Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Bunchorntavakul C. et al. (2015) Distinct features in natural history and outcomes of acute hepatitis C. J *Clin Gastroenterol,* 49(4):e31-40.
Date of Review:	March 6, 2016
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☒ **Social Science** ☐ **Programmatic Review** ☐
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **Acute HCV patients** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **United States** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	Primary research; to analyze the clinical and demographic features in acute HCV patients.
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Data was not used for decision-making.
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developed countries?	☐	☒	☐	The results of this study are not applicable to other countries as methodology involved only requiting patient

				population from the medical centers in United States. The clinical and demographic characteristics found would not be applicable to other locations.
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☐	☒	☐	
The research study/tool/data dictionary is easily accessed/available electronically	☒	☐	☐	Open access of the article can be found on http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4112167/
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	Cost effective analysis was no conducted.
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☐	☐	☐	This study was funded by the NIH Grants, the Philadelphia VA Medical Research. NIH/NIDDK Center of Molecular Studies in Digestive and Liver Diseases and its Molecular Biology and Cell Culture Core Facilities, and the NIH Public Health Service Research Grant.
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☒	☐	☐	Patients were enrolled in the study since 2000.
Are these data regularly collected at and/or below a national level?	☒	☐	☐	Patients were recruited from Philadelphia VA Medical Center, Hospital of University of Pennsylvania and Brooklyn VA Medical Center.
Are these data collected manually or electronically?	☐	☐	☐	Manually

RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	Journal of Clinical Gastroenterology
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	New data/information

OPEN

Distinct Features in Natural History and Outcomes of Acute Hepatitis C

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Background: Acute hepatitis C (AHCV) provides a diagnostic challenge with diverse clinical presentations.

Goals: This study was aimed to examine the clinical and demographic features as well as outcomes in AHCV patients identified from inpatient and outpatient hospital settings.

Study: Patients with suspected AHCV were recruited from Philadelphia VA Medical Center, Hospital of University of Pennsylvania and Brooklyn VA Medical Center between 2000 and 2010. AHCV was diagnosed by acute serum alanine aminotransferase elevation with anti-hepatitis C virus (HCV) seroconversion, HCV-RNA fluctuations above 1 log, and/or recent high-risk exposure without prior HCV infection, excluding those with human immunodeficiency virus infection. Clinical and therapeutic outcomes were monitored for at least 6 months.

Results: A total of 40 AHCV patients were enrolled with a median follow-up of 129 weeks. They were mostly men (68%) and whites (73%) with median age of 43 years, diverse risk factors (33% injection drugs, 20% health care–associated, 3% sexual, and 45% unknown), and wide variations in peak alanine aminotransferase (143 to 3435 U/L) and total bilirubin levels (0.4 to 19.3 mg/dL). Viremia resolved spontaneously in 23% and persisted without therapy in 27%, whereas 50% received interferon α-based therapy with 90% cure (18/20). Distinct clinical scenarios included: (1) wide viremic fluctuations >1 log (65%) and intermittent HCV-RNA negativity; (2) autoantibodies (25% antinuclear antibodies, 69% antismooth muscle antibodies) or autoimmune features; (3) delayed spontaneous viral clearance in 2 patients; (4) rapid cirrhosis progression in 2 patients.

Conclusions: AHCV is a heterogenous disease that requires careful monitoring. The lack of apparent risk factor in high proportion of patients and its diverse presentations warrant diagnostic vigilance.

Key Words: hepatitis C virus, acute hepatitis, RNA fluctuation, clinical presentation, autoantibody

(*J Clin Gastroenterol* 2015;49:e31–e40)

Chronic hepatitis C virus (HCV) infection is a leading cause of chronic liver disease worldwide. Although the incidence of acute hepatitis C (AHCV) has been declining in recent years, such cases continue to occur in the community in the setting of injection drug use (IDU), health care–associated (HCA) procedures, and/or sexual exposures as well as unknown risk factors.[1–7] While most untreated AHC progresses to chronicity, antiviral therapy–based on interferon α (IFNα) has been more effective when initiated during AHCV rather than with established chronic hepatitis C.[8–11] Thus, a timely diagnosis and therapy of AHCV can prevent liver disease progression while limiting further spread of HCV infection.

However, diagnosis of AHCV can be challenging due to a wide spectrum of clinical presentation from completely asymptomatic to acute icteric and symptomatic hepatitis as well as fluctuating course of viremia and transaminase elevation.[2,3,8,12,13] Diagnostic criteria for AHCV can include documented anti-HCV seroconversion (77%), alanine aminotransferase (ALT) elevation (68%), and HCV-RNA detection (63%).[14] It remains unclear as to when anti-HCV seroconversion occurs relative to the timing of clinical presentation and laboratory testing.[3,6,13] HCV seroconversion may not even occur with low-level exposures.[15] In this regard, >1 log viremic fluctuations and low-titer HCV-RNA (uncommon in established chronic hepatitis C) support the diagnosis of AHCV.[12,16]

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C.B.: study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript; L.M.J., M.K., and A.A.: acquisition of data; M.E.V., D.E.K., and F.A.N.: patient recruitment and acquisition of data; K.R.R.: study concept and design, patient recruitment, interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision; K.-M.C.: study concept and design, patient recruitment, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, obtained funding, administrative support, and study supervision. The content of this article does not necessarily reflect the views of the Department of Veterans Affairs or of the US government.

The authors declare that they have nothing to disclose.

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The virological outcome of AHCV is associated with various host and viral factors including age, gender, presence of symptoms and/or jaundice, antiviral T-cell responsiveness, immunogenetic polymorphisms, and viral coinfections.[2,3,8,16–21] Typically, patients with self-limited AHCV have sustained viral clearance within the first 12 weeks of disease onset, whereas viremia beyond 6 months generally indicate chronic evolution (CE).[5,8,10] If viremia is not spontaneously resolved within 12 weeks, IFNα-based treatment can achieve excellent sustained virological response (SVR) rate above 80% regardless of treatment regimen (monotherapy combined with ribavirin) or duration (typically 12 to 48 wk).[1,8,9,11,22] However, up to 30% of the patients are not treated due to comorbidities that may present challenges to IFNα-based therapy.[1,22] Chronic hepatitis C therapy is rapidly evolving into an IFN-free and directly acting antiviral regimens, with or without ribavirin, for as short a duration as 8 to 12 weeks and with high response rates.[23] Although such regimens have not yet been fully evaluated in AHCV, they can be used in such cases as reported by Fierer et al[24] and possibly even prophylactically after HCV exposure although the latter is contentious.

