22 – Acute Hepatitis

Speaker: David Thomas, MD, MPH

2020 INFECTIOUS DISEASE BOARD REVIEW

Acute Hepatitis

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Acute Hepatitis

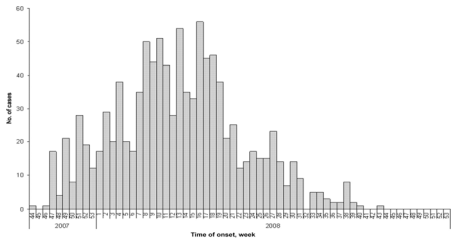
- 42 year old female has malaise and RUQ pain; she just returned from 6 month stay at an IDP camp in north Uganda. She endorses tick and other 'bug' bites and swam in the Nile. 1st HAV vaccine 2 days before departure. Prior HBV vaccine series.
- Exam shows no fever, vitals are normal. RUQ tender. Mild icteric. ALT 1245 IU/ml; TB 3.2 mg/dl; WBC 3.2k nl differential.

Question #1

Which test result is most likely positive?

A. Ebola PCR
B. IgM anti-HEV
C. IgM anti-HAV
D. Schistosomiasis "liver" antigen
E. 16S RNA for Rickettsial organism

1. There are HEV outbreaks, eg. North-Ugandan IDP Camp



Teshale CID 2010

2. Vaccination works vs immune globulin to prevent hepatitis A *even after* exposure

End Points	Per-Protocol Population		Modified Intention-to-Treat Population†	
	Vaccine Group (N=568)	Immune Globulin Group (N=522)	Vaccine Group (N=740)	Immune Globulin Group (N=674)
	number (percent)			
Clinical				
Primary				
Any symptom plus IgM-positive and ALT ≥ twice ULN	25 (4.4)	17 (3.3)	26 (3.5)	18 (2.7)
Secondary				
Any symptom plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR‡	29 (5.1)	19 (3.6)	30 (4.1)	20 (3.0)
Jaundice plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR	18 (3.2)	12 (2.3)	19 (2.6)	12 (1.8)

Victor NEJM 2007

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3. Boards aren't in alphabetical order

Hepatitis E: Key Epidemiologic Points

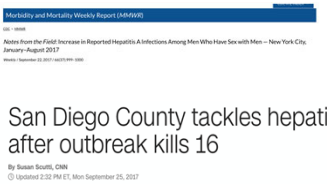
- –Outbreaks – contaminated water in Asia/Africa
- –Sporadic - undercooked meat (BOAR, deer, etc)
- –Overseas travel typical
- –USA: endemic rare, genotype 3, IgG serology positive far more than can be explained by cases - can be hard to interpret

Hepatitis E: Key Clinical Points

- –Diagnosis: RNA PCR; IgM anti-HEV
- –Fatalities in pregnant women
- –Can be chronic in transplant (rarely in HIV)
- –GBS and neurologic manifestations (vs other hep viruses)
- –Pancreatitis

Hepatitis A: Key Epidemiologic Points

- There are outbreaks all over the world now: <u>people</u>


Morbidity and Mortality Weekly Report (*MMWR*)

Notes from the Field: Increase in Reported Hepatitis A Infections Among Men Who Have Sex with Men — New York City, January–August 2017

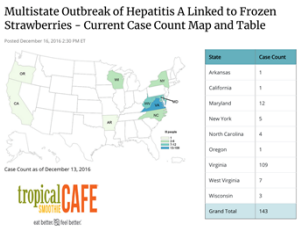
San Diego County tackles hepatitis A after outbreak kills 16

By Susan Scutti, CNN

Updated 2:32 PM ET, Mon September 25, 2017

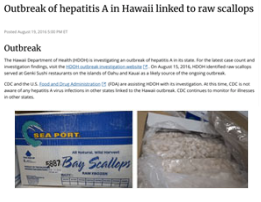
Hepatitis A: Key Epidemiologic Points

- There are outbreaks all over the world now: <u>places/products</u>


Multistate Outbreak of Hepatitis A Linked to Frozen Strawberries – Current Case Count Map and Table

