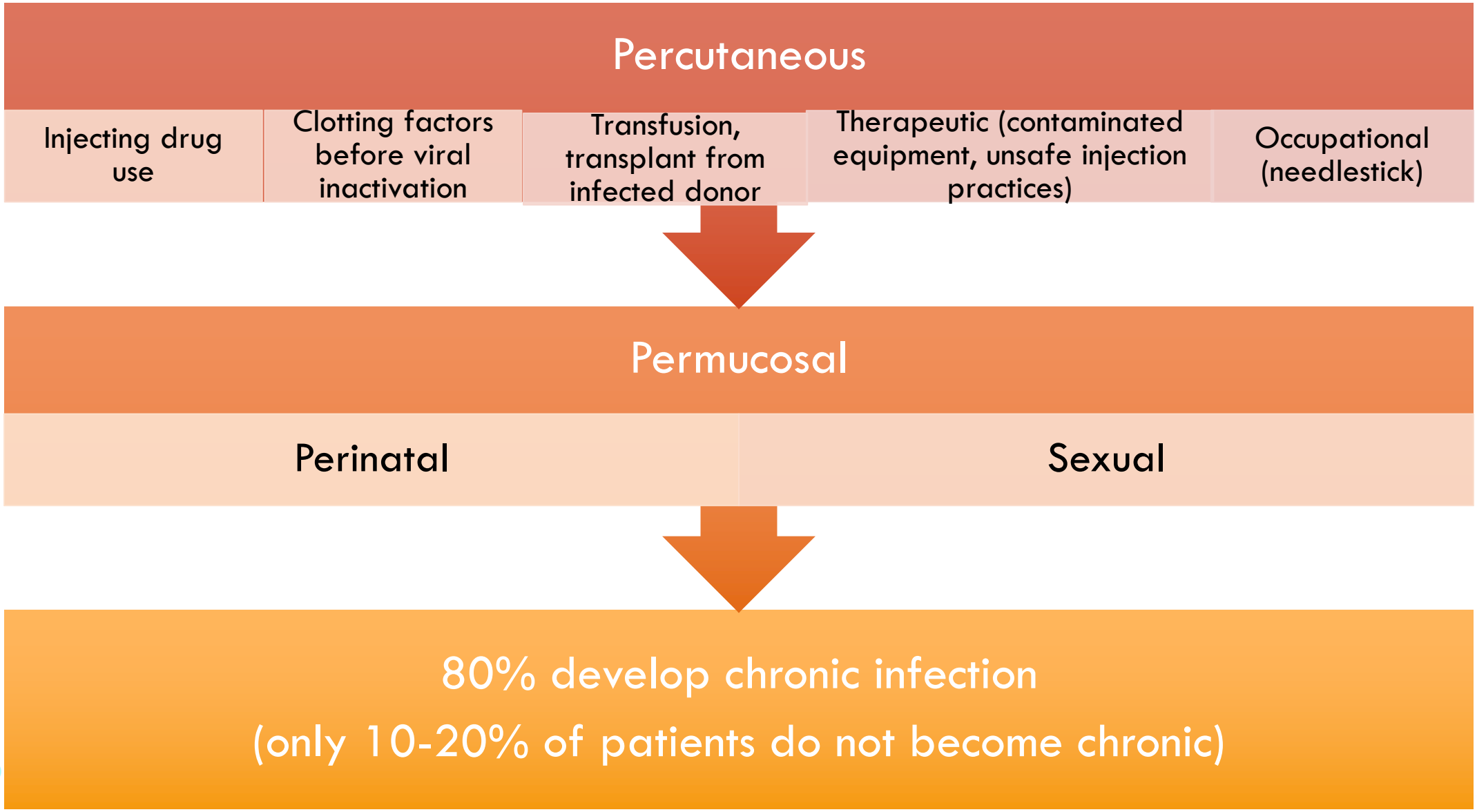
Question #7

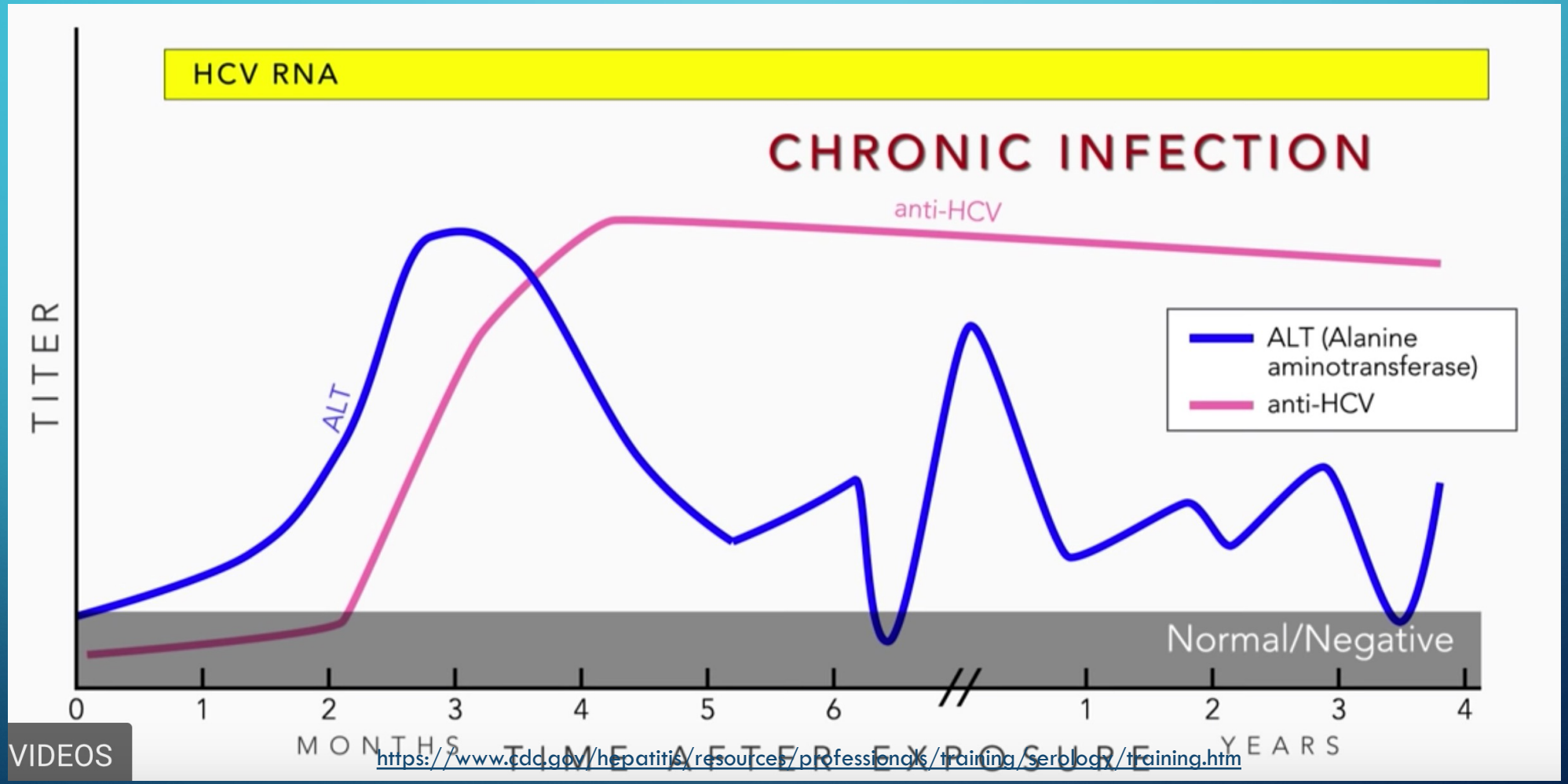
In order to distinguish acute from chronic HCV, which of the following testing protocols is most appropriate?