In our center, we have been prospectively enrolling AHCV patients since 2000 to examine the role of cellular immunity in HCV infection.[16,17] In this study, we analyzed the clinical and demographic findings in our patient cohort recruited over a decade of IFNα-based therapeutics to highlight their natural history and outcomes.

MATERIALS AND METHODS

Patient Recruitment and Diagnosis

Patients with suspected AHCV were recruited between 2000 and 2010 at the Philadelphia VA Medical Center, Hospital of the University of Pennsylvania and Brooklyn VA Medical Center with written informed consent approved by the respective Institutional Review Boards. All patients underwent detailed qualitative interview and review of medical record by the clinical research coordinator and/or physicians for risk factor history including HCA procedures (eg, transfusion, surgical/medical procedures), piercing, tattooing, IDU, recreational drug use, and sexual exposures within a year of clinical onset as well as other history relevant for liver disease. Laboratory parameters included standard liver function parameters as well as serology for hepatitis A/B and human immunodeficiency virus (HIV). All patients were enrolled within 1 year of clinical onset and monitored for at least 6 months. Serum HCV-RNA, HCV genotype, and anti-HCV status were determined by standard commercial assays through the clinical laboratory (see Supplementary document for details, Supplemental Digital Content 1, http://links.lww.com/JCG/A122).

AHCV was diagnosed by acute serum ALT elevation with documented HCV seroconversion, spontaneous serum HCV-RNA fluctuations over 10-fold, and/or risk history within 1 year of clinical onset without a history of prior HCV infection or other causes of liver disease.[12,14,16] HIV-coinfected patients were excluded. Among 50 AHCV patients initially identified, 10 were excluded for HIV coinfection or follow-up duration of <6 months, resulting in 40 AHCV patients with documented seroconversion (70%) and/or viremic fluctuations above 10-fold (65%) (Fig. 1). As the timing of HCV exposure was difficult to define, the clinical onset was operationally defined as the time of first documented ALT elevation. Among those with HCV seroconversion (70%), the median time from a negative HCV Ab test to clinical onset of AHCV was 16 weeks, although some may have been "recent" rather than "acute" hepatitis C.

Patient Grouping

Patients were grouped as: (1) spontaneous resolution (SR) with undetectable serum HCV-RNA and ALT normalization on at least 2 consecutive occasions at 3 or more months apart; (2) CE with persistent HCV-RNA for over 6 months; (3) IFN group who received 2 or more doses of IFNα ± ribavirin.

HCV Therapy

HCV therapy included nonpegylated to pegylated IFN either alone or with ribavirin, initiated by the primary clinical provider based on clinical indications and contraindications as well as patient's motivation.[25] Treatment was defined as early or late, based on their initiation before or after 6 months (or 26 wk) from clinical onset, respectively. SVR was defined as undetectable HCV-RNA at 24 weeks from treatment cessation.

Statistical Analysis

Categorical variables were analyzed using the Pearson χ^2 or the Fisher exact test. Continuous variables were examined using nonparametric Mann-Whitney U or Kruskal-Wallis test, with P-value below 0.05 considered significant.

RESULTS

Patient Characteristics

A total of 40 subjects with AHCV were enrolled between 2000 and 2010 as described in Materials and methods section and monitored over a median duration of 129 weeks. They included 9 patients with SR (23%), 11 patients with CE without therapy (27%), and 20 with IFNα-based therapy (50% IFN) (Tables 1, 2). The patients were 68% males, 73% white, and wide in age range (18 to 75 y). IL28B genotype was defined in 38/40 subjects as 53% CC, 30% CT, and 13% TT (Table 1B). HCV genotype 1 was most prevalent (80%) followed by genotype 3 (13%) (Table 1C). HCV clearance was ultimately achieved in 27/40 (68%) including 9 SR, 16 IFN patients achieving SVR with initial therapy, and 2 IFN patients who initially relapsed but achieved SVR with second therapy.

All patients had elevated ALT activity consistent with our inclusion criteria, whereas 24/40 (60%) displayed jaundice with total bilirubin ≥ 3 mg/dL (Tables 1, 2, Fig. 2A). Severe liver inflammation and/or jaundice occurred in 17/40 (43%) with ALT above 1000 U/L (Table 1D), including 5/40 (13%) with ALT above 2000 U/L and 11/40 (28%) with total bilirubin above 10 mg/dL. As for HCV-RNA, median peak HCV-RNA titer was 6.1 $\log_{10}$ IU/L with titers above 7 log in 11/40 patients (28%). ALT activity was associated with total bilirubin levels (R's = 0.57, $P = 0.00014$) but not HCV-RNA titers (Fig. 2B). The patient groups did not differ in clinical or demographic parameters or IL28B genotype distribution.