Case Count as of December 13, 2016

State	Case Count
Arkansas	1
California	1
Maryland	12
New York	5
North Carolina	4
Oregon	1
Virginia	109
West Virginia	7
Wisconsin	3
Grand Total	143


Outbreak of hepatitis A in Hawaii linked to raw scallops

Outbreak

Hepatitis A: Key Clinical Points

- There are outbreaks all over the world now
- The most common cause of acute hepatitis in USA
- Clinical syndrome
  - –fulminant on HCV
  - –relapsing: symptoms/jaundice recur <12 mo

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Vaccination to Prevent Hepatitis A

- *Pre-exposure:* vaccinate
  - Inactivated vaccines USA (HAVRIX,VAQTA)(TWINRIX)
  - HCV or HBV positive persons/chronic liver disease/homeless/MSM/PWID/Travelers/HIV pos/adoptee exposure
  - All children receive hepatitis A vaccine at age 1 since 2006
- *Post-exposure:* vaccinate (and possibly IG)
  - Unless > 40 years or immunosuppressed then IG is 'preferred' (see slide 7)
  - Close exposure (sex or IDU partner) not casual (eg office worker)

Victor NEJM 2007; MMWR May 19, 2006 / 55(RR07) MMWR October 19, 2007 / 56(41);1080-1084

Case 2: Tired and jaundiced

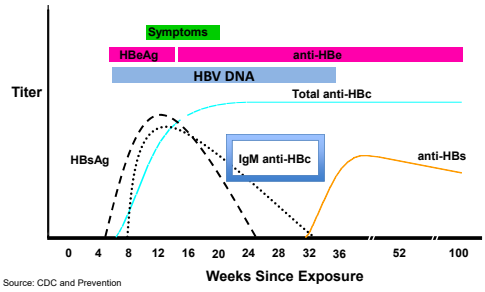
- 21 year old male presents with fatigue and dark urine. PMH neg; MSM, Hx STD, not very careful and at least 1 new ptr. No IDU. No rashes. No penile ulcer or discharge.
- Exam shows no fever, vitals are normal. Mild icteric. ALT 1945 IU/ml; AST 1239 IU/ml; TB 4.2 mg/dl; WBC 3.2k nl differential.
- Total HAV pos; HAV IgM neg; HCV RNA neg; IgM anti-HBc pos; HBsAg pos; RPR neg

Question #2

Which is easiest to justify medically?

A. Anti-HBs for partner
B. Repeat HBsAg in 1 month to see if cleared
C. Discuss TAF/FTC for HBV and HIV PREP
D. HIV testing
E. Repeat HCV RNA with test for HCV antibodies

1. Diagnose acute HBV infection with IgM anti-HBc



2. Recognize HIV can co-occur

- Shared risk factors
- HIV/HBV coinfection is common
- TDF/TAF active against HIV and HBV so status of both needed
- Test for other STD

3. No treatment is needed for acute HBV prevention by HBIG + vaccine

- HBsAg and anti-HBs screening of partners
- Vaccine and HBIG if susceptible

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Acute Viral Hepatitis B Key Points

- Most linked to sex, drugs, nosocomial
  - –Nosocomial (fingerstick devices, etc)
  - –Most transmissible (HBV>HCV>HIV)
- Clinical
  - –Acute immune complex disease
  - –Diagnose: IgM anti-core, HBsAg and HBV DNA
  - –New infection vs reactivation (can be IgM pos)

Acute Viral Hepatitis Delta Key Points

- HDV
  - –HBV coinfection
    - Fulminant with acute HBV
  - –HBV superinfection
    - Acute hepatitis in someone with chronic HBV
  - –Test for HDV RNA

Acute Viral Hepatitis C Key Points

- HCV
  - –IDU link (hepatitis in Appalachia)
  - –HIV pos MSM
  - –Acute RNA pos but AB neg or pos
  - –"most likely" in IDU or HIV pos MSM with neg HBsAg

