Chronic liver disease in Aboriginal North Americans

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Abstract

A structured literature review was performed to detail the frequency and etiology of chronic liver disease (CLD) in Aboriginal North Americans. CLD affects Aboriginal North Americans disproportionately and is now one of the most common causes of death. Alcoholic liver disease is the leading etiology of CLD, but viral hepatitis, particularly hepatitis C, is an important and growing cause of CLD. High rates of autoimmune hepatitis and primary biliary cirrhosis (PBC) are reported in regions of coastal British Columbia and southeastern Alaska. Non-alcoholic liver disease is a common, but understudied, cause of CLD. Future research should monitor the incidence and etiology of CLD and should be geographically inclusive. In addition, more research is needed on the treatment of hepatitis C virus (HCV) infection and non-alcoholic fatty liver disease (NAFLD) in this population.

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INTRODUCTION

Aboriginal North Americans, which include American Indians and Alaska Natives (AI/ANs), Canadian First Nations, and native Greenlanders, are disproportionately affected by chronic liver disease (CLD). CLD for the purpose of this review includes the diagnoses of cirrhosis, end-stage liver disease (ESLD) and its complications, and chronic elevation of transaminase enzymes. In the United States, CLD was the twelfth leading cause of death in the general population in 2003, but was the fifth leading cause of death in AI/AN populations[11]. Likewise, cirrhosis is a disproportionate cause of death in Canadian First Nations[2]. Very little is known about the prevalence and incidence of CLD in native Greenlanders, although chronic hepatitis B incidence is known to be high in this population[8]. Of great concern, between 1990 and 1998, the overall annual CLD mortality rate in the United States declined by 4.5% but increased 11% among AI/AN populations[9]. Despite these striking disparities, studies examining the incidence, prevalence and etiology of CLD in Aboriginal North Americans are scarce. The goal of this paper is to summarize the etiology, natural history, and mortality rates of CLD in Aboriginal North Americans.

LITERATURE RETRIEVAL

English language articles were identified by a search of the PubMed database from 1966 to August 2007. Because articles on Aboriginals from Mexico and Central America were frequently in non-English, we restricted our study to Aboriginals in the United States, Canada, and Greenland. Search terms included the following 7 individual medical conditions: chronic hepatitis, alcoholic liver disease, liver cirrhosis, fatty liver, hemochromatosis, hepatolenticular degeneration, and hepatitis A. Variants of these terms were also used; for example, in addition to fatty liver, other key words included non-alcoholic steatohepatitis (NASH). To identify publications focused on Aboriginal peoples, our search terms were American Indian(s), Alaska Native, native Alaskan, Native American, North American Indian(s), Greenland, and Inuit(s). Next, the bibliographies of the retrieved
This finding was unexpected. These frequency of specific etiologies for chronic liver disease among AI/AN was 25.5-28.7 per 100,000 compared to 6.0-15.4 deaths per 100,000. Specific mortality data from Canadian data did not include separate categories for hepatitis B and C. Data not available on Canadian First Nations peoples and native Greenlanders specifically. Data adapted from Statistics Canada[4] and Vong[7].

In this review, we refer to the 7 disorders above as CLD. A meta-analysis, or other forms of systematic analyses, was not possible to conduct owing to the number of CLDs, variations in study designs, methods (particularly participant selection and case definitions), heterogeneous nature of the population, pockets of certain liver diseases, and the quality of the investigations.

Studies assessing patients with at least 1 CLD that included information on at least one North American Aboriginal population were included. In addition, we excluded studies which had no confirmed diagnosis, such as self-reported symptoms. We focused on publications that reported three kinds of data: prevalence, etiology, and patient characteristics. Prevalence data are summarized in Table 1. Next, we outlined information on discrete diagnoses. These studies, which are more clinically useful than population studies, are shown in Table 2. For each study, information was abstracted on the patient groups and the diagnostic criteria applied, the methods, and the major findings. The sources of the authors’ funding had no role in the collection or interpretation of the data. Based on these tables, we summarized information for the sections below.

