Toxic and Idiopathic diseases

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OUTLINE

Normal anatomy & function
Hepatobiliary injury and responses
Manifestations of hepatic failure
Developmental anomalies and miscellaneous lesions
Circulatory disturbances
Metabolic & nutritional disturbances
Infectious diseases of the liver (hepatitis)
Toxin-induced liver diseases
Diseases of uncertain cause
Proliferative lesions of the liver
Diseases of the gallbladder and bile ducts
Mycotic infections may cause:

- Hemorrhagic infarcts
  - Cattle – resulting from mycotic rumenitis

- Granulomatous hepatitis
  - *Blastomyces dermatitidis*
  - *Histoplasma capsulatum*

Yeasts of *Histoplasma* in the cytoplasm of Kupffer cells and macrophages

(c) 2012, Richard M. Jakowski, DVM, PhD, DACVP

**Nematodes**

*Ascaris suum*

- Adults live in the intestine of pigs
- Larvae migrate through the liver
  - Tunnel → hemorrhage → eosinophilic infiltration/coagulative necrosis → fibrosis
  - Multifocal fibrosis = “Milk spots”
Nematodes

Dirofilaria immitis

- Fatal vena caval (postcaval) syndrome in heavy infections
  - DIC, Intravascular hemolysis, acute hepatic failure
Cysticercosis

- Adult tapeworm in GIT
- Larval tapeworms (cysticerci) encysted within tissues or on serosal surfaces
- Usually incidental
**INFECTIOUS DISEASES OF THE LIVER – PARASITIC INFECTIONS**

**Cestodes**

*Echinococcus granulosus*

**Hydatosis**

- Adult tapeworm in canid GIT
  - Larval form encysts in viscera of sheep, also many other species (accidental)
  - Zoonotic – people can get hydatid cysts

**Cestodes**

**Echinococcus multilocularis**

**Alveolar echinococcosis**

- **Adult tapeworm in canid GIT**
  - Larval form encysts in viscera of rodents, also many other species (accidental)
  - Zoonotic – people can get alveolar hydatid cysts

- In Canada, was mostly restricted to the northern tundra and south AB, MB, SK
- A few cases have occurred in Ontario recently in dogs as intermediate hosts

CDC/Dr IKagan
Cholangitis, *Fasciola hepatica*, liver, cow

**Trematodes**

- *Fasciola hepatica*
- *Fasciola gigantica*
- *Fascioloides magna*
- *Dicrocoelium*
- *Opisthorchis*
- *Platynosum*
**Trematodes**

- Immature flukes: Hemorrhage/necrosis during migration
  - May activate Clostridial spores if present
- Adults: Cause mechanical/chemical irritation/physical obstruction
  - Fibrosing cholangitis (pipestem liver) - *F. hepatica*
  - Parenchymal cysts and pigment - *F. magna*
Protozoa

Histomoniasis

“Black head”

*Histomonas meleagridis*

- Turkeys > Chickens
- Typhlitis
- Target-like areas of Hepatic necrosis
- Transmitted in the ova of *Heterakis gallinarum*
** Protozoa **

** Hepatic Coccidiosis **

*Eimeria stiedae*

- Disease of rabbits
- Coccidia live in biliary epithelial cells
- Proliferative cholangitis

www.askjpc.org/wsc/wsc/images/2008/080403-1
Liver is the most common site of toxic injury because:

- Ingested toxins $\rightarrow$ GIT $\rightarrow$ Liver
- Biotransformation of endogenous / exogenous substances for excretion
  - Bioactivation $\rightarrow$ more toxic
- Predictable or idiosyncratic
- Common Lesions:
  - **Acute**: Hydropic degeneration, lipidosis & necrosis, often **centrilobular**
  - **Chronic**: Fibrosis, biliary hyperplasia and nodular regeneration (= cirrhosis)
Classification of hepatotoxic liver injury

Biotransformation (most common)
- Cytochrome p450 system (in centrilobular area)
- Phase I: Bioactivation – reactive intermediates
- Phase II: Conjugation
- Phase III: Excretion (via bile)

Hepatic injury:
- Stimulation of autoimmunity
- Stimulation of apoptosis
- Disruption of calcium homeostasis
- Canaliculal injury causing cholestasis
- Mitochondrial injury

Hepatoxic Agents
- Toxic plants
- Mycotoxins
- Cyanobacteria
- Chemicals
- Therapeutic agents
• Pyrrolizidine Alkaloid Poisoning
• Alsike Clover
Pyrrolizidine Alkaloid Poisoning

- Occur worldwide
- Pigs > cattle > horses > goats and sheep
- Alkaloids \( \rightarrow \) cytochrome p450 system \( \rightarrow \) Toxic pyrrolic esters
  - Alkylating agents – react with nuclear and cytosolic proteins and nucleic acid: antimitotic
  - Prevent cell division but not DNA synthesis*
- Toxic compound in milk \( \rightarrow \) transferred to neonates
- Acute
- Chronic*