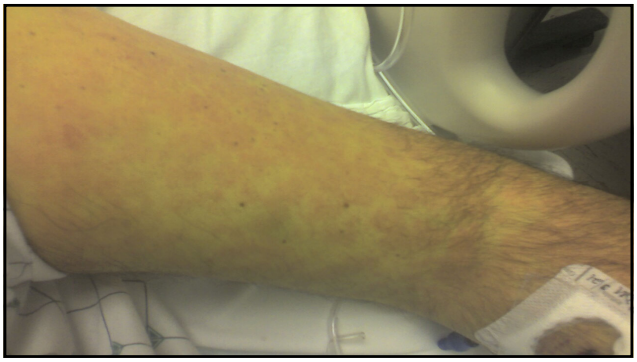
Cox CID 2005

Case 3. 48 year-old with jaundice

- 48 year old found minimally responsive and brought by friends to ED
  - – 1 week malaise, chills, headaches, leg pain and weakness
  - – Eats disposed "food"
- PMH – ETOH, IDU, kidney stones
- SH – homeless
- Baltimore for 20 years, previously Missouri
- FH, ROS non-contributory

Case 3. 48 year-old with jaundice, con't

- T 39.1; BP 80/50; P 110; 95% 4L; sleepy
- Icteric, non-injected, no murmurs or lymphadenopathy
- Diffuse red maculopapular rash
- WBC 98,000 (79 P, 4 B, 5 My/Meta); Hb 7.7; Plt 31,000
- Creatinine 3.9; UA 1+pro; Bicarb 8; INR 2.5; Tbili 41 (direct 31); ALT/AST 146/213
- HCV Ab pos, HIV Ab neg



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Case 3. 48 year old with jaundice

The cause of his illness is:

A. Acute hepatitis A
B. Babesia microti
C. Ehrlichia chaffeensis
D. Leptospira icterohaemorrhagiae
E. Zika

Leptospirosis

1. Exposure to fresh water (eg rafting in Hawaii or Costa Rico) OR rats (Baltimore)

Leptospirosis

2. Systemic findings (kidney, eyes, skin, muscle, lungs)

Liver and muscle: flu, adeno, EBV, HIV, malaria, Rickettsia/Ehrlichiosis, tularemia, TSS, coxsackie

Leptospirosis

3. Liver enzymes < bilirubin

Case 4. Hepatitis in the Coast Guard*

- 40 y/o coast guard presents with 1 fever and watery diarrhea
- Has B cell lymphoma; s/p CHOP x4 and 1 week post rituximab
- Lives on E Shore of MD, recent travel to NC with fresh water swimming; extensive travel before including SW USA (recurrent), S America (1 yr); daughter just returned from Ecuqador 1 wk before onset. Has dog, no ticks noted

**Courtesy J Rocco*

Pilot Case History, con't

- T 38.1, Vitals nl; no rash, neuro- WNL
- Hb 11 g/L, WBC 600 (ANC 320), Plt 35,000
- Creat 3.5; no rbc casts
- AST 600, ALT 320, Alk Phos nl, alb 2.6, TBR 2.2
- Ferritin: 180,000

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Hepatitis in a pilot

What agent caused this illness?

A. Leptospira icterohaemorrhagiae

B. Hepatitis A virus

C. EBV

D. Ehrlichia chaffeensis

E. Hepatitis G (GB virus C)

Hepatitis with bacterial infections

1. Think Rickettsia/Ehrlichia with exposure, low PMN, and especially low platelets

Hepatitis with bacterial infections

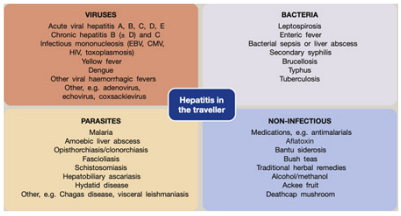
2. Coxiella burnetti and spirochetes (syphilis and lepto) also in ddx but tend to be cholestatic

Hepatitis with bacterial infections

3. Hepatitis F or G are WRONG answers

Hepatitis with travel to developing country

There is a broad differential



Jones Medicine 2017

Hepatitis with travel

Viral: remember dengue (below), Chickungunya, or Zika

Ref.	Patients	Raised AST	Raised ALT	AST > ALT	Hyper-bilirubinemia	> 10 fold rise (AST, ALT)
Kuo et al[37]	270	93.30%	82.20%	+	7.20%	11.1%, 7.4%
Souza et al[39]	1585	63.40%	45%	+	-	3.4%, 1.8%
Itha et al[41]	45	96%	96%	Equal	30%	-
Wong et al[40]	127	90.60%	71.70%	+ in 75.6%	13.4%	10.2%, 9.5%
Parkash et al[33]	699	95%	86%	+	-	15%
Trung et al[36]	644	97%	97%	+	1.7%	-
Lee et al[14]	690	86%	46%	-	-	1%
Karoli et al[34]	138	92%		+	48%	-
Saha et al[35]	1226				16.9%	