**EPIDEMIOLOGY OF CLD**

Two studies from the past decade reported the overall, age-adjusted death rates due to CLD in AI/AN populations was 25.5-28.7 per 100,000 compared to 10.4-11.6 per 100,000 in the general population[1,2]. Moreover, CLD disproportionately strikes young adults; it was the second-leading cause of death among AI/ANs 25-44 years old[3]. In another study, researchers classified underlying conditions contributing to death by ICD-9 (International Statistical Classification of Diseases, version 9) codes as listed on death certificates[6]. In 1998, the top contributors to CLD mortality in AI/AN were: alcohol (65%), hepatitis C virus (HCV) (8%), hepatitis B virus (HBV) (2%), and primary biliary cirrhosis (PBC) (1%). Notably, 24% of the deaths had no attributable cause.

Among AI/AN patients living with CLD, researchers observed a similar theme of high disease burden from viral hepatitis and alcohol, in conjunction with a large proportion of unexplained liver disease. In a study of AI/ANs obtaining outpatient and inpatient services in Phoenix, AZ, San Bernardino, CA, and Anchorage, AK, 5%-7% of AI/ANs had evidence of CLD[6,7]. These studies defined CLD as two elevated AST, ALT, or total bilirubin levels separated by 6 mo. Alcohol and HCV were the most common causes of CLD; however, non-alcoholic fatty liver disease (NAFLD) was also a major etiology and a significant proportion had no identified etiology (Figure 1).

In the general population of Canada, CLD is the 13th most common cause of death[8], accounting for 6.0-15.4 deaths per 100,000. Specific mortality data from CLD in Canadian First Nations was not available in published form or directly from Statistics Canada.

No mortality statistics are available for Greenland. However, in a study of hospitalized patients, the prevalence of cirrhosis, as determined by ICD-10 (International Statistical Classification of Diseases, version 10) discharge diagnoses, was lower in Greenlanders (0.19%) than in a similar cohort in Denmark (0.54%)[9]. This finding was unexpected because Inuit Greenlanders are known to have high rates of viral hepatitis and thought to consume more alcohol on average than their Danish counterparts living in Greenland.

CLD in Aboriginal North American populations is heterogeneous, with certain causes of CLD found in unique geographic regions, such as HBV in the circumpolar regions and PBC in coastal British Columbia (Figure 2).

### HEPATITIS A

Before the implementation of hepatitis A virus (HAV) vaccination, this disease caused large outbreaks,
cycling every 5-7 years in many AI/AN communities. Although US national prevalence statistics have not been published, incidence rates of hepatitis A in AI communities in South Dakota have been reported as 33

Table 2  Major causes of viral hepatitis in Aboriginal North Americans

| Aboriginal group          | Study populations                        | Hepatitis A       | Hepatitis B       | Hepatitis C       | Comments                                                                 |
|--------------------------|------------------------------------------|-------------------|-------------------|-------------------|--------------------------------------------------------------------------|
| Native Americans          | South Dakota NA                           | Pre-vaccine incidence was 96/100000 | N/A               | Seroprevalence: 76% | Hepatitis A incidence now is comparable to general population: 1.0-2.0/100 000 |
|                          | Navajo NA                                 |                   |                   |                   |                                                                          |
|                          | Urban and Veterans populations            |                   |                   |                   |                                                                          |
| Alaska Natives            | Random distribution of AN tribes          | 49% seroprevalence pre-vaccination | 6% sAg+, 24% core IgG+ | 0.8% seroprevalence | Heavy burden of hepatitis a prior to vaccination. Hepatitis B endemic to AN with high rates of HCC in certain regions, vaccination has lead to decreased incidence |
| First Nations (Canada)    | Manitoba FN                               | Seroprevalence of 90% in those < 40 yr; 31/100000 incidence pre-vaccine | 5% sAg+, 27% core IgG+ in circumpolar regions, much lower outside circumpolar areas | 1.1% seroprevalence in Inuit, 2%-20% in non-Inuit | Similar patterns of hepatitis as seen in US. |
|                          | British Columbia FN                       |                   |                   |                   |                                                                          |
|                          | Inuit                                     |                   |                   |                   |                                                                          |
| Native Greenlanders       | Inuit                                     | 54% seroprevalence | 7%-12% sAg+, 42% core IgG+ | < 1% seroprevalence | Hepatitis B may be spread sexually more frequently than other Aboriginal populations. HCC also less common |
| (Inuit)                   |                                          |                   |                   |                   |                                                                          |

Figure 2  Common causes of chronic liver disease in Aboriginal North Americans.
HEPATITIS B

A recent national study of hepatitis B in AI/ANs indicated that HBV accounted for just 11 deaths, a rate of 0.60/100,000 persons. In contrast, hepatitis B is an important cause of CLD in AN living in the circumpolar region. Among AN, high rates of acute, icteric hepatitis B were first reported in the 1970s. Subsequent studies found that 6.4% of ANs were surface antigen-positive and 24.2% were positive for hepatitis B core antibody.