Senecio vulgaris (www.cals.ncsu.edu/plantbiology)

- Common genera:
  - *Senecio*, *Crotalaria*, *Heliotropium*, etc
Pyrrolizidine Alkaloid Poisoning

**Lesions**

**Acute:** (rare)
- Centrilobular necrosis

**Chronic (common)**

**Gross**
- Small firm finely nodular liver

**Histology**
- Megalocytosis (antimitotic effect)
- Fibrosis
- Biliary Hyperplasia
- Minimal nodular hepatocyte regeneration
Horses
  - **Chronic** liver disease
  - Photosensitization (2º)

Histo
  - **Portal hepatitis and fibrosis**
  - Biliary hyperplasia

Toxic principle unknown
  - Possibly a mycotoxin
    - “Sooty blotch”
• Aflatoxins
• Phomopsin
• Poisonous mushrooms
**Aflatoxins**

- 4 major aflatoxins: B1, B2, G1, G2
  - Aflatoxin B1*

**Occur in mouldy feed**
- Corn, peanuts, cottonseed
  - Pig, poultry/ducks, calves
- Commercial dog food
  - Dogs

**Most common in stored feed when temperatures are warm and humid**
- Bioactivated (cytochrome p450) in liver
  - *Toxic intermediates bind to DNA, RNA, protein*
- Toxic and Carcinogenic

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**Aspergillus flavus & A. parasiticus**

- Cornell Veterinary Medicine
Acute intoxication
• Dogs
• Centrilobular to massive necrosis, hemorrhage and lipidosis

TOXIN INDUCED LIVER DISEASE - MYCOTOXINS

Diagnosis: Submit food / stomach content / vomit for aflatoxin testing
Chronic intoxication
- Pigs, horses > cattle
- Lipidosis
- Fibrosis
- Biliary hyperplasia
- Mild megalocytosis

Phomopsin

**Diaporthe toxica** (*Phomopsis leptostromiformis*)

- Grows on lupins
- Chronic damage in cattle, sheep, and horses:
  - Small livers, finely nodular
  - Mitotic abnormalities and fibrosis
  - Photosensitization
Poisonous Mushrooms

- *Amanita phalloides* (Death Cap)
  - Produce toxic cyclopeptides:
    - *Amatoxin*
      - *Inhibits of RNA polymerase II function*
    - One mushroom is sufficient to kill
  - Acute damage:
    - Shrunken hemorrhagic liver
    - Centrilobular to massive lipidosis, necrosis and hemorrhage

Phase I – latent: 6-12 hrs
Phase II – GI signs: 6-24 hrs
Phase III – false recovery: 12 – 24 hrs
Phase IV – hepatic failure: 36-48 hrs

Diagnosis: Test for α-amanitin in serum, urine, gastric content, liver
Cyanobacteria – more like bacteria than fungi
- Grows as blooms on lakes and ponds
- Late summer or early fall
- **Microcystin** (pre-formed toxin)
  - *Inhibits protein phosphatase and causes cytoskeletal damage and cell death*
- Livestock, dogs, and cats
- Signs develop rapidly
  - Diarrhea, Prostration and Death

**Microcystis**
- **Anabaena**
- **Aphanizomenon**
- **Nodularia**
Lesions
- Acute hemorrhagic gastro-enteritis
- Red swollen liver:
  - Centrilobular to massive necrosis
  - Often die within a few hours
- Chronic liver disease in survivors

Diagnosis: Test gastrointestinal content /vomit or liver for Microcystin
• Xylitol
• White Phosphorus
• Metals
  – Iron
    • Iron dextran in pigs
    • Ferrous fumarate in foals
  – Copper (already covered)

TOXIN INDUCED LIVER DISEASE – HEPATOXIC CHEMICALS

- Vomiting
- Weakness
- Incoordination
- Tremors
- Depression or lethargy
- Seizures / Coma

Xylitol
- Artificial sweetener
- Acute toxicity in dogs – 0.5 mg/kg
- Hyperinsulinemia and marked hypoglycemia
- Centrilobular to massive hepatic necrosis
• Some are predictable
  – Acetaminophen – cats (↓ glucuronyltransferase activity)
• Idiosyncratic reactions – rare individuals affected
  – Usually centrilobular hepatocytes; often via unknown mechanisms
  – Species and individual variation
    • Trimethoprim-sulfonamide - Doberman pinschers
    • Carprofen - Labrador retrievers
    • Anticonvulsants (primidone, phenytoin and phenobarbital) → end stage liver in some dogs
    • Diazepam – acute hepatic failure in some cats
Questions?