Sexually acquired severe acute hepatitis C infection in men who have sex with men

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Case 1

A 33-year-old man with no notable medical history presented to the emergency department with 4 days of severe malaise and jaundice. He had returned to Canada from a trip to Miami, Florida, 2 weeks earlier, where he had engaged in sexual intercourse with multiple partners without barrier protection, including receptive anal and oral intercourse. Three days before the onset of malaise and jaundice, he started a course of doxycycline for chlamydial urethritis. However, he had stopped taking the medication when he developed these symptoms, as he was concerned they were related to the drug. He reported no history of alcohol or drug use.

The patient's initial examination was notable only for jaundice, and blood tests showed markedly elevated levels of liver enzymes and total bilirubin. His alkaline phosphatase was at the upper end of the normal range at 125 U/L and the international normalized ratio (INR) was high at 1.6 (Table 1). His serum albumin, platelet and glucose levels were normal. We diagnosed severe acute hepatitis, but he did not meet criteria for acute liver failure as he did not have hepatic encephalopathy. The initial work-up for causes of hepatitis was negative.

We did not admit the patient to hospital because we were able to monitor him closely as an outpatient. Within 1 day of discharge from the emergency department, he was seen by a hepatologist, who deemed acute hepatitis C virus (HCV) infection to be the most likely diagnosis. We ordered an HCV polymerase chain reaction (PCR) test, but the request was denied days later because the patient tested negative for anti-HCV antibodies. The PCR test was performed after an appeal to the laboratory and showed a very high viral load of 9.12×10^7 IU/mL.

Given the patient's severe symptoms and presentation, we immediately started him on treatment with sofosbuvir–velpatasvir, before knowing that the patient had an HCV genotype 1a infection. After 4 doses of treatment, his blood test results started to normalize (alanine aminotransferase 936 U/L, total bilirubin 256 µmol/L, INR 1.2), and his symptoms improved substantially.

Key points

- Acute infection with hepatitis C virus (HCV) is a cause of severe acute hepatitis.
- Sexual transmission of acute HCV is uncommon, but risk is accentuated in individuals who engage in receptive anal sex.
- In acute HCV infection, testing by polymerase chain reaction (PCR) returns positive results, but results from tests of anti-HCV antibodies are typically negative for several weeks after exposure.
- Some public health laboratories allow for HCV PCR testing only if the anti-HCV antibody test result is positive, which can make diagnosing acute HCV infection challenging.

Case 2

A 43-year-old man with HIV who was on long-term treatment with lamivudine–abacavir–dolutegravir presented to the emergency department. He had no other notable medical history. He had recently travelled to Miami, Florida; while there, he had engaged in receptive anal and oral intercourse with multiple partners, without barrier protection. He had used intranasally administered cocaine but gave no history of substantial alcohol use. While in Florida, he had been admitted to hospital with acute hepatitis, after developing jaundice and malaise. Investigations for causes, including testing for anti-HCV antibodies, were negative. The discharge diagnosis was drug-induced liver injury from lamivudine–abacavir–dolutegravir.

When the patient returned to Canada, he presented to the emergency department for further evaluation. He was mildly symptomatic with residual jaundice and malaise and had elevated levels of liver enzymes and total bilirubin; his INR was in the normal range at 1.0 (Table 1). The severe hepatitis transitioned to chronic hepatitis without treatment and his symptoms resolved 3 weeks after presentation to the emergency department. A week after returning to Canada, he was notified that the HCV PCR test done in Florida had returned a positive result. Given the patient's mild symptoms and improving laboratory results, we started him on sofosbuvir–velpatasvir only once provincial funding for treatment was secured.

