Work Up of Abnormal Liver Enzymes

Bruce D. Askey, MS, ANP-BC
Associate Lecturer
Fitzgerald Health Education Associates
North Andover, MA
Adult Nurse Practitioner
Dept. of Bariatric Medicine
Guthrie Clinic
Sayre, PA

Disclosure

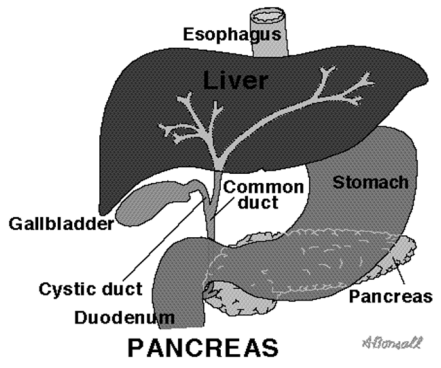
- No real or potential conflict of interest to disclose.
- No off-label, experimental or investigational use of drugs or devices will be presented.

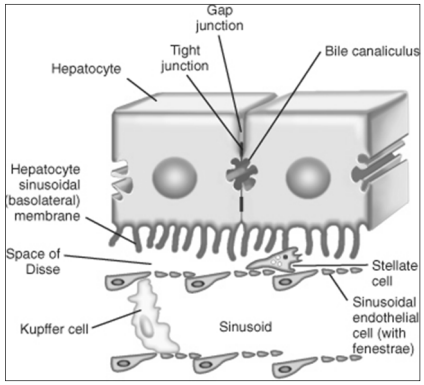
Objectives

- At the end of this presentation, the participant will be able to:
  - Identify the true markers of liver function.
  - Describe the difference between cholestatic and hepatocellular patterns of injury, including drug-induced hepatic problems.
  - Identify the appropriate diagnostic measures for hepatocellular and cholestatic patterns of liver injury.

References

Additional References at End of Presentation





Source: Gastrointestinal and Liver Disease 8e

Liver Function Tests

True Liver Function Tests

- Prothrombin time (INR)
- Albumin
- Bilirubin

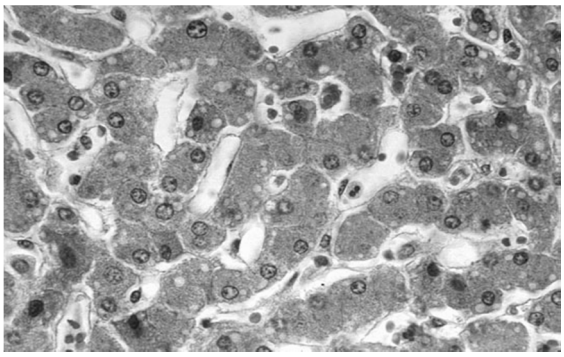
Prothrombin Time (INR)

- Prothrombin is synthesized (manufactured) by liver cells.
  - Normal level indicates normal hepatocellular (liver cell) synthetic function (ability to do work).
  - Elevated INR occurs in decompensated cirrhosis and impending hepatic failure.

Albumin

- Synthesized (manufactured) in the liver
  - Albumin levels drop as hepatic synthetic function declines.
    - Also decreases in malnutrition and acute and chronic illness

Hepatocytes



Hepatocellular (Liver Cell) Enzymes

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST)
  - Levels increase with hepatocellular inflammation.
- Measure of severity of hepatocellular inflammation
  - Severe elevations (>5 × ULN) often result from toxins (meds, infection, herbals) or shock liver.

Hepatocellular Enzymes (continued)

- AST elevations in excess of ALT elevations often occur with alcohol (EtOH) use.
- ALT is more specific to liver.
  - "L"=Liver

Causes of Elevated Hepatocellular Enzymes

- Infection
- Alcohol
- Medications
- Steatohepatitis
- Metabolic disorders
- Celiac disease
- Autoimmune hepatitis
- Alpha-1 antitrypsin deficiency