Samanta World J Cases 2015

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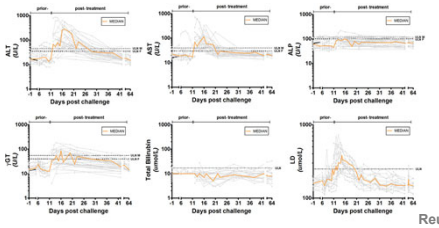
Hepatitis with travel

Malaria –



Acute human challenge studies

Reuling Ebio Med 2018

Case 5. Hepatitis in Pregnancy

- 24yo 33 wks gestation with nausea and vomiting and RUQ pain. Taking acetaminophen 1gm q 4-6; has dog and bird; recent visit to mom in NC.
- T 37.2; BP 158/110;2/6 SEM; RUQ tender; no rash.
- Plt 103K; Hct 26; WBC 6.6 10%L; PMN 82%; G 85; creat 0.6; ALT 225; AST 559; TB 1.4; CRP 15.8; PT WNL; fibrinogen NL.

Hepatitis in pregnancy

What is the best diagnosis?

A. HELLP
B. Acute fatty liver of pregnancy
C. HAV infection
D. HSV infection
E. HEV

Hepatitis in pregnancy

1. Rule out HSV

~50% have muco-cutaneous lesions

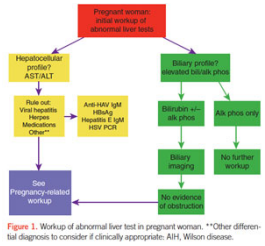


Figure 1. Workup of abnormal liver test in pregnant woman. **Other differential diagnosis to consider if clinically appropriate: AIH, Wilson disease.

ACOG 2016

Hepatitis in pregnancy

2. HELLP
   – HTN and can occur post partum
   – Fibrinogen high vs. sepsis and AFLP

3. AFLP – severe and low glucose, inc INR, low fibrinogen (Swansea criteria)

Case 6. Fulminant hepatitis

- 65 year old man with hx of jaundice. 2 weeks before finished amoxacillin/clavulanate acid for sinusitis. Hx of HTN on HCTZ and rosuvastatin. ETOH: 2 drinks per day.
- TB24; ALT 162 U/L; AST 97 U/L ALK P 235 U/L. IgM anti-HAV neg; IgM anti-HBc neg; HCV RNA neg. RUQ US neg.

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Question: Fulminant Hep

Which of the following is the most likely cause of hepatitis:

A. **toxicity from amox/clav**
B. **alcohol**
C. **porphyria flare**
D. **leptospirosis**
E. **statin**

Drug related liver toxicity

1. Amoxicillin/clavulanate is most common

- **Cholestatic or mixed**
- **Often AFTER stopping**
- **1/2500 Rx**
- **DRB1*1501**
- **clavulanate>amoxicillin**

Rank	Agent	Year of FDA Approval	No. (%)†	Major Phenotypes
1	Amoxicillin-clavulanate	1984	91 (10.1)	Cholestatic or mixed hepatitis
2	Isoniazid	1952	48 (5.3)	Acute hepatocellular hepatitis
3	Nitrofurantoin	1953	42 (4.7)	Acute or chronic hepatocellular hepatitis
4	TMP-SMZ	1973	31 (3.4)	Mixed hepatitis
5	Minocycline	1971	28 (3.1)	Acute or chronic hepatocellular hepatitis
6	Cefazolin	1973	20 (2.2)	Cholestatic hepatitis
7	Azithromycin	1991	18 (2.0)	Hepatocellular, mixed, or cholestatic hepatitis
8	Ciprofloxacin	1987	16 (1.8)	Hepatocellular, mixed, or cholestatic hepatitis
9	Levofloxacin	1996	13 (1.4)	Hepatocellular, mixed, or cholestatic hepatitis
10	Diclofenac	1988	12 (1.3)	Acute or chronic hepatocellular hepatitis
11	Phenytoin	1946	12 (1.3)	Hepatocellular or mixed hepatitis
12	Methyldopa	1962	11 (1.2)	Hepatocellular or mixed hepatitis
13	Azathioprine	1968	10 (1.1)	Cholestatic hepatitis

