

Acute Hepatitis A Outbreak Among Men Who Have Sex With Men in Krakow, Poland; February 2017–February 2018

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Abstract

Since February 2017 in Poland, an increasing number of acute hepatitis A (AHA) cases have been reported; a noteworthy increase to 3,072 cases of AHA in 2017 compared to 35 cases in 2016 was reported by the National Institute of Public Health (NIPH). The aim of this study was to evaluate the demographic features, clinical manifestations, laboratory results, and sexually transmitted coinfections. All cases of AHA diagnosed between February 2017 and February 2018 at the University Hospital in Krakow were analyzed. A total of 119 cases of hepatitis A virus (HAV) were reported; 105 (88%) were males and 14 (12%) were females, with a mean age 31 years (range 19–62). In 84 patients (71%), the HAV was transmitted by oral–anal sexual contact between men. Six women were infected by close house contact with men infected with HAV. The route of transmission was not identified for 29 cases, and 88 patients (74%) required hospitalization. Among the cases, the following coinfections were already diagnosed: HIV 36 patients (30%), chronic hepatitis C virus (HCV) 4 patients (3%), and chronic hepatitis B virus (HBV) 2 patients (1.5%). During AHA diagnosis, some new sexually transmitted infections (STIs) were detected; syphilis eight patients (6.7%), HIV/syphilis seven patients (6%), HIV//HCV/syphilis one patient, and acute retroviral syndrome/*Shigella flexneri* one patient. Overall, AHA outbreak in Poland in 2017 affected primarily men who have sex with men (MSM) and was connected with oral–anal sexual contacts, and the majority of patients did not have HAV vaccination. These results show a clear need for routinely offering HAV vaccination to at-risk populations and that awareness among health-care workers about HAV sexual transmission may help introduce prevention methods.

Keywords

hepatitis A, outbreak, MSM, coinfections, HIV, syphilis

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Hepatitis A is an acute liver infection caused by *Hepatitis A virus* (HAV) in the family Picornaviridae, genus *Hepatitis A virus*. Humans are the only reservoir of infection and transmission is via the fecal–oral route (Lin et al., 2017). HAV is the most common cause of acute hepatitis worldwide, with a predominance of infections occurring in developing countries including Africa, Asia, and South America. Up to now, most of the cases were connected with the consumption of contaminated water or food; virtually any food can be contaminated with HAV, especially food that is not properly heated after contamination (Lin et al., 2017). Low socioeconomic conditions and poor sanitation are considered to be important risk factors of infection (Ciccullo et al., 2018; Lin et al., 2017). The last outbreak in Europe

and North America once again revealed that HAV should be considered a sexually transmitted infection (STI) via oral–anal sex, but also digito–anal and genito–oral sex. Due to these sexual activities, men who have sex with men (MSM) are known to be a high-risk group (Boucher

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et al., 2018; Ciccullo et al., 2018; Lin et al., 2017; Ndumbi et al., 2017).

The HAV incubation period ranges between 15 and 50 days. A lot of the cases have mild severity; symptoms such as fever, nausea, fatigue, loss of appetite, diarrhea, and jaundice predominate in the clinical picture (Lin et al., 2017). Severe courses and fulminant hepatic failure are reported in less than 1% of cases, with a death rate of less than 0.3% (Lin et al., 2017).

The last Europe-wide outbreak of HAV was in 2008, where marginalized populations such as MSM and HIV-positive individuals were the most affected in various parts of Europe including the Czech Republic, Slovakia, Latvia, Spain, Italy, Ireland, as well as Poland (Bordi et al., 2012; Dabrowska et al., 2011; Sfetcu et al., 2011). Past research has reported that MSM are at high risk for HAV infections (Bialek et al., 2018). From the end of 2016 to the end of 2017, an increasing number of acute hepatitis A (AHA) cases, especially among MSM in Europe, were observed (Lanini et al., 2017; Ndumbi et al., 2017; Rodríguez-Tajes et al., 2018). According to available epidemiological data from the European Center for Diseases Prevention and Control, the number of outbreak-confirmed cases of AHA from 22 European Union/European Economic Area (EU/EEA) since June 1, 2016, until September 7, 2018, was 4,475. In 2017 the National Institute of Public Health (NIPH) in Poland reported 80 times more cases than in 2016. The main route of transmission was sexual, oral–anal contacts among MSM, with the rapid spread of HAV to close house contacts. The aim of the study was to investigate demographic and clinical features of 119 cases of AHA treated in the University Hospital in Krakow, Poland, from February 1, 2017, to February 1, 2018.