Infection

- Hepatitis A, B, C, D, E, G
- Epstein-Barr
- Cytomegalovirus
- Many viruses

Baby Boomers

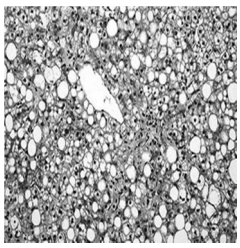
- Those born between 1945–1965 (baby boomers) should be offered a 1 × screening for hepatitis C.
  - 5 × more likely than other adults to have hepatitis C
  - 75% of adults with hepatitis C are baby boomers.
    - Source: https://www.cdc.gov/hepatitis/hcv/pdfs/hepctesting-diagnosis.pdf

Medications

- Any medication can cause elevated liver enzymes in susceptible people.
- Phase 1 reaction
  - Liver converts drug to active metabolite.
  - Active metabolite is potentially toxic.
  - This metabolite is then converted to a nontoxic substance (phase 2 reaction).
- Idiosyncratic reaction (unpredictable)

Steatohepatitis Fatty Deposition within the Hepatocyte

- Nonalcoholic fatty liver disease (NAFLD)
  - Liver enzymes are normal.
- Nonalcoholic steatohepatitis (NASH)
  - Liver enzymes are elevated.
  - Biopsy is needed to make diagnosis.



Steatohepatitis
Fatty Deposition within the Hepatocyte
(continued)

- Nonalcoholic steatohepatitis (NASH) (cont.)
  - Hepatocellular enzymes are abnormal (ALT/AST).
  - Obesity
  - Hyperlipidemia
  - Diabetes mellitus

Steatohepatitis
Fatty Deposition within the Hepatocyte
(continued)

- Nonalcoholic steatohepatitis (NASH) (cont.)
  - Thyroid disease
  - Biopsy shows increased fat and inflammation.
  - Can lead to cirrhosis

Metabolic Disorders

- Hemochromatosis (iron overload)
  - Iron, total iron binding capacity (TIBC), ferritin, genetic analysis
  - Liver biopsy
  - Leads to cirrhosis, diabetes, arthritis, impotence, cardiomyopathy
  - Damage can be prevented/minimized by phlebotomizing routinely based on ferritin level (50–100).

Metabolic Disorders
(continued)

- Wilson's disease (copper overload)
  - Decreased ceruloplasmin
  - Increased 24-hour urinary copper excretion
  - Liver biopsy
  - Kayser-Fleischer rings (slit lamp)

Celiac Disease

- Intolerance to gluten, resulting in malabsorption
  - Elevated hepatocellular enzymes may be only early manifestation.
  - Positive tissue transglutaminase antibody and villous atrophy on small bowel biopsy

Autoimmune Hepatitis

- Autoimmune disorder in which immune cells are "attacking" the liver.
  - More common in women but also occurs in men.
  - Positive antinuclear antibody (ANA)
  - Positive anti-smooth muscle antibody

Autoimmune Hepatitis (continued)

- Positive anti-liver-kidney microsomal-1 antibody
- Soluble liver antigen
- Total proteins are often elevated.
- Liver biopsy confirms diagnosis (preponderance of plasma cells).

Fitzgerald Health Education Associates 25

Autoimmune Hepatitis (continued)

- Treatment of autoimmune hepatitis
  - Prednisone 10–40 mg daily
    - If long term, must wean off
    - Adverse effects include weight gain, hyperglycemia, mood swings, and insomnia
  - Start concurrently with long-term immunosuppressive agent (azathioprine [Imuran®]) as azathioprine often takes several months to exert full effects.

Fitzgerald Health Education Associates 26

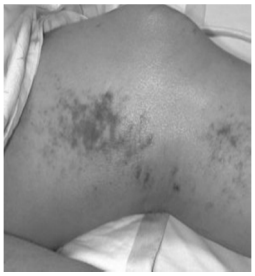
Immunosuppressive Agent

- Azathioprine (Imuran®, Azasan®)
  - 1 mg to 2 mg/kg/day
  - Bone marrow suppression: Monitor CBC
  - Monitor renal and liver studies
  - Pancreatitis
  - Lymphoma (BOXED WARNING)