Diverse Risk Factors for AHCV

Potential risk factors for HCV transmission included (Table 1A): IDU (33%), HCA (20%), sexual exposures (3%). No risk factors were identified in 19/40 (45%). There

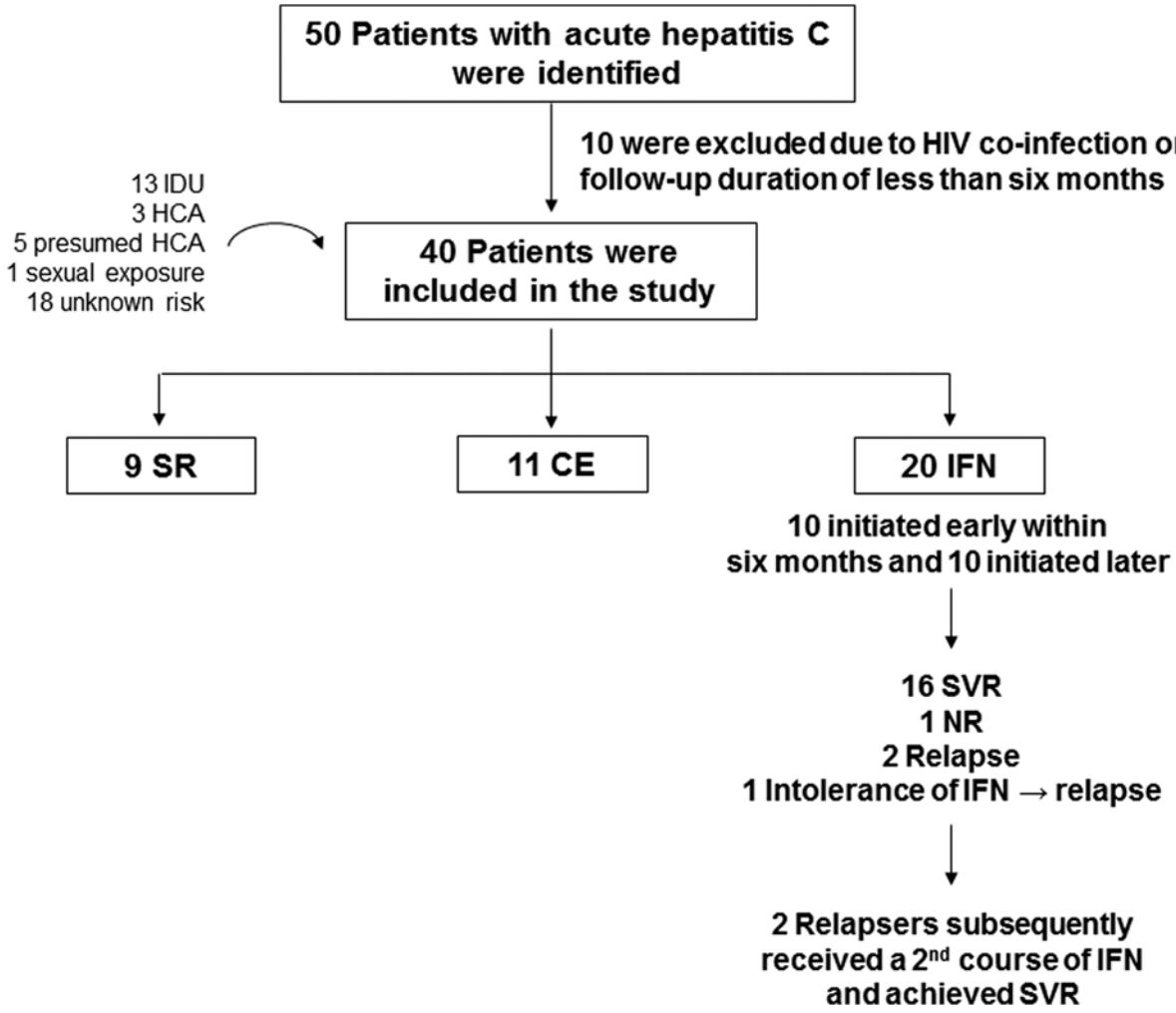

FIGURE 1. Study flow. CE indicates chronic evolution; HCA, health care–associated; HIV, human immunodeficiency virus; IDU, injection drug users; IFN, interferon; NR, nonresponse; SR, spontaneous resolution; SVR, sustained virological response.

were no associated recent transfusions, piercing, or tattoos. As shown in Table 3, persons who inject drugs (PWID) included mostly young white males who started injection drugs within 1 to 2 years. They were enriched for HCV genotype 3 compared with non-PWID (31% vs. 4%, $P = 0.032$) with a tendency for lower total bilirubin level ($P = 0.055$). PWID also showed a tendency for greater CE (46% vs. 18%, $P = 0.13$) and less treatment initiation (31% vs. 59%, $P = 0.18$) in part due to poor follow-up with ongoing drug use and/or incarceration, highlighting a need to systematically motivate, educate, and treat PWID and persons in correctional facilities.[26,27] There was no difference in %SVR between PWID and non-PWID (75% vs. 81%, $P = 1.0$), similar to previous reports.[28]

Among 8 patients with HCA risk factors, 2 had documented HCV exposures: IFN01 was a nurse with HCV-contaminated needle-stick accident, whereas IFN13 received HCV-contaminated tendon graft. Another patient was on chronic hemodialysis—a known risk factor for HCV infection. In the remaining 5 patients in HCA group, the precise mode of transmission was not defined except for recent medical/surgical procedures (eg, cardiac catheterization, prostate biopsy, upper endoscopy, or abdominal surgery within 6 mo of clinical presentation). HCV risk factor was presumed to be sexual in a 58-year-old female patient IFN17 (3%) who was newly married to an HCV-infected male in the absence of other known risk factors, although specific details of their sexual practice were not obtained. Thus, IDU accounted for only 30% of HCV transmission in our AHCV cohort, whereas the majority had either no apparent risk factor (47%) or only temporal associations with medical/surgical procedures (20%).

Virological Outcome to IFNα-based Antiviral Therapy

Twenty patients received IFNα therapy (standard or pegylated) either alone or combined with ribavirin (Table 2B). Median time from onset to treatment initiation was 25.8 weeks (range, 2 to 105 wk). Median treatment duration was 30 weeks (range, 2 to 68 wk). Antiviral therapy was initiated within 6 months in 10 patients (IFN01 to 10) and beyond 6 months in 10 others (IFN11 to 20). The later therapy was in part due to fluctuating viremia with transiently low to undetectable HCV-RNA in 7 as well as delayed referral, concurrent medical issues, and/or personal preference.