Patients and Methods

All cases of AHA treated in the University Hospital in Krakow from February 2017 to February 2018 were analyzed, including those hospitalized in the Infectious Diseases Department as well as those who stay under the control of the Outpatient Clinic. Twenty-eight of the patients already diagnosed with HIV were under the constant control of the Outpatient Clinic of the Infectious Diseases Department. Others were referred to the University Hospital from general practitioner (GP) doctors' offices, emergency rooms, or other hospitals in Krakow and the southeast part of Poland. Informed consent was obtained and patients were informed about the purpose of the study. All patients voluntarily confirmed their willingness to participate by signing consent forms and none of the patients refused collection of data. Therefore, approval from the local ethics committee was not obligatory. The cases of HAV were confirmed by

testing for hepatitis A–specific immunoglobulin M (IgM) antibodies (HAV IgM) via enzyme-linked immunosorbent assay (ELISA) among patients with symptoms of viral hepatitis.

Data on epidemiology, probable route of transmission, and clinical manifestations were collected. Additional information about risky sexual behavior, including oral–anal, digito–anal, and genito–oral sex, medical history, previous STIs, as well as preexposure prophylaxis (PrEP) of HIV was obtained through face-to-face interviews with physician. The interviews were conducted on the basis of a standard questionnaire for AHA, which is used in our hospital. All coinfections diagnosed at the moment of AHA diagnosis were recorded. Serology tests were used to screen concomitant infections with hepatotropic viruses, HIV and *Treponema pallidum* (HBs antigen (Ag); anti-HBc antibody (Ab); anti-HBs Ab; anti-HCVAb, fourth-generation enzyme immunoassays (EIA) for p24Ag/HIV1&HIV2Ab, and rapid plasma regain (RPR) and *T. pallidum* hemagglutination (TPHA) tests); if positive, appropriate molecular tests were done (HBV-DNA, HCV-RNA, HIV-RNA). Analysis of laboratory test results of patients with AHA (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] at the time of diagnosis) were made. We evaluated the rate of hospitalization among investigated groups and any differences in the clinical course of AHA and in lab values between patients with and without HIV coinfection.

For the statistical analysis, we used SPSS software version 24.0. Initially, Kolmogorov–Smirnov tests were done, which showed that our data did not differ significantly from a normally distributed scale. An unpaired *t* test was then performed to assess the statistical significance between the two groups.

Results

Between February 2017 and February 2018, 119 cases of AHA were reported in the Outpatient Clinic and Infectious Diseases Department of the University Hospital in Krakow. One hundred and five patients were male (88%) and 14 were female (12%), with a median age of 31 years (range 19–62). Table 1 presents the age range and sex distribution for the total number of patients. Eighty-four of the patients (71%) identified themselves as MSM.

The highest number of HAV cases were diagnosed from June 2017 to September 2017 (June—17 cases, August—28 cases, September—28 cases). Figure 1 presents the number of cases for each of the 12 months and the corresponding number of male and female cases. The most common way of hepatitis A transmission was sexual contact—84 patients (71%). All of the MSM patients

Table 1. Characteristics of Investigated Group.

Characteristics	Number (n)	Percentage (%)
Sex		
Male	105	88
Age range		
0–19	2	2
20–39	83	79
40–59	20	19
60+	0	0
Female	14	12
Age range		
0–19	0	0
20–39	7	50
40–59	5	35.7
60+	2	14.3
MSM		
Yes	84	80
Travel in 2 months before symptoms onset		
Yes	8	7
Hospitalized for AHA		
Yes	88	74
HIV infected before AHA		
Yes	28	23
On antiretroviral therapy		
Yes	25	89
HIV-RNA <50 copii/mL	24	86
HIV- RNA >50 copii/mL	1	4
No	3	11
Chronic HBV		
Yes	2	1.5
Chronic HCV		
Yes	3	3
Other STDs diagnosed with AHA		
HIV	8	7
HCV	1	1
Syphilis	8	7
<i>Shigella flexneri</i>	1	1
HAV mode of transmission		
Risky sexual behaviors/MSM	84	71
Foodborne/unknown		
Male	21	18
Female	14	12

Note. AHA = acute hepatitis A; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; MSM = men who have sex with men; RNA = ribonucleic acid.

reported risky sexual behaviors without the use of protection with multiple partners in the period of 2 months before the diagnosis of AHA: oral–anal sex 81 (68%), digito–anal 83 (70%), and genito–oral 84 (71%). None of the investigated patients was on PrEP.

