

Clinical Manifestations of Hepatitis A Infection



Brian J McMahon MD, Scientific and Clinical Director
Liver Disease and Hepatitis Program
Alaska Native Medical Center
Guest Researcher, AIP/CDC

Conflict of Interest

- Spouse owns 100 shares of GlaxoSmithKline stock in her Individual Retirement Fund (IRA)
 - GSK makes one brand of hepatitis A vaccine
- There will be no discussion of non FDA approved drugs or uses of approved drugs in my presentation

Outline of Talk

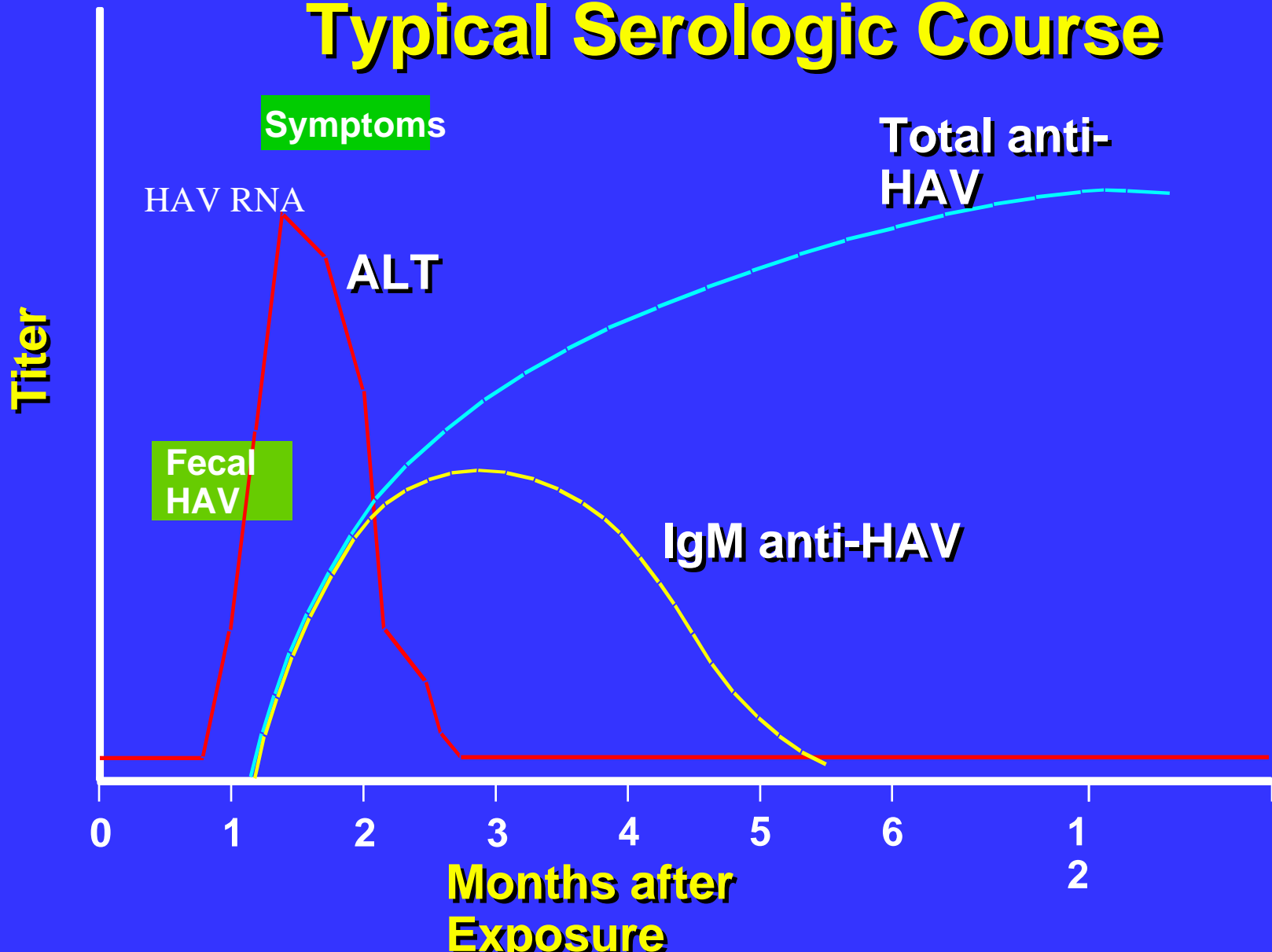
- Clinical spectrum of acute hepatitis A
- Clinical features of acute hepatitis A
- Fulminant hepatitis A
- Hospitalization from hepatitis A
- Hepatitis A in chronic liver disease
- Symptomatic Hepatitis A in emerging nations

