Liver Disease in Horses

Kara Lascola DVM, MS, DACVIM
Auburn University

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Hepatic Disease in Horses

- Common, progression to liver failure is rare
- **~60-70% of liver must be affected for function to be impaired**
  - ***Hepatic disease can be present without hepatic failure***
- **Causes:**
  - Toxic
  - Infectious (bacterial, viral)
  - Metabolic/vascular
  - Neoplastic
  - Hypoxic

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The story of "Holly" and "Roxy"

ACUTE ONSET HEPATIC DISEASE & HEPATOENCEPHALOPATHY IN TWO MARES

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Holly: Signalment

- 5-year-old previously healthy QH mare
- 2-month-old foal by her side
- Presented for evaluation of acute lethargy and anorexia

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Holly: History

- Normal foaling two months ago
- Mare and foal administered tetanus toxoid and antitoxin at foaling and mare up-to-date on vaccinations
- Maintained on pasture with other horses
- All other horses and foal are healthy
- Owners believe mare has lost weight acutely over the previous week

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Holly: Initial Evaluation

- Recumbent and minimally responsive on trailer
- HR 20 BPM
- Mucous membranes hyperemic with prolonged CRT
- Poor jugular fill
- **Venous blood gas:** ***Glucose 19 mg/dL***
  lactate 8.3 mmol/L
  pH 7.33 HCO_3 15 mmol/L
  iCa^{++} 1.2 mmol/L
  PCV 52%

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Holly: Immediate therapy

- 1L Hypertonic saline; LRS with 2.5% dextrose and calcium supplementation
- HR 60, RR 20, T 102.3
- Mare stood with assistance on trailer
- Menace response absent & PLRs present bilaterally
- The mare appeared mildly ataxic and very depressed but was able to exit the trailer
- CBC & chemistry submitted

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Holly Additional Diagnostics

- **CBC w/ Fibrinogen**
  - Hypofibrinogenemia (91 mg/dL); neutrophilic leukocytosis (21.9 X 10^3)
- **Serum Biochemistry**
  - **GGT** 145 U/L (4-20); **GLDH** 47.7 (1-5); **Tbili** 24.3 (0.5-2.3);
  - AST 2394 (150-294); Alk Phos 1027 (41-137)
- **Abdominal Ultrasound**
  - Hepatomegaly, decreased echogenicity
- **Ammonia**
  - 274 (15-45)
- **Serum bile acids**
  - 111.4 (0-20)
- **PT & PTT**
  - 25 (8-15); 56.7 (33-47)

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Holly Additional Therapy

- Anti-inflammatory therapy: flunixin meglumine
- Maintenance intravenous fluid therapy with electrolyte supplementation, dextrose and antioxidants (thiamine and vitamin C)
- Lactulose 120ml PO every 6 hours for hyperammonemia

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Roxy: Signalment

- 5-year-old previously healthy QH mare
- 2-month-old foal by her side
- Presented for evaluation of acute lethargy, anorexia, and ataxia of 48 hours duration

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Roxy: History

- Normal foaling two months ago
- Mare and foal administered tetanus toxoid and antitoxin at foaling and mare up-to-date on vaccinations
- Mare has previously been healthy

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Roxy: evaluation prior to referral

- Physical Examination:
  - Icterus
  - Ataxia
  - Pyrexia (102.3F)
- Biochemistry:
  - GGT 157 U/L;
  - TBIL 15.2 mg/dL;
  - ALK Phos 453 U/L

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Roxy: Initial evaluation

- HR 60; RR 24
- Mucous membranes: icteric/dark red; CRT >3 sec; prolonged jugular fill time; petechia
- Marked ataxia, head pressing and compulsive circling
- Appeared nonvisual; + PLR & menace bilaterally
- Abrasions, lacerations and diffuse edema over face and muzzle

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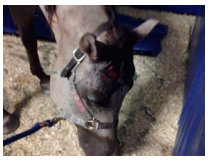
Roxy Initial Evaluation

- **Venous Blood Gas:**
  - **pH** 7.298
  - **LAC** 18.1 mmol/L
  - **HCO_3** 15 mmol/L
  - ***iCa^{++} 0.9 mmol/L***
  - **Mg^{++}** 1.26 mmol/L
- **PCV** 55% and **TP** 7.6 g/dL



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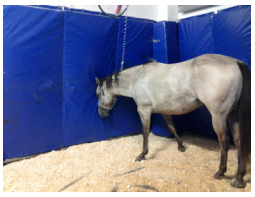
Roxy: Treatment

