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Rare Birds in North America: Acute Hepatitis C Cohorts

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In this issue, the Comment from the Editor highlights 8 cohorts of acute hepatitis C patients and the dedicated investigators who are tracking these rarely identified patients in variety of unusual settings— collectively identifying 643 patients since 1996. The identification, enrollment, prospective monitoring and treatment of patients with acute HCV infections require enormous collaborative efforts and networking among individuals and institutions in addition to multiple sources of research funding. Acute hepatitis C provides a critical window of opportunity to understand the early and dynamic host-virus interactions that define the outcome of HCV infection, an opportunity that is lost once HCV persistence or resolution is firmly established. These cohorts continue to provide valuable insights about the natural history, outcome, therapy and immune pathogenesis of acute hepatitis C in various populations while offering important collaborative opportunities.

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1. ACUTE HEPATITIS IN INJECTION DRUG USERS

Baltimore Cohort (1996-present), Johns Hopkins University Principal Investigators (PIs): Andrea L. Cox, David L. Thomas

Since 1996, the Baltimore cohort has identified acute hepatitis C among active injection drug users (IDUs) through community outreach and street-based recruitment in neighborhoods frequented by high-risk youth (mostly 19-35 years old). Participants are enrolled if they are active IDUs and test negative for anti-HCV antibodies; they receive counseling before and after testing and are referred to drug treatment and needle exchange programs. The protocol is designed for monthly follow up with testing for HCV RNA as well as anti-HCV. Therefore, subjects are identified without regard to the presence of symptoms. The cohort investigators also follow a smaller number of subjects who were identified through common source outbreaks or on the basis of symptoms. Subjects with acute HCV infection are educated about the potential benefits of early therapy and referred for evaluation for treatment. Subjects are also educated about the risks of re-infection and cleared subjects are screened via RNA testing for re-infection. Acutely infected subjects are counseled regarding the benefits of therapy and referred for comprehensive evaluation and treatment.

This cohort has provided significant new insights on epidemiology and immune pathogenesis of acute hepatitis C: HCV transmission between IDU's as older drug users show new users how to inject ¹; the induction of HCV-specific CD8+ T cell responses in most patients with acute hepatitis C and their decline with progression to chronicity without development of new responses ²; the characteristics of humoral immune response in acute HCV infection (delayed, low in titer and restricted primarily to the IgG1 subclass ³); mechanisms of HCV persistence whereby sequence evolution contributes to viral escape from CD8+ T cell responses and optimization of replicative capacity^{4,5}; high level expression of an inhibitory molecule on HCV-specific CD8+ T cells with progression to chronicity in the absence of escape ⁶. The Baltimore cohort study has been funded by U19 AI040035.

San Francisco Cohort (2000-present), UFO Acute HCV Study PI: Kimberly Page, University of California San Francisco; Co-investigators: Judith Hahn, Paula Lum, Stewart Cooper, Eric Delwart and Michael Busch

In San Francisco, prospective studies of HCV in young (<30 years old) active IDUs have been underway since January 2000. Young IDUs were recruited in 3 waves and followed prospectively in "The UFO Study". Details of this cohort were previously published⁷ and subsequent UFO Study participants were recruited in 2003-2004 and again in 2006 using the same methodology.

Participants found to have new and acute HCV infections (based on quarterly anti-HCV assays and nucleic acid amplification testing [NAT_(KI)]) were followed prospectively in the "UFO Acute HCV" study cohort to track infection outcome (clearance or persistent infection), predictors of outcome and treatment feasibility. Each month, UFO Acute HCV participants were interviewed and blood samples were collected to: (1) quantify HCV (anti-

HCV and HCV RNA) and alanine aminotransferase (ALT) levels; (2) assess immunological responses, (3) perform virological analyses, (4) determine treatment candidacy and (5) bank specimens. Referrals to care and assessments for HCV treatment were conducted in conjunction with a network of community-based providers. Acute HCV infection was classified as either a baseline incident acute infection (anti-HCV negative but HCV RNA positive by nucleic acid amplification testing NAT_[k2]) or a prospective incident acute infection (initially HCV negative by antibody and RNA testing but with confirmed positive HCV infection on follow-up). Viral clearance was defined as 2 consecutive serum-negative HCV RNA tests (by NAT) after confirmed acute or incident infection.

A total of 135 participants with acute or incident HCV have been identified, 95 (70.4%) studied longitudinally. Spontaneous HCV clearance was documented in 20 (21.1%); 68 (71.6%) showed persistent viremia; the remaining 7 (7.4%) could not be classified. Ongoing studies are assessing immunologic correlates of viral clearance, reinfection, infectivity and transmission dynamics between injecting partners and acute HCV treatment. The UFO Acute HCV Study has been funded by the National Institutes of Health (NIDA 2-R01 DA016017). Dr. Page has also received funding from NIAID (U19 AI040034).