TABLE 1. Summary of Demographic, Virological, and Clinical Parameters

	All (n = 40)	SR (n = 9)	CE (n = 11)	IFN (n = 20)	*P* (SR vs. CE vs. IFN)
Demographic factors					
Median age (y)	43	40	39	49	0.76
% Males	68	67	91	55	0.10
Median weeks of follow-up	129	100	182	121	0.38
Racial distribution (%)					
Asians	5	11	9	0	0.24
Blacks	20	22	9	25	0.59
Hispanic	3	0	9	0	0.50
White	73	67	73	75	0.90
Risk factors (%)					
IDU	33	33	55	20	0.15
Health care–associated	20	22	18	20	1.0
Sexual exposure	3	0	0	5	1.0
Unknown	45	44	27	55	0.36
IL28B genotype (%)					
CC	53	78	45	45	0.25
CT	30	11	45	30	0.26
TT	13	11	9	15	0.10
Unknown	5	0	0	10	0.72
Virological factors					
HCV genotype 1	80	78	73	85	0.68
HCV genotype 2	3	0	0	5	1.0
HCV genotype 3	13	11	27	5	0.16
HCV genotype 3	3	11	0	0	0.23
HCV genotype unknown	3	0	0	5	1.0
Median peak HCV-RNA (log IU/mL)	6.1	6.4	6.8	5.9	0.13
HCV seroconversion (%)	70	67	91	60	
%HCV viremic fluctuation >1 log	65	78	64	60	0.63
%HCV-RNA + beyond 6 mo	68	22	100	70	0.0008
%HCV clearance (± therapy)	68	100	0	90	< 0.0001
Clinical parameters					
Median peak ALT (U/L)	868	869	677	1016	0.70
% with peak ALT above 1000 U/L	43	44	27	50	0.49
Median total bilirubin (mg/dL)	5	7.6	2.1	7.3	0.27
% with peak total bilirubin >3 mg/dL	60	67	45	35	0.37

ALT indicates alanine aminotransferase; CE, chronic evolution; IDU, injection drug users; IFN, interferon; SR, spontaneous resolution.

SVR was achieved in 16/20 (80%) with initial therapy, including 2/3 patients with IL28B TT genotype. Paradoxically, all 4 SVR-negative patients received early IFN therapy, resulting in a lower %SVR in early than late IFN group (60% vs. 100%, $P = 0.087$). In particular, IFN02 was refractory to antiviral treatment and maintained viremia above 5 logs throughout 49 weeks of combination IFNα and ribavirin therapy. IFN03 was intolerant of IFN therapy and required treatment cessation at 19 weeks with subsequent virological relapse. Two patients (IFN01, IFN08) with viremic relapses after 24 and 12 weeks, respectively, achieved SVR after a second round of therapy. Of note, IFN01 has IL28B TT genotype, whereas IFN08 had IL28B CC genotype. There were no apparent differences in demographic, clinical, and virological characteristics between early and late IFN groups or between SVR + and SVR − patients (data not shown), although our sample size was small. Thus, the overall treatment response was excellent in our AHCV cohort regardless of early and late therapy or IL28B genotype.

Distinct Features in Natural History and Outcomes of AHCV

There were several distinct features in our AHCV cohort as shown below.

Viremic Course in Early and Late Phase of AHCV

Spontaneous viremic fluctuations over 10-fold (median 1.5 log fold) were observed in 26/40 (65%) patients, irrespective of IL28B genotype. This included rapid and sustained loss of detectable HCV-RNA titers in most SR patients within the first 6 months and multiple bouts of intermittent HCV-RNA negativity followed by continued viremia in some CE patients (eg, CE2 in Fig. 3B and IFN11 in Supplementary Figure 1S, Supplemental Digital Content 2, http://links.lww.com/JCG/A123). Interestingly, 2 SR patients (SR06, SR08) with stable viremia in the early phase cleared viremia beyond 6 months from onset. As shown in Figure 3C, SR06 was persistently viremic with the latest documented viremia at week 46, before becoming temporarily lost to follow-up for recurrent drug use, incarceration, and pregnancy. She then returned with undetectable HCV-RNA and normal ALT at weeks 191 and 241. Similarly, SR08 was viremic up to 98 weeks, but became repeatedly HCV-RNA-negative at weeks 119, 194, and 235 with normal ALT. Neither patients showed evidence of concurrent HBV infection that can influence HCV outcome[29] and were negative for HBsAg, anti-HBc, and anti-HBs. Both patients had IL28B CC genotype and had not received antiviral therapy. Thus, among 20 patients without antiviral therapy, 2 (10%) achieved delayed viral clearance

TABLE 2. Demographic, Clinical, and Virological Parameters in Individual Patients