The vast majority of HBV infection in AN is acquired horizontally, usually before the age of five. A small pocket of AN with genotype C (Asian variant) transmit HBV vertically (personal communication, Brian McMahon). As a result, most AN have an intermediate risk of becoming chronic carriers. Of those AN children exposed before the age of five, 28.8% will be chronic carriers. Once chronically infected, AN carriers of HBV rarely clear the infection. A large study of HBsAg positive AI/AN patients showed an average annual seroreversion rate to anti-HBs of 0.3%; however, patients over 40 years had a much higher seroreversion rate (4.4%) than those under 40 years (1.7%) [22].

Another survey of 1536 HBsAg positive AN people demonstrated that 42% were HBeAg positive at baseline [23]. Of those who were HBeAg positive, 73% cleared HBe-antigen within 10 years. After a median of 20.5 years of follow-up, 8% remained HBc antigen positive and 22% became anti-HBe positive but then reactivated to HBe antigen-positivity. Among those who were anti-HBe positive and HBe antigen negative at the beginning of the study, 86% remained anti-HBe positive throughout the period of observation [24]. The time to clearance was shorter for those who were HBeAg negative than for those who were HBeAg positive.

Several sequelae are common amongst hepatitis B carriers, most notably ESLD and hepatocellular carcinoma (HCC). These combined outcomes occur at a rate of 2.3 per 1000 carrier-years; the majority of events (82%) are HCC [25]. The link between chronic hepatitis B and HCC was first observed in the 1970s, when the incidence of HCC was reported to be five times greater in an Alaska Native population than the US white population [26]. Most of that excess risk was attributable to chronic hepatitis B carriage rather than alcohol consumption. In a study of 1400 HBsAg positive AI/ANs, 13 of the 60 deaths (22%) and 57% of all fatal neoplasms during the study were due to HCC [25]. The incidence of HCC is higher in AN men, 2.3 per 1000 carrier years, versus 1.2 per 1000 carrier years in AN women. The relative risk of developing HCC for an HBsAg carrier is 148 times greater compared to a non-carrier, as documented in a more recent study [22].

Within HBsAg positive AI/AN populations, HCC is observed more frequently in older patients, those with reversion to HBeAg positivity, those of Yupik ethnicity, and carriers with genotype F [23, 25]. An living in the Yukon delta region of western Alaska develop HCC at very young ages, in the context of no cirrhosis [27]; however, more recent studies found that half (15/30) of the cases of HCC elsewhere in AN were found in cirrhotics [26]. It is possible that the genotype F variant seen in this part of Alaska confers a very high risk of developing HCC.

Among Canadian Inuit living in the Arctic region, 5% were surface antigen-positive and 27% had been exposed [29]. However, Canadian First Nations members living outside of the circumpolar region have similar chronic infection (0.3%-3%) and exposure rates (10%-22%) as compared to non-Aboriginals engaging in similar activities [29].

Among native Greenlanders, 7%-12% were surface antigen-positive carriers and 42% had evidence of past infection [18, 30]. The peak incidence occurs in young adults,
suggesting that sexual acquisition is the predominant route of exposure\[30\]. This route of transmission differs from the perinatal or early horizontal transmission seen in AN\[21\]. Among native Greenlanders, the incidence of HCC is not higher than in the general Danish population (1.9 vs 2.2 cases per 100 000), despite the high prevalence of chronic hepatitis B\[31\]. There are several possible explanations for this discrepancy in HCC rates seen in the circumpolar region. First, native Greenlanders acquire HBV later in life and more frequently clear the virus. Second, chronic carriers tend to have low viral loads (median: 40 000 copies/mL\[32\]). Finally, the majority of native Greenlanders with chronic HBV appear to have a new genotype (Bj variant), which may be less carcinogenic than other genotypes.