A. Anti-HCV antibody test
B. HCV RNA antigen test
C. Single HCV RNA antigen and ALT test
D. Multiple HCV RNA antigen and ALT tests

Hepatitis C


Percutaneous
Injecting drug use
Clotting factors before viral inactivation
Transfusion, transplant from infected donor
Therapeutic (contaminated equipment, unsafe injection practices)
Occupational (needlestick)
Permucosal
Perinatal
Sexual
80% develop chronic infection
(only 10-20% of patients do not become chronic)

Acute Hepatitis C Virus Infection Progressing to Chronic Infection



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Hepatitis C

EIA (Screening tests)

- Assays detect >95% of infected patients
- Don't distinguish acute vs chronic vs resolved infection
- Seronegative window (6-8 weeks)
- False positives in populations with low prevalence

RIBA (Recombinant Immunoblot Assay)

- Confirmatory test for detection of HCV antibodies
- Use if EIA gives indeterminate or questionable results

Hepatitis C

NAT for HCV RNA - Qualitative	• Confirmation of infection • Final assessment of treatment response
NAT for HCV RNA – Quantitative	• Predict response to therapy • Monitor response to therapy
Goal of therapy = Sustained Viral Response (SVR)	• no detectable virus 6 months after AVT completed

Hepatitis D

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Question #8

Which of the following Hepatitis infections are more likely to become chronic?

A. HDV infection
B. HBV and HDV superinfection
C. HBV and HDV co-infection
D. None of the above

Hepatitis D

Occurs only with co-infection with HBV
(infects about 4% of acute HBV cases), or as superinfection in chronic HBV carriers.