- Hypertonic saline
- LRS: dextrose, CMPK, Vit C, thiamine
- TMS & lactulose via small bore NGT

Over next 18 hours mare's condition worsened with episodes of unpredictable aggression



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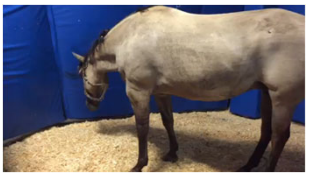

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- Clinical Signs
- Diagnostic Testing:
  - Biochemical testing: liver specific enzymes, tests of liver function, nonspecific hematological abnormalities
- Histopathology

RECOGNIZING AND DIAGNOSING HEPATIC DISEASE

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Indicators of hepatic disease

- Variable and often non-specific
- Depend upon: duration; type (hepatocellular, biliary) and extent of hepatic damage; specific cause
- Holly & Roxy
  - Clinical signs:
    - CNS (blindness, circling, mentation, ataxia); icterus; pyrexia; anorexia; petechia
  - Biochemical abnormalities
    - Increased specific (GLDH, GGT) and nonspecific (AST, ALP) liver enzymes
    - Altered liver function (bile acids, ammonia, bilirubin)
    - Other: coagulopathy, hypoproteinemia, hyperlactatemia, hypoglycemia

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Clinical Signs of Hepatic Insufficiency

- **Common**
  - *Icterus*
  - Weight Loss*
  - Anorexia
  - Colic
  - *Pyrexia*

- **Less Common**
  - *Hepatic encephalopathy**
  - Photosensitization *

- **Uncommon**
  - Epistaxis (coagulopathy)
  - Ascites, edema
  - Diarrhea

**more common chronic*
***more common acute*

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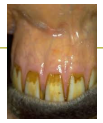
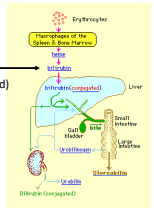
Icterus



- **Hyperbilirubinemia** with deposition of pigment in tissues
- *Total serum bilirubin = **Indirect** (unconjugated) > **Direct** (conjugated)*
  - DIRECT and INDIRECT both increased with hepatic disease
  - DIRECT more specific
    - Biliary outflow obstruction: direct bilirubin > 30% of total bilirubin

Increases
Liver disease
Hemolysis
GI disease
Anorexia

Indirect (unconjugated)



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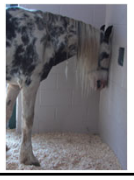
Hepatic Encephalopathy

- Abnormal mentation & hepatic disease
- Clinical signs - often progressive
  - Depression, yawning, behavior changes
  - Proprioceptive deficits, ataxia
  - Head-pressing, circling/pacing, central blindness
  - Episodes of aggression and/or somnolence
- Presumptive diagnosis:
  - Neurologic signs of cerebral dysfunction
  - Clinical findings of hepatic disease
  - Increased serum ammonia



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Hepatic Encephalopathy

- Severity correlates with degree of hepatocellular damage
- Exact pathophysiology is complex and elusive
  - ***Characteristically associated with hyperammonemia (CSF, blood)***
    - Gut-derived neurotoxin (NH_3)
  - Other contributors:
    - Additional neurotoxins, cerebral and systemic inflammation, cerebral vascular dysfunction, neuroendocrine abnormalities
- Alzheimer Type II astrocytes may be identified in brain

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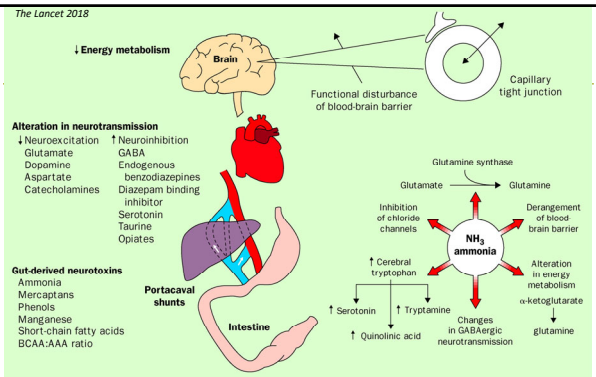

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Diagnosis of hepatic disease: biochemical testing

- **Liver specific enzymes**
  - Sorbitol dehydrogenase (SDH), Glutamate dehydrogenase (GLDH); Gamma-glutamyl transferase (GGT)
- **Nonspecific indicators of liver disease**
  - Alkaline phosphatase (ALP), aspartate aminotransferase (AST), lactate dehydrogenase (LDH)
  - Plasma proteins, metabolic indicators
- **Tests of liver function**
  - Bile acids, bilirubin (direct and indirect), ammonia, coagulation tests

