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Review Article

Severe Acute Hepatitis of Unknown Etiology in Indonesia: What Has Been Learned?

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Abstract

The world has witnessed increased incidences of severe acute hepatitis in children since early 2021, in which the total number of global cases was over 1,000 in July 2022. Those cases of severe acute hepatitis were intriguing, as they were not caused by the common hepatitis A-E viruses. Additionally, the cause remains unknown to date, thus named as severe acute hepatitis of unknown etiology. The World Health Organization, supported by regional and national health agencies, has issued the working case definitions in order to closely monitor the development of this disease worldwide. As one of its member states, Indonesia has also adopted the case definitions and subsequently issued a health decree to increase public awareness and to conduct an early surveillance on this illness. It remains to be seen whether this updated public health policy would be successful to control the numbers of cases of severe acute hepatitis of unknown etiology in Indonesia.

Introduction

On April 5, 2022, severe acute hepatitis of unknown etiology was observed in 10 previously healthy children in the United Kingdom. Since then, by the time this review was written, a total of 1,010 probable cases were further reported in 35 countries, including 18 cases in Indonesia.[1] Hepatitis, an inflammation of the liver, is a serious health condition predominantly caused by a viral infection although other triggers, such as drugs, toxins, alcohol, and autoimmune diseases, also account for a small percentage of the reported cases.[2–4] Despite some similarities in the pathophysiology of the severe acute hepatitis of unknown etiology with the one due to common hepatitis A-E viruses, the cause remains elusive to date.[1,5] This opens a possibility that the case might be an entirely new infectious agent previously unconnected to viral hepatitis.

As the COVID-19 pandemic remains, the elevated global incidences of severe acute hepatitis of unknown etiology in children compel the World Health Organization (WHO) and its member states to stay on high alert in anticipating another potential outbreak. Interestingly, a similar phenomenon had been observed, in which increased cases of hepatitis with jaundice had been reported in New York in 1923 after the 1918 influenza pandemic. Approximately 700 cases of jaundice were reported, and most of the cases were from children aged 5–14 years.[6,7] Similarly, laboratory diagnostics at that time had been unable to pinpoint the pathogen that caused jaundice. It was speculated that those cases of hepatitis had occurred due to a social containment during the pandemic, thus leading to lower susceptibility of children against certain viruses that in normal situations would not cause severe acute hepatitis.[6,7] Whether this hypothesis would be valid for the current situation as well remains to be seen.

The WHO has issued working case definitions for monitoring severe acute hepatitis of unknown etiology in children.[1] The current definition, although incomplete, allows the WHO member states (including Indonesia) to monitor probable cases of severe acute hepatitis, control its spread, design appropriate interventive measures to minimize any associated morbidity and mortality, as well as ultimately identify the culprit of this illness. In this review, we aim to summarize information on known hepatitis-inducing viruses with the hope of shedding some light on this still mysterious

Keywords: Severe acute hepatitis; Unknown aetiology; Working case definitions; Indonesia; Public health policy.

Abbreviations: AAV2, adeno-associated virus 2; AdV, adenovirus; ALF, acute hepatic failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; COVID-19, Coronavirus disease 2019; EBV, Epstein-Barr virus; ECDC, European Center for Disease Prevention and Control; DNA, deoxynucleic acid; HAV, hepatitis A virus; HBsAg, hepatitis B s antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDAg, hepatitis D antigen; HDAg-s, small hepatitis D antigen; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; kb, kilobase; IgG, immunoglobulin G; IgM, immunoglobulin M; NK cells, natural killer cells; ORF, open reading frame; qPCR, quantitative polymerase chain reaction; RNA, ribonucleic acid; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

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Table 1. Summary of hepatitis-inducing viruses