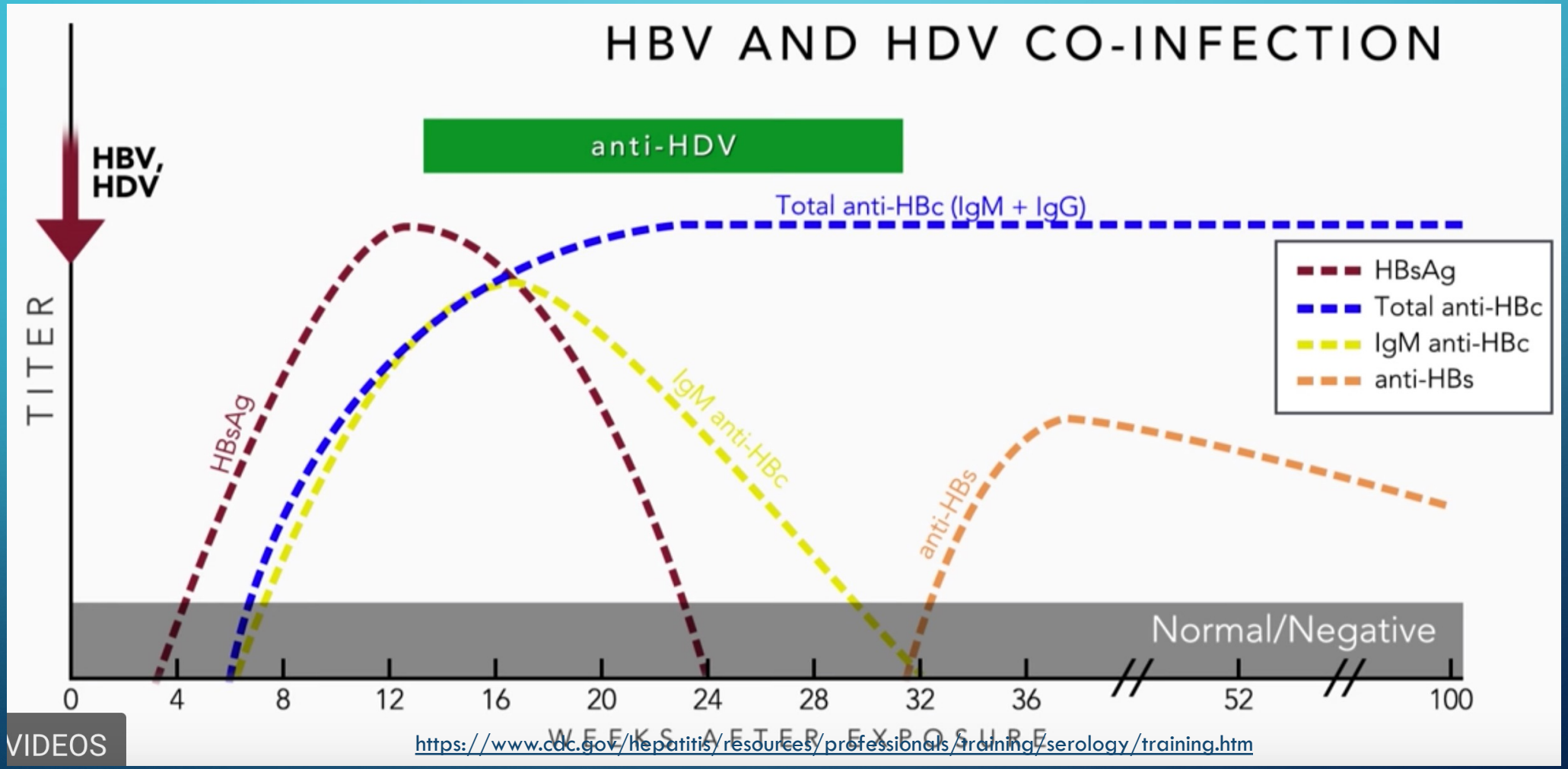
Co-infection

Increases severity of acute HBV infection	Decreases risk of chronic infection

Superinfection

Usually develop chronic HDV infection	High risk of severe chronic liver disease

