Trifecta!
Kentucky Leads in Viral Hepatitis A, B, & C

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Objectives

At the end of this presentation, participants will
1. Recognize Kentucky leads the nation in viral hepatitis A, B, & C, and how to diagnose these infections
2. Describe primary, secondary, and tertiary prevention of viral hepatitis
3. Name a treatment or therapy for hepatitis A, B, & C

Outline

1. Viral hepatitis epidemiology in the US and Kentucky
2. Viral hepatitis prevention
3. Review screening and diagnosis, and how to determine immunity/susceptibility
4. Review supportive care for HAV and treatment indications and options for HBV and HCV
5. Review vaccinations
6. Questions & Answers

Case Study: Tyler

Disclosures

Grant/Research Support: Intercept, Conatus, Gilead, AbbVie, Janssen, Merck
Speaker Bureaus: AbbVie, Gilead, Salix
Consultant: Dova
Advisory Boards: AbbVie, Gilead

My spouse, Matt Cave:
Grant/Research Support: Intercept, Conatus, Gilead, AbbVie
Speaker Bureaus: AbbVie, Gilead, Merck, Dova, Intercept
Advisory Boards: Gilead

There will be no off-label discussion in this presentation.

Pick Your Virus, Pick Your Places!
Meet Tyler

- 26 y/o WM from Perry County
- Medications: Albuterol, Montelukast, ibuprofen PRN
- PMH: Asthma
- SH: Smokes ½ PPD or Vapes daily; denies ETOH intake; 11th grade education; works in a fast food restaurant; has 2 children who live with their mother; reports frequent marijuana use, recreational IV heroin use
- Chief complaint: “My pee is brown and my stomach hurts.”
- ROS: + nausea, recent diarrhea, abd pain, fever 3 days ago, fatigue

Viral Hepatitis Epidemiology

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Viral Hepatitis Symptoms

Viral Hepatitis Risk Factors

Acute Chronic

- Nausea/Vomiting
- Abdominal Pain
- Fever/Chills
- Dark Urine
- Jaundice
- Fatigue
- Anorexia
- Joint Pain
- Grey stools
- Fatigue
- Extrahepatic Manifestations
- Usually asymptomatic until cirrhosis develops

Hepatitis A: Contact with food, objects, or drinks contaminated by the virus by an infected person

Hepatitis B: Unprotected sex, born to HBV-infected other, sharing contaminated equipment such as needles (this includes unregulated tattoos and body piercings, and vaccinations done at a time or in a place with poor infection control measures!), glucose monitors, toothbrushes, shaving razors

Hepatitis C: Same as above although sexual transmission is more predictable among MSM; receipt of blood products before 1992; Viet Nam Era military veterans, Baby Boomer (born 1945-1965)

Hepatitis A Virus (HAV) in the U.S.

Multiple Outbreaks in Recent Years

2013: Multistate outbreak: Pomegranate seeds from Turkey
2016: Multistate outbreak: frozen strawberries from Egypt
2016: Hawaii outbreak: raw scallops
2017-Present: Multistate outbreak r/t person-to-person contact, especially amongst those who use injection AND NON-INJECTION drugs, and homeless persons

Hepatitis B Virus (HBV) in the U.S.

- Prevalence: 850,000-2.2 million
- 2013 was the first year acute HBV infections increased after declining over the 20 previous years
- Rates of new HBV infection highest among people aged 30-49
- Most common risk factor for new infection: injecting drugs
- Rates of chronic HBV infection are highest in foreign-born individuals (Asia, Pacific Islands, Africa): they account for more than half of cases in the U.S.

CDC: https://www.cdc.gov/hepatitis/abc/index.htm

Hepatitis C Virus (HCV) in the U.S.

2010 HCV Antibody Prevalence


Let’s Look at Kentucky.

