Neuroscience Education Institute

LIFE DEPENDS ON THE LIVER: A PRACTICAL GUIDE TO LIVER FUNCTION TESTS

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Learning Objectives

1. Understand the blood panels that test for liver function and damage
2. Discern the components of blood panels and what each can tell you
3. Identify liver damage and disease due to differential causes (alcoholic liver disease, hepatotoxicity from medications, etc)

"Hepatic Function Panel"

Hepatic Function Panel

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Hepatic Function Panel (7)				
Protein, Total, Serum	6.5		g/dL	6.0 - 8.5
Albumin, Serum	4.5		g/dL	3.5 - 5.5
Bilirubin, Total	1.0		mg/dL	0.0 - 1.2
Bilirubin, Direct	0.17		mg/dL	0.00 - 0.40
Alkaline Phosphatase, S	54		IU/L	39 - 117
AST (SGOT)	20		IU/L	0 - 40
ALT (SGPT)	28		IU/L	0 - 44

- Standard term used by most major laboratories
- Panel of 7 tests

Comprehensive Metabolic Panel

- 14 tests
- Basic metabolic panel (BMP; "Chem-7") + Hepatic Function Panel

Comp. Metabolic Panel (14)

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Comp. Metabolic Panel (14)				
Glucose	70		mg/dL	70-99
BUN	15		mg/dL	8-27
Creatinine	0.76		mg/dL	0.76-1.27
eGFR	102		mL/min/1.73	>59
BUN/Creatinine Ratio	20			10-24
Sodium	134		mmol/L	134-144
Potassium	3.5		mmol/L	3.5-5.2
Chloride	96		mmol/L	96-106
Carbon Dioxide, Total	20		mmol/L	20-29
Calcium	8.7		mg/dL	8.6-10.2
Protein, Total	6.0		g/dL	6.0-8.5
Albumin	3.8		g/dL	3.8-4.8
Globulin, Total	2.2		g/dL	1.5-4.5
A/G Ratio	1.7			1.2-2.2
Bilirubin, Total	0.1		mg/dL	0.0-1.2
Alkaline Phosphatase	44		IU/L	44-121
AST (SGOT)	15		IU/L	0-40
ALT (SGPT)	12		IU/L	0-44

May Also Give Calculated Test Results

Protein, Total	8.0		g/dL	6.0-8.5
Albumin	**5.2**	**High**	g/dL	4.1-5.1
Globulin, Total	2.8		g/dL	1.5-4.5
A/G Ratio	1.9			1.2-2.2
Bilirubin, Total	**1.8**	**High**	mg/dL	0.0-1.2
Alkaline Phosphatase	70		IU/L	44-121
AST (SGOT)	**112**	**High**	IU/L	0-40
ALT (SGPT)	**73**	**High**	IU/L	0-44

1. Serum **globulin**: total protein minus albumin
2. **Albumin/Globulin ratio** (A/G ratio)
3. **Indirect bilirubin**: total bilirubin minus direct bilirubin

NOT Included in Hepatic Function Panel

Also tests of liver function

But, if needed, have to order them separately from the Hepatic Function Panel

Let's talk about each...

1. Serum **gamma-glutamyl transferase (GGT)**
2. Plasma **ammonia**
3. **Prothrombin time (PT)**

1. Serum gamma-glutamyl transferase (GGT)

GGT	287	High	IU/L	0-65

- Also called glutamyl transpeptidase
- If alcoholic use disorder or alcoholic liver disease are suspected, **consider ordering it separately**

Reus et al. Am J Psychiatry. 2018 Jan 1;175(1):86-90.
Dixit and Singh. J Clin Diagn Res. 2015 Dec;9(12):VC01-VC04
Woreta and Alqahtani. . Med Clin North Am. 2014 Jan;98(1):1-16.
Giannini et al. CMAJ. 2005 Feb 1;172(3):367-79.

2. Plasma Ammonia

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Ammonia, Plasma	74		ug/dL	30 - 130

Why is this a test of liver function?