Despite the heavy disease burden from chronic HBV in Aboriginal North Americans, there are still many unanswered questions. For example, it is unclear why the natural history, routes of transmission, and risk for HCC differ so dramatically within the circumpolar region. In addition, the route of transmission and natural history has not been thoroughly studied in AI/AN living in the lower 48 states of the US.

**HEPATITIS C**

Hepatitis C is one of the most common and important causes of CLD in AI/AN (Table 1, Figure 1). However, seroprevalence studies have come to disparate conclusions regarding the prevalence of hepatitis C in AI/AN. For example, in the largest study of AI/AN, the overall seroprevalence was just 0.82%\[33\], which is lower than the overall seroprevalence in the US (1.8%)\[34\]. In contrast, studies of pregnant AI women in the US Southwest, urban AI/AN in the US Midwest, and AI/AN in the Veterans Affairs system showed seroprevalence rates of 11.5%, 3%, and 32%, respectively\[35\]-\[37\]. Part of the discrepancy in findings may be attributable to selection bias; the study from Alaska was a true population-based study\[33\], whereas the others were convenience samples.

The route of transmission appears to be similar to the general US population; namely, injection drug use and blood transfusions. In a study of HCV-positive Alaska Natives, 60.1% had a history of intravenous drug use and 14.0% had a history of blood transfusion\[33\]. Similarly, in a study from an urban US Midwest city, intravenous drug and cocaine use accounted for the majority of those who were HCV positive\[38\]. Other identified risk factors were tattoos > 5 years old and having a sexual partner with HCV.

In the US general population, genotype 1 accounts for the majority of chronic HCV (72%), followed by genotypes 2 (15%) and 3 (6%)\[39\]. In AI/AN, the more easily-treated genotypes are more common: 60% have genotype 1, 23% have genotype 2, and 14% have genotype 3\[31\]. In this Alaska cohort, 73% tested positive for HCV RNA; men were more likely to have higher levels of HCV RNA.

Studies of antiviral efficacy in AI/AN are limited to one small study from Alaska. However, the results indicate that antiviral therapy may be markedly less efficacious than in American whites (35% vs 52%)\[39,40\]. The rate of sustained virologic response (SVR) was 7% (1/15) in patients with genotype 1, 54% (7/13) in genotype 2, and 50% (6/12) in genotype 3.

Studies of First Nations members in Canada show a similar pattern as those done in the US. In a study of Canadian Inuit, the seroprevalence of HCV was 1.1%\[29\], but in areas outside of the circumpolar region, the seroprevalence ranged from 2.2% to 20%\[16,41\]. Among First Nations Canadians who used injection drugs, the seroprevalence was 33%\[41\]. Interestingly, Aboriginal North Americans may have an increased ability to clear the virus, a finding reported in both Canada and the US\[16,42\]. In native Greenlanders, the seroprevalence is similarly low, < 1%\[30\].

**HEPATITIS D AND E**

Hepatitis D (or delta) virus (HDV) is a very small RNA virus which is dependent on HBV for its life cycle; therefore, in humans it is only seen in the context of concurrent HBV infection. HBV-infected patients who become super-infected with HDV are more likely to develop acute fulminant liver failure than if they just had HBV\[43\]. Similarly, HBV/HDV co-infected patients progress more rapidly (1–2 years in some cases) and more frequently (70%) to cirrhosis\[43,44\]. HDV is believed to be uncommon in most Aboriginal North American populations, with the exception of Greenland, where 40% of those with HBV also have HDV\[44\].

Hepatitis E virus (HEV) is also an RNA virus but is spread by the fecal-oral route, similar to HAV. It is predominantly seen in developing countries. However, a recent study showed that 3% of a population of Canadian Inuit had IgG antibodies to HEV (none were viremic). HEV infection has been linked to consumption of deer and caribou, although local caribou were all HEV-negative in this study\[45\].

**ALCOHOLIC LIVER DISEASE**

Alcohol has long been recognized as the most important cause of cirrhosis and liver-related death in AI/AN\[46\] and continues to be the most common cause of CLD (Figure 1). In one study, 65% of all deaths from CLD were attributable to alcoholic cirrhosis\[46\]. Moreover, the excess cirrhosis mortality observed in AI/AN men is independent of socioeconomic status\[47\].

