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Abstract:

The Hepatitis C (formerly NANB Hepatitis) epidemic started in the 1950’s and peaked in 2001.1 With identification of the Hepatitis C virus (HCV) in 1989 and development of effective antibody detection tests and institution of educational programs, the incidence of HCV infection has dropped precipitously.2,3 Recent, development of direct acting antiviral (DAA) agents (telaprevir and boceprevir) added to standard of care (SOC) pegylated interferon-alpha (PEG-IFN) and ribavirin regimens have provided a major advance in the effective treatment of the most common and difficult to treat form of HCV seen in the U.S., genotype 1.4 The next step in stamping out the epidemic of HCV is to identify the more that 2 million Americans that are unaware that they are infected with the HCV and initiate effective antiviral therapy, before this indolent and potentially lethal virus inflicts irreversible liver disease and death.5

Hepatitis C is a blood borne illness primarily associated with exposure to the hepatitis C virus (HCV) found in contaminated needles, bodily fluids, blood, blood products and/or donated organs.1 In 1965, the estimated annual incidence hepatitis C was very low, about 18 cases per 100,000 persons in the US.1,2 However, the practice of Intravenous Drug Abuse (IVDA), sharing of needles and promiscuous sexual practices of the 1960’s led to a silent epidemic of asymptomatic HCV.6 At the same time, medical advances made with the use of blood, blood products and organ transplant common place.7 Paid blood donation programs became a gateway for IVD abusers to secure money to perpetuate their addiction, while the unknowing public received countless units of blood and blood products infected with hepatitis C.8 A perfect storm was looming, comprised of a pool of unknowing and asymptomatic HCV infected blood donors, and physicians needing to provide blood and blood products for their patients. By the 1980’s, roughly 230,000 new hepatitis C infections were seen each year.5 Elimination of the practice of paid blood donation by Congress in 1978,9 the introduction of surrogate markers to screen blood donors for hepatitis C in 1990,10 and decreased IVDA are responsible for dramatic improvement in blood supply safety and a precipitous decline in the incidence of acute HCV infections, Figure 1.3,5

Michael Houghton and his team identified and characterized the hepatitis C virus in 1989.11 This key scientific discovery was closely followed by the development of multi-antigen serologic assays for the testing of the blood, blood products and organs.12 Use of these screening tests by blood banks has reduced today’s risk for HCV transmission to an estimated one in a million chance from a blood transfusion.12 Currently, 170 million persons worldwide and ~ 3.7 million in the United States are infected with hepatitis
C virus (HCV). Unfortunately, 75% of infected U.S. residents (~2.8 million) remain undiagnosed and 25% already have cirrhosis (~925,000). Only ~20% of acute hepatitis C infections are cleared spontaneously. Most of HCV infections become chronic, indolent, and asymptomatic disease. Data from observed HCV cases monitored over 20 years indicate that ~20-30% of infected persons will progress from fibrosis to cirrhosis and as many as 5% will die from HCV related disease, Figure 2.6,14

The sharp and steady increase in the prevalence of Chronic HCV since 1950, plateaued in 2001 is now rapidly declining due to blood screening practices and educational programs about IVDA and unsafe sexual practices, see Figure 3. Those persons infected during the peak years of HCV infection (1970-1990) comprises a cohort of roughly 1 million persons, most of whom (75%) are unaware of their HCV infection.5 This 1970-1990 HCV cohort is “frame-shifted,” 20-40 years from the time initial infection and just now beginning to manifest medical complications. In 2005, Grant, et al examined trends in health care costs related to HCV.15 Economic analysis showed HCV infection was already associated with profound increases in health care costs related to the number and complexity of hospital days, medications, physician visits and liver transplant.15,16

The 20 to 40 year delay in the indolent development of complications from hepatitis C is dramatically and graphically demonstrated by the evolution of HCV related cirrhosis, see Figure 3. In 1989, cirrhosis accounted for about 5% of diagnosed and undiagnosed cases of HCV and that percentage has roughly doubled each decade since then [1989 (5%), 1998 (10%), and 2010 (25%)], see Figure 4.17 Today, it is estimated that 25% of patients with HCV currently have cirrhosis and it is projected that we will see 1 million cases of HCV related cirrhosis by 2020. The total number of HCV cases will decline by 2030, but the percentage of HCV cirrhosis is projected to peak at 45% by 2030.17 The window of opportunity to intervene in the progression of this silent epidemic of HCV is rapidly closing. The large cohort of individuals infected with hepatitis C in the 1970s and 1990s moving into their fourth decade with HCV infection. This asymptomatic and unknowing epidemic is a looming health care crisis that is approaching the American health care system with “Tsunami” like implications.
The incredible success of the programs implemented to prevent the spread of HCV are deeply contrasted by the catastrophic failure of the CDC (1998) guideline to identify HCV-infected persons, see Table 1. In 2012, seventy-five percent of asymptomatic Americans with HCV infection are still unaware, undiagnosed and not offered new and effective, antiviral treatment.

Table 1. CDC (1998) Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease.

**CDC (1998) Recommendations For Prevention and Control of Hepatitis C Virus**

**Routine HCV testing is recommended for**

- Persons who ever injected illegal drugs, including those who injected once or a few times many years ago and do not consider themselves as drug users.
- Persons with selected medical conditions, including
  - persons who received clotting factor concentrates produced before 1987;
  - persons who were ever on chronic (long-term) hemodialysis; and
  - persons with persistently abnormal alanine aminotransferase levels.
- Prior recipients of transfusions or organ transplants, including
  - persons who were notified that they received blood from a donor who later tested positive for HCV infection;
  - persons who received a transfusion of blood or blood components before July 1992; and
  - persons who received an organ transplant before July 1992.