HAV Outbreak in Kentucky

Statewide HAV outbreak declared in November 2017.
As of 11/17/18:
Total cases reported: 2,769
Hospitalizations: 1,438
Deaths: 17 (<1%)
Boyd, Carter, Elliott, Magoffin, Martin, Menifee, Montgomery, Whitley, Johnson, Floyd, and Bath Counties have incidence rates <200 per 100,000 people
Outbreak linked to California and Utah HAV outbreaks through viral genotyping

HAV in Louisville

https://chfs.ky.gov/agencies/dph/dehp/idb/Pages/Hepatitis%20A%20Outbreak.aspx

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HBV in Appalachia

Incidence of acute HBV infection, by year—U.S. and KY, TN, and WV 2006-2013

Harris, A.M. et al., 2016

HBV Is Increasingly A Rural Problem

Incidence of acute HBV infection by urban/non-urban county of residence—KY, TN, & WV, 2006-2013

Harris, A.M. et al., 2016

New Cases of HBV in Kentucky:
We are #2 in the Nation.

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<tr>
<th>Year</th>
<th># Cases</th>
<th>Rate</th>
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<td>2016</td>
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WV Year | # Cases | Rate |
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<tr>
<td>2016</td>
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<td>14.6</td>
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CA Year | # Cases | Rate |
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<tr>
<td>2015</td>
<td>160</td>
<td>0.4</td>
</tr>
<tr>
<td>2016</td>
<td>115</td>
<td>0.3</td>
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Acute HCV in the Region

(Whalen, 2015)

Acute HCV in Kentucky

2017 Acute HCV Update: Infections are Increasing

Map provided by CDC (2016). Available at: https://www.cdc.gov/hepatitis/statistics/2016surveillance/index.htm#tabs-5-1

Acute HCV in the Region

Scourge in the Heartland

(Whalen, 2015)
From 2011-2014, Kentucky was #1 in Acute cases of HCV (Koneru, Nelson et al. 2016).

A 2013 study of rural Appalachian drug users showed the HCV antibody rate was as high as 54.6% (Havens, Lofwall et al., 2013).

Viral Hepatitis Prevention

Primary:
- Vaccinate
- Avoid contact with known ill persons
- Hand washing

Secondary:
- See a healthcare provider for diagnosis
- Stay home if you are ill; avoid sex until well
- Seek healthcare for severe symptoms

Secondary:
- Screening of blood products/organisms
- Syringe Exchange Programs
- Do not share toothbrushes, shaving razors
- Tattoos/piercings should only be placed in a professional setting by a licensed artist

Tertiary:
- Hepatology, Gastroenterology, or Infectious Disease Specialists can determine if/treatment is necessary

HCV Infections are Up in Kentucky

Changing HCV Epidemiology
Massachusetts 2002 v. 2009

Prevention

Primary: Avoid or prevent

Secondary: Screen for the disease and link to treatment early

Tertiary: Treat the disease; try to limit complications of advanced disease

HAV Prevention

Primary:
- Vaccinate
- Screening of blood products/organs
- Syringe Exchange Programs
- Do not share toothbrushes, shaving razors
- Tattoos/piercings should only be placed in a professional setting by a licensed artist

Secondary:
- Screening in pregnant women; treat during pregnancy if indicated
- Risk-based screening
- HBIG/vaccines for exposed infants

Tertiary:
- Hepatology, Gastroenterology, or Infectious Disease Specialists can determine if/treatment is necessary

HBV Prevention
HCV Prevention

Primary:
- Screening of blood products/organisms
- Syringe Exchange Programs
- Do not share toothbrushes, shaving razors
- Tattoos/piercings should only be placed in a professional setting by a licensed artist

Secondary:
- Screening in pregnant women: limiting exposure to maternal blood during birth
- Risk-based universal screening of all adults
- Early linkage-to-care for HCV infected individuals

Tertiary:
- Provide HCV Treatment (PCP, Addiction Centers, GI/Hepatology, Infectious Disease)
- Hepatology care for those with advanced liver disease


Viral Hepatitis Screening & Diagnosis

- Chief complaint: "My pee is brown and my stomach hurts."
- ROS: + nausea, recent diarrhea, abd pain, fever 3 days ago, fatigue

Review of his chart shows he is down 6 pounds from his last visit.