Montreal Cohort (2005-present), Centre de Recherche du Centre Hospitalier de l'Université de Montréal

PIs: Julie Bruneau, Naglaa H. Shoukry; Co-investigators: Mark Daniel, Marc Bilodeau

This cohort includes acute HCV cases identified in the Saint-Luc Cohort study (established in 1998 to follow IDUs in Montreal) and through partnership with methadone maintenance clinics and needle exchange programs in the Montreal area.

Since January 2005, participants at high risk for HCV acquisition, defined as those who share injection material or have an HCV-positive partner, are examined every 3 months. At each visit, participants are tested for HCV RNA and baseline plasma and peripheral blood mononuclear cell (PBMC) samples are collected. Between 2005 and 2008, 60 cases of acute hepatitis C were identified, defined by a positive anti-HCV and/or HCV RNA test following a negative test within the last 6 months. The cohort is mostly Caucasian, with a median age of 33 years, and is 58% genotype 3a, 31% genotype 1a and 1b, and 11% other genotypes. Acute HCV patients are then followed at a monthly interval for 1.5 years. All patients who test positive for HCV RNA at 12 weeks are offered standard-of-care therapy through the Quebec Universal Health Care system and followed by a multidisciplinary team of clinicians, nurses and social workers in the outpatient clinic of the Addiction Medicine Division of the Centre Hospitalier de l'Université de Montréal.

Based on data from this cohort, researchers hope to understand correlates of the innate and adaptive immune responses to the outcome of HCV during the acute phase and early interferon therapy⁸, as well as the impact of acute HCV infection and antiviral treatment on the behaviours and quality of life of active IDUs who have access to IDU-targeted health services⁹. The work with this cohort was supported by grants from the Canadian Institutes for Health Research (CIHR) (MOP-74524, MOP-74581, MOP-84451), Fonds de la

Recherche en Santé du Quebec (FRSQ) (FRSQ-12428) and the FRSQ-AIDS and Infectious Disease Network (SIDA-MI).

2. ACUTE HEPATITIS IDENTIFIED IN DIVERSE RISK GROUPS

Boston/New England Cohort (1998-present), the Massachusetts General Hospital
Group PI: Georg Lauer, Arthur Kim

This cohort includes 150 patients primarily in the Boston/New England area acutely infected with HCV, identified through partnerships with the Massachusetts Department of Public Health, Massachusetts Department of Corrections, and local physicians from multiple area hospitals. The majority of individuals report IDU as their primary risk factor, within the context of a rise of HCV prevalence in Massachusetts among youth related to heroin use. Initially, most subjects were identified based on symptoms, but a recent risk factor-based screening program for inmates entering the Massachusetts correctional system has increased the number of cases in the cohort, adding a substantial number of non-symptomatic cases. All patients are referred for comprehensive evaluation and treatment; over 50 individuals have been treated. Patients are recruited to participate in translational studies regarding the early immunopathogenesis of disease as well as studies on viral evolution. This local cohort is complemented by a cohort of over 70 subjects with acute HCV infection from Rio de Janeiro; these patients are all symptomatic, have acquired HCV through routes other than drug use and have a spontaneous clearance rate of over 50%. Studies in this cohort produced several important scientific findings, including the first description of a successful early immune response against HCV¹⁰; the first observation of HCV escape from CD8+ T-cell responses¹¹; a longitudinal analysis of full-length viral sequences regarding the mechanisms underlying the rate of viral evolution¹²; the first direct *ex vivo* analysis of human virus-specific CD4+ T-cells using class II tetramer technology¹³; and an understanding the dynamics of cell-mediated immunity in patients on interferon-based therapies¹⁴. The cohort has also sparked numerous collaborations with other groups worldwide^{15, 16}. Work with this cohort has been funded by U19AI066345, K23AI054379, R01AI031563, and R01AI067926.

Denver Cohort (2002-present), University of Colorado Health Sciences University
(Multi-center Study of Acute HCV in Community Settings and Academic Medical Centers) PI: Hugo R. Rosen

This cohort has prospectively followed 81 patients with acute HCV infection from 6 cities in the U.S. (Portland, Seattle, Los Angeles, Memphis, Pittsburgh and Denver), identified through partnerships with health departments, needle exchange programs, plasmapheresis and blood centers, and academic university practices. All individuals are counseled about risks of transmission, disease progression and treatment options. The definition of acute hepatitis C and the demographic features of this cohort¹⁷ include: (1) a positive anti-HCV or HCV RNA test from a participant with a documented negative anti-HCV result within the past year, (2) a positive anti-HCV test from a participant with clinical hepatitis, detectable serum HCV RNA, a ALT >10 times the upper limit of normal, and negative results of tests for HBsAg and anti-HAV IgM; or (3) by direct sequence analysis. Diagnoses of acute hepatitis C were made after patients sought medical attention for symptoms, including

nausea, anorexia, abdominal pain, malaise, fever and jaundice. Diagnoses were made by physicians specializing in hepatology or infectious diseases after evaluation of the patient's clinical presentation and laboratory data. Both the presence of symptoms and female gender increase the likelihood of spontaneous recovery.