ID #	Age (y)	Gender	Race	HCV Risk	HCV Genotype	Peak ALT (U/L)	Peak Bili (mg/dL)	Peak HCV-RNA (log IU/mL)	IL28B	IFN Start Time (wk)	Total Weeks on IFN	Total Weeks of FU	Outcome
SR01	62	M	W	HCA	4	1152	1.1	5.3	CC	—	—	100	
SR02	49	M	W	HCA	1b	453	19	0.0	CC	—	—	443	
SR03	39	F	B	NK	1	1744	9.9	0.0	TT	—	—	63	
SR04	55	M	A	NK	1a	820	14.9	4.4	CC	—	—	39	
SR05	47	F	B	NK	1b	867	12	6.4	CC	—	—	40	
SR06	35	M	W	IDU	3a	869	1.1	7.9	CC	—	—	241	
SR07	24	M	W	IDU	1a	1618	7.6	7.3	CC	—	—	206	
SR08	22	F	W	IDU	1b	328	1.2	6.8	CC	—	—	235	
SR09	31	M	W	NK	1b	1444	3.2	7.6	CT	—	—	31	
CE01	42	M	W	IDU	1b	677	4.9	6.5	CT	—	—	362	
CE02	31	M	W	IDU	3a	2426	10.3	5.3	CT	—	—	429	
CE03	71	M	B	NK	1b	590	5	5.8	CT	—	—	367	
CE04	75	M	W	HCA	1	175	0.8	7.1	CT	—	—	129	
CE05	63	M	W	HCA	1b	811	1.3	7.3	CC	—	—	308	
CE06	25	M	A	IDU	1a	620	0.6	7.0	CC	—	—	113	
CE07	38	M	W	IDU	1b	997	1.2	6.7	CT	—	—	182	
CE08	23	M	W	IDU	3a	3435	2.1	7.2	CC	—	—	128	
CE09	67	M	W	NK	1b	280	3.6	6.8	CC	—	—	232	
CE10	31	F	H	NK	3a	1745	9.3	5.9	CC	—	—	27	
CE11	23	M	W	IDU	1	143	0.5	6.9	TT	—	—	118	
IFN01	25	F	W	HCA	1a	843	13.1	6.0	TT	2	24	210	Relapse*
IFN02	52	M	B	NK	1a	710	3.3	5.6	CT	15	49	472	NR
IFN03	52	M	W	NK	1a	1359	7.8	5.9	CC	20	19	255	Intolerant
IFN04	24	F	W	IDU	1b	2353	10.1	6.3	NK	18	48	122	SVR
IFN05	55	F	B	NK	1	1790	6.9	3.9	CT	25	2	111	SVR
IFN06	18	M	W	IDU	1a	300	0.4	4.2	CC	11	48	184	SVR
IFN07	40	F	W	IDU	3a	1910	5.8	3.8	CC	14	4	83	SVR
IFN08	20	M	W	IDU	1a	823	2.2	7.5	CC	10	12	36	Relapse*
IFN09	69	M	W	HCA	1	1947	10.4	7.2	CC	4	23	117	SVR
IFN10	43	M	W	NK	1a	226	1	5.8	TT	21	68	118	SVR
IFN11	35	F	W	HCA	1b	1979	7.7	5.1	CC	97	48	320	SVR
IFN12	49	M	W	NK	1b	2788	19.3	5.9	NK	49	48	290	SVR
IFN13	34	M	W	HCA	1a	918	0.9	5.9	CT	82	48	167	SVR
IFN14	53	F	W	NK	NK	2000	16.5	3.4	CT	105	35	366	SVR
IFN15	36	M	W	NK	1a	1471	18.4	7.6	CC	36	14	140	SVR
IFN16	63	M	B	NK	2a	155	1.2	6.6	CT	27	24	120	SVR
IFN17	58	F	B	Sex	1a	471	0.5	4.7	CT	46	39	95	SVR
IFN18	61	F	B	NK	1a	1113	15.2	5.0	TT	48	24	99	SVR
IFN19	62	F	W	NK	1	143	0.6	6.2	CC	33	48	74	SVR
IFN20	49	M	W	NK	1a	308	7.8	6.2	CC	45	25	120	SVR

*2 relapsed patients achieved SVR with second round of therapy.

A indicates Asian; ALT, alanine aminotransferase; B, black; CE, chronic evolution; F, female; FU, follow-up; H, Hispanic; HCA, health care–associated; IDU, injection drug users; IFN, interferon; M, male; NK, not known; NR, nonresponse; peak bili, peak total bilirubin level; SR, spontaneous resolution; SVR, sustained virological response; W, white.

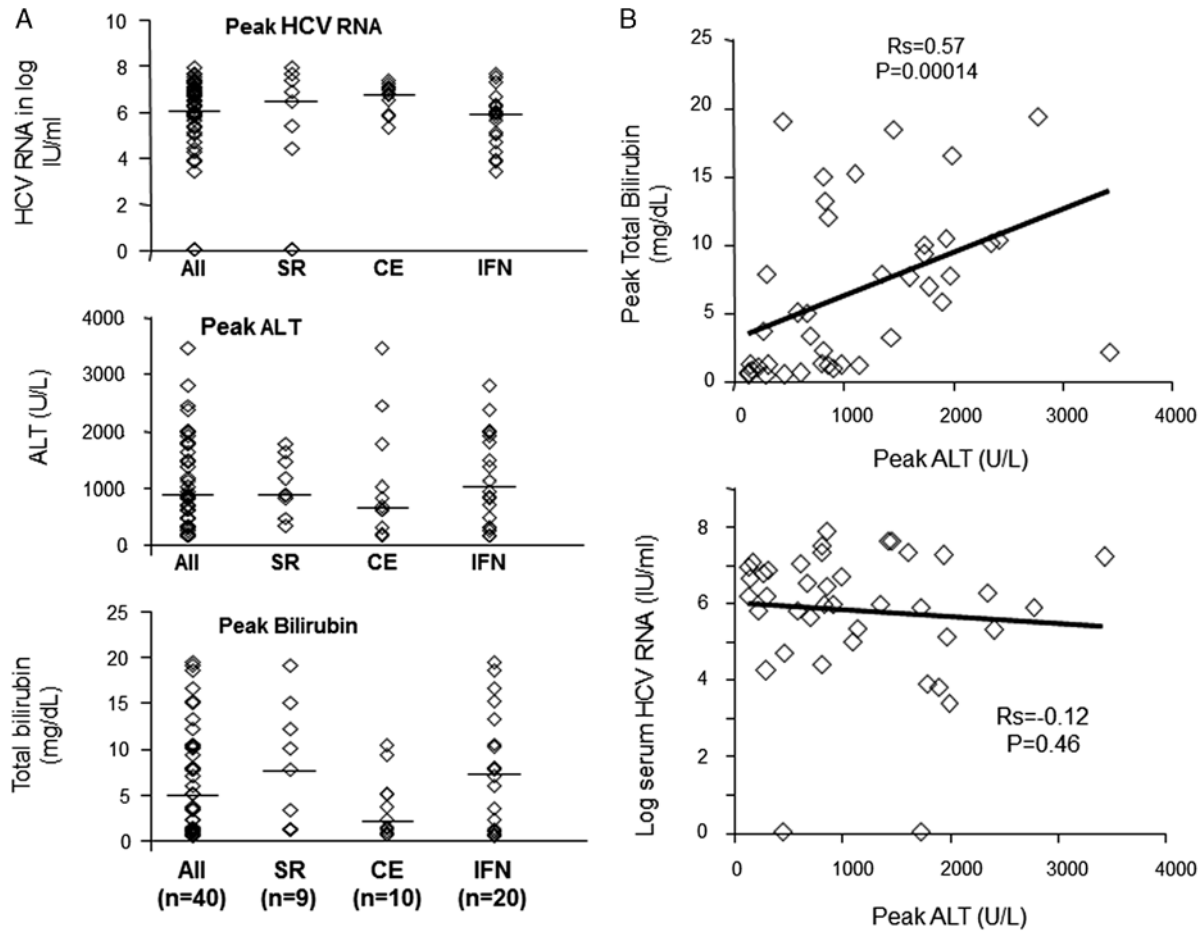

FIGURE 2. Clinical and virological course in acute hepatitis C with spontaneous resolution or chronic evolution. ALT indicates serum alanine aminotransferase; CE, chronic evolution; IFN, interferon; SR, spontaneous resolution.