Virus	Genome	Route of infection	Mechanism of hepatitis
Hepatitis A virus	RNA	Fecal-oral; exposure to contaminated fecal matter or blood products.	Immune-mediated liver damage.
Hepatitis B virus	DNA	Percutaneous or mucosal contact with blood products and bodily fluids (saliva, tears, semen, vaginal secretions, urine, or sweat).	Immune-mediated liver damage.
Hepatitis C virus	RNA	Exposure to contaminated blood products.	Immune-mediated liver damage.
Hepatitis D virus	RNA	Exposure to contaminated blood or through sexual activity.	Direct cytopathogenicity and/or immune-mediated liver damage.
Hepatitis E virus	RNA	Hepatitis E virus (HEV) 1 and 2: fecal-oral; HEV 3 and 4: zoonosis; through undercooked meat and occupational exposure; Transfusion-related transmission was also found in some subtypes.	Immune-mediated liver damage.
Other viruses			
Epstein-barr virus	DNA	Body fluids.	Immune-mediated liver damage.
Cytomegalovirus	DNA	Body fluids.	Immune-mediated liver damage.
Parvovirus	DNA	Respiratory secretion, blood and blood, products.	Direct cytopathogenicity and/or immune-mediated liver damage.
Adenovirus	DNA	Respiratory secretion, infected tissue and blood, through the mouth or eyes contact with infected objects, and fecal-oral.	Still elusive.

DNA, deoxynucleic acid; RNA, ribonucleic acid.

disease and on how Indonesia has prepared itself in anticipating this potential outbreak.

Viral hepatitis

Viral hepatitis is a group of diseases specifically characterized by inflammation of the liver triggered by a viral infection. There are five distinctly different viruses denoted as the hepatitis A, B, C, D and E viruses, which are known to infect the liver and induce an immunological response leading to the pathophysiology of the disease.[4] A detailed review and updates on the patient care of hepatitis A-E can be found in review articles, such as the review by Almeida, *et al*.[8] In a less frequent occurrence, other viruses, such as the Epstein-Barr virus, cytomegalovirus, human parvovirus B19, and adenovirus, could also cause liver inflammation, which have been commonly referred as X or non A-E hepatitis.[9,10] Several essential information of the common hepatitis-inducing viruses are presented below and summarized in Table 1.

Hepatitis A virus

Hepatitis A virus (HAV), which was first identified and characterized in 1973, is a non-enveloped virus of 27 nanometers in diameter that belongs to the family *Picornaviridae* and genus *Hepatovirus*.[11,12] Molecular analysis of the HAV genome revealed a single positive-strand RNA of 7.5 kilobases (kb) in length with a single open reading frame (ORF) encoding a huge polyprotein.[13] There are two forms of the infectious virion: the quasi-enveloped virions commonly found in the blood, and naked virions usually excreted in the feces. The quasi-enveloped virions are membranous vesicles enveloping an RNA-containing capsid. When these virions pass through the biliary canaliculus during hepatocyte invasion and viral propagation, the membranous vesicles are degraded by the action of bile salts, thus leaving a naked virion to enter the gastrointestinal tract and shed in the feces.[13,14]

HAV is the primary cause of acute viral hepatitis globally and one of the culprits in the foodborne disease outbreaks, particularly in developing and some regions of developed countries.[13] Although the incidence of hepatitis A greatly depends on the hygienic, sanitary and socio-economic status, childhood exposure to this virus in developing countries is usually asymptomatic, consequently contributing to an endemicity with less reported cases and less common outbreaks. In contrast, people in developed countries are more commonly exposed to this virus at later stages in life and could suffer from greater symptoms, thereby leading to more reported cases and outbreaks.[15,16] Hepatitis A outbreak has occurred several times in Indonesia, predominantly in Java,[17] in which it is the second most common viral hepatitis after hepatitis B. It has afflicted an estimated 19.3% of the population across Indonesia. According to the Basic Health Research survey in 2013, three provinces in Indonesia with the highest cases of hepatitis A were the Riau Islands, Lampung, and Banten.[18]

The high viral titers shed in feces underlies the main transmission of this virus (i.e., fecal-oral route), either directly through contact with infected patients or indirectly through the ingestion of contaminated food or water.[12,13] On rare occasions, transmission could also happen through blood transfusion, sexual activities, and organ transplantation.[12] Moreover, there are specific risk groups reported to be more susceptible to hepatitis A particularly in developed countries, such as travelers to endemic countries, men who have sex with men, drug users, people with chronic liver disease, and HIV patients.[12,19]