Labs ordered: CBC, CMP, Acute Hepatitis Panel

Case Study: Tyler

Acute Hepatitis Panel: What it Does

- Hepatitis A IgM or- Hepatitis A Ab Total
- Hepatitis B Surface Antigen Screen with reflex
- Hepatitis B Core Antibody IgM
- Hepatitis C Antibody

Acute Hepatitis Panel: Shortfalls

- If hepatitis A Total Ab used, then you do not know if IgG or IgM is positive
- Confusing when only hepatitis B Core Antibody is positive
- May miss acute hepatitis C infection (6-8 weeks after exposure needed to develop HCV antibody)

Remember: immunocompromised patients take longer to generate IgM antibodies

Solution? Draw HAV, HBV, or HCV viral load if there is strong suspicion of a specific exposure, and/or check HAV IgG, HBV Surface Antibody for evidence of immunity
Acute HAV Diagnosis

Keep it simple:
Symptoms of viral hepatitis, jaundice and/or elevated ALT or AST, HAV IgG +

Clinical Description
Acute hepatitis A is caused by ingestion of food or water contaminated with feces from an infected individual.

Laboratory Criteria for Diagnosis
HAV IgM + on acute phase serum or stool

Chronic HBV

Keep it simple: No symptoms or evidence of liver disease needed
HBV core IgM – with HBV sAg +, HBeAg +, or HBV DNA +

Clinical Description
Chronic hepatitis B is an infection of the liver lasting more than 6 months.

Laboratory Criteria for Diagnosis
HBV DNA +, HBeAg +, or anti-HBe + twice at least 6 months apart

HBV Status Assessment: Clearing Things Up

Interpretation HBV sAg HBV sAb HBV core IgM
HBV core IgG (or Total) HBeAg HBe Ab

Susceptible - - -
Immune from natural infection - + - -
Immune by vaccination - + - -
Chronic Infection + - - + +/- +/-

Check HBV DNA PCR (viral load) and HBeAg/Ab

Adapted from CDC.gov/hepatitis
Acute HCV

Keep it simple:
Symptoms of viral hepatitis, elevated ALT >200 and/or jaundice
HCV Ab+ and HCV RNA +

Chronic HCV

Keep it simple:
Asymptomatic
May have evidence of chronic liver disease HCV Ab+ and HCV RNA +

ALT levels are very high during the first few months after infection

The Natural History of Hepatitis C

No such thing, but:
• How does one recognize exposure versus infection?
• Cure after treatment?
• Re-infection?

Case Study: Tyler’s Lab Results
Clear evidence of acute viral hepatitis
HAV IgM+ → He has acute hepatitis A infection
HBV sAg+ → He has chronic hepatitis B infection because HBV core IgM was negative
What about hepatitis C infection?
Remember: diagnosis HCV requires both HCV Ab and HCV RNA.
Tyler’s HCV RNA: 5,490 IU/mL
Is it acute or chronic HCV???

- Infection is self-limiting (avg. 28 days, range 15-50 days)
- Supportive care for most cases
- AST/ALT may be >1000 with levels peaking about 4 weeks after exposure
- Hospitalization may be necessary to manage complications, dehydration, or liver failure
- Remember: VACCINATE household contacts

Adapted from CDC.gov/hepatitis
Check HBV DNA PCR (viral load) and HBe Ag/Ab
HBV Long-Term Needs

- Counsel on transmission prevention
- Hepatocellular carcinoma screening in:
  - All cirrhotics
  - High-risk pts: Asian or black men >40 y/o, Asian women >50 y/o
  - Children/adolescents with F3 or cirrhosis AND have a 1st degree family member with HCC

HCV: Moving Through the Treatment Pathway

- Screening
- Diagnosis
- Genotyping
- Fibrosis Assessment
- HCV Treatment Experience
- Treatment Readiness: Social, Financial, etc.
- Insurance Formulary
- Costs
- Drug-Drug Interactions
- Treatment Selection

HCV: Genotyping

- Invasive:
  - Liver Biopsy
- Non-invasive:
  - APRI, FIB4
  - Fibrosure/Fibrotest/Fibrospect
  - Vibration Controlled Transient Elastography (Fibroscan)
  - Liver Multiscan
  - MR Elastography
  - US Elastography

Fibrosis Assessment

HCV Treatment Experience

- Interferon/ribavirin
- Protease Inhibitors
  - First generation
  - Second generation
  - Third generation
- NS3 Inhibitor
- Resistance Associated Variants
- Resistance Associated Substitutions