The remaining 35 patients, including 21 men who identified themselves as heterosexual, did not report any risky sexual behaviors. Among the patient pool, there were only 14 women (12%); 6 of the women infected with AHA lived in close quarters with men with AHA (3 mothers, a patient's sister, the wife of a patient, and one sharing a flat with a man infected with AHA). These cases represent the result of the spreading of the epidemic through a close physical environment.

The mode of transmission was not identified in 29 patients; 21 men (18%) and 8 women (8%) identified themselves as heterosexual. The most probable mode of transmission in this group was foodborne contamination with HAV. One patient traveled to Ukraine in the period of 6 weeks before the diagnosis of AHA.

The majority of the patients were exposed to HAV in Poland, with a minority of eight cases (7%) reporting a travel history outside of Poland (Ukraine—2, Spain—3, Israel—1, Oman—1, and Cyprus—1) during the assumed period of possible infection. Among these patients, seven identified themselves as MSM reporting risky sexual behavior during travel. Detailed characteristics of the investigated group are presented in Table 1.

Concomitant STIs acquired before and at the moment of AHA diagnosis were evaluated in detail. Thirty-six patients with AHA had HIV, eight (22%) of whom were newly diagnosed. Of these patients, one presented with acute retroviral disease and *Shigella flexneri* infection. The patient revealed a history of passive and active unprotected anal sex with multiple male partners during the period of 3 months before the diagnosis. There were 28 (78%) patients diagnosed with HIV before the AHA diagnosis. Twenty-four (67%) were on effective antiretroviral (ARV) therapy with HIV-RNA viral load below 20 copies/mL. In this group, 4 patients were diagnosed with HIV less than 12 months before AHA (minimum 1 month, maximum 11 months), 7 patients 2 years before AHA (minimum 12 months, max 2 years), and 13 patients more than 2 years before AHA (minimum 3 years, maximum 10 years)

Three patients (8%) were not treated with ARV drugs (HIV-RNA range from 14.9×10^3 copies/mL to 23.2×10^4 copies/mL). One patient (3%) who started antiretroviral therapy (cART) 1 month before AHA had a detectable viral load of 952 copies/mL at the time of diagnosis. All cases of coinfection with HIV were reported among MSM.

Four patients had HAV/HCV coinfection, but only one patient was diagnosed with both HCV and syphilis at the time of AHA diagnosis. This patient was already infected with HIV and was on an effective ARV therapy. He reported multiple risky sexual contacts without protection.

Eight patients (7%) with HAV were diagnosed with *T. pallidum* and required treatment with penicillin; six of

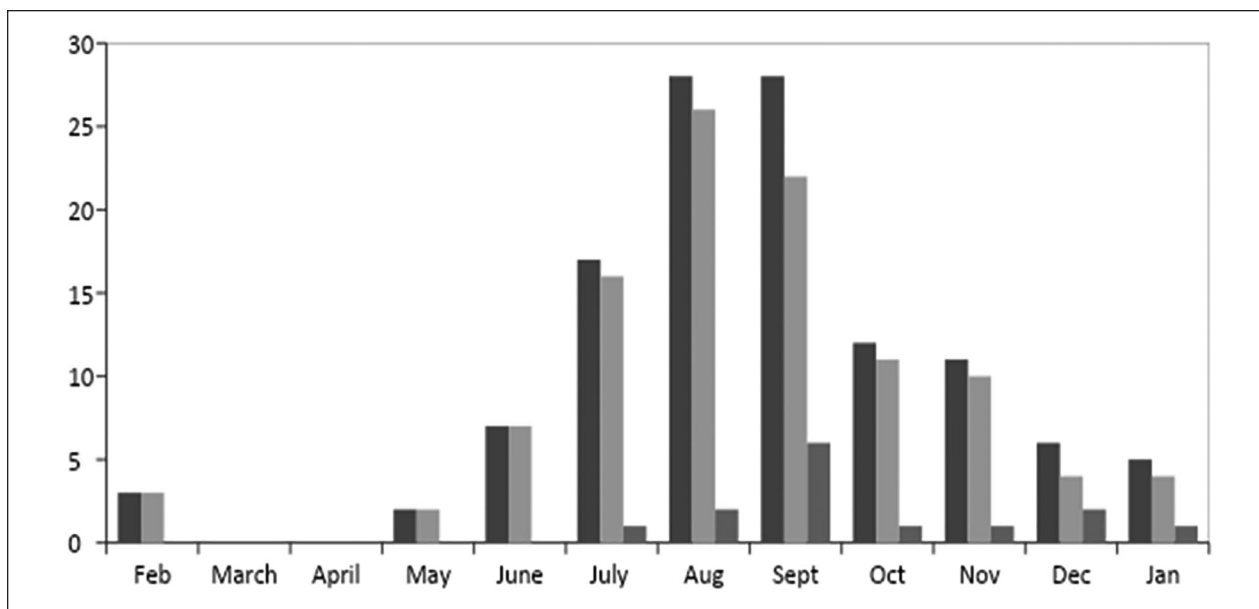


Figure 1. Total number of HAV cases and the number of male and female patients for each month. HAV = hepatitis A virus.