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Liver Specific Enzymes

- Glutamate dehydrogenase (GLDH):
  - Hepatocellular (mitochondrial); $T_{1/2}$ ~14h
- Sorbitol dehydrogenase (SDH)
  - Hepatocellular (cytosolic); $T_{1/2}$ <12h
- Gamma-glutamyl transferase (GGT):
  - Biliary epithelium; $T_{1/2}$ ~3D
    - Cholangiohepatitis; biliary disease

Severe and/or long-standing liver disease may result in a similar increases in both hepatocellular and biliary enzymes

magnitude of increase in enzymes may not correspond to the functional status of the liver or with prognosis

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Diagnosis: tests of liver function

Bile Acids (most common)
Indicator of functional reserve of liver
Excellent screen of liver failure (> 20 µmol/L)
Not specific for type of disease
Better indicator of prognosis with chronic disease

Bilirubin (especially Direct)
Magnitude of increase corresponds to failure
Indirect – hepatocellular
Direct – biliary disease (>25% total)

Ammonia
Neurotoxic by-product of metabolism of nitrogen containing compounds (urea cycle)
Inconsistently increased with liver disease
Increased also with GI disease

Coagulation (Clotting) Factors
Increased PT and APTT
Decreased Factor 7 (+/- other factors)
Clinical bleeding uncommon

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Diagnosis: nonspecific laboratory abnormalities

Enzymes
- Aspartate aminotransferase (AST):
  - Hepatocellular damage; half-life 7d
- Alkaline phosphatase (ALP):
  - Biliary disease ; half-life 3d
- Lactate dehydrogenase (LDH):
  - Isoenzyme 5 – hepatocellular disease

Protein
- Hypoalbuminemia:
  - Severe/chronic disease
- Hyperglobulinemia:
  - Liver failure
- Fibrinogen:
  - Variable; decreased in liver failure

Metabolic
- Hypoglycemia in liver failure
  - Impaired gluconeogenesis
- Hypertriglyceridemia is nonspecific

Hyperlactatemia
- Liver failure
  - Reduced clearance, increased production

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Most useful diagnostics for liver disease

- Laboratory
  - SDH (or GLDH)
  - GGT
  - Bile acids
  - Total and direct bilirubin
- Liver US and biopsy
- ***Prognosis for liver disease is best determined by:***
  - ***(1) Persistent abnormalities in tests of liver function, (2) etiology, (3) extent of fibrosis, and (4) hepatic encephalopathy***


Journal of Equine Veterinary Science

Bile Acids, Direct Bilirubin and Gamma-glutamyltransferase as Prognostic Indicators for Horses with Liver Disease in the Eastern United States: 82 Cases (1997-2019)

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Systemic disease and hepatic enzymes

- Inflammation, vascular, hypoxic, toxic insults from non-hepatic primary diseases
- Intestinal disorders
  - E.g. LC displacement, GGT, direct bilirubin
  - E.g. reduced prognosis with increased bile acids
- Maladjustment to training
  - Thoroughbred racehorses and GGT

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Outcome: Holly & Roxy

- Rapid clinical deterioration:
  - Euthanized within 18-24 hours
- Necropsy Liver:
  - severe to massive hepatocellular degeneration and necrosis
  - Hemorrhage, stromal collapse & fibroplasia
  - Gross and microscopic findings consistent with **serum hepatitis (Theiler's disease)** → **Tetanus antitoxin**
- Necropsy Brain (gray matter):
  - Alzheimer Type II astrocytosis (hepatoencephalopathy)

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Serum Hepatitis

- 1918: Africa Horse Sickness vaccine
  - Theiler's Disease
- Epidemiology
  - Administration of biologic product of equine origin
    - ***Tetanus antitoxin*** (post 1960's), botulism antitoxin, pregnant mare serum, *Strep equi* antiserum
    - Plasma for colloid support (Aleman 2005)
    - Allogenic stem cells
  - Non-biologic cases
    - In-contact (infectious)
    - Isolated case clusters
- Cause elusive historically

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Serum Hepatitis – Theiler's Disease