beyond the first 6 months, similar to delayed viral clearance in 3/15 Italian patients during an AHCV outbreak.[30]

Autoantibodies and/or Autoimmune Hepatitis (AIH)

On the basis of the associations between HCV infection and autoimmune markers,[31,32] serum antinuclear antibodies (ANA) and antismooth muscle antibodies (ASMA) were obtained in 28 and 16 patients, respectively. ANA were detected in 7/28 patients tested (25%) and ASMA were detected in 11/16 patients tested (69%) although mostly at low titers ($\leq$1:80) and without preexisting autoimmune conditions. However, higher ANA titers (1:2560) were detected in IFN11, a 35-year-old white woman without associated autoimmune condition. A second patient (IFN14) was a 53-year-old white woman with liver histology showing interface hepatitis suggestive of AIH but no detectable autoantibodies that developed an ALT flare upon corticosteroid therapy. Fortunately, both patients achieved SVR upon subsequent IFNα-based therapy. Their clinical details are described in Supplementary document and Figure 1S (Supplemental Digital Content 2, http://links.lww.com/JCG/A123).

Rapid Liver Disease Progression

Cirrhosis generally develops gradually over decades of chronic hepatitis C.[33] However, rapid fibrosis progression into frank clinical cirrhosis occurred in CE05 and IFN02 without a prior history of liver disease. As shown in Table 2, CE05 was a 63-year-old white male with CE of AHCV who did not undergo antiviral therapy due to concurrent medical issues and chaotic lifestyle due to homelessness. Unfortunately, he developed clinically apparent cirrhosis with thrombocytopenia, splenomegaly, and ascites within 5 years of AHCV presentation. The second patient (IFN02) was a 52-year-old African American male who remained persistently viremic despite multiple rounds of IFNα-based antiviral with platelet count spontaneously declining below 130 k within 7 years from AHCV and F4 fibrosis on liver biopsy within 10 years.

On the basis of these findings, fibrosis progression was estimated in a noninvasive manner using Fib-4 index based on the formula previously defined: age ([y] $\times$ AST [U/L])/((platelets [10^9/L]) $\times$ (ALT [U/L])(1/2)).[34,35] As shown in Figure 4, transient Fib-4 index elevations were observed during initial acute hepatitis due to high AST levels (eg, SR02, SR04, CE03, and CE08). Fib-4 index elevations were seen in both patients with IL28B CC and non-CC genotypes. Prolonged Fib-4 index elevation during the first 2 year was also seen in CE09 whose liver biopsy during acute hepatitis showed moderate to bridging fibrosis, although cirrhosis could not be assessed due to competing medical issues (metastatic lung cancer, prostate cancer, and

TABLE 3. Characteristics of People Who Inject Drugs

	PWID (n = 13)	Non-PWID (n = 27)	*P* Between PWID vs. Non-PWID
Median age (y)	24	52	< 0.0001
%Males	77	63	0.48
%White	92	63	0.068
%Black	0	30	0.037
%Genotype 1	69	85	0.40
%Genotype 3	31	4	0.032
Median ALT (U/L)	869	867	0.63
Median total bilirubin (mg/dL)	2.1	7.7	0.055
Log HCV-RNA	6.8	5.9	0.06
%SR	23	22	0.69
%CE	46	19	0.13
%Treated	31	59	0.18
%SVR	75 (3/4)	81 (13/16)	1.0

ALT indicates serum alanine aminotransferase; CE, chronic evolution; PWID, people who inject drugs; SR, spontaneous resolution; SVR, sustained virological response.

cardiovascular disease). By contrast, both CE05 and IFN02 showed Fib-4 index levels persistently above 3.25 within the first 3 years of AHCV (Fig. 4B), consistent with their clinical cirrhosis progression. Otherwise, prolonged Fib-4 elevation and clinical cirrhosis was not seen in patients with spontaneous or IFN-related HCV clearance. Thus, rapid fibrosis progression was observed in 2/13 (15%) patients with persistent viremia after AHCV and in 2/40 (5%) of the overall AHCV cohort.

DISCUSSION

In this study, we examined AHCV patients identified from inpatient and outpatient hospital settings by clinical symptoms, exposure history, and/or clinical laboratory abnormalities. Our cohort is characterized by predominantly white ethnicity, male gender, HCV genotype 1 infection, and wide viremic fluctuations as well as relatively high levels of ALT and total bilirubin. HCV infection spontaneously resolved in 23%, resolved with therapy in 90% of those treated, and persisted regardless of therapy in 33% with several distinct demographic and clinical features. AHCV identified in the context of clinical suspicion may differ in natural history and outcome, with a greater likelihood for SR when compared with clinically silent cases,[2,8,19] although SR was observed in only 23% of our cohort.

