Lecture 1
Normal anatomy & functions; Hepatobiliary injury & responses

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Winter 2015
Outline of Lectures

I. Normal anatomy & functions
II. Hepatobiliary responses
III. Manifestations of hepatic failure
IV. Developmental anomalies & Miscellaneous lesions
V. Circulatory disturbances
VI. Metabolic & nutritional disturbances
VII. Infectious diseases of the liver (hepatitis)
VIII. Toxin-induced liver diseases
IX. Diseases of uncertain cause
X. Proliferative lesions of the liver
XI. Diseases of the Gallbladder
General considerations

- Largest visceral organ
- 25% cardiac output
  - 67% portal vein
  - 33% hepatic artery
- Functions – multiple
- Injurious agents: myriads
- Clinical signs: variable
- Size
  - Carnivores 3-4% body weight
  - Omnivores 2% body weight
  - Herbivores 1% body weight
I. Normal anatomy & function

- The traditional structural unit (or hepatic lobule)
  - Hexagonal structure 1-2 mm wide
  - Central vein (terminal hepatic vein) at the centre
  - Portal triads
    - Bile ducts (BD)
    - Branches of portal vein (PV)
    - Hepatic artery (HA)
    - Nerves and lymphatics
  - Limiting plate
1.1 Normal structure

Portal tract. Composed of an hepatic artery (HA), bile duct (BD), portal vein (PV), and several lymphatic vessels (LV). These structures are surrounded by a collagenous extracellular matrix that forms an abrupt border with a circumferential row of hepatocytes, termed the limiting plate (LP—dotted line).
Zone 1 or centroacinar (periportal) surrounds the portal triads
Zone 2 or midzone is the intermediate or midlobular area
Zone 3 or periacinar (centrilobular) surrounds the central veins
Normal liver (trichrome stain). Note the blood-filled sinusoids and cords of hepatocytes; the delicate network of reticulin fibers in the subendothelial space of Disse stains light blue.
1.2 Functions of the liver

Bilirubin metabolism

- Formation of bilirubin
- Binding to albumin
- Hepatocellular uptake
- Conjugation
- Secretion into intestine
- Degradation to urobilinogens
- Excretion & reabsorption of urobilinogens

Schematic diagram of Bilirubin metabolism and elimination
Other liver functions

• Bile acid metabolism
  – Maintenance of cholesterol homeostasis
  – Stimulation of bile flow & digestion
  – Absorption of fats & fat soluble vitamins

• Carbohydrate metabolism
  – Conversion of glucose to glycogen & back

• Lipid metabolism
  – Production & degradation of plasma lipids
Other liver functions

• Xenobiotic metabolism
  – Inactivation of toxins (cytochrome p450 enzymes)

• Protein synthesis
  – Albumin, transport proteins, lipoproteins, etc

• Immune functions
  – Kupffer cells, production of acute phase proteins, recirculation of IgA
II. Hepatobiliary injury and responses - Background

- Clinical Signs
  - Similar regardless of the cause
  - If functional reserve and regenerative capacity are overwhelmed or impaired bile flow

- Liver lesions
  - Location and type
  - Histopathology is essential for diagnosis
Portals of entry of injurious agents

- Portals of entry
  - Hematogenous
  - Retrograde through biliary & pancreatic ducts
  - Direct extension through liver capsule
    (Penetrating trauma through the abdominal wall, rib cage, lumen of the GI tract)
2.1 Patterns of hepatocellular degeneration & necrosis

2.1.1 Random

- Single cell necrosis
- Multifocal necrosis
- Piecemeal necrosis?
Multifocal hepatic necrosis (white foci), foal with equine herpes virus infection

Multifocal hepatic necrosis and inflammation (N), pig, salmonellosis. P = Normal


Multifocal hepatic necrosis (N), tularemia (higher magnification). P = normal parenchyma
2.1 Patterns of hepatocellular degeneration & necrosis

2.1.2 Zonal

- Centrilobular
- Paracentral
- Midzonal
- Periportal
- Bridging
- Massive
Centrilobular necrosis (n), pig
C = central vein

Paracentral degeneration/necrosis (n), cow.
C = central vein

Midzonal necrosis (n), pig
C = central vein, P = portal area

Periportal necrosis (n), horse P = portal area

*Pathologic Basis of Veterinary Disease (2006), 4th ed., Mosby-Elsevier*
Massive necrosis, liver, dog. It involves entire lobule or contiguous lobules. The entire population of hepatocytes within the lobule has undergone necrosis. $P$, Portal area.
2.2 Patterns of hepatic inflammation

- Acute hepatitis
- Chronic hepatitis
- Cholangitis
- Cholangiohepatitis

**Acute, multifocal, necro-suppurative hepatitis**

**Chronic, multifocal, granulomatous hepatitis (Mycobacteriosis)**
Diagrammatic representations of the morphologic features of acute and chronic hepatitis. Fibrosis only happens in chronic hepatitis.
Acute, suppurative **cholangitis**, horse. Note the neutrophils (n) in and around bile ducts (arrows).

Chronic, lymphocytic **cholangitis**, cat. Numerous lymphocytes (L) surround and infiltrate a dilated bile duct (b)

Acute, suppurative **cholangiohepatitis**, rat. Note neutrophils (n) around a bile duct and invading the parenchyma (p)
2.3 General responses of liver to injury

- Three ways:
  - Regeneration of parenchyma
  - Replacement by fibrosis
  - Biliary hyperplasia

- Clinical signs
  - Loss of 75% of functional reserve
  - Liver enzymes can be elevated earlier
2.3.1 Regeneration

- Very good ability
- Oval (stem) cells
- For optimal regeneration (without scarring):
  - Intact framework
  - Good blood supply
  - Patent bile ducts
- Nodular proliferations if chronic (with scarring)

A single regenerative nodule (N) is surrounded by abundant fibrous tissue (F)

Black reticulin fibers (reticulin stain), hepatic extracellular matrix, normal liver, dog.

Oval cell proliferation, liver, rat

*Pathologic Basis of Veterinary Disease (2006), 4th ed., Mosby-Elsevier, chapter 8*
2.3.2 Fibrosis

- Increased amount of connective tissue within the liver

- Ito (stellate) cells

- Significance is dependent upon effects on normal hepatic function, blood and biliary flow
Patterns of fibrosis

- Focal/multifocal fibrosis
- Diffuse hepatic fibrosis
- Biliary fibrosis

Diffuse fibrosis in a cirrhotic, liver. Thick fibrous bands (blue) surrounding regenerative nodules. Trichrome stain

“Milk spotted liver”, pig (multifocal fibrosis)

Biliary fibrosis in chronic cholangitis due to *Fasciola hepatica*, cow
2.3.3 Biliary hyperplasia

Proliferation of new bile ducts within the portal areas

- Bile drainage obstruction
- Often seen in chronic hepatotoxicity
  - pyrrolizidine alkaloid
  - aflatoxin poisoning
- Can occur quickly in young animals
- An attempt to regenerate hepatocytes?

2.3.4 End-stage liver (Cirrhosis)

Final irreversible result of different hepatic diseases characterized by
- Nodular regeneration
- Fibrosis
- Bile duct hyperplasia

Liver architecture is very distorted so the initial pattern or cause can no longer be determined

Cirrhotic liver, Masson trichrome stain

Cirrhotic liver, dog

From Noah's arkive