them had early latent syphilis, one patient had primary syphilis with ulceration of the urogenital area, and one patient had neurosyphilis. Seven patients were already diagnosed with HIV. Twenty-six patients (22%) were previously diagnosed with syphilis and treated at least 1 year before the episode of AHA. All of these patients were from the MSM group.

Two patients (1.5%) had HBV/HAV coinfection, which was not treated previously. Both of these patients were from MSM group and were treated for syphilis in the past. From the patient pool, 21 men (18%) identified themselves as heterosexual. Among this group, there were no coinfections diagnosed. One of the men was a cousin of a patient from the MSM group infected with HAV and one traveled to Ukraine before diagnosis. In the rest of the cases, the mode of transmission was not clear. There were no concomitant STIs among the women group.

Vaccination history against HAV, which is completely voluntary in Poland, was evaluated. Only one patient of all subjects was vaccinated against HAV before the symptoms appeared. The patient was vaccinated by one dose after exposure to close contact with HAV infection.

Eighty-eight of the patients (74%) required hospitalization. Criteria for hospital admission are presented in Table 2 and only one of the criteria had to be met for admission. Mean duration of hospitalization was 11 days (range 3–40 days). The decision about the discharge of the patient from the hospital was set individually, where clinical improvement and a decrease in high laboratory test results were observed. No cases of acute liver damage were reported during the analysis. There were only

18 patients with elevated INR ratio (range 1.22–1.46). Mean value of ALT during recognition in all patients was 1948 U/L (min 58 U/L, max 5,216 U/L) and the mean value of maximum ALT presented was 2143 U/L (min 133 U/L, max 5,126 U/L).

All enzyme values at the time of diagnosis and the maximum value during the clinical course of HAV between HIV and non-HIV patients are reported in Table 3. Patients with HIV presented with significantly higher mean values of gamma-glutamyl transpeptidase (GGTP) at the time of diagnosis compared to patients without HIV. The difference between the max GGTP value in patients with HIV and non-HIV was statistically significant ($p = .05$).

Discussion

From February 2017 until February 2018, an increasing number of HAV cases were reported with a high male-to-female ratio during the outbreak, with MSM (71%) being particularly affected. The primary mode of transmission was determined to be risky sexual practices with multiple sexual partners between males. Only a small number of cases were the result of spreading of the epidemic through social environment and 7% of patients associated with traveling outside Poland. The highest number of HAV cases diagnosed from June 2017 to September 2017 can be connected with higher sexual activity and unsafe sex during the summer vacation. It should be stressed that among travelers, 88% were from MSM group and they were engaged in high-risk sexual behavior, including

Table 2. Criteria for Hospital Admission Patient With AHA.

Criteria for hospital admission patient with AHA.

- Age >50 years
- Intensive nausea or vomiting with signs of dehydration
- INR ratio >1.2
- Coinfection of HCV or HBV
- Ascites
- Consumption of more than 3 g of paracetamol/day during the past week
- Newly diagnosed HIV
- Uncontrolled chronic diseases (i.e., chronic renal insufficiency, diabetes mellitus)

Note. AHA = acute hepatitis A; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio.

Table 3. The GGTP Values of HIV and Non-HIV Individuals Infected AHA (significant values are noted with a *).

	HIV	Non-HIV	p value
ALT at the time of diagnosis (U/L)	1,877	2,202	.544
Maximum ALT	1,956	1,970	.199
GGT at the time of diagnosis (U/L)	357	259	.033*
Maximum GGT (U/L)	364	300	.055
Bilirubin at the time of diagnosis (μmol/L)	132	118	.151
Maximum bilirubin (μmol/L)	172	150	.131

Note. ALT = alanine aminotransferase.

oral–anal, digito–anal, and genito–oral sex while traveling abroad. Most of the patients were young, with a higher attack rate before 40 years of age. Analysis of AHA cases in clinic follows the European trend, where from January 2017 to December 2017, 20,067 cases of HAV (15,591 male and 4,476 female) in European countries were reported. The highest increase was between March and July 2017 with a predominance of MSM affected (Boucher et al., 2018; Fierro, 2019; Lanini et al., 2017).