**Persons who should be tested routinely for HCV-infection based on a recognized exposure**

- Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood.
- Children born to HCV-positive women.
Both patients and health care providers are responsible for the failure of these targeted measures to identify the estimated ~3.0 million Americans with asymptomatic HCV infection. First, many patients are either forgetful of remote indiscretions or so consumed by guilt, that they deny any history of risky behaviors.\footnote{19} Second, health care providers have access to numerous published guidelines on the appropriateness of screening,\textsuperscript{20,21,22,23,24,25} but surveys have shown that over 40% of primary care physicians are unfamiliar with these guidelines\textsuperscript{26} and less than 50% of physicians ask their patients sensitive questions related to high risk behaviors.\textsuperscript{27}

Failure of the CDC (1998) risk-based guidelines to identify the majority of HCV asymptomatic patients coupled with the recent availability of new and more effective direct antiviral therapies have prompted the CDC to examine alternative methods to better identify asymptomatic HCV infection.\textsuperscript{18} Dr. David Rein and colleagues,\textsuperscript{28} examined the utility of expanding HCV screening recommendations to cover the birth cohort born from 1945 through 1965 (among whom HCV prevalence is highest) to complement to current risk-based screening recommendations. The authors used a Markov chain Monte Carlo simulation model of the prevalence of hepatitis C antibody stratified by age, sex, race/ethnicity, and history of injection-drug use and of the natural history of chronic hepatitis C. Applying HCV prevalence data from the National Health and Nutrition Examination Survey (NHANES, for 2001 through 2006), they divided this population into 40 mutually exclusive groups stratified by age, race/ethnicity, history of injection drug use, and prescription drug coverage.\textsuperscript{29} They further stratified these cohorts into those with and those without antibody to HCV and divided those with antibodies into those with chronic (75%) and those with cleared (25%) infections.\textsuperscript{30,31} They estimated that 28% of chronically infected patients were already aware of their infection and would not benefit from additional screening.\textsuperscript{31,32,33,34} This modeling estimated that 66.9 million Americans born between 1945 and 1965 visited a primary care provider at least once in 2006. Of these, 2.4 million were antibody positive for HCV, 1.9 million were chronically infected and 1.2 million were chronically infected and unaware of their status.\textsuperscript{28} Using the HCV birth-cohort screening model, Rein, et al, estimated over 1 million new cases of HCV would be identified and 552,000 patients would be treated.\textsuperscript{28} Using a conservative estimate of efficacy of 54% SVR for triple therapy (Interferon and Ribavirin plus a DAA agent) would project 311,00 persons would achieve SVR and 121,000 deaths would be prevented.\textsuperscript{28} Overall, Smith, et. al., predict that when compared to the status quo HCV Risk Based Screening, that the implementation of the HCV birth-cohort screening would identify and prevent 808,580 additional cases and 82,000 HCV-related deaths, at a screening cost of $2874. The HCV birth-cohort screening would detect 4 times more cases of undiagnosed HCV than CDC (1998) Risk Based screening.

In August 2011, the CDC convened a 2-day consultation with the HCV Birth Cohort Testing Work Group members to review and evaluate the quality of evidence of effectiveness of the proposed strategy of one-time testing of all members of the 1945-1965 birth cohort for Anti-HCV.\textsuperscript{35} The group offered a consensus recommendation for birth cohort HCV screening (1945 – 1965, ages 47 to 67) added to existing risk based screening, see \textbf{Table 2}. The new CDC (2012) HCV screening guideline has been reviewed and published.\textsuperscript{35} Now Gastroenterology, Hepatology and Infectious Disease specialists need to update and educate the “gatekeepers” in primary care on HCV birth-cohort screening for their patients aged, 47-67 yrs. Perhaps the more difficult problem will be providing health care access to the bolus of 800,000 Americans that will be identified with HCV birth-cohort screening method. This is a problem that we all look forward to solving as we stamp out the epidemic of Hepatitis C.
Table 2. CDC (2012) Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic diseases.35

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<tr>
<th>Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born during 1945–1965*</th>
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<td>* Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.</td>
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<td>* All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.</td>
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Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults & Adolescents†
* HIV-infected patients should be tested routinely for evidence of chronic HCV infection. Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV) in blood.

Recommendations for Prevention & Control of Hepatitis C Virus Infection & HCV-Related Chronic Disease§
§ Routine HCV testing is recommended for:
* Persons who ever injected illegal drugs, including those who injected once or a few times many years ago and do not consider themselves as drug users.
* Persons with selected medical conditions, including:
  - persons who received clotting factor concentrates produced before 1987;
  - persons who were ever on chronic (long-term) hemodialysis; and
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* Prior recipients of transfusions or organ transplants, including:
  - persons who were notified that they received blood from a donor who later tested positive for HCV infection;
  - persons who received a transfusion of blood or blood components before July 1992; and
  - persons who received an organ transplant before July 1992.

Routine HCV testing is recommended for persons with recognized exposures, including:
  - Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood.
  - Children born to HCV-positive women.

References:


2. Centers for Disease Control and Prevention C. Viral Hepatitis Surveillance, United States 2009: Centers for Disease Control and Prevention, CDC.