http://livertox.nlm.nih.gov; Hoofnagle NEJM 2019

Drug related liver toxicity

2. Watch for hypersensitivity

Dilantin, Abacavir, Nevirapine,

http://livertox.nlm.nih.gov

Acute hepatitis in HIV

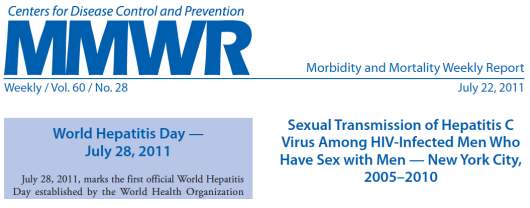
46 y/o HIV pos male, CD4+ lymphocyte 235/ml^3, HIV RNA undetect; HBsAg pos; no symptoms on TDF/FTC/RAL. Liver enzymes increased from ALT of 46 to 1041 IU/L. TB was 2.3. He has a long history of various ART regimens. He is sexually active with other men.

Acute hepatitis in HIV

Which of the following is the most likely cause of hepatitis:

A. **toxicity from the RAL**
B. **acute HCV infection**
C. **IRIS**
D. **resistant HBV**
E. **HDV**

Recognize acute HCV in HIV POS MSM



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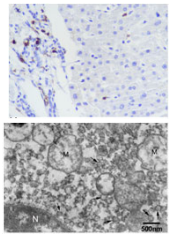
Hepatitis in 2020: SARS-CoV-2

Table 2. Laboratory and radiographic findings of patients with COVID-

	All patients (N = 788)
Leukocytes, $\times 10^9$/L	4.8 (3.8-6.0)
Neutrophils, $\times 10^9$/L	3.0 (2.2-4.0)
Lymphocytes $\times 10^9$/L	1.2 (0.9-1.6)
$\geq 0.8 \times 10^9$/L	654 (83.0)
$< 0.8 \times 10^9$/L	134 (17.0)
Platelets, $\times 10^9$/L	181 (147-221)
$\geq 100 \times 10^9$/L	761 (96.6)
$< 100 \times 10^9$/L	27 (3.4)
Hemoglobin, g/L	138.0 (127.0-151.0)
International normalized ratio	1.02 (0.97-1.09)
Albumin, g/L	41.4 (38.3-43.8)
Alanine aminotransferase, U/L	21.1 (15.0-33.0)
Aspartate aminotransferase, U/L	25.0 (19.6-33.0)

Hao Am J Gastro 2020



Wang J Hepatol 2020

Acute Hepatitis Summary

- Acute A: vaccine effective
- HEV: chronic in transplant and/or boar
- HIV: acute HCV in MSM
- Ehrlichial or rickettsial
- Find the lepto case (jaundice>hepatitis)

BREAK

Case 4. Hepatitis in a pilot

- 70 y/o pilot presents with 1 week of fever, diarrhea and sweats, then "collapse"
- Tooth extraction 1 month before, E. Shore of Maryland and extensive travel, chelation "treatment"
- T 38.1, 135/70, 85, 18, 97% on 2L; few small nodes, soft systolic M, petechial rash on legs, neuro- WNL

Pilot Case History, con't

- Hct 33%, WBC 1.4 K (81% P 10% L), Plt 15,000
- Creat 2.8
- AST 495, ALT 159, Alk Phos 47, alb 2.6, TBR 0.8
- CPK 8477
- CXR: infiltrate LLL

Hepatitis in a pilot

What agent caused this illness?

A. Leptospira icterohaemorrhagiae
B. Hepatitis A
C. EBV
D. Ehrlichia chaffeensis
E. Hepatitis G (GB virus C)