Hepatitis B and Hepatitis D Co-Infection



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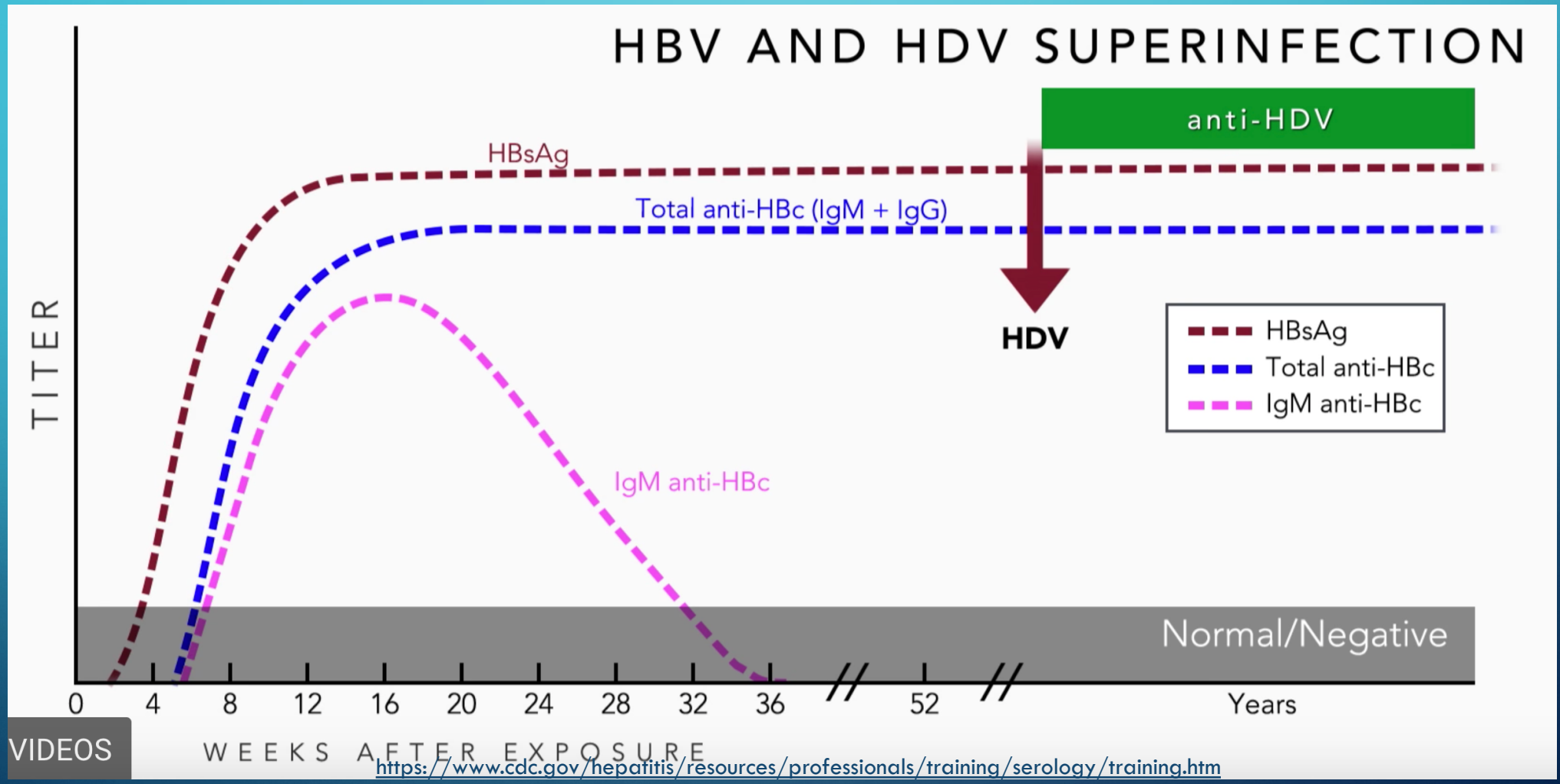
Hepatitis B and Hepatitis D Superinfection