HAV infection typically does not progress to chronicity. Clinical symptoms are usually present on 14–50 days after infection and resolve within 4–7 weeks.[20,21] Symptoms manifested in patients are similar to other types of viral hepatitis, including fever, ab-

dominal pain, nausea, malaise, anorexia, vomiting, elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as jaundice in more severe cases.[11,22] The mortality rate of hepatitis A ranges between 0.1–2.1% with a higher incidence occurring in adults over 49 years of age.[20]

Hepatitis A is clinically indistinguishable from other viral hepatitis; thus, a specific detection approach is required to determine the status and types of viral infection. In the presence of the symptoms, the most used method to detect HAV infection is a serologic testing targeting anti-HAV immunoglobulin M (IgM) antibodies.[23] These antibodies are typically detectable within 5–10 days after infection and represent an active infection as the titers would progressively decrease until undetectable within 6 months.[23,24] Anti-HAV immunoglobulin G (IgG) antibodies typically would rise later than IgM and stay detectable for the rest of the patient's life, hence could be used to assess immunity to past infection or vaccinations.[25] Confirmation tests for patients, either asymptomatic or symptomatic, could be performed via molecular techniques, such as nucleic acid amplification tests (NAATs), by detecting the presence of HAV RNA.[23]

The mechanism of acute hepatitis caused by HAV remains to be completely understood. HAV does not cause any direct cytopathic effect, and studies done to elucidate the mechanism have pointed toward the role of cell-mediated immune responses in causing and worsening the hepatitis. HAV-specific $CD8^+$ T cells hold the main role in the apoptosis of infected hepatocytes during HAV infection, in which specific $CD8^+$ T cells are not only contributing to the viral clearance, but also causing liver damage, particularly if this happens in an extended time and/or excessive manner.[26] In addition, elevated levels of interleukin-15 (IL-15) in the sera of hepatitis A patients induced the cytolytic activity of non-specific $CD8^+$ T cells toward both infected and uninfected hepatocytes.[21] Genetic variations and mutations in certain individuals also contributed to higher levels of cytolytic activity of Natural Killer (NK) and Natural Killer T (NKT) cells against hepatocytes.[22]

Hepatitis B virus

Hepatitis B is caused by the hepatitis B virus (HBV), which belongs to the family *Hepadnaviridae* and genus *Orthohepadnavirus*.[27] The genome of HBV consists of 3.2 kb partially double-stranded relaxed circular DNA (rcDNA) with four ORFs that are contained within icosahedral protein capsid.[27,28] Covering the nucleocapsid is a lipid bilayer membrane envelope composed of three types of surface proteins commonly referred to as hepatitis B surface antigen (HBsAg).[28] Unlike hepatitis A that is only associated with acute hepatitis, hepatitis B manifests as acute and chronic hepatitis that can progress to life-threatening liver failure, cirrhosis, and hepatocellular carcinoma (HCC).[29] In 2019, the WHO estimated at least 296 million people worldwide were suffering from chronic hepatitis B, although only 10.5% of the number were aware of their infection due to the commonly asymptomatic and chronic nature of the disease.[30] Together with hepatitis C, hepatitis B accounts for the majority of hepatitis deaths worldwide with an estimation of 820,000 deaths due to hepatitis B alone in 2019.[30,31] In Indonesia, HBV is the primary cause of viral hepatitis.[18] Around 21.8% of the population was infected by HBV in 2013.[18] In the latest data provided by Indonesia's Ministry of Health, Bangka Belitung, Maluku, and West Sulawesi were the top three provinces with the highest prevalence of hepatitis B.[18]

Transmission of HBV occurs through percutaneous or mucosal contact with infectious blood or body fluids, such as saliva, sweat, urine, vaginal secretions, semen, and tears.[32,33] Vertical transmission from mothers to neonates, which constitutes the main transmission route for this virus, could occur through the placenta, during delivery, or during postpartum care and breastfeeding.[34] Horizontal transmission could occur from person to person through sexual activities, administration of infected blood and its derivatives, administration of contaminated needles in intravenous drug injection, contaminated medical instruments, unsterile medical procedures, and sharing of personal hygienic products, such as razors and toothbrushes.[34,35]