While binge alcohol use is common (up to 16% in a phone survey of AI/AN)\[48\], there is also evidence that alcohol consumption in Native American populations is not significantly greater than consumption in other ethnic groups but rather that alcohol has more serious effects on AI/AN populations\[49\]. A study of alcohol consumption and subsequent health effects showed that Native Americans did not drink more alcohol per day or drink for longer periods of time than their Caucasian, Hispanic, and Afro-American counterparts, but...
suffered significantly higher rates of alcoholic hepatitis and cirrhosis. In addition, AI/AN in this study had a much lower survival rate, although small sample sizes prevented statistical significance. Such results suggest that AI/AN populations have a genetic predisposition to alcohol liver injury, a finding that has been suggested by other studies[59].

Data from Canada presents a more mixed picture regarding the influence of alcohol on CLD. One study found that the death rate from alcoholism and cirrhosis was three times greater in Canadian First Nations as compared to the general population[59]. However, a study reviewing indications for liver transplants in Aboriginal populations in British Columbia found that while alcoholic cirrhosis was the third leading indicator for transplant recipients in the general population, it was not an indicator for any of the fifteen Aboriginal patients who received a transplant. Instead, PBC and autoimmune hepatitis were the two most common reasons (13/15) for liver transplantation in Canadian First Nations[59].

Native Greenlanders have a high per capita alcohol intake. However, when comparing patients in alcohol treatment programs in Greenland vs Denmark, the Greenlanders less frequently had abnormal liver function tests (42% vs 91%) and cases of cirrhosis or advanced fibrosis (0 vs 13)[59]. This study suggests that Greenland Inuit may be more resistant to the hepatotoxic effects of alcohol.

Prevention and treatment of alcohol abuse in Aboriginal populations has been an area of active research[54].

AUTOIMMUNE HEPATITIS

AI/AN have one of the highest rates of autoimmune hepatitis (AIH) in the world. A review of AI/AN in Alaska with AIH between 1984 and 2000 found a point prevalence of definite or probable AIH (using International Autoimmune Hepatitis Group criteria[89]) of 42.9/100,000[59]. Revisited data from this cohort through 2005 showed a point prevalence of 61.7/100,000[59]. The only other population-based study of AIH was from Norway and reported a prevalence of 16.9/100,000[59]. Fortunately, AI/AN with AIH responded to treatment with systemic steroids with normalization of ALT more rapidly than in previously reported studies[59].

AIH is similarly more common in First Nations peoples in British Columbia[59]. A study of indications for liver transplants in British Columbia showed that 7% of recipients the overall population received transplants with AIH as their primary diagnosis, whereas 27% of aboriginal recipients had AIH as their primary diagnosis. Autoimmune hepatitis was fourth leading indication for liver transplant overall, but was the second leading indication within the Aboriginal population. Among those referred for transplant evaluation with AIH, a statistically significant proportion, 12/68 (18%), were First Nations, when compared to their overall proportion in the general population (4.4%)[59]. Most cases appear to be type 1 AIH[59].

There are no studies on AIH in native Greenlanders.

PBC

PBC, like autoimmune hepatitis, is an autoimmune disease that has a strikingly high prevalence in Alaska Natives and British Columbia’s First Nations population. A genetic predisposition and female gender are the primary risk factors for developing PBC.

In a study of AN persons with autoimmune liver disease, a combined prevalence rate of antimitochondrial antibody (AMA)-positive and AMA-negative persons with PBC was 21/100,000, including a prevalence of 71.5/100,000 in Southeast Asian Indian persons[59]. Five of 23 persons (22%) had AMA-negative PBC and only 1/23 persons was male.

Outside of Alaska, PBC affects AI/AN populations less frequently than the general population. PBC accounted for 0.18 deaths per 100,000 in the general population in 1998, but a slightly lower rate of 0.11 deaths per 100,000 in the AI/AN population. The death rate from PBC in AI/AN was 0.28 per 100,000. Furthermore, this rate remained static in the AI/AN population during the 1990s[60].