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Hepatitis E

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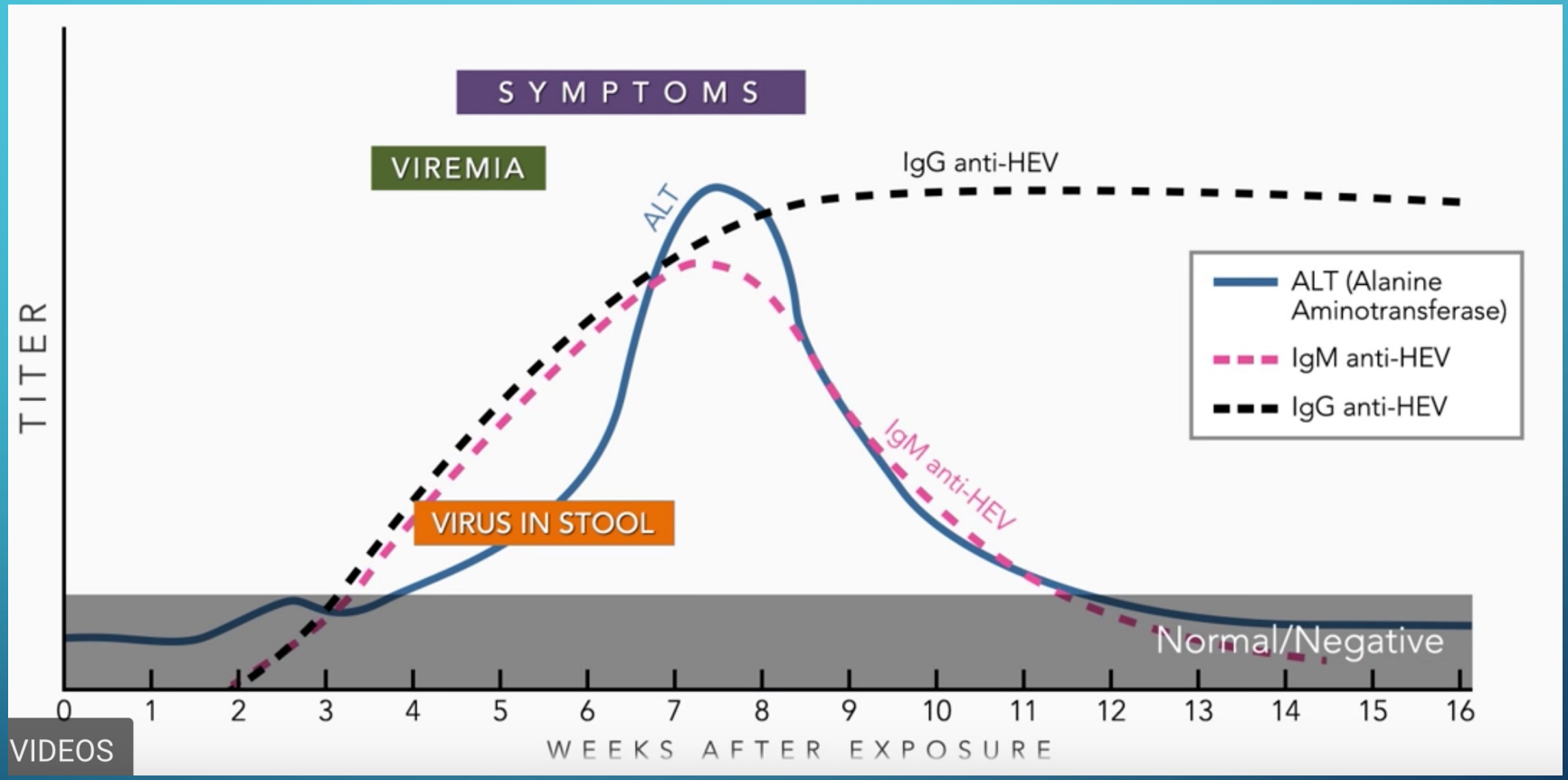
Hepatitis E