High number of previously diagnosed and new episodes of STI coinfections were reported among MSM patients with AHA treated in the University Hospital in Krakow including HIV, *T. pallidum*, HBV, HCV, and *S. flexneri*. As many as 43% of MSM patients were already infected with HIV, most of them on effective cART. All of them reported unprotected sex with unsteady partners. In this group, previous episodes of other STIs were also diagnosed. This high rate of HIV coinfection can be attributed to the fact that the study was conducted in a referral hospital for individuals living with HIV. Another reason for HAV and HIV coinfection in MSM population may be due to shared features such as having casual sex with multiple male partners, oral–anal sex, inconsistent condom use, and intravenous drug use. Furthermore, HIV can be considered a risk factor for AHA infection, as coinfection can exacerbate HAV-associated liver diseases and prolong the fecal excretion of HAV (Ndumbi et al., 2017). Coinfections with HAV and HIV were reported

before in Italy, Spain, and Poland (Dabrowska et al., 2011; Lin et al., 2017). Eight new cases of HIV, including one episode of acute retroviral disease, were detected during the outbreak of AHA. None of the patients, in spite of high-risk sexual behavior, was on PrEP.

The medical staff at the clinic was engaged in the care of HIV-infected patients and MSM with other STIs. Physicians and nurses should work to enhance educational methods regarding safe sexual practices, barrier methods, PrEP, and the importance of regular testing to prevent transmission.

HCV infection was diagnosed in 4.7% of the MSM pool, but only in one case acute hepatitis C was confirmed. Recent outbreaks of HAV, as well as HCV among MSM, showed that these viruses can be effectively spread through anogenital contact (Soriano & Romero, 2019). Some of the patients were newly diagnosed with more than one STI at the time of the AHA diagnosis and required treatment for concomitant diseases.

Results of the study indicate a higher risk of coinfections with other sexually transmitted diseases (STDs) among MSM with AHA. This may be in connection with risky sexual behaviors including chemsex, sexual disinhibition, and multiple sexual partners. One limitation of the study is that we did not collect data about chemsex among the investigated group as well as the number of sexual contacts and partners, participation in sexual parties, and using sexual networking applications to locate such sexual parties.

It should be emphasized that HAV is preventable by an effective and safe vaccine, which has been available since 1995. The vaccination is recommended by the European and Polish Guidelines among vulnerable populations such as HIV-infected individuals. There is no official recommendation to vaccinate people in the MSM group. The study revealed that none of the patients, including those already infected with HIV, was vaccinated against HAV, except one who received one dose of vaccine as postexposure prophylaxis. This confirmed that vaccination coverage is very low, even among people from high-risk groups. Ndumbi et al. (2017) reported that 92% of analyzed patients during the last outbreak in the EU and EEA were unvaccinated, which corresponds with our data. In other research, authors emphasized low immunity levels and highlighted the importance of HAV vaccinations among MSM (Latash et al., 2017). Other researchers proved increasing susceptibility to HAV infection among younger corporate professional employees in large cities in Poland (Juszczak et al., 2018). During the outbreak in Poland, there was a temporary nonavailability of vaccinations. Other European countries experiencing the HAV outbreak, such as Denmark, France, Spain, Norway, and Great Britain, also reported a low vaccine availability (Petersen et al., 2019). Regan et al. have suggested that vaccine coverage in the vicinity of >70% is required for MSM populations in most large Western metropolitan centers to prevent an outbreak of HAV (Regan et al., 2016). Taking into considerations all these facts, the medical staff should be educated about the importance of HAV vaccines among MSM. Promoting vaccines among gay community events as well as providing no-cost or subsidized vaccinations in such settings as sexual health clinics have been postulated (Regan et al., 2016). Modeling studies suggested that immunity among MSM must exceed 70% to prevent further transmission of HAV (Charre, 2017). Postvaccine testing can be considered among HIV-positive patients as the effectiveness of vaccination is not ensured (Fritzsche et al., 2018). Prevention campaigns that target MSM population and promote protective sexual behaviors seem to be an important supplementary method, especially among men who have multiple anonymous partners. Also further investigations regarding routine sexual practices among MSM populations may help the development of more effective control measures.

Results of investigations proved that health-care professionals should determine MSM status during workup with AHA patients, collect information regarding “chem-sex,” “slam sex,” PrEP, and other factors, which can be connected with a higher risk of STI transmission. Trained health-care professionals in regard to STIs and possible methods of prevention such as offering vaccinations, behavior interventions, and management of drug abuse

seem to be essential (Charre, 2017; Soriano & Romero, 2019).

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