Fitzgerald Health Education Associates 27

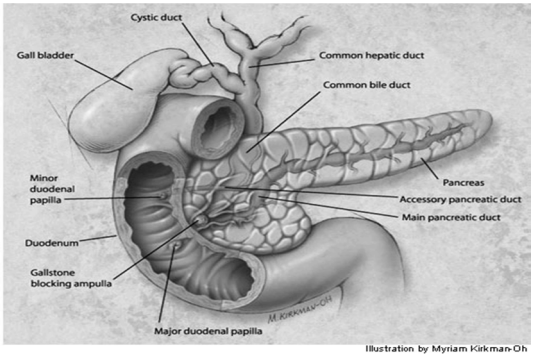
Alpha-1 Antitrypsin Deficiency

- Deficiency of alpha-1 antitrypsin resulting in cirrhosis
- Genetic predisposition to decreased alpha-1 antitrypsin levels
- May develop panniculitis (photo)



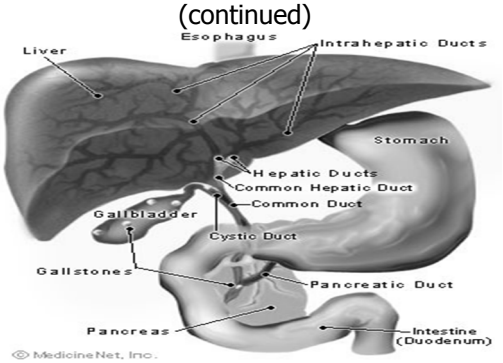
Fitzgerald Health Education Associates 28

Cholestasis (Obstruction of Bile Flow)



Fitzgerald Health Education Associates 29

Cholestasis (continued)



Fitzgerald Health Education Associates 30

Biliary Enzymes

- Alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase (GGT), 5'-nucleotidase
- Elevated in "cholestatic" (obstructive) conditions
  - Primary biliary cirrhosis (cholangitis)
    - Antimitochondrial antibody
  - Primary sclerosing cholangitis
    - Endoscopic retrograde cholangiopancreatography (ERCP)

Cholestasis

- Mechanical obstruction (tumor, gallstone)
  - CT/ultrasound, ERCP/MRCP
- Medications/herbals

Alkaline Phosphatase

- Arises from liver, bone and intestine
  - Alkaline phosphatase isoenzymes
  - GGT/5'-nucleotidase
- If clearly arising from the liver, an infiltrative process should be suspected.
  - Tumor
  - Fatty liver
  - Ultrasound, MRI or CT

Alkaline Phosphatase (continued)

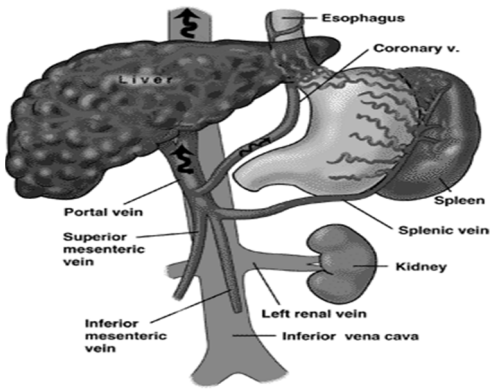
- GGT or 5'-nucleotidase
  - Parallel hepatic but not other sources of alkaline phosphatase
  - Confirms that elevated alkaline phosphatase is truly originating from the liver
  - GGT– Often elevated with alcohol use

Bilirubin

- Indirect bilirubin (unconjugated)
  - Released from red blood cells when they reach the end of their natural life
  - Not water soluble
    - Will not show up in urine
  - Increase occurs outside of liver
  - Increases with hemolysis
    - Hemolytic-uremic syndrome
    - Ribavirin (medication)
  - Increased in Gilbert's syndrome

Direct (Conjugated Bilirubin)

- Indirect bilirubin travels to the liver, where a molecule of glucuronic acid is added, making it water soluble, now referred to as "conjugated" or "direct" bilirubin.
- Elevated in cholestatic liver abnormalities
- Elevated secondarily with decreased hepatocellular function



Fitzgerald Health Education Associates 37

MELD Score
Assessing Severity of Liver Disease

- https://reference.medscape.com/calculator/meld-score-end-stage-liver-disease
- Input the bilirubin, creatinine and INR
- The higher the score, the more severe the liver damage and the greater the need for transplant.