HCV risk factors in our cohort were diverse with several notable features. First, we were struck by the lack of defined HCV-associated risk factors in 18/40 (45%) patients. Moreover, among 8 subjects with HCA risk factors, exposure was only presumed without a clear source in 5 with recent medical, surgical, and/or dental interventions. This ultimately resulted in 23/40 without a clear route of HCV transmission (58%). Our findings contrast from the MMWR surveillance summary listing PWID as the highest risk factor (48%), followed by multiple sexual partners (42%) and unknown (35%).[36] These differences reflect

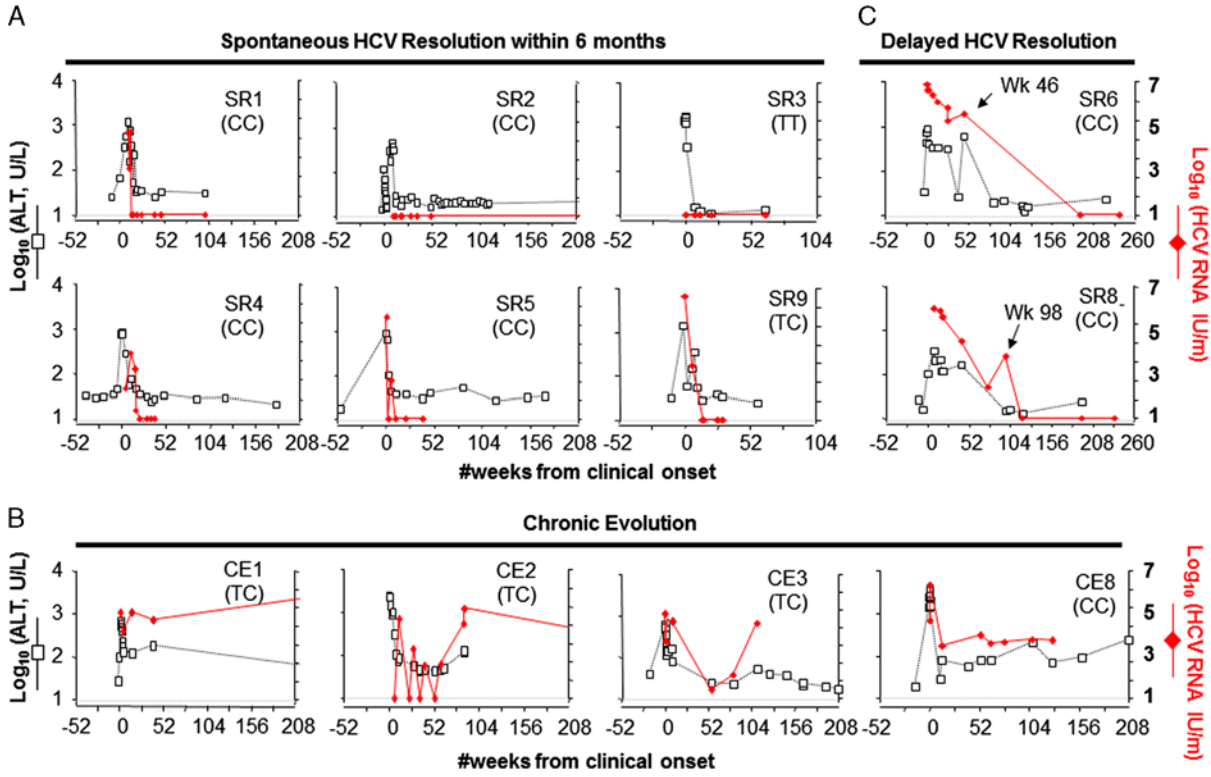

FIGURE 3. Clinical and virological parameters in acute hepatitis C relative to outcome and IL28B genotype. Letters in parentheses (CC, TT, CT) are IL28B genotypes. ALT indicates serum alanine aminotransferase; SR, spontaneous resolution; CE, chronic evolution.