- Oral/fecal transmission, similar to HAV
- Endemic in developing countries (Mexico, Asia, Africa)
- Can detect anti-HEV or test for HEV antigen with PCR
- Should be part of differential diagnosis if travel to endemic areas has occurred

Hepatitis E Virus Infection



https://www.cdc.gov/hepatitis/resources/professionals/training/serology/index.htm

Hepatitis Lab Panels

- Acute Hepatitis Panel
  - Anti-HAV IgM
  - HBsAg
  - Anti-HBc IgM
  - Anti-HCV IgM
- Chronic Hepatitis B Panel
  - HBsAg
  - Anti-HBs
  - HBeAg
  - Anti-HBe

Case Study # 1

- A 37 year old female presents to your primary care practice complaining of feeling very weak and tired for the past two weeks. She is not aware of any blood loss and has had no problems with chest pain, palpitations or abdominal discomfort. No palpable hepatosplenomegaly is identified. She has a history of lupus with an elevated ANA.

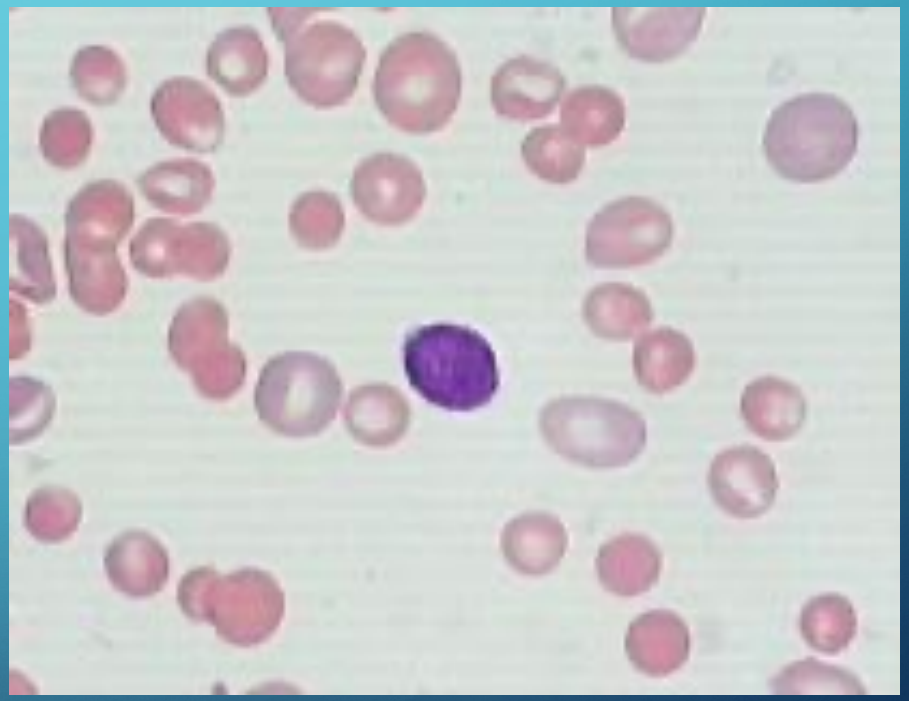
Case Study # 1 Lab Results

- Hepatic Function Panel
  - AST = 22 U/L (N: 7 – 40 U/L)
  - ALT = 31 U/L (N: 7 – 40 U/L)
  - ALP = 109 U/L (N: 30 – 115 U/L)
  - Total Bilirubin = 2.9 mg/dL (N: 0.2-1.5 mg/dL)
  - Direct Bilirubin = 0.5 mg/dL (N: 0.2-0.5 mg/dL)

Case Study # 1 Lab Results

CBC

- WBC = 5,600/mm^3
- Hgb: 4.6 g/dl
- Hct: 15%
- MCV: 114 fL
- MCHC: 31.7%
- Plt: 186,000/mm^3
- Retics: 26.1%



Question #9

What is the most likely diagnosis for this patient?