Fitzgerald Health Education Associates 38

Childs Pugh Scoring System

- Total serum bilirubin
  - Bilirubin <2 mg/dL: 1 point
  - Bilirubin 2–3 mg/dL: 2 points
  - Bilirubin >3 mg/dL: 3 points
- Serum albumin
  - Albumin >3.5 g/dL: 1 point
  - Albumin 2.8–3.5 g/dL: 2 point
  - Albumin <2.8 g/dL: 3 point
- INR
  - INR <1.70: 1 point
  - INR 1.71–2.2: 2 point
  - INR >2.2: 3 point
- Ascites
  - No ascites: 1 point
  - Ascites controlled medically: 2 point
  - Ascites poorly controlled: 3 point
- Encephalopathy
  - No encephalopathy: 1 point
  - Encephalopathy controlled medically: 2 point
  - Encephalopathy poorly controlled: 3 point

Case Studies

Fitzgerald Health Education Associates 40

Case Study #1

- AST 2054 unit/L
  - N 15–46
- ALT 3056 unit/L
  - N 7–56
- Alk. phos. 186 unit/L
  - N 43–122
- Total bili. 26.2 mg/dL
  - N 0.2–1.3
  - 448.02 µmol/L (0.342–22.23)
- Direct bili. 17.1 mg/dL
  - N 0–0.4
  - 292.4 µmol/L (0–6.84)
- Albumin 2.7 g/dL
  - N 3.4–5.0
  - 27 g/L (34–50)
- INR 1.93
  - N 0.79–1.21

Fitzgerald Health Education Associates 41

Case Study #1
(continued)

- 57-year-old male
- Recently placed on lisinopril
- Subsequently underwent liver transplant
- >10 years later, he is doing well and enjoying his grandchildren!

Fitzgerald Health Education Associates 42

Case Study #2

- AST 21687 unit/L
  - N 15–46
- ALT 9501 unit/L
  - N 7–56
- Alk. phos. 112 unit/L
  - N 43–122
- Total bili. 7.0 mg/dL
  - N 0.2–1.3
  - 119.7 µmol/L (3.4–22.23)
- Direct bili. 4.1 mg/dL
  - N 0–0.4
  - 70.11 µmol/L (0–6.84)
- Albumin 3.5 g/dL
  - N 3.4–5.0
  - 35 g/L (34–50)
- INR 2.88
  - N 0.79–1.21

Case Study #2 (continued)

- 41-year-old female
- 1 bottle of rum q 2 days for several months
- Recent toothache
- Acetaminophen (Tylenol®) 500 mg, she has been taking 4 pills q 4 hours

Case Study #2 (continued)

- Acetylcysteine (Mucomyst®) 140 mg/kg PO, then 70 mg/kg q 4 hours
- Airlifted to transplant center where she was monitored and recovered

Case Study #2 Follow-up Labs 1 Month Later

- AST 23 unit/L
  - N 15–46
- ALT 17 unit/L
  - N 7–56
- Alk. phos. 84 unit/L
  - N 43–122 unit/L
- Total bili. 0.7 mg/dL
  - N 0.2–1.3
  - 11.97 µmol/L (3.42–22.23)
- Direct bili. 0.1 mg/dL
  - N 0–0.4
  - 1.71 µmol/L (0–6.84 µmol/L)
- Albumin 3.7 g/dL
  - N 3.4–5.0
  - 37 g/L (34–50)
- INR 0.91
  - N 0.79–1.21

Case Study #3

- AST 196 unit/L
  - N 15–46
- ALT 104 unit/L
  - N 7–56
- Alk. phos. 1149 unit/L
  - N 43–122
- Total bili. 4.8 mg/dL
  - N 0.2–1.3
  - 82.08 µmol/L (3.42–22.23)
- Direct bili. 1.9 mg/dL
  - N 0–0.4
  - 32.49 µmol/L (0–6.84)
- Albumin 2.0 g/dL
  - N 3.4–5.0
  - 20 g/L (34–50)
- INR 1.08
  - N 0.79–1.21

Case Study #3 (continued)

- 55-year-old female
- Pancreatic cancer

Case Study #4

- AST 80 unit/L
  - N 15–46
- ALT 45 unit/L
  - N 7–56
- Alk. phos. 112 unit/L
  - N 43–122
- Total bili. 1.7 mg/dL
  - N 0.2–1.3
  - 29.07 µmol/L (3.42–22.23)
- Direct bili. 0.8 mg/dL
  - N 0–0.4
  - 13.68 µmol/L (0–6.84)
- Albumin 1.5 g/dL
  - N 3.4–5.0
  - 15 g/L (34–50)
- INR 1.42
  - N 0.79–1.21