Symptoms of hepatitis B usually appear 60–180 days after infection.[36] Early symptoms include fever, malaise, fatigue, vomiting, diarrhea, abdominal pain, nausea, and anorexia. As the hepatitis progresses, patients may suffer from hepatosplenomegaly and jaundice accompanied by visibly dark urine and clay-colored feces.[36] In most cases, patients suffering from acute hepatitis typically recover within 4–6 weeks. However, 5–10% of patients, who developed chronic hepatitis, were diagnosed through the presence of HBsAg in the serum of the patients who had had it for at least 6 months since the infection.[36,37] The risk of chronic patients to develop severe complications, such as cirrhosis and HCC, greatly depends on a range of host, viral, and environmental factors.[37] Fulminant hepatitis, which constitutes only 1% of all hepatitis B infections, could lead to liver failure, change in brain function, and mortality.[36]

Clinical diagnosis of HBV infection is usually performed through a range of serologic and molecular tests. Serologic markers used in the detection of HBV are hepatitis B antigen (HbsAg), hepatitis B e-antigen (HBeAg), antibodies against hepatitis B surface antigen (anti-HBs), antibodies against hepatitis B e-antigen (anti-HBe), and antibodies against hepatitis B core antigen (anti-HBc). The presence of HBsAg in the patients' serum is one of the most important indicators of active HBV infection, which can be detected within 1–10 weeks from the onset of infection, and persistence for more than 6 months indicates the establishment of chronic infection.[38] On the other hand, the presence of anti-HBs antibodies implys a resolved infection or the patient has been vaccinated with hepatitis B vaccine.[38] Molecular approaches, such as branched-chain DNA and quantitative polymerase chain reaction (qPCR), could specifically target HBV DNA and quantitatively measure the viral load and replication activity of the virus. These methods are increasingly being used in clinical settings due to their accuracy and reliability for monitoring the progression of the disease.[38,39]

Pathologically, HBV does not impose direct cytopathic effects, as no hepatocyte damage is observed at the early phase of infection.[40] The immune responses, especially cell-mediated immunity, instead play a major role in causing liver damage because the inhibition of the cellular immune responses by certain medication leads to the survival of hepatocytes despite high numbers of the virus.[40] For patients with chronic hepatitis, alternating phases of immunologic activity and inactivity could occur multiple times during a lifetime.[41] During the active phase, liver inflammation is established and pro-inflammatory cytokines secreted by hepatic immune cells lead to recruitment and on-site activation of other immune effectors, such as macrophages, NK cells, and most importantly $CD8^+$ T cells that directly kill infected hepatocytes and contribute to tissue damage.[42] This phase is followed by immune downregulation and tissue repair, including the deposition of extracellular matrix (ECM). When this happens repeatedly during the chronic HBV infection, accumulation of ECM and incomplete wound repair due to persistence of antigenic stimuli could lead to progressive liver fibrosis and cirrhosis.[42,43]

Patients with chronic hepatitis B have also been reported to have 15–20 times greater chance of developing HCC compared to uninfected individuals.[44] Similar to the hepatitis C and D viruses, progression into HCC could be mediated through several processes, including repeated and continuous liver inflammation and oxidative stress damage during the course of chronic infection, as well as oxidative damage and disruption of cell signaling directly induced by viral proteins.[27] In addition, since HBV is a DNA virus, it could integrate into the host genome and introduce mutations that could lead to changes in the expression levels of tumor-associated genes.[27]

Hepatitis C virus

The hepatitis C virus (HCV) was first discovered in 1989 and categorized as a bloodborne hepatotropic virus that belongs to family *Flaviviridae* and genus *Hepacivirus*.[45] It has a 9.6 kb positive-sense single-stranded RNA genome, which contains one long ORF.[45] Its genome is located inside a nucleocapsid, which is surrounded by a lipid bilayer membrane envelope with two subunits of viral glycoproteins (E1 and E2) that have important roles in viral entry.[45,46] In 2019, the WHO estimated that at least 58 million people worldwide contracted chronic hepatitis C, in which 290,000 of them died mostly due to end-stage liver diseases, including cirrhosis and HCC.[47] According to the data collected in 2013, approximately 2.5% of Indonesia's total population were infected with HCV.[18] Despite the lower prevalence of hepatitis C as compared to hepatitis A or B in Indonesia, it was estimated in 2014 that 9% of those HCV-infected patients would develop cirrhosis, HCC, or require a liver transplantation.[18,48] This number is projected to continue increasing in the coming years and would reach 15% in 2030. The provinces in Indonesia with the most cases of HCV infection in 2013 were the Riau Islands, West Sumatera, and Bali.[18,48]