A. Prehepatic jaundice
B. Hepatic jaundice
C. Post-hepatic jaundice
D. None of the above

Case Study # 1 Diagnosis

- Direct Coombs Test = positive
- The peripheral blood findings coupled with an increased unconjugated (indirect) bilirubin, and positive direct Coombs point to a diagnosis of:

Autoimmune Hemolytic Anemia

Case Study # 2

- A 37 year old housewife comes to see you in the office with the complaint of three weeks of general fatigue, several days of dark urine, and two days of yellow eyes. She denies any vomiting, but does complain of mild, continuous pain in the right upper quadrant and some nausea.

Case Study # 2

- On exam you note icteric sclera. No signs of palmar erythema or spider angiomas. The liver is tender and enlarged. The spleen is not enlarged. The rest of the exam is normal.

Case Study # 2 Lab Results

- Hepatic Function Panel
  - AST = 1100 U/L (N: 7 – 40 U/L)
  - ALT = 1320 U/L (N: 7 – 40 U/L)
  - ALP = 190 U/L (N: 30 – 115 U/L)
  - Total Bilirubin = 5.5 mg/dL (N: 0.2-1.5 mg/dL)
  - Direct Bilirubin = 3.2 mg/dL (N: 0.2-0.5 mg/dL)
- CBC = Within Normal Limits

Question #10

What is the most likely diagnosis for this patient?

A. Prehepatic jaundice
B. Hepatic jaundice
C. Post-hepatic jaundice
D. None of the above

Case Study # 2 Lab Results

- Acute Hepatitis Panel
  - Anti-HAV IgM = negative
  - Anti- HCV IgM = negative
  - HBsAg = positive
  - Anti-HBc IgM = positive

Case Study # 2 Diagnosis

- AST and ALT markedly elevated (x 20)
  - de Ritis ratio = 0.83
- ALP mildly elevated
- Direct Bilirubin > 50% of total
- Hepatitis B markers positive

Acute Hepatitis B

Case Study # 3

- A 32 year old woman was seen in the ER because of recurrent epigastric pain and colicky pain in the RUQ. The current episode began four hours after a “heavy” dinner and was characteristic of previous episodes. The pain has become more severe during the more recent episodes. VS are normal; patient afebrile; tenderness without rebound in RUQ; bowel sounds normal. Urine slightly dark.

Case # 3 Lab Results

- Hepatic Function Panel:
  - Bilirubin, total = 2.4 (0.2-1.0 mg/dL)
  - Bilirubin, direct = 1.4 (0.0-0.2 mg/dL)
  - AST = 80 (9-30 U/L)
  - ALT = 60 (10-28 U/L)
  - ALP = 675 (124-255 U/L)
  - GGT = 210 (5-85 U/L)
- CBC = Within Normal Limits

Question #11

What is the most likely diagnosis for this patient?

A. Prehepatic jaundice
B. Hepatic jaundice
C. Post-hepatic jaundice
D. None of the above

Case Study # 3 Diagnosis

- ALP and GGT elevated x 3
- AST and ALT mildly elevated (x 2)
  - de Ritis ratio = 1.3

Extrahepatic cholestasis (cholecystitis)

Question #12

Do all patients with elevated hepatic function tests have viral hepatitis, alcoholic hepatitis, or gall bladder disease?

A. Yes

B. No

TAKE HOME POINTS

- Evaluation of total, direct and indirect bilirubin results can be useful in the differentiation of pre-hepatic, hepatic and post-hepatic jaundice
- Unique patterns in elevation of hepatic enzymes can be used to differentiate hepatobiliary diseases
- Hepatitis A, B, C, D, and E have unique serologic patterns which can aid in determining clinical staging and clinical outcome

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