Case Study #4
(continued)

- 38-year-old male
- Chronic hepatitis B
- Cirrhosis

Case Study #4
Antiviral Medications for Heb B

- Pegylated Interferon alpha 2a
  - 180 mcg SQ weekly
  - Adverse effects
    - Flu-like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders
  - Monitoring on treatment
    - CBC, TSH q 3 months, monitoring for adverse effects

Case Study #4
Antiviral Medications for Heb B

- Lamivudine
  - 100 mg PO daily
  - Adverse effects
    - Pancreatitis, lactic acidosis
  - Monitoring on treatment
    - Pancreatic enzymes, lactic acid levels if a clinical concern for the development of pancreatitis or lactic acidosis

Case Study #4
Antiviral Medications for Heb B

- Telbivudine
  - 600 mg PO daily
  - Adverse effects
    - Creatine kinase elevations/myopathy, lactic acidosis, peripheral neuropathy
  - Monitoring on treatment
    - Creatine kinase, lactic acid levels if a clinical concern for the development of myopathy or lactic acidosis

Case Study #4
Antiviral Medications for Heb B

- Entecavir
  - 0.5–1 mg PO daily
    - 1 mg if lamivudine or telbivudine experienced or if decompensated cirrhosis is present
  - Adverse effects
    - Lactic acidosis
  - Monitoring on treatment
    - Lactic acid levels if a clinical concern for the development of lactic acidosis

Case Study #4
Antiviral Medications for Heb B

- Adefovir
  - 10 mg PO daily
  - Adverse effects
    - Acute renal failure, lactic acidosis, nephrogenic diabetes insipidus, Fanconi syndrome

Fitzgerald Health Education Associates 55

Case Study #4
Antiviral Medications for Heb B

- Adefovir (cont.)
  - Monitoring on treatment
    - Baseline creatinine clearance
    - Annual and PRN creatinine clearance, phosphate, urine glucose/protein if at risk for renal impairment
    - Baseline and PRN bone density if h/o fracture or risk factors for osteopenia
    - Lactic acid levels if a clinical concern for the development of lactic acidosis

Fitzgerald Health Education Associates 56

Case Study #4
Antiviral Medications for Heb B

- Tenofovir
  - 300 mg PO daily
  - Adverse effects
    - Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis

Fitzgerald Health Education Associates 57

Case Study #4
Antiviral Medications for Heb B

- Tenofovir (cont.)
  - Monitoring on treatment
    - Baseline creatinine clearance
    - Annual and PRN creatinine clearance, phosphate, urine glucose/protein if at risk for renal impairment
    - Baseline and PRN bone density if h/o fracture or risk factors for osteopenia
    - Lactic acid levels if a clinical concern for the development of lactic acidosis

Fitzgerald Health Education Associates 58

Case Study #5

- AST 46 unit/L
  - N 15–46
- ALT 28 unit/L
  - N 7–56
- Alk. phos. 223 unit/L
  - N 43–122
- Total bili. 1.6 mg/dL
  - N 0.2–1.3
  - 27.36 µmol/L (3.42–22.23)
- Direct bili. not available
  - N 0–0.4 mg/dL
  - 0–6.84 µmol/L
- Albumin 4.0 g/dL
  - N 3.4–5.0
  - 40 g/L (34–50)
- INR 2.39
  - N 0.79–1.21

Fitzgerald Health Education Associates 59

Case Study #5
(continued)

- 85-year-old male referred for "abnormal liver enzymes"
- Direct bili. was added and found to be normal at 0.3 mg/dL (N 0–0.4) (5.13 µmol/L [N 0–6.84]).
- Gamma-GT was added and found to be normal at 42 unit/L (N 7–50).