Transmission of HCV occurs primarily through contamination with infected blood and its products.[49] This could occur via needle sharing and unsafe injection, both in healthcare and recreational drug settings, unsterile tattoo and piercing practices, as well as sexual activities, particularly in HIV-infected patients. Vertical transmissions have also been reported, but in a lesser extent than HBV infection.[49,50] HCV infection can cause both acute and chronic hepatitis, in which most infected people (60–80%) end up with chronic infection.[51] Acute HCV infection is typically asymptomatic and only 25–30% of patients with acute hepatitis C develop symptoms, such as jaundice, nausea, fever, vomiting, or abdominal pain.[49,52] A small proportion of these acutely infected adults (15–25%) achieved spontaneous resolution within one year after the onset of infection, while the remainder suffered from persistent infection.[49,50] The silent onset of the disease partly contributes to wide transmissibility within the population and delays the appropriate treatment since many infected people are unaware of their condition.[50]

Similar to hepatitis B, chronically HCV-infected patients have a much higher risk to develop fibrosis, which could progress into cirrhosis, liver decompensation, and HCC.[50] The progression rate to fibrosis varies between patients and depends on factors, such as age, gender, level of alcohol intake, co-infection with HIV, level of ALT, and level of steatosis.[50] It has been reported that as many as 10–20% of patients with chronic hepatitis C develop cirrhosis, which could manifest decades after the onset of infection.[50] After the establishment of cirrhosis, the risk of HCC increases 1–5% annually and the risk of hepatic decompensation increases 3–6% annually, thus highlighting the importance of a timely and accurate diagnosis as well as treatment for the disease.[53]

Clinical detection of HCV infection could be done either serologically through detection of HCV antigens or antibodies against HCV antigens, or molecularly through direct amplification of HCV RNA.[54] Serologic assays targeting antibodies against the HCV core and NS3-NS5 viral antigens are typically used to screen infected patients.[54,55] However, due to its low correlation with the viral load and actual HCV replication, molecular techniques, such as qPCR, need to be conducted to confirm diagnosis as well as to follow-up patients during treatment.[54] In regions with limited equipment, reagents and skilled laboratory staff, detection of HCV core antigens using techniques, such as chemiluminescent microparticle immunoassay, automated chemiluminescent enzyme immunoassays and ELISA, have demonstrated good potential and have been reported to have a good correlation with HCV RNA and was slightly less sensitive than qPCR.[55]

HCV does not only replicate within the liver, but could also be inside the lymphatic system, which would mediate its effects on the immune cells and facilitate its escape from immune surveillance and elimination.[56] HCV is not known to be cytopathic; hence, the induction of liver damage would be largely due to the action of the immune responses and the stress imposed on the hepatocytes over the course of infection.[57] Additionally, continuous secretion of pro-inflammatory cytokines secreted by activated immune cells at the site of the infection would maintain the state of liver inflammation and contribute to the formation of liver fibrosis.[51] With their cytolytic nature, NK and $CD8^+$ T cells play a major role in hepatitis C pathogenesis by directly targeting the infected hepatocytes and inducing their apoptosis.[58] It has also been reported that during chronic HCV infection, multiple cell-death-related factors, including Fas ligand and TNF-related apoptosis-inducing ligand (TRAIL), were upregulated.[51] Furthermore, the ability of HCV to induce metabolic reprogramming could lead to the promotion of steatosis, which in turn would support the development of fibrosis and HCC.[27]