Proteins broken down → ammonia → converted by the urea cycle in the liver to urea

If this fails (for example, if acute hepatic failure), **serum ammonia level rises → hepatic encephalopathy**

Urea Cycle Disorders Conference group. J Pediatr. 2001;138(1 Suppl):S1-5.
Kipervasser et al. Acta Neurol Scand. 2017;136(5):401-406.

Individual Tests in the Hepatic Function Panel

1. Total Protein, 2. Albumin

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Decrease serum albumin can indicate either:

1. A **decrease in the liver's synthesis ability** (also prothrombin time), OR
2. **Abnormal loss of albumin** (most importantly from leaking of albumin into the urine due to kidney disease)

3. Total Bilirubin, 4. Direct Bilirubin

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Hepatic Function Panel (7)				
Protein, Total, Serum	6.5		g/dL	6.0 - 8.5
Albumin, Serum	4.5		g/dL	3.5 - 5.5
Bilirubin, Total	1.0		mg/dL	0.0 - 1.2
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Total bilirubin = Direct bilirubin + Indirect bilirubin

Kwo et al. Am J Gastroenterol. 2017 Jan;112(1):18-35.
Woreta and Alqahtani Med Clin North Am. 2014 Jan;98(1):1-16.

Bilirubin Production and Excretion

1. Old RBCs are destroyed

2. Hemoglobin is converted into bilirubin

3. Bilirubin is not water-soluble and cannot be excreted easily. **The liver combines ("conjugates") the bilirubin** with some molecules that make the bilirubin water soluble

4. Conjugated bilirubin is then excreted by the liver through the bile duct into the intestine

Total bilirubin = Direct bilirubin + Indirect bilirubin

Woreta and Alqahtani. . Med Clin North Am. 2014 Jan;98(1):1-16.

What Could Cause ↑ Total Bilirubin?

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Total bilirubin increased:

1. ↑ hemolysis
2. ↓ conjugation of bilirubin (will see ↑ unconjugated bilirubin)
3. ↓ excretion of conjugated bilirubin (will see ↑ conjugated bilirubin)

What is "Direct" Bilirubin?

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Unconjugated bilirubin = **In**direct bilirubin

Conjugated bilirubin = Direct bilirubin

5. Alkaline Phosphatase (ALP)

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Albumin, Serum	4.5		g/dL	3.5 - 5.5
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↑ serum alkaline phosphatase → **usually, liver OR bone disease**

To differentiate liver vs. bone → look at <u>other</u> test results (for example, serum GGT)

If ↑ alkaline phosphatase is d/t liver disease → **cholestasis** (blockage of excretion of conjugated bilirubin somewhere)

6. AST and 7. ALT

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Hepatic Function Panel (7)				
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Albumin, Serum	4.5		g/dL	3.5 - 5.5
Bilirubin, Total	1.0		mg/dL	0.0 - 1.2
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AST: aspartate aminotransferase

ALT: alanine aminotransferase

↑ AST and ALT → hepatocellular injury (generalized damage to liver cells)

AST and ALT: We Should Also Look At..

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Hepatic Function Panel (7)				
Protein, Total, Serum	6.5		g/dL	6.0 - 8.5
Albumin, Serum	4.5		g/dL	3.5 - 5.5
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1. AST and ALT: **How high?**
2. AST vs. ALT: **Which one is elevated more?**
3. AST/ ALT **ratio?**

Interpreting Elevated AST and ALT

- AST and ALT levels can increase markedly with even mild liver damage
- One way of interpreting the severity of liver damage:
  - **Mild** elevation = **≤ 5 times** the upper limit of normal
  - **Moderate** elevation = **5 to 10 times** the upper limit of normal
  - **Marked** elevation = **> 10 times** the upper limit of normal

Combine with other information to judge the severity of liver damage

Giannini et al. CMAJ. 2005;172(3):367-79

Also Look at Total Bilirubin

Protein, Total	g/dL	6.0-8.5	7.5
Albumin	g/dL	4.1-5.1	4.9
Globulin, Total	g/dL	1.5-4.5	2.6
A/G Ratio		1.2-2.2	1.9
Bilirubin, Total	mg/dL	0.0-1.2	1.7 ^
Alkaline Phosphatase	IU/L	44-121	68
AST (SGOT)	IU/L	0-40	261 ^
ALT (SGPT)	IU/L	0-44	102 ^