Hepatitis A - Clinical Features

- Incubation period:
 - Average 30 days
 - Range: 15-50 days
- Range of symptomatic period:
 - Few days to 6 or more months
- Chronic Sequelae:
 - None

Hepatitis A Virus Infection

Typical Serologic Course



Hepatitis A Infectious Period

- Infectious period: In Sera
 - HAV RNA detected average 17 days before ALT peak (J Clin Virol 2004;29:254-9)
 - HAV RNA present up to 490 days post onset icterus at levels 1×10^3 - 1.25×10^4 HAV genome equivalents*

*JID 2000;182:12-7 and J Med Virol
2004;72:10-6

Hepatitis A Infectious Period

- Infectious period: HAV RNA in Stool
 - Neonates: HAV RNA found 4-5 months after identified as infected (JID 1991;164;476-82)
 - Adults: HAV RNA found from 3 to 89 days post onset icterus (Hepatology 1996;24:10-3)

Clinical Variants of Hepatitis A Infection

- Asymptomatic (anicteric) disease
 - Children under 6 years of age, > 90%
 - Children from 6-14 years old, 40-50%
- Symptomatic (icteric) disease
 - Adults and children over 14, 70-80%

Clinical Spectrum of Acute HAV Infection

- Inapparent: Anti-HAV IgM+ without any clinical illness or rise in aminotransferase levels
- Sub-clinical: No symptoms but rise in aminotransferase levels and anti-HAV IgM+
- Anicteric Clinical: Symptoms without jaundice but rise in aminotransferase levels plus anti-HAV IgM+
- Icteric Clinical: Jaundice and increased rise in aminotransferase levels

Symptoms in the Prodrome of Acute Symptomatic Hepatitis A

| Symptom | Frequency |
|----------------------------|-----------|
| Anorexia | 58%-98% |
| Malaise, fatigue | 48%-79% |
| Fever | 32%-75% |
| Headache | 17%-72% |
| Myalgia, arthralgia | 52%-69% |
| Upper Respiratory Symptoms | 0-20% |

Reported Frequency of Symptoms in Diagnosed Acute Symptomatic HAV

| Symptom | Frequency |
|---------------------|-----------|
| Dark Urine | 58%-96% |
| Anorexia | 41%-90% |
| Jaundice, Icterus | 41%-88% |
| Nausea, vomiting | 26%-87% |
| Malaise, fatigue | 48%-79% |
| Fever | 32%-75% |
| Abdominal pain | 37%-65% |
| Diarrhea | 17%-58% |
| Light colored stool | 24%-58% |

Liver Related Variants of Acute Hepatitis A

- Cholestatic Hepatitis A
 - Rising direct bilirubin, normal prothrombin time and falling ALT and marked pruritus
 - Benign: Responds to corticosteroids
- Relapsing Hepatitis A
 - One or more flares of aminotransferase elevation, rise in bilirubin and return of symptoms
 - Can recur for 12-18 months from initial onset
- Fulminant Hepatitis A

Non-Hepatic Complications of Acute Hepatitis A

- Incidence of complications unknown
- Types of complications:
 - Acute cholecystitis
 - Renal
 - Pancreatitis
 - Aplastic anemia
 - Neurological: Vasculitis, Guillain`Barrè syndrome, meningoencephalitis
 - Autoimmune hepatitis following acute HAV
 - Pregnancy: no increase risk to mother or fetus

Fulminant Hepatitis A in USA

- Leading type of viral hepatitis that leads to liver transplant
 - Occurred in 3.1% of patients hospitalized from 1998-2005 in US* Acute Liver Failure Study Group. (Hepatology 2006;44:1589-97)
 - 55% recovered spontaneously
 - 31% transplanted
 - 14% expired
- *decrease in proportion of cases from 5% to 0.8% during period

Fulminant HAV in Developing World

- Acute symptomatic HAV in children ≤ 15 years in Pakistan
 - 232/2735 (8.5%) admitted to hospital
 - 30/232 (13%) had fulminant hepatitis
 - 83% had encephalopathy; 48% grade 4 (coma)
 - 37% died