Fitzgerald Health Education Associates 60

Case Study #5
(continued)

- Alkaline phosphatase isoenzymes indicated a bone source of elevation. (Subsequent work-up revealed that he has Paget's disease.)
- On warfarin (Coumadin®)
  - Explains elevated INR

Case Study #6

- AST 1005 unit/L
  - N 15–46
- ALT 1310 unit/L
  - N 7–56
- Alk. phos. 194 unit/L
  - N 43–122
- Total bili. 11.1 mg/dL
  - N 0.2–1.3
  - 189.81 µmol/L (3.42–22.23)
- Direct bili. 5.3 mg/dL
  - N 0–0.4
  - 90.63 µmol/L (0–6.84)
- Albumin 4.1 g/dL
  - N 3.4–5.0
  - 41 g/L (34–50)
- INR 1.12
  - N 0.79–1.21

Case Study #6
(continued)

- 47-year-old female
- Work-up indicated acute hepatitis C
- Cleared virus spontaneously and is virus free with normal liver studies >10 years later

Case Study #7

- AST 51 unit/L
  - N 15–46
- ALT 63 unit/L
  - N 7–56
- Alk. phos. 104 unit/L
  - N 43–122
- Total bili. 1.1 mg/dL
  - N 0.2–1.3
  - 18.81 µmol/L (3.42–22.23)
- Direct bili. 0.2 mg/dL
  - N 0–0.4
  - 3.42 µmol/L (0–6.84)
- Albumin 4.9 g/dL
  - N 3.4–5.0
  - 49 g/L (34–50)
- INR 1.02
  - N 0.79–1.21

Case Study #7
(continued)

- 51-year-old female
- Work-up indicated celiac disease
- Liver enzymes have normalized on a gluten-free diet.

End of Presentation
Thank you for your time and attention.

Bruce D. Askey
MS, ANP-BC
www.fhea.com bruce@fhea.com

References

- Agrawal, A, et al. Evaluation of abnormal liver function tests. *Journal of Postgraduate Medicine 2016*; 92:223–234.
- Armstrong, MJ, et al. Presence and severity of nonalcoholic fatty liver disease in a large prospective primary care cohort. *Journal of Hepatology 2012*; 56:234–240.
- Askey, B. Abnormal liver studies: What happens next? *The Clinical Advisor. April, 2006*; 23–30.

References (continued)

- Ferri, F. (2014) *Ferri's Best Test: A Practical Guide to Clinical Laboratory Medicine and Diagnostic Imaging,* 3rd Edition, St. Louis: Elsevier Health Sciences. Available at fhea.com
- Kwo, P, et al. ACG clinical guideline: Evaluation of abnormal liver chemistries. *American Journal of Gastroenterology, 2017, January*; 112: 18–34.

References (continued)

- Longo, DL. *Harrison's Principles of Internal Medicine.* New York: McGraw-Hill, 2012.
- Singal, AK, Kamath, PS. Model for End-stage Liver Disease. *J Clin. Exp. Hepatology. 2013*;3:50–60.

- Images/Illustrations: Unless otherwise noted, all images/ illustrations are from open sources, such as the CDC or Wikipedia or property of FHEA or author.
- All websites listed active at the time of publication.

Copyright Notice

Statement of Liability

- The information in this program has been thoroughly researched and checked for accuracy. However, clinical practice and techniques are a dynamic process and new information becomes available daily. Prudent practice dictates that the clinician consult further sources prior to applying information obtained from this program, whether in printed, visual or verbal form.
- Fitzgerald Health Education Associates disclaims any liability, loss, injury or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents of this presentation.

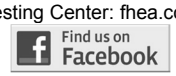
Fitzgerald Health Education Associates

85 Flagship Drive

North Andover, MA 01845-6154
978.794.8366 Fax-978.794.2455

Website: fhea.com

Learning & Testing Center: fhea.com/npexpert



www.facebook.com/fitzgeraldhealth

@npcert

Fitzgerald Health Education Associates 73

Cholestasis (Obstruction of Bile Flow)