Studies of this cohort focus on understanding the mechanisms governing cytotoxic T-cell escape¹⁸, the importance of CD4+ T-cell help¹⁹, characterization of T cell thresholds associated with recovery¹⁹, the suppressive function of regulatory T cells in the early stages of infection²⁰, dysregulation of interleukin-7Ra and persistence²¹, and the innate immune response, particularly of natural killer and natural T cells²². Collaborations have been established with the Massachusetts General Hospital/Broad Institute and the Johns Hopkins University groups to address novel questions utilizing this rare population of individuals. Work with this cohort has been funded by NIH RO1 DK60590

3. ACUTE HEPATITIS IDENTIFIED IN CLINICS AND HOSPITALS

Atlanta Cohort (2004-current), Emory University PIs: Arash Grakoui, Hank Radziewicz, Co-investigator: Kimberly Workowski

This cohort, initiated in 2004, comprises 8 patients (6 male and 2 female) acutely infected with HCV to study immune mechanisms of HCV persistence, with a focus on adaptive T cell immunity. All patients were enrolled in Atlanta from either the Emory/Crawford Long Hospital/Clinics or from Grady Hospital/Clinics. Patients were initially identified based on increased ALT levels and recognition by the medical provider of the possibility for acute HCV infection.

Risk factors included sexual transmission for 6 patients and IDU for 2 patients. Four of the patients are HIV-positive. The community clinician or individual physician caring for the patient dictates treatment practices. To date, 3 patients completed combination therapy with pegylated interferon and ribavirin with sustained viral responses. One patient is currently on treatment, 2 others will receive treatment if viremia persists and one has refused therapy.

Acute HCV infection is defined by a positive HCV antibody test with a negative HCV antibody test within the past 1 year; hepatitis with concomitant HCV viremia; or, if a previous HCV antibody test had not been performed (or negative antibody test performed >1 year prior) and the patient presents with positive anti-HCV results, a syndrome of clinical hepatitis with an identified risk factor encounter for HCV (without another identified source for hepatitis) and HCV viremia.

In this cohort, the researchers study T cell functional deficits and the role of co-inhibitory receptors such as PD-1 in regulating HCV-specific immune responses²³. Clinicians at the Atlanta VA collaborate in research to better understand the immune response to HCV and host determinants of infection outcome. We acknowledge the support from the Grand Challenges in Global Health Initiative, EVC/CFAR Flow Cytometry Core P30 AI050409, Cancer Research Institute Investigator Award (AG), the Yerkes Research Center Base Grant RR-00165 and the Public Health Service [K08 AI072191 (HR), AI070101 (AG)].

Philadelphia Cohort (1999-present), University of Pennsylvania and Philadelphia VA Medical Center PI: Kyong-Mi Chang; Co-investigator: David E. Kaplan

This cohort was established in 1999 using a referral network through various gastrointestinal (GI)/Hepatology, Infectious Disease and Primary Care clinics within the Hospital of University of Pennsylvania as well as the Primary Care, Addiction Recovery Unit, GI and ID Clinics at the Philadelphia VA Medical Center (PVAMC). Important clinical collaborators include K. Rajender Reddy (the Director of Hepatology at Penn) and Frederick A Nunes at Pennsylvania Hospital. Ayse Aytaman (the Chief of GI at the Brooklyn VA Medical Center) provides same-day blood samples from New York City. Among 36 patients that met the criteria for acute hepatitis C, 30 have defined outcomes: 6 spontaneously resolved; 3 became chronically infected without therapy; 15 were treated (10 have achieved an SVR). Investigators of the New York Mount Sinai Cohort collaborate in research.

Acute hepatitis C is diagnosed by a combination of clinical and serological findings including documented HCV seroconversion and/or spontaneous viremic fluctuations in patients with recent increases in liver enzymes without other causes of liver diseases as recently described ²⁴. Patients are asked a series of questions to identify the potential source, timing and circumstance of HCV inoculation. With patient's consent, relevant clinical laboratory measures are communicated to the patient and the primary hepatologist for clinical decisions—to be made entirely at the discretion of each patient's primary hepatologist with the patient. Active follow-up is maintained by the research coordinator; blood samples are collected to monitor the clinical and virologic course as well as immunological parameters (particularly the adaptive immune response). Studies of this cohort have resulted in a number of observations regarding the relevance of antiviral effector and regulatory T-cell, as well as neutralizing antibody, responses in patients with acute hepatitis C ^{24, 25}. Moreover, studies are examining the relevance of immune inhibitory or costimulatory molecules in HCV immune pathogenesis ²⁶. The work with this cohort has been funded by the National Institutes of Health (NIAID, RO-1 AI47519) and the WW Smith Charitable Foundation.