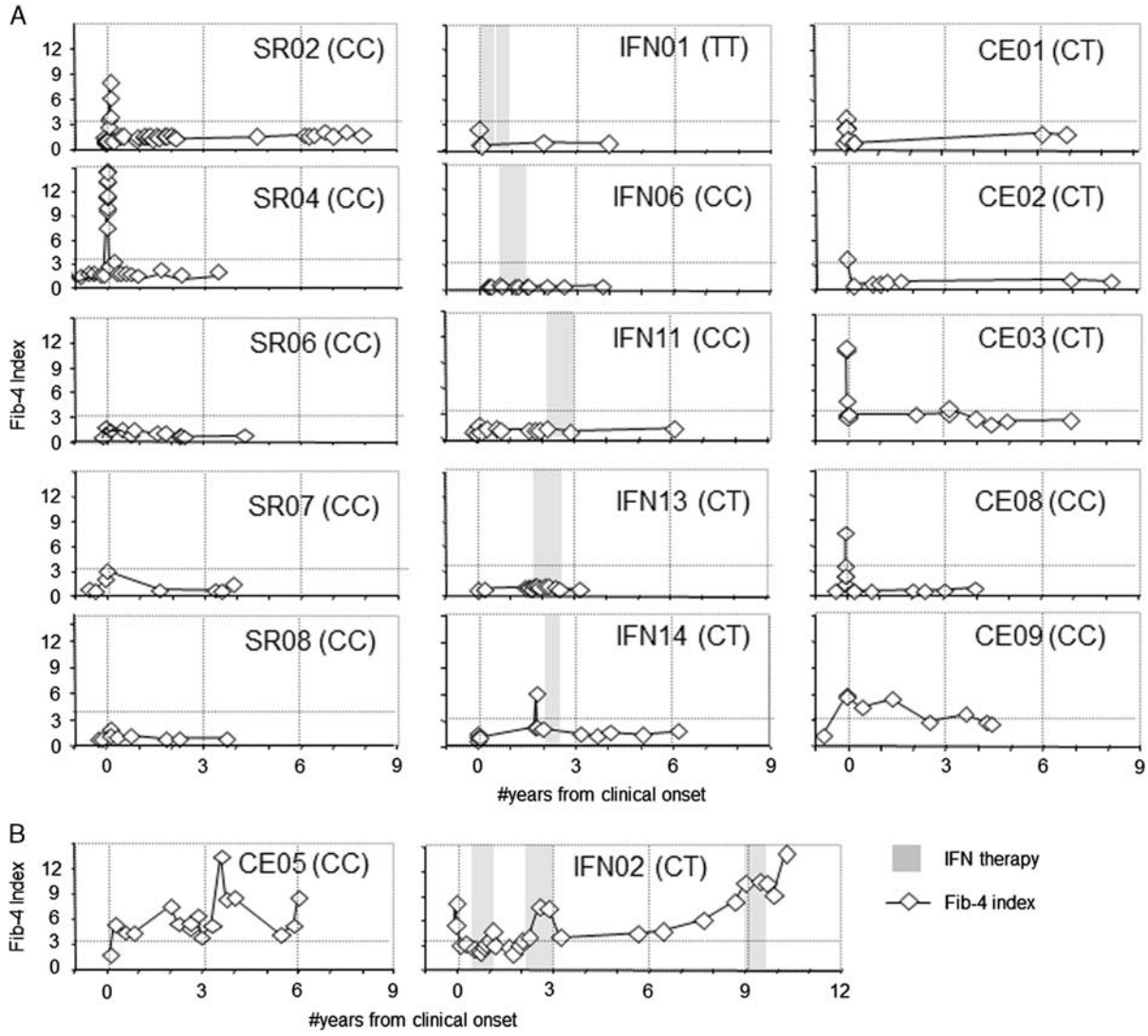

FIGURE 4. Evolution in Fib-4 index during and after acute hepatitis C. Letters in parentheses (CC, TT, CT) are IL28B genotypes. CE indicates chronic evolution; IFN, interferon; SR, spontaneous resolution.

different data collection methodologies and populations examined. For example, we did not collect explicit information on sexual exposures or non-IDU (eg, methamphetamine), as described in HIV-infected men who have sex with men in the New York City epidemic.[37] Nevertheless, a lack of identifiable risk factor, as was noted in our AHCV cohort, can result in psychological distress for the patients (and their families) while limiting preventative strategies. Second, our findings suggest that AHCV should be considered in all persons presenting with acute hepatitis, even without apparent risk factors. Indeed, 2 patients in our cohort were over 70 years old and AHCV may not have been considered given their age. Recent hospitalizations with presumably an exposure to HCV infection may have been the mode of acquisition in one of these patients. Of note, risk factors for AHCV may differ between HIV-negative and HIV-positive patients with rising incidence of AHCV observed among HIV-positive men who have sex with men.[37–40] Third, CE was more frequent in PWID compared with others (46% vs. 19%, $P = 0.13$). Although the difference did not reach statistical significance, this could reflect reinfection or superinfection previously reported among recently HCV-infected patients with ongoing IDU.[41]

Overall, SVR was achieved in 80% upon initial therapy and in an additional 2/2 patients with repeat therapy (overall 90% in treated patients) regardless of IL28B genotype. All 4 patients with initial treatment failure received early therapy within 6 months of clinical onset, contrasting with a superior therapeutic response associated with early therapy in some but not all studies.[8–10] The rate of SVR was similar among patients who acquired AHCV through injection drugs and other routes (75% vs. 81%, $P = 1.0$) as reported previously.[28,42] Of note, 90% SVR in our AHCV cohort is higher than the 50% SVR rates reported for patients with chronic HCV genotype 1 infection.[43] Among 2 patients who failed IFN therapy, IFN02 showed primary IFN resistance, whereas IFN08 was intolerant. Limited initial treatment duration may have been a factor in IFN01 and IFN08 who relapsed but achieved SVR with

retreatment. However, short-term therapy can be effective for AHCV, as IFN05 and IFN15 achieved SVR with only 2 and 14 weeks of therapy, respectively. Thus, virological response to IFN-based therapy was generally excellent in AHCV regardless of timing and duration of therapy, IDU, or IL28B genotype.

The rate of fibrosis progression in HCV-infected patients can depend on various host, environmental, and viral factors.[44] One large systematic review of 111 studies estimated the prevalence of cirrhosis after 20 years of infection to be 14% to 19%.[45] In our cohort, 2 patients (CE05, IFN02) rapidly progressed to cirrhosis within 5 to 8 years without HIV coinfection or HBV coinfection[46,47] or immunosuppression.[48] Although CE05 also suffered from diabetes and obesity, IFN02 had no known factors associated with liver disease progression. Unfortunately, CE05 was not a candidate for IFNα-based therapy, whereas IFN02 was IFN resistant likely related to African American heritage and HCV genotype 1 infection[49] as well as IL28B non-CC genotype.

It is important to emphasize the potential benefits of timely AHCV diagnosis. For example, this can provide valuable window of opportunity for risk reduction counseling, disruption of transmission networks, evaluation for other blood-borne or sexually transmitted infections, education about HCV and liver disease, therapeutic options, and monitoring strategies to ultimately limit health risks at the individual and population levels. Our finding of AHCV in young IDUs also highlights a continued need to screen this population and for preventative interventions (eg, access to clean syringes, addiction treatment, and opiate replacement therapy).

Of interest is the delayed spontaneous HCV clearance beyond 46 to 98 weeks of infection in 2 patients with IL28 CC genotype. Such a phenomenon has been reported in 3/15 Italian patients with AHCV,[30] although the IL28B genotype of the Italian patients is unknown. One can only speculate that the dynamic host-virus interactions in early HCV infection may be protracted and that such a phenomenon might be related to IL28B polymorphism.

Chronic hepatitis C has been associated with autoimmune conditions[50] and AIH with serum autoantibodies detected in up to 18% although not anti-KLM.[31,32] Although pathogenetic mechanisms remain unclear, continued antigenic exposure during chronic HCV infection could lead to B-cell stimulation. Autoantibodies were frequent in our AHCV cohort (25% ANA, 69% ASMA), suggesting that their induction does not require long-term HCV persistence. As for their clinical relevance, the presence of autoantibodies in HCV-infected patients may mislead clinicians to diagnose and treat for AIH. Indeed, corticosteroid administration for suspected AIH resulted in worsening transaminases in IFN14, whereas high ANA titers contributed to delayed treatment in IFN11. In both patients, however, IFNα therapy led to resolution of hepatitis without an apparent AIH flare, indicating that their autoimmune features were HCV-mediated and innocent bystanders.

In conclusion, AHCV can present in a heterogenous manner. A heightened awareness regarding AHCV is needed, given the high proportion of patients with no apparent HCV-associated risk factor and its diverse presentations. Although therapeutic outcome of AHCV is excellent with IFNα-based therapy, greater improvement is anticipated with the use of direct-acting antivirals, provided that there is accurate and timely diagnosis of AHCV.

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