- Clinical signs observed 4-10 weeks post exposure:
  - Acute onset, rapidly progressive, fulminant liver failure
  - Lethargy, anorexia, icterus, fever, encephalopathy
  - Marked increase in liver enzymes & B.A., hypoglycemia, hemoconcentration
- Mortality 50-90% in clinically affected horses
  - Morbidity in outbreak < 10%
  - ***Subclinical cases only increased liver enzymes***
- Diagnosis
  - Histopathology: lymphocytic hepatitis, severe centrilobular necrosis, hepatocyte loss and damage
  - Recently: antemortem hepatic viral testing

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Journal of Veterinary Internal Medicine ACVIM

STANDARD ARTICLE

Viral testing of 18 consecutive cases of equine serum hepatitis: A prospective study (2014-2018)

Joy E. Tomlinson[1] | Amit Kapoor[2] | Arvind Kumar[2] | Bud C. Tennant[3] | 2019

- 18 cases: 12 TAT, 3 plasma, 3 allogenic stem cells
- Equine Parvovirus EqPV-H
  - serum and/or liver tissue (10/10 TAT)
- Other viruses identified but inconclusive:
  - Equine Hepacivirus (EqHV); Equine Pegivirus 1 (EqPgV1), Theiler's Disease Associated Virus (TDAV; EqPV2),
- Roxy & Holly:
  - Serum & liver positive
  - TAT from same lot EqPV-H positive

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Equine Parvovirus Hepatitis (EqPV-H)

- Hepatotropic DNA virus
  - Consistently identified - experimental & biologic exposure, outbreaks
- Unknown why causes disease – possible immune response to virus
  - Increased viremia associated with acute disease
  - Most infections subclinical
- Seroprevalence 15-30% (multiple countries)
  - >60% seroprevalence during outbreaks
- Spread
  - Biologics: virus resistant to many preservatives
  - Insect spread proposed in outbreaks

EqPV-H and EqHV PCR testing through Cornell Animal Health Diagnostic Center

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Other Viruses

- Equine Hepacivirus (EqHV)
  - Hepatotropic, RNA virus *very* closely related to Hepatitis C virus
    - **Peak viremia:** mild/transient increase in hepatic enzymes, lymphocytic portal inflammation with mild & diffuse hepatocyte necrosis
      - Viral clearance approximately 6 months post viremia
  - USA: 2-7% infection rate & 30% seropositivity in adult horses
- Equine Pegivirus 1 (EqPV1) and Equine Pegivirus 2 (EqPV2)
  - RNA viruses, NO hepatotropism, NO liver disease
  - EqPV1: relatively common nonclinical infection in horses
  - EqPV2: Uncommon; formerly Theiler's Disease Associated Virus (TDAV)

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Hepatic Disease in Horses

- **Causes:**
  - Toxic
  - Infectious
  - Metabolic/vascular
  - Neoplastic
  - Hypoxic

→ **HEPATITIS (acute or chronic)**
Primary viral
Ascending bacterial
Toxicosis
Other: idiopathic, EIA, mycotoxin, fungal

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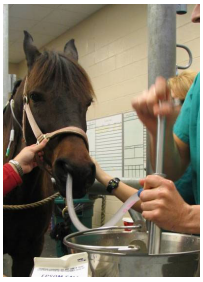
Ascending Bacterial Hepatitis - Cholangiohepatitis

- Cause
  - Primary gastrointestinal disease
    - duodenitis, colonic displacement, Ileus
- Pathology
  - Portal tract and bile duct inflammation
- Clinical signs
  - Fever, colic, icterus, increased GGT, bilirubin
- Treatment
  - May resolve if correct underlying cause
  - Antimicrobials, anti-inflammatory



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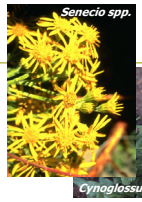
Toxicosis Associated Hepatitis

- **Pyrrolizidine alkaloid-containing plants**
  - Potent hepatotoxins
  - Chronic exposure (4 weeks - 6 months)
  - Hepatic necrosis, megalocytosis, biliary hyperplasia, portal fibrosis
- Other toxin sources
  - Alsike clover
  - Panicum grasses



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Less Common Causes of Hepatitis

- Mycotoxicosis
  - Fumonisin
- Fungal
- EIA
- Idiopathic

JAVMA AVMA

A seasonal idiopathic hepatitis syndrome in horses presented to a Midwestern veterinary teaching hospital

Sandra D. Taylor, DVM, PhD[1*]; Janice E. Kritchevsky, VMD, MS[2]; Patrick Huang, DVM[2]; Carla Olave, DVM, PhD[2]; Sarah J. Waxman, DVM, MS[2]; Margaret A. Miller, DVM, PhD[2]

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