Assessing social and financial concerns
- Planning and coordinating support
- Ensuring continuous insurance coverage (open enrollment, January 1 plan changes)
- Sobriety?
Insurance Formulary and Costs

- Commercial Coverage: all manufacturers offer $5/fill coupons
- Medicaid Coverage: $0-8
- Medicare Coverage: Subject to drug benefit deductible but grant programs are available. Most pay less than $10

Formularies change every 6-12 months
Some plans have parity with multiple preferred agents
Non-preferred agents are accessible when needed

Importance of Reviewing Potential Drug-Drug Interactions

Is the patient taking any drugs that could have a potential drug-drug interaction with a DAA?

<table>
<thead>
<tr>
<th>Antiarhythmic e.g. digoxin, amiodarone</th>
<th>PPI/acid reducing agents</th>
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<tbody>
<tr>
<td>Herbal supplements</td>
<td>HIV antivirals e.g. tenofovir, lamivudine/lovotenovir</td>
</tr>
<tr>
<td>Renally cleared drugs</td>
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Is a co-medication contraindicated or is a dose adjustment required?
Can plasma levels of co-medications be easily monitored to ensure they remain within the established therapeutic range?

Taking all HCV Elements Into Consideration...

- Virtually everyone is eligible for HCV treatment
- Treatment 8-12 weeks for most
- HIV or HBV co-infected patients can be cured of HCV
- 95% or higher chance for cure
- Primary Care Providers are treating
- Specialty Pharmacies help keep patients and providers on track

Modern HCV Treatments: Direct Acting Antivirals

<table>
<thead>
<tr>
<th>Direct-Acting Antiviral Agents</th>
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<tbody>
<tr>
<td>NS3/4A Inhibitors</td>
</tr>
<tr>
<td>Nucleotide</td>
</tr>
<tr>
<td>Daclatasvir</td>
</tr>
<tr>
<td>Elbasvir</td>
</tr>
<tr>
<td>Grazoprevir</td>
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<tr>
<td>Velpatasvir</td>
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Current HCV Treatments

As Recommended by AASLD Guidelines and Availability on Insurance Plan Formularies

- elbasvir/grazoprevir (Zepatier)
- glecaprevir/ribavir (Mavyret)
- ledipasvir/sofosbuvir (Harvoni)
- sofosbuvir/velpatasvir (Epclusa)
- sofosbuvir/velpatasvir/voxilaprevir (Vosevi)
Vaccines

HAV Vaccine

Indications: All children between 12 and 24 months age
Any adult wishing to be vaccinated
Members of high-risk populations
• 2 dose series
• Allergic reaction is rare
• AE’s: soreness at injection site, low-grade fever, h/a, fatigue
• Trade names: Havrix (Glaxo-Smith Kline), Vaqta (Merck)
• Availability: pre-filled syringe or single dose vial

Louisville: <83,000 HAV vaccines
Targeted vaccination strategy: homeless, people who inject drugs, food service employees, healthcare workers
HAV vaccines for all children was first included on the CDC Recommended Childhood Immunization Schedule in 2000.
Jefferson County Public Schools: HAV vaccines now a requirement

HAV Vaccine

HBV Vaccination for Children

• Indicated for all children under the age of 19 who have not yet been vaccinated
  • First dose given within 1st day of life
• Series of 3 vaccines
• Vaccine combined with HBiG in infants with vertical exposure
• CDC has recommended birth dose since 1991
• Immunity is not life-long!
  • Check titers after ~20 years

HAV Vaccine

HBV Vaccine Options for Adults

Having all doses of HBV vaccine confers immunity in >90% of adults and 95% of children
Heplisav B: 2 dose option indicated for ADULTS only, FDA approved in November 2017
Preventive vaccine will utilize multiple immunologic approaches
- Protective neutralizing antibody (nAb) is a key component
- High levels of nAb associated with increased viral clearance by host; low levels of nAb associated with chronic HCV infection
- Vaccine may cover gaps for those at high-risk of acquiring infection but limited access to treatment
- 4 phase 1 studies as of 2016; 3 animal models
- Do not expect an FDA-approved vaccine before 2026

References