4. ACUTE HEPATITIS C IN HIV-INFECTED PATIENTS

New York Mount Sinai Cohort (2006-current), Mount Sinai School of Medicine, NY PI: Daniel Fierer, Andrea Branch

This dynamic cohort was established in 2006 in response to the current HCV outbreak in New York City. It includes 35 subjects with acute HCV infection. Most are HIV-infected men that have sex with men (MSM; median age 41 years). Acute HCV infection was defined using 3 criteria in combination: seroconversion, marked increases in ALT levels, and $>1 \log_{10}$ fluctuations in HCV viral load. The majority of infections were likely sexually acquired, although percutaneous exposures were reported by some subjects. A detailed risk factor questionnaire is administered at the initial visit and blood samples are collected for PBMC, plasma, and serum analyses every 2 weeks during the initial 12-week observation period. Liver biopsy and treatment are offered if spontaneous clearance is not apparent within this period.

Histopathology studies on this cohort showed that fibrogenesis occurred early and was markedly accelerated in this group of subjects²⁷: 17 of the first 20 biopsies, performed at a median of 4.3 months after the first noted increase in ALT levels, revealed Stage 2 (of 4, Scheuer scale) fibrosis, a much greater number than reported in patients who acquired HCV infection before HIV infection. Age and male sex may contribute to this rapid fibrosis progression but no other known risk factors for fibrosis explain these findings. Treatment with pegylated interferon and weight-based ribavirin during the acute phase resulted in a 70% SVR rate. Early spontaneous clearance occurred in approximately 15% of patients but was not related to the occurrence of symptomatic hepatitis. Ongoing work centers on understanding factors contributing to the accelerated fibrosis progression, maximizing treatment response, and characterizing factors that are contributing to this ongoing outbreak of acute HCV infection among HIV-infected MSM in New York City. Investigators of the Philadelphia Cohort collaborate in this study to characterize early immunological responses in HIV-infected patients.

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Acute Hepatitis C Cohorts in North America

City	Institutions	Contact	Inception	* HCV risk group	#Patients recruited	Treatment	Funding	Ongoing research
Baltimore	Johns Hopkins University	Andrea Cox, David Thomas	1996	I	138	educated and referred	NIAID, NIDA	factors affecting incidence and outcomes, immunology, viral sequence evolution, HIV coinfection, genetics
San Francisco	University of California in San Francisco	Kimberly Page	2000	I	135	referred and facilitated	NIDA; NIAID	incidence of infection, clearance, re-infection, re-clearance, infectivity and transmission dynamics, immunology, lipids, genetics, acute treatment candidacy and outcome, HCV vaccine trial preparedness
Montreal	CRCHUM-Centre de Recherche du Centre Hospitalier de l'Université de Montréal	Julie Bruneau, Naglaa H. Shoukry	2005	I	60	offered	CIHR, FRSQ	individual-related and social epidemiology, immune pathogenesis, treatment outcomes including quality of life
Boston	Massachusetts General Hospital	Georg Lauer, Arthur Kim	1998	C, CI, S/H, P	150	offered	NIAID	screening strategies, immune pathogenesis, viral evolution
Denver	University of Colorado	Hugo Rosen	2002	I, C, D, S/H, O/I	81	offered or referred	NIDDK	immune pathogenesis, viral escape
Atlanta	Emory University	Arash Grakoui, Hank Radziewicz	2004	S/H, C, CI	8	offered or referred	NIAID	immune pathogenesis, virus-host interactions, anti-viral therapy
Philadelphia	Philadelphia VA Medical Center and the University of Pennsylvania	Kyong-Mi Chang	1999	C, D, CI	36	offered, or referred	NIAID, WW Smith Charitable Foundation	immune pathogenesis, outcomes
New York City	Mount Sinai School of Medicine	Andrea Branch, Daniel Fierer	2006	CI, C, S	35	offered	NIDA, NIDDK	fibrosis progression, treatment response, outcomes, outbreak investigation, epidemiology

I. Injection drug use cohort

P. Prison inmate cohort

C. patients identified from the community and clinics via HCV seroconversion, ALT flares and HCV viremic fluctuations

CI. HIV+ patients identified from the community/clinics via HCV seroconversion, ALT flares and HCV viremic fluctuations

D. Drug and alcohol rehabilitation

S/H. Sexual or household exposure

O/I. Occupational/iatrogenic

CIHR: Canadian Institutes for Health Research

FRSQ: Fonds de la Recherche en Santé du Québec

* **HCV Risk Groups**