Pediatrics 2000;105:436-8

Treatment of Fulminant Hepatitis

- Supportive Care
- Liver Transplant
- Everything else is experimental and no evidenced-based data that any other treatment modality works

Age-specific Mortality Due to Hepatitis

A

| <u>Age group (years)</u> | <u>Case-Fatality (per 1000)</u> |
|------------------------------|-------------------------------------|
| <5 | 3.0 |
| 5-14 | 1.6 |
| 15-29 | 1.6 |
| 30-49 | 3.8 |
| >49 | 17.5 |
| Total | 4.1 |

Source: Viral Hepatitis Surveillance Program, 1983-1989

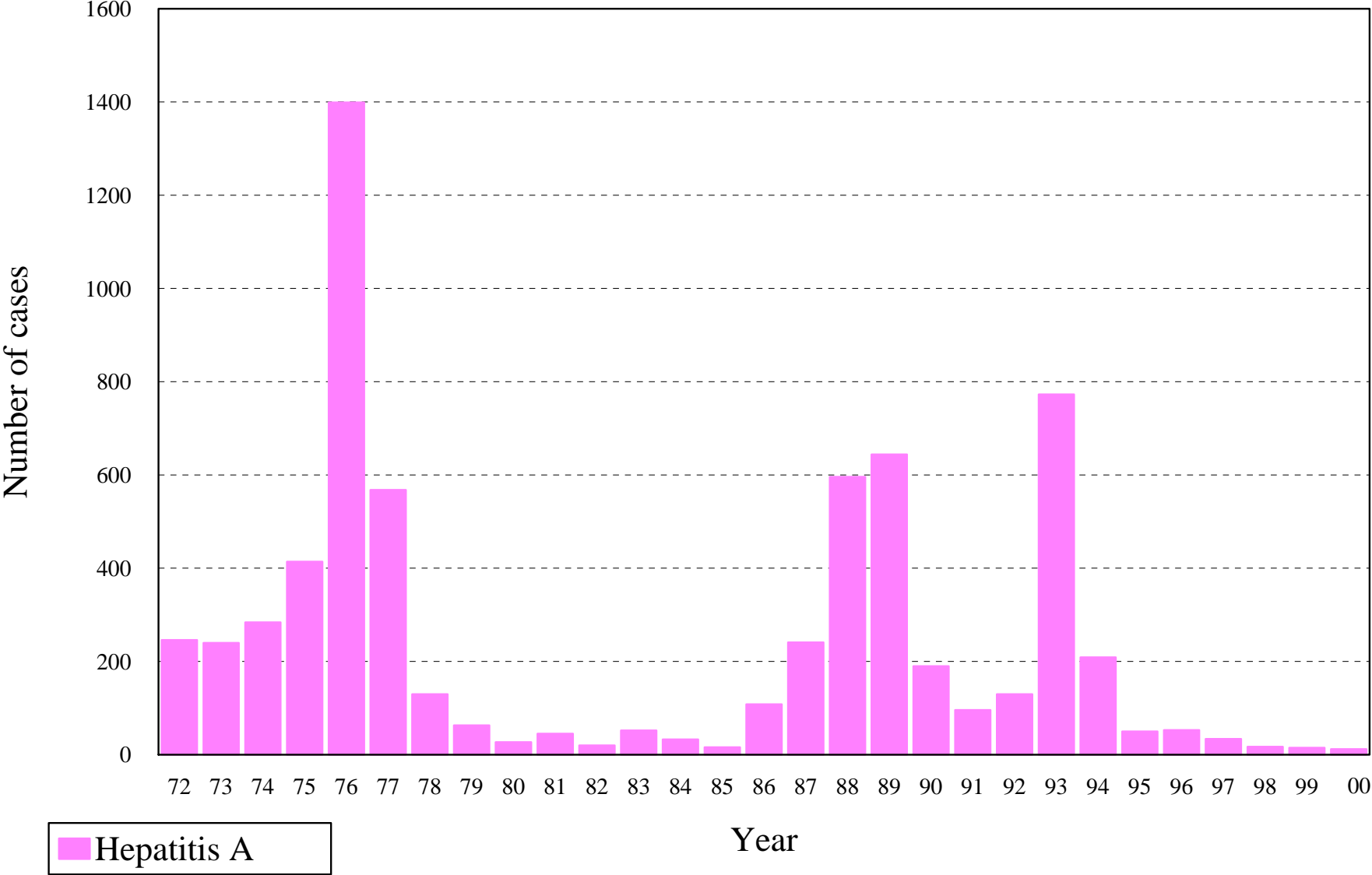
Factors that May Be Associated with Increased Risk of Hospitalization or Fulminant Hepatitis A