Native populations in British Columbia, like AN, have a high PBC prevalence. For example, in British Columbia, First Nations people comprise 4% of the population, yet account for 25% of those needing liver transplants due to PBC[61]. From 1989 to 1998, PBC was the leading indication for a liver transplant in British Columbia First Nations patients[61]. First Nations patients were also referred for liver transplants at a much younger age than non-First Nations patients[89]. Of those First Nations patients referred for liver transplantation, most (33/34) are female.

Several factors indicate a strong genetic component to the occurrence of PBC. Within a population of British Columbia First Nations patients with PBC, 19/24 reported at least one other autoimmune condition and 33% had a family history of PBC[60]. First Nations patients were unusual in that 18% tested negative for AMA, which are normally present in 95% of PBC patients.

There are no studies of PBC in native Greenlanders.

NAFLD

NAFLD is the deposition of fat in the liver, commonly as a consequence of obesity and diabetes mellitus type 2. This condition may progress to NASH, in which there is inflammation, sometimes with resulting fibrosis and cirrhosis. NAFLD was the fourth most common cause of CLD in a study from the Southwestern US, accounting for one-eighth of the total cases (Figure 1). Preliminary results from a retrospective study of abnormal ALT values in AI/AN indicate that NAFLD is the second most common etiology[7].

It is not surprising that NAFLD accounts for a significant proportion of CLD, given the high prevalence of risk factors for NAFLD in AI/AN (obesity, hypertriglyceridemia and diabetes mellitus type 2). For example, the prevalence of obesity among AI/AN is 24%-40%, the highest rate in any American ethnic group[89]. Similarly, the prevalence of diabetes is higher...
in AN/AI than any other ethnic group, ranging from 9.7%-19.7%[48,63]. Rates of these conditions are expected to rise in the general population, so NAFLD can likewise be expected to increase in the future.

There are no available studies of NAFLD in Canadian FN and native Greenlanders.

GENETIC

Inherited causes of liver disease are an uncommon cause of cirrhosis in North American Aboriginal populations. One exception is in the Ojibway-Cree population in Northwestern Quebec where North American Indian childhood cirrhosis (NAIC) has been described[64]. This autosomal recessive trait is carried by 10% of the local population and 1/250 to 1/750 are believed to have the condition. A missense mutation on chromosome 16q22 causes a change in the secondary structure of cirrhin, a protein crucial in embryonic liver development[65]. Intrahepatic cholestasis develops and manifests clinically as a sustained elevation in the alkaline phosphatase level. Children born with this condition have transient neonatal jaundice, with rapid progression to biliary cirrhosis and portal hypertension. In a case series of 30 children with NAIC, 14 (47%) died, mostly from complications of ESLD[66]. Liver transplantation is the only cure. A syndrome termed focal familial cholestatic syndrome has been reported in Greenland Eskimo children[67]. This autosomal recessive disease is associated with dwarfism, osteodystrophy, jaundice, and malnutrition. Death in infancy is common and there is no specific treatment available.

Hemochromatosis, an autosomal recessive trait leading to iron overload and cirrhosis, is common in persons of northern European descent, affecting about 5 of every 1000 persons[68]. Initial studies screening patients from primary care clinics in Alabama suggested that patients with AI ancestry may have greater ferritin and lower mean transferrin levels, findings which are suggestive of hemochromatosis[69]. However, genetic testing of 80 patients with hemochromatosis did not show a difference in phenotype among those with and without AI ancestry[70].

Familial clusters of HCC have been observed in AN, sometimes in childhood. Because p53 mutations have been observed in 29% of patients with HCC, researchers hypothesized that p53 mutations might account for the early onset and clustering[71]. However, they found no antibody, immunohistochemical or DNA evidence of p53 mutations in 14 AN patients with HCC. It is still possible, however, that a germline mutation in a tumor suppression gene exists.

There are no studies examining Wilson’s disease in Aboriginal North Americans.

CONCLUSION

CLD is an important cause of morbidity and mortality in Aboriginal North Americans. Alcohol abuse is the most common etiology of CLD in this population and incidence rates remain stable. However, the incidence of CLD due to viral hepatitis, especially HCV, is rising. In addition, NAFLD is an understudied, but an increasingly more common, cause of CLD. Taken together, this population can be expected to increase in the coming decade. Accordingly, future studies should continue to monitor the incidence and etiology of CLD and should be geographically inclusive. In addition, future research should focus on the treatment of HCV and NAFLD.

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