Hy's Law

At risk of **death** or **needing a liver transplantation** if all three of the following are seen on the Hepatic Function Test results:

1. **ALT and/or AST** increased to **> 3 times** the upper limit of normal
2. **Total bilirubin** increased to **> 2 times** the upper limit of normal
3. **Alkaline phosphatase** is **< 2 times** the upper limit of normal. That is, it is **NOT significantly increased** (normal or only minimally increased)

Chalasani et al. Am J Gastroenterol. 2021 May 1;116(5):878-898.
Voican et al. Am J Psychiatry. 2014 Apr;171(4):404-15.
Temple R. Pharmacoepidemiol Drug Saf. 2006 Apr;15(4):241-3.

Hy's Law Explained

1. **ALT and/or AST** increased to **> 3 times** the upper limit of normal

Indicates damage to liver cells (hepatocellular injury)

2. **Total bilirubin** increased to **> 2 times** the upper limit of normal

The liver has a lot of extra capacity for conjugating and excreting bilirubin. So, **total bilirubin increases significantly only if the damage to liver cells is HUGE**

Regev and Björnsson. Gastroenterology. 2014;147(1):20-4

Hy's Law Explained

3. **Alkaline phosphatase** is **< 2 times** the upper limit of normal. That is, it is **NOT significantly increased** (normal or only minimally increased)

Increased serum total bilirubin could also be due to blockage of excretion of bilirubin after conjugation and not due to extensive hepatocellular damage

If alkaline phosphatase is not ≥ 2 times the upper limit of normal, rules out cholestasis as the cause of increased total bilirubin → must be hepatocellular damage

Regev and Björnsson. Gastroenterology. 2014;147(1):20-4

If Conditions of Hy's Law Are Present...

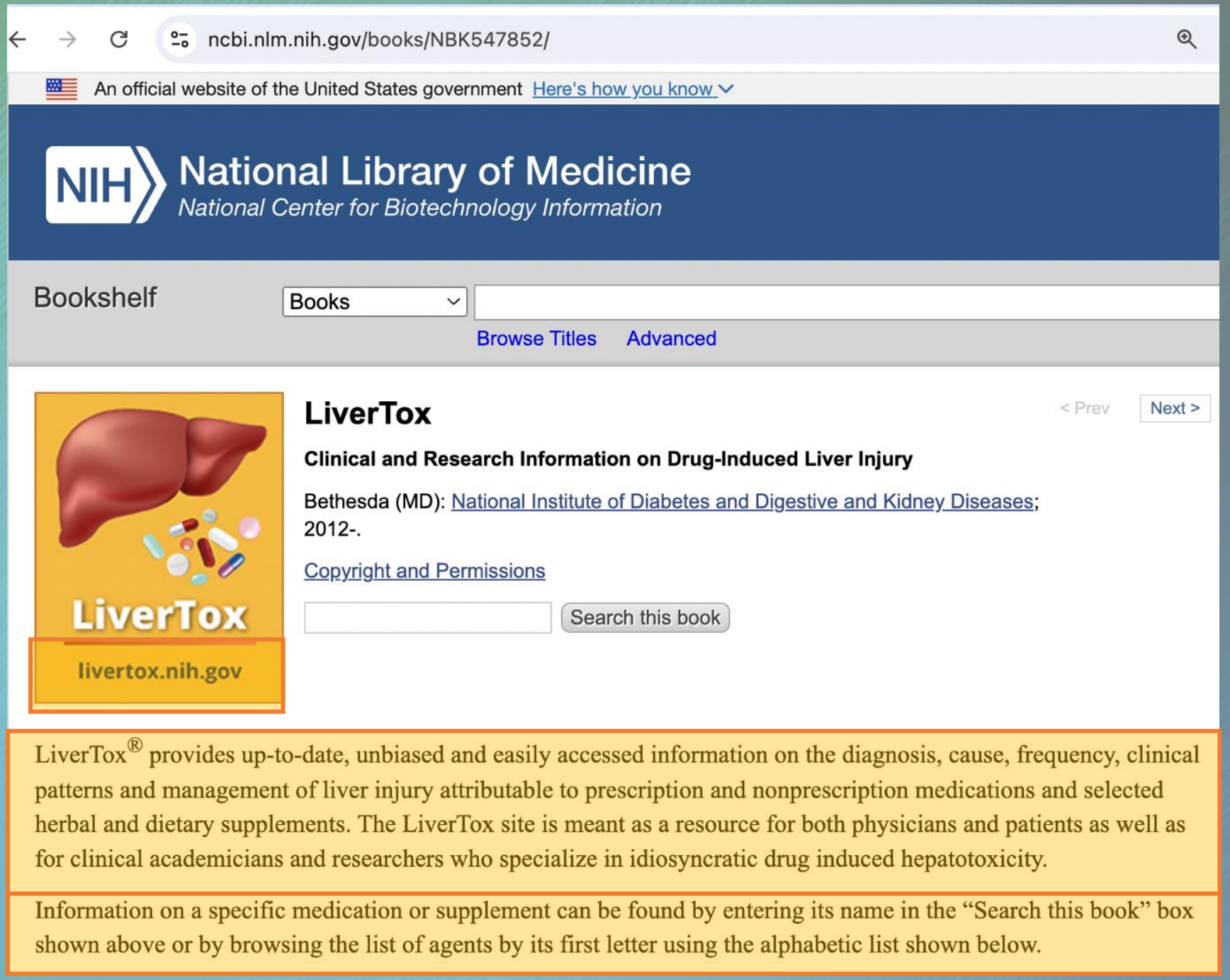
True medical emergency!