Table 1: Results of laboratory testing over time in 2 patients with acute severe HCV infection

Day relative to ED presentation	Laboratory investigation								Treatment
	ALT, U/L	AST, U/L	ALP, U/L	INR	Albumin, g/L	Bilirubin, mmol/L	Anti-HCV	HCV PCR	
Case 1									
−2809	38	27	73	1.11		12			
−985							Negative		
0	2948	2618	125	1.60	43	110			
1	5358	5226	167	1.85	43	202	Negative	Test ordered	
4	5201	4465	202	1.8	40	420			
5	4480	3808	196	1.8	39	482			
7	2525	4090	174	1.7		343		Result reported: genotype 1a 9.12×10^7 IU/mL	Started patient on sofosbuvir–velpatasvir
11	936	250	124	1.2	37	256			
26	120	71	82	1.1	46	71			
47	25	21	67	1.1	47	26			
Case 2									
−158	24	20	67			9	Negative		
−7	2286	1399	232		34	173			
0	679	468	171			107			
1	764	497	158			112		Test ordered	
2	1170	922	186	1.0	39	139	Negative		
3	1001	681	205			112			
13	125	41	126			36			
20	173	75	120			26			
22	125	46	103	1.0	42	27	Positive		
34								Result reported: genotype 1a 3.52×10^5 IU/mL	
44	130	73	113			13			
75	169	54	111			8			
98									Started patient on sofosbuvir–velpatasvir

Note: ALT = alanine aminotransferase, ALP = alkaline phosphatase, anti-HCV = antibodies to hepatitis C virus, AST = aspartate aminotransferase, ED = emergency department, HCV PCR = hepatitis C virus polymerase chain reaction, INR = international normalized ratio.
*Normal levels as follows: ALT 7–40 U/L, AST 5–34 U/L, ALP 40–150 U/L, INR 0.9 –1.2, albumin 38–50 g/L, bilirubin ≤ 22 mmol/L.

Discussion

For both patients, clinicians initially considered the diagnosis of acute HCV unlikely, as no parenteral risk exposures were reported (although sharing straws for intranasal cocaine is a potential source of infection), the transaminitis was severe (> 1000 U/L) and the anti-HCV antibody test returned negative results. Furthermore, the reported incidence of acute HCV infection is low in Toronto at 0.7 per 100 person-years.[1] An approach to the investigation of severe hepatitis — defined as alanine aminotransferase (normal < 45 U/L) and aspartate aminotransferase (normal < 40 U/L) levels at least 10 times greater than normal — is outlined in Box 1.

Although acute HCV infection has generally been thought to be asymptomatic or pauci-symptomatic, presenting with subclinical viremia and subsequent seroconversion,[3] severe acute HCV infection leading to fulminant hepatitis is a well-characterized entity, as viral genomes from such cases have been isolated in vitro.[4] As such, the focus in practice has been on screening for chronic HCV infection rather than detecting acute infection.

Current testing regimens are based on a 2-step process whereby the patient is first assessed for the presence of anti-HCV immunoglobulin (Ig) G antibodies. The HCV viral load is assessed by PCR as the second step, only if the serology is positive for

Box 1: Approach to investigating and managing severe hepatitis*

- Viral hepatitis:
  - Hepatitis A (HAV): test for immunoglobulin (Ig) M anti-HAV antibodies
  - Hepatitis B (HB): test for HB surface antigen, IgM anti-HB core antibodies, anti-HB surface antibodies
  - Hepatitis C (HCV): test for anti-HCV antibodies and test by HCV polymerase chain reaction
- Drug-induced liver injury: establish history of prescribed and non-prescribed drugs, or toxins
- Ischemic liver injury: establish history of hypotension and acute kidney injury
- Hepatic congestion: order imaging to detect enlarged heterogeneous liver, thrombus in hepatic vein or dilated hepatic vein from right-sided heart failure
- Acute biliary obstruction: order imaging to detect dilated bile ducts. Biliary obstruction can initially present with hepatitis, but evolves to a cholestatic pattern over time.
- Autoimmune hepatitis: test for anti-nuclear antibodies, smooth muscle antibodies, elevated IgG. Initially, tests may be negative. Severe autoimmune hepatitis is a diagnosis of exclusion.[2]

*Alanine aminotransferase (normal < 45 U/L) and aspartate aminotransferase (normal < 40 U/L) levels at least 10 times greater than normal.