- Alcoholism
- Malnutrition
- Underlying chronic liver disease
 - Alcoholic liver disease
 - Hepatitis B
 - Hepatitis C
 - Cirrhosis of any etiology
- Acetaminophen use during prodrome

Burden of Disease for Hepatitis A: The EUROHEP.NET Survey

- Survey done 1997-2001 in 22 countries
- % cases hospitalized: range 0 to 100%
- Hospitalized cases/100,000: range 0 to 97.8/100,000
- Above values depend on a variety of circumstances such as country policy
- Deaths:
 - Number: Range 0 to 17
 - Mortality per 100,000: Range 0 to 0.26
 - Case fatality rate: Range 0 to 11.1 (all but one country < 1.0)

Figure 1: Reported Cases of Hepatitis A in the State of Alaska, 1957-2000



Hospitalizations Due to Hepatitis A: Alaska Outbreak Experience

- Hepatitis A outbreak 1992-1993
 - 443 icteric cases
 - 53 hospitalized (12%)*
 - Number of days hospitalized: 345 (mean 6.5 days)
 - 8 ICU days
 - Elevated Prothrombin time: 37/52 (71.2%)
 - >1.5 times upper limit normal: 25/52 (48.1%)
 - Encephalopathy: 11/52 (21%)

*Similar to ~15% in outbreak in Tennessee (Ann Intern Med 1998;128:111-4)

Possible Contributing Factors to Hospitalization for HAV and Costs in Alaska

- Acetaminophen use in acute hepatitis A
 - 15/39 (38.5%) took acetaminophen in therapeutic doses during prodrome*
- Alcohol use in acute hepatitis A
 - 16/35 (45.7%) had used alcohol preceding onset of acute hepatitis A
- Cost of hospitalization in 1994 dollars
 - \$436,959.92

*Two other studies found acetaminophen factor in fulminant HAV
Hepatology 2003;38:613-8 and Gastroenterol Clin Biol 2006;30:763-8

Hospitalization and Clinic Visit Rates Since Hepatitis A Vaccine

- Pre-vaccination era to 2004 in US
 - Hospitalizations due to hepatitis A declined by 68.5% (from 0.81 to 0.26 per 100,000 population, $P < 0.001$)
 - Ambulatory visits declined by 41.5% (from 12.9 to 7.5 per 100,000 population, $P < 0.001$)

Vaccine. 2007 May 4;25(18):3581-7

Hepatitis A in Chronic Liver Disease

- Previously studies showed a high a higher rate of death in HBsAg+ or chronic liver disease in patients with acute hepatitis A
- Recent studies: no evidence of increase risk of death (Dig Liver Dis 2003;35:404-8)
 - 25 deaths in acute hepatitis Italy 2000-2005.
 - No deaths acute HAV on HBV (n=309) or HCV (n=166)
 - Acute HAV cleared HBsAg if few cases (Clin Infect Dis 2006;43:1536-43)

Other Consequences of Acute Symptomatic Hepatitis A

- Loss of Work Time
 - Impact on economics of family and community
- School absenteeism:
 - May delay child's advancement to next grade

Hepatitis A in Emerging Nations

- Large outbreaks of HAV have occurred in Emerging Nations where safe water is available in urban but not rural areas due to cohort of children and young adults living in cities not infected early in life
 - Examples
 - Shanghai epidemic (292,301 cases) 1988 (JID 1991;164:852-9)
 - Kuwait in children <16 years, 2000-2002 (Med Princ Pract 2006;15:266-9)

Conclusions

- Hepatitis A is a significant cause of morbidity in developed and some emerging nations
 - Vaccination of children in US has decreased incidence of hospitalization and clinic visits
- Mortality due to hepatitis A is low but is the leading cause of liver transplant for acute viral hepatitis:
 - Rates of fulminant hepatitis A have decreased in US likely due to hepatitis A vaccine

Conclusions Continued

- More widespread use of hepatitis A vaccine would have a major impact on future hospitalization rates and rates of fulminant hepatitis due to HAV
 - In US vaccination of adults could eliminate hospitalizations and fulminant hepatitis due to hepatitis A
 - In emerging nations use of hepatitis A vaccine could decrease symptomatic and fulminant HAV