If suspect drug-induced liver injury → **we** should **stop the medication immediately** pending further evaluation

In the hospital: other causes of severe liver damage (for example, viral hepatitis) need to be ruled out

Chalasani et al. Am J Gastroenterol. 2021 May 1;116(5):878-898.
Voican et al. Am J Psychiatry. 2014;171(4):404-15.

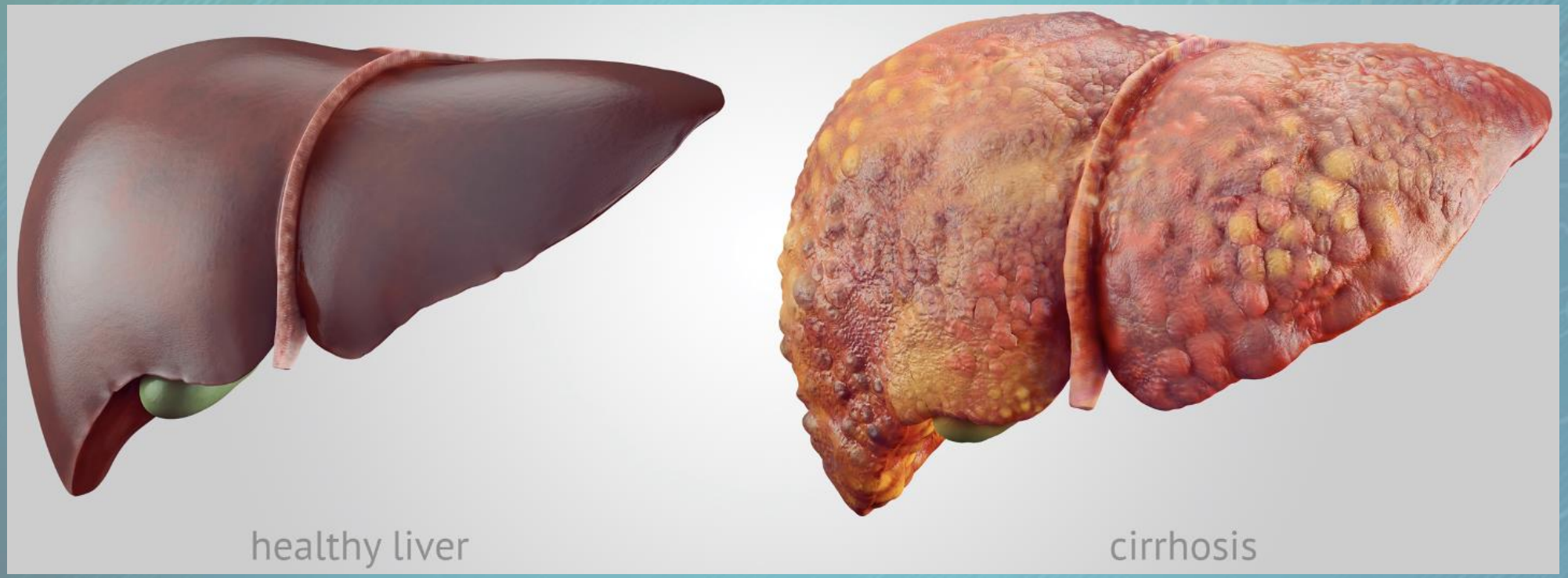
LiverTox is a fantastic resource for determining the hepatotoxicity of medications