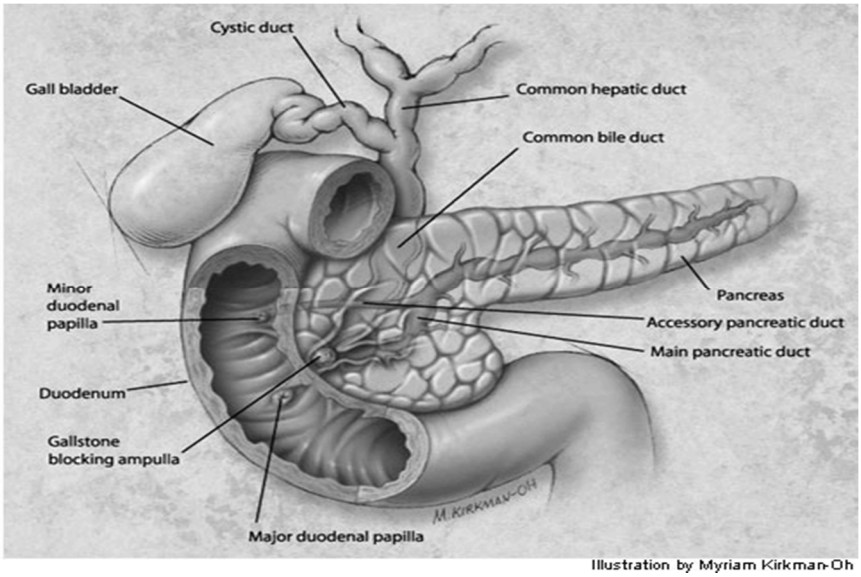
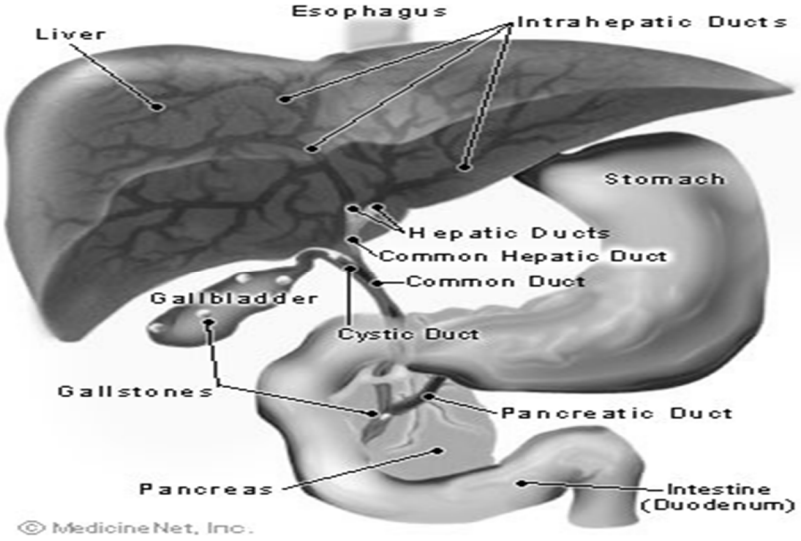


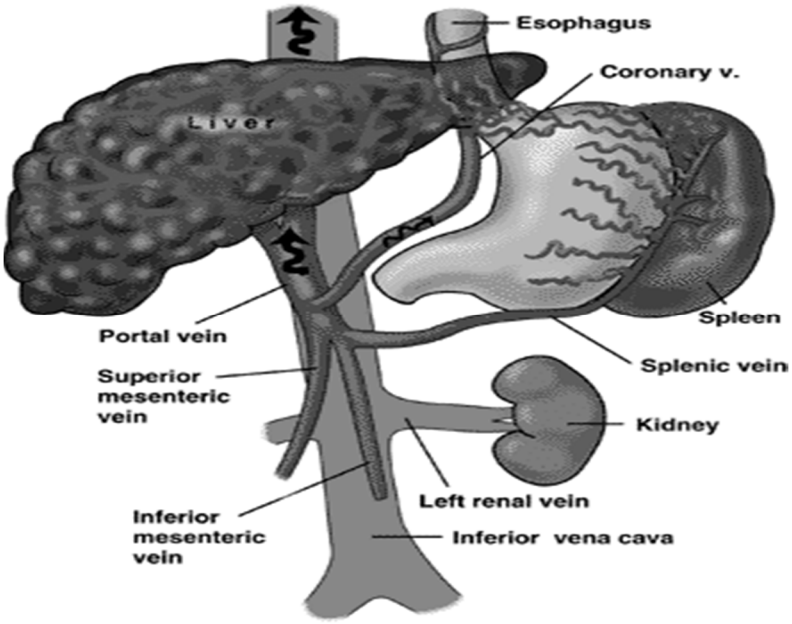
Illustration by Myriam Kirkman-Oh

Fitzgerald Health Education Associates 29

Cholestasis (continued)



Fitzgerald Health Education Associates 30



Fitzgerald Health Education Associates 37