Hepatitis D virus

In 1977, Rizzetto *et al*.[59] observed a novel antigen dubbed as delta antigen in patients with chronic HBV infection. It was subsequently found that the delta antigen originated from the hepatitis D virus (HDV), which belongs to the genus *Deltaviridae*.[60] HDV is a single-stranded RNA virus, which contains around 1,700 nucleotides and six ORFs.[61,62] Until now, only ORF1 has been known to be translated. ORF1 encodes the hepatitis D antigen (HDAg) that exists in two isoforms, i.e., small HDAg (HDAg-S; 195 nucleotides) and large HDAg (HDAg-L; 214 nucleotides).[61,62] While HDAg-S is important for viral replication, HDAg-L inhibits the replication, but it is important for viral morphogenesis by anchoring the HDV ribonucleoprotein to the HBV surface antigen (HBsAg).[61,62] This mechanism explains how HDV uses HBsAg as its envelope and also why HDV cannot replicate without HBV.[61,62] Therefore, HDV infection could only occur while a person is actively infected by HBV.

There are eight different subtypes of HDV that are found in various parts of the world.[61,63] HDV-1 is the most predominant strain in the world, which is found in Europe, the Middle East, Asia, Africa, North America, and South America. HDV-2 is found primarily in Asia and Russia. HDV-3 is mainly found in South America and some parts of Asia. HDV-5 is found in Europe and Africa. HDV-4, 6, and 8 are found exclusively in Africa. In addition, HDV-8 is also found in some parts of South America.[61,63]

Stockdale *et al*. estimated that there were 12 million people around the world who were infected with HDV.[63] Based on their

findings, Mongolia has the most prevalence of HDV infection, and the regions with the most prevalence of HDV in consecutive order were the WHO Regions of Africa, the Americas, the Eastern Mediterranean, Europe, Southeast Asia, and the Western Pacific.[63] Unfortunately, there are no data on the prevalence of HDV in Indonesia, but estimation could be calculated based on the latest data on hepatitis B. Based on national research by Indonesia's Health Minister in 2013,[18] there was 21.8% of the total Indonesian population or around 18 million people afflicted with hepatitis B and by using data from Stockdale *et al*.,[63] the prevalence of HDV in Indonesia in 2013 would be approximately 126,000 people.

HDV is a bloodborne virus. It is transmitted parenterally, for example through shared injection or blood products and through sexual activity.[64] Acute HDV infection has an incubation period of around one month.[65] After the incubation period, clinical symptoms, such as fatigue, nausea, loss of appetite, and jaundice, may arise in patients with hepatitis D.[65] HDV infection causes a very high mortality rate of around 2–20%.among viral hepatitis sufferers.[66] Chronic infection of HDV is the most dangerous of all chronic viral hepatitis, in which 70–80% of patients develop cirrhosis within 5–10 years, and once cirrhosis has been developed, their mortality rate is between 51–60%.[64]

Clinical diagnosis of HDV is initially performed by detecting HBsAg serologically. Subsequently, patients are tested serologically for anti-HDV IgG antibodies.[61,65] As positive results of this test could not inform whether HDV infection is still active, the infection would be confirmed by using a molecular approach, i.e., qPCR for HDV RNA.[61,65]

The pathogenicity of acute hepatitis D has not been thoroughly elucidated. Cole *et al*. reported through an *in vitro* study that by using HDAg-S, HDV could directly induce cytopathic activity in hepatocytes.[67] However, the majority of other studies supported the notion that HDV did not cause direct cytopathy, but drove immune-mediated cytotoxicity.[68,69] In addition to cytotoxic $CD8^+$ T cells in mediating the cytolysis of hepatocytes, perforin-expressing $CD4^+$ T cells have also been reported to play an important role in aggravating liver damage, in which their presence was found to be higher in the peripheral blood of HDV patients compared to the ones of HCV or HBV patients.[68,69] Therefore, more studies would be required to determine the exact mechanism of HDV pathophysiology and the interplay between HDV and HBV in mediating the disease progression.[68,69]