Serrano J. Clin Liver Dis (Hoboken). 2014 Jul 25;4(1):22-25.

When Can AST and ALT be Misleadingly Normal or Even LOW?

- **Cirrhosis** of liver: most advanced stage of liver disease
- Due to destruction and scarring of liver tissue, **AST and ALT levels may be misleadingly normal or even *low***



Look at AST vs ALT

ALT: high concentration in liver cells; very low concentrations in other tissues

AST: found in many other tissues including muscle, kidney, and brain

So, **ALT is a more specific marker for liver injury**

Mnemonic: **L is more specific for Liver**

In most forms of chronic liver disease (including drug-induced liver injury) **ALT > AST (except in alcoholic liver disease)**

Kwo et al. Am J Gastroenterol. 2017 Jan;112(1):18-35.
Woreta and Alqahtani Med Clin North Am. 2014 Jan;98(1):1-16.

AST vs ALT in Muscle Injury

Injury to skeletal muscle (for example, strenuous exercise, rhabdomyolysis)

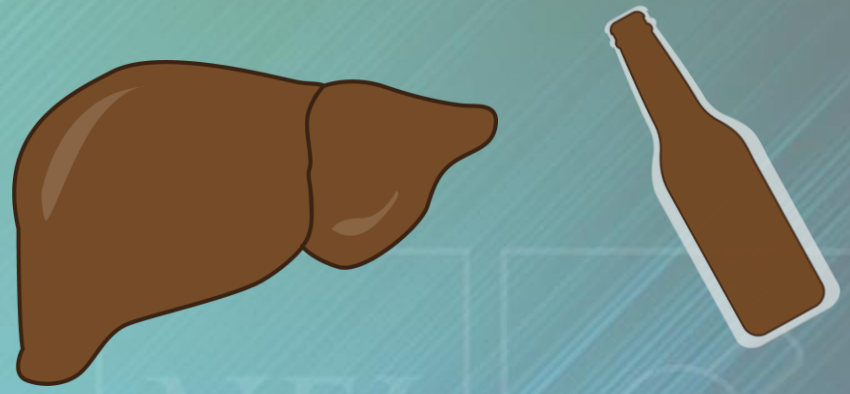
Which one will increase more – AST or ALT?

1. **AST** will be
2. **ALT** will be
3. So, the **AST/ALT ratio** will be

Alcoholic Liver Disease

Summary: Alcoholic Liver Disease

1. AST and ALT:
   - **<u>Both</u> AST and ALT are elevated**
   - **Typically <u>not</u> more than 400 IU/L**



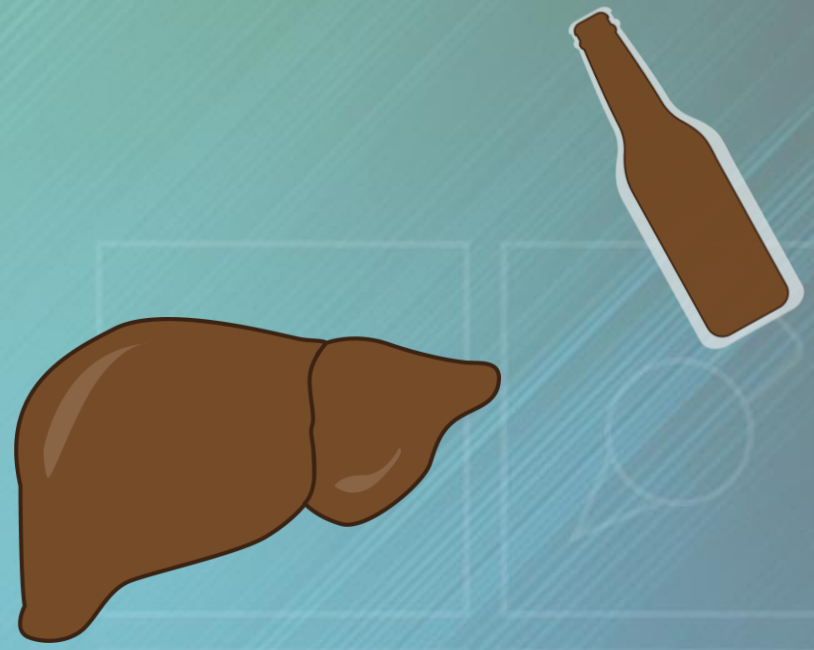
2. Relative elevation of AST vs. ALT: **AST/ALT ratio > 2**
3. Alkaline phosphatase: **Normal /<u>only slightly</u> elevated**
4. Gamma-glutamyl transferase (GGT): **Elevated**
5. Carbohydrate Deficient Transferrin (CDT) : **Elevated**

1. AST and ALT

Both AST and ALT are elevated

But, AST and ALT are **typically not more than 400** IU/L

Rule of thumb: AST and ALT **more than 1000** IU/mL **almost never due to alcoholic liver disease alone**



AST and ALT

Thoughts?

Protein, Total		7.0			g/dL
Albumin		4.7			g/dL
Globulin, Total		2.3			g/dL
A/G Ratio		2.0			
Bilirubin, Total		0.7			mg/dL
Alkaline Phosphatase		59			IU/L
AST (SGOT)			**84**	**High**	**IU/L**
ALT (SGPT)			**108**	**High**	**IU/L**

2. Relative elevation of AST vs ALT

Contrary to our general rule, in alcoholic liver disease, **AST is elevated more than ALT**

(Due to the effect of alcohol on mitochondria which releases AST)

Wrong: “In alcoholic liver disease, AST/ALT ratio is 2:1”

Correct: In alcoholic liver disease, **AST/ALT ratio is typically 2 or more**

Kwo et al. Am J Gastroenterol. 2017 Jan;112(1):18-35.
Tran and Lim. Ann Intern Med. 2021 Sep;174(9):ITC129-ITC144.

3. Alkaline Phosphatase (ALP)

NOT significantly increased

(Normal or only slightly elevated)

4. Gamma-glutamyl transferase (GGT)

1. With heavy alcohol use, **GGT** may be increased to **> 2 times the upper limit of normal**

2. But, **GGT can also be elevated in other (non-liver) conditions**

   - So, if GGT is elevated, we must also **look at alkaline phosphatase (ALP)**
   - **Alkaline phosphatase (ALP)**: **normal** or **only slightly elevated**
   - So, **GGT/ALP ratio > 5**

Reus et al. Am J Psychiatry. 2018 Jan 1;175(1):86-90.
Dixit and Singh. J Clin Diagn Res. 2015 Dec;9(12):VC01-VC04
Woreta and Alqahtani. . Med Clin North Am. 2014 Jan;98(1):1-16.
Giannini et al. CMAJ. 2005 Feb 1;172(3):367-79.

5. Optional: Carbohydrate Deficient Transferrin (CDT)

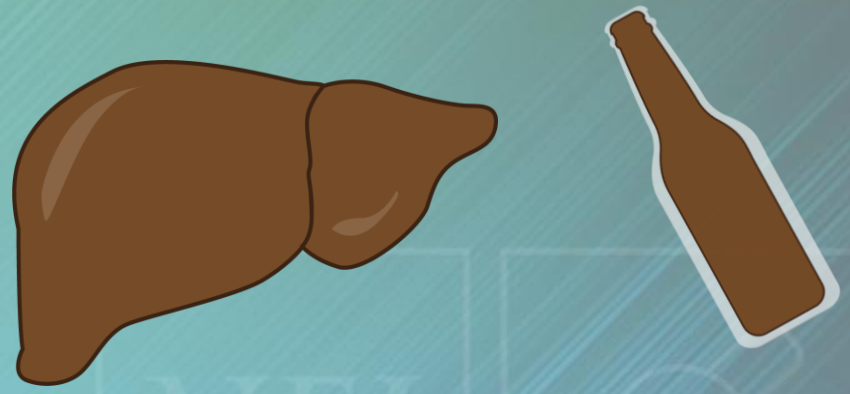
(Heavy alcohol use → reduction in the normal number of carbohydrate molecules attached to transferrin)

Carbohydrate Deficient Transf.				
CDT	**5.7**	**High**	**%**	0.0-1.3
			Normal	**<1.4**
			Inconclusive	**1.4 - 1.6**
			Elevated	**>1.6**
Clinical use only. Not specific for medico-legal purposes.				
This test is not suitable for the evaluation of patients suspected of having congenital glycosylation disorders.				
Comment				
A Carbohydrate Deficient Transferrin (CDT) result >1.6% is considered to be elevated and associated with chronic alcohol use during the previous two weeks.				
GGT	**108**	**High**	IU/L	0-65

Piano et al. Liver Transpl. 2014 Jul;20(7):815-22.

Summary: Alcoholic Liver Disease

1. AST and ALT:
   - **<u>Both</u> AST and ALT are elevated**
   - **Typically <u>not</u> more than 400 IU/L**



2. Relative elevation of AST vs. ALT: **AST/ALT ratio > 2**
3. Alkaline phosphatase: **Normal /<u>only slightly</u> elevated**
4. Gamma-glutamyl transferase (GGT): **Elevated**
5. Carbohydrate Deficient Transferrin (CDT) : **Elevated**

Plasma Ammonia

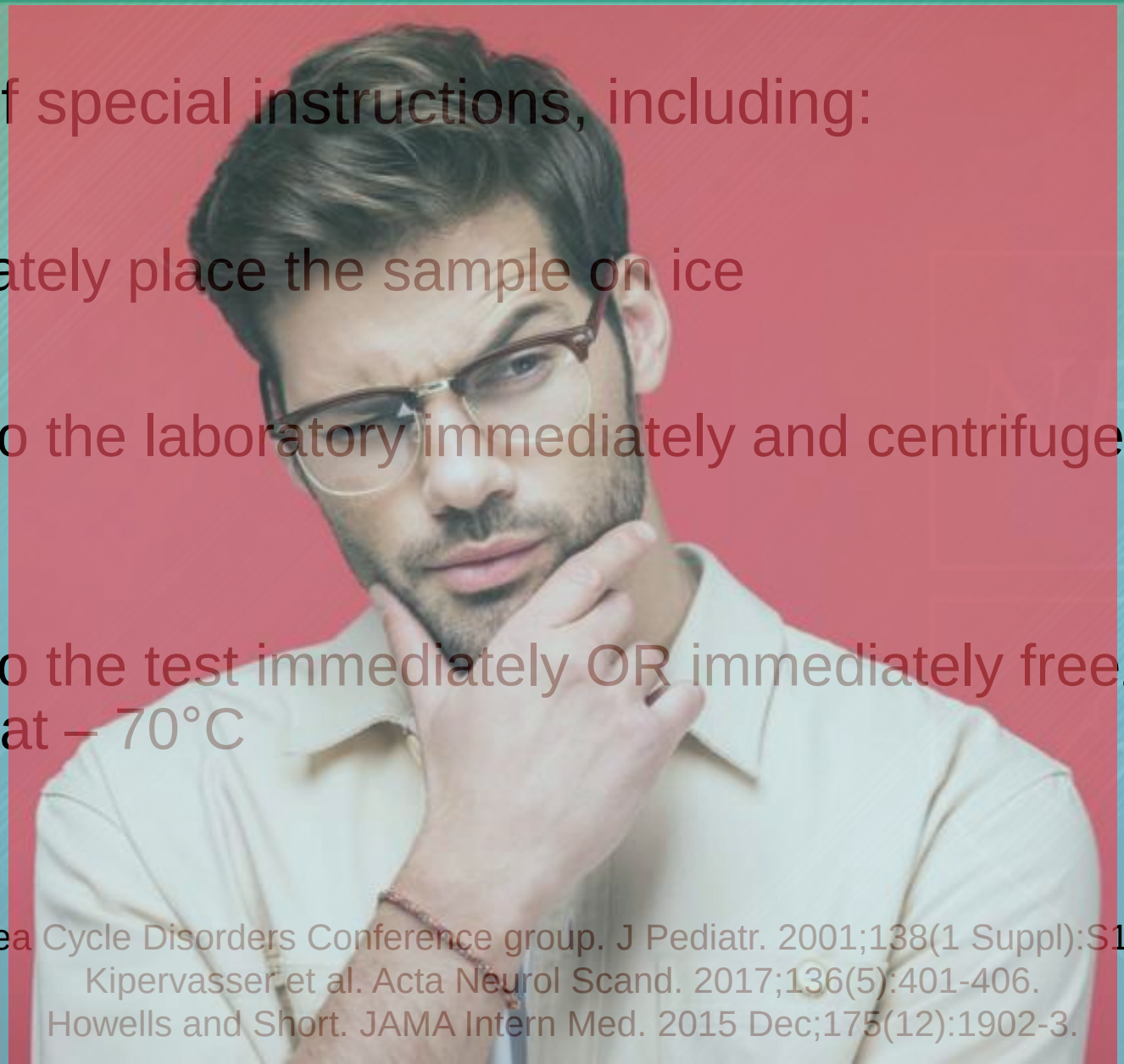
2. Plasma Ammonia

- Ammonia → converted in the liver to urea
- If ↑ plasma ammonia level → hepatic encephalopathy
- Valproate can cause hyperammonemia even with:
  - Valproic acid level: therapeutic
  - AST/ ALT: normal (or only slightly elevated)
- So, we may check plasma ammonia if a patient on valproate seems confused, has unstable gait, etc.

Urea Cycle Disorders Conference group. J Pediatr. 2001;138(1 Suppl):S1-5.
Kipervasser et al. Acta Neurol Scand. 2017;136(5):401-406.

False Positive Increased Ammonia Level?

- Long list of special instructions, including:
  - Immediately place the sample on ice
  - Take it to the laboratory immediately and centrifuge it right away
  - Either do the test immediately OR immediately freeze the plasma at – 70°C



Urea Cycle Disorders Conference group. J Pediatr. 2001;138(1 Suppl):S1-5.
Kipervasser et al. Acta Neurol Scand. 2017;136(5):401-406.
Howells and Short. JAMA Intern Med. 2015 Dec;175(12):1902-3.

Summary

- Get Hepatic Function Panel results for all patients on medications
- If **AST/ ALT are elevated**, look at the **Total bilirubin** and **Alkaline phosphatase** (Hy's law)
- In **Alcoholic liver disease**:
  1. AST/ ALT elevated but below 1000;
  2. AST > ALT;
  3. AST/ ALT ratio of 2 or more;
  4. Alkaline phosphatase NOT significantly increased
- Add **GGT and CDT** to the tests you consider for **identifying excessive alcohol use and detecting relapse**
- **Plasma ammonia** commonly false positive due to special requirements

Posttest Question 1 of 3

Which of the following is not included in a standard "hepatic function panel" and must be ordered separately?

1. Serum gamma-glutamyl transferase (GGT)
2. Serum albumin
3. Prothrombin time (PT)
4. Both 1 and 3
5. All of the above

Posttest Question 2 of 3

In alcoholic liver disease, which of the following is true regarding ALT and AST?

1. Both ALT and AST tend to be increased equally
2. ALT tends to be increased more than AST
3. AST tends to be increased more than ALT
4. All of the above are often present

Posttest Question 3 of 3

Hy's law refers to the conditions in which the patient is at risk of death or needing a liver transplantation if three conditions are met on the Hepatic Function Tests. Which of the following are conditions that are part of Hy’s law?

1. ALT and/or AST increased to > 3 times the upper limit of normal
2. Total bilirubin increased to > 2 times the upper limit of normal
3. Alkaline phosphatase is > 2 times the upper limit of normal
4. Both 1 and 2
5. All of the above