these antibodies.[5,6] The primary aim of this approach is to distinguish between active and resolved HCV infection. In acute infection, however, HCV serology can return negative results, as illustrated by our 2 cases. In the natural history of infection, symptoms begin 3–4 weeks after exposure, but detectable seroconversion with the appearance of anti-HCV IgG antibodies occurs around 8–11 weeks for most people.[3]

Therefore, a negative anti-HCV antibody test early in the course of acute hepatitis does not rule out acute HCV infection. However, public health organizations in British Columbia and Ontario currently recommend testing for anti-HCV antibodies in cases of suspected hepatitis,[5,6] and testing for viral load by HCV PCR is typically not permitted unless the serology is positive. A negative antibody test is interpreted as absence of infection. This approach poses a challenge for the detection of acute HCV infection, potentially leading to unnecessary invasive tests and hospital admission.

A compounding challenge to diagnosis lies in beliefs about how HCV is transmitted. Multiple sources, including the World Health Organization[7] and some provincial health organizations,[5,6] continue to emphasize that HCV is a bloodborne infection, with risk factors for transmission including sharing or reusing medical equipment, using intravenous drugs and receiving unscreened blood products. However, HCV has been detected in the semen of about one-third of viremic men;[8] sexual transmission among men who have sex with men (MSM) from exposure to semen and rectal fluid is an ongoing concern.

The transmission of HCV between heterosexual couples is exceedingly rare, estimated at 1 infection per 190 000 episodes of sexual contact.[9] In the MSM population, however, sexual transmission is thought to be driven by microdamage to the mucosal barrier in the rectum during intercourse. Practices including fisting, use of sex toys and group sex, as well as the presence of anogenital ulcerative disease, have been associated with five- to ninefold increases in the risk of HCV transmission.[10] Recent studies suggest that HCV transmission occurs in both HIV-positive and HIV-negative MSM, including people on HIV pre-exposure prophylaxis.[9]

Between 2012 and 2019, the incidence of HCV in Toronto, for example, was estimated to be 0.7 per 100 patient-years, very low compared with chlamydia, gonorrhea and syphilis at 49.2, 36.3 and 5.2 per 100 patient-years, respectively.[1] The risk of sexual transmission of HCV in Toronto appears to have fallen, likely because local health care providers for the at-risk population have aggressively screened for and treated patients with chronic HCV infection. In these 2 cases, the patients had been screened for HCV previously by their primary care providers (Table 1).

Globally, incidence estimates for HCV infection range from 0.6–4.8 per 100 patient-years, with higher estimates reported in Europe.[11] The prevalence of HCV antibodies in Florida was 4 times the average of the United States in 2019 at 4.1%.[11] Phylogenetic analyses of HCV genome sequences in Europe, Australia and the US show overlapping clusters by geography, but also between networks of MSM and people who inject drugs.[9] This reflects the international interconnectedness of social and transmission networks, which drives primary infection and reinfection.[9] Thus, reliance on local HCV incidence rates can be misleading when assessing risk in the MSM population.

Considered together, these issues highlight several areas of concern. Acute HCV infection is often overlooked as a cause for acute transaminitis, with or without liver failure, and routine methods of testing are not sensitive for ruling out infection. The active transmission of HCV in the MSM population is globally interconnected through overlapping social networks, which poses a risk of both primary and re-infection for people who are active in these networks. As public health measures implemented during the COVID-19 pandemic are lifted and international travel rebounds, an increase in HCV cases is to be expected. In both of these cases, the patients' risk of infection was increased by travel in early 2022 to Florida, where international social networks overlap.

Reliance on current testing regimens can lead to delays in diagnosis of 6 months or more as these regimens do not account for time to detectable seroconversion. This may potentiate ongoing transmission as patients are unaware of their infectious status. These cases emphasize the importance of assessing for acute HCV infection with viral PCR in patients presenting with marked transaminitis, especially if they have risk factors such as being part of the MSM population, being positive for HIV or having travelled to an area with higher endemic rates of HCV.

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