Hepatitis E virus

Hepatitis E virus (HEV) is a single positive-strand RNA virus that belongs to the genus *Orthohepevirus*.[70] There are four species of known *Orthohepevirus*, i.e., *Orthohepevirus* A-D. Most HEV infection cases in humans are caused by *Orthohepevirus* A, which contains eight different genotypes.[70] The genome of *Orthohepevirus* A consists of 7,200 bp nucleotides containing three ORFs.[70] ORF1 encodes a polyprotein that is important for virus replication. ORF2 encodes the viral capsid. ORF3 encodes a multifunctional protein that is involved in the morphogenesis and pathogenesis of HEV.[71] An additional ORF4 has been found to overlap with ORF1 in genotype 1 of *Orthohepevirus* A. This ORF would only be translated in the event of endoplasmic reticulum stress, in which its function would be to help facilitate viral replication.[72–74]

According to the WHO, there are approximately 20 million cases of hepatitis E annually in the world, and among those, 3.3 million cases are estimated to be symptomatic hepatitis E.[75] Genotypes 1 and 2 are found predominantly in Mexico, Africa, and South and Southeast Asia.[71,76] Both genotypes are waterborne and transmitted through the fecal-oral route. Genotypes 3 and 4 are found predominantly in Asia and Africa.[71,76] Both genotypes mainly infect animals, such as pigs, and are transmitted to humans through undercooked meat and occupational exposure. Genotype 6 only infects animals and no record yet shows any human infection.[71,76] Genotypes 5, 7, and 8 are known to infect humans through animals similar to genotypes 3 and 4.[71,76] While genotype 5 is found in wild boars in Japan, genotypes 7 and 8 are found in camels in the Middle East and China, respectively.[71,76] Although it has been hypothesized that HEV is transmitted exclusively by the fecal-oral route and zoonosis, a recent investigation has proved that transfusion-related transmission could occur.[72,76]

The first documented outbreak of HEV in Indonesia was in West Kalimantan in 1987, in which Corwin *et al*. found that HEV persisted in the area two years later with 59% of the population testing positive for anti-HEV IgG antibodies.[77] The primary reason for this endemicity was how most of the population used the river water to cook and drink, wash clothes, bathe, and to dispose of their excretes.[77,78] The most recent documented outbreak was in Bondowoso Regency in Java in 1998.[79] Based on the investigation completed in 2002 by Sedyaningsih-Mamahit *et al.*, 59% of the tested population were either positive for anti-HEV antibodies when tested using an immuno-based assay or positive for the HEV gene when tested using PCR. They also discovered that people in that area primarily used the river as their water source similar to what had happened in West Kalimantan.[79] A study to determine the prevalence of genotype 3 HEV in Indonesia was done in 2013 by Widasari *et al*., in which they observed that in a subset of the population in Java, there was a 5.1% prevalence of HEV and among those, 66.67% were swine farmers.[80] They also noted that high numbers of swine (70.3% in Java and 81.5% in Bali) tested positive for HEV.

Common clinical symptoms of hepatitis E include fatigue, nausea, vomiting, and jaundice.[72,81] These symptoms may appear after an incubation period of 1.5–8 weeks.[72,81] These symptoms may resolve after a few days or weeks. Acute HEV has a low mortality rate of 0–10%, but this rate increases among pregnant and immunocompromised individuals.[72,81] Additionally, HEV may cause chronic infection in HIV patients, leukemia patients, lymphoma patients, solid organ transplant recipients, and other immunocompromised patients.[72,82] Among these patients, an infection of HEV can lead to a 60% chance of chronic hepatitis E. Moreover, chronic hepatitis E may even develop into cirrhosis, HCC, and lead to death.[72,82]

HEV infection can be detected clinically through serological and molecular approaches. Serological diagnosis of HEV uses ELISA to detect HEV antigens (encoded by ORF2 and/or ORF3) and anti-HEV IgG or IgM antibodies.[76] Detection of antigens encoded by ORF2 has 100% specificity but lower sensitivity, as compared to the detection of anti-HEV IgM antibodies.[76] Therefore, detection of anti-HEV IgM is the main serological method for HEV diagnosis in resource-limited countries.[76] NAATs using patients' blood and stool are sensitive and reliable, as they can detect HEV as low as 7 IU/mL.[76] There are many available reagents for NAATs, and the WHO has established an international standard for the molecular testing of HEV. In many places, both the serological and molecular approaches are used concurrently to diagnose hepatitis E.[76]

HEV causes hepatocellular injury by increasing numbers and activities of $CD4^+$ T cells, $CD8^+$ T cells, NK cells, and monocytes, which in turn damage the liver tissue.[83] Furthermore, it has been found that HEV through its ORF2 is capable of inhibiting the

Table 2. The working case definitions of the WHO/ECDC for acute hepatitis of unknown aetiology[1,5,99]

Parameter	Case definition
Confirmed	Not available at present.
Probable	Presenting acute hepatitis with elevated levels of AST or ALT more than 500 IU/L: (ii) Negative for hepatitis A-E; (iii) Subject is 16 years old or younger; (iv) Since October 1, 2021.
Epidemiologically linked	Presenting acute hepatitis with elevated levels of AST or ALT more than 500 IU/L: (ii) Negative for hepatitis A-E; (iii) Subject of any age with a history of close contact with a probable case; (iv) Since October 1, 2021.
Pending classification	Presenting acute hepatitis with elevated levels of AST or ALT more than 500 IU/L; (ii) Waiting for laboratory results of hepatitis A-E; (iii) Subject is 16 years old or younger; (iv) Since October 1, 2021.
Discarded	Having other explanations for the severe acute hepatitis.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECDC, European Center for Disease Prevention and Control; WHO, World Health Organization.

NF-κß pathway. Specifically, ORF2 inhibits the ubiquitination of IκBα, thereby inhibiting its degradation and the subsequent activation of NF-κß.[84] Various *in vivo* experiments in a murine model have analyzed the link between the significant downregulation of NF-κß and hepatic injury, including HCC.[85–87]

Other hepatitis-inducing viruses

Viral hepatitis is the most common cause of acute hepatic failure (ALF).[2,88] Data has shown approximately 20% of ALF was due to non-hepatitis A-E, in which most of those cases were caused by a viral infection.[2,88] There are a few other viruses that are able to induce hepatitis, such as the Epstein-Barr virus, cytomegalovirus, parvovirus, and adenovirus.[2,88] Unfortunately, there is a lack of data to describe the whole epidemiology of these hepatitis-inducing viruses partly due to hepatitis being a rare manifestation of these viral infections.

Epstein-Barr virus (EBV) belongs to the family *Herpesviridae* and its infection is commonly asymptomatic but, in several cases, it may lead to acute or chronic hepatitis.[89–91] The common symptoms of EBV-induced hepatitis, include fever, sore throat, and adenopathy (i.e., infectious mononucleosis).[89–91] Other symptoms may also be exhibited by those patients, such as jaundice (≤5%), abdominal discomfort, and nausea (2–15%).[89–91] Elevation of hepatocellular enzymes up to three times higher than the normal value may also be detected.[89–91] Hepatitis by EBV can also cause ALF in immunocompromised individuals.[89–91] EBV infection may progress to chronicity and could lead to severe, fatal liver disease.[89] Hepatic injury due to EBV infection is immune-mediated and mostly caused by $CD8^+$ T cells.[90,91]

Cytomegalovirus (CMV) is a common pathogen that also belongs to the family *Herpesviridae* and has broad cellular tropism and can infect many types of cells, including hepatocytes.[92] In certain cases, CMV infection can cause acute and chronic hepatitis. In immunocompetent people, CMV-induced hepatitis is asymptomatic and only 10% of patients would develop some symptoms.[92] In immunocompromised patients, however, particularly liver transplant recipients, the rate of infection could reach up to 32.5%.[92] Common symptoms of CMV-induced hepatitis, both in immunocompetent and immunocompromised patients, are fever and malaise.[92] Additionally, immunocompetent patients may develop rash, jaundice, and abdominal discomfort. CMV-induced hepatitis can cause indirect cytopathogenicity in the liver because of the accumulation of cytotoxic $CD8^+$ T cells.[92] Furthermore, infection of CMV in hepatocytes may lead to direct cytopathogenicity in the liver as was shown in the *in vitro* culture and murine experiments.[92]

Parvovirus B19 of the family *Parvoviridae* is a DNA virus that can infect children and adults. This viral infection is known to be more severe in children than in adults.[93] It is transmitted through respiratory droplets, household contacts, and blood products.[93] It can infect all cells that have globosides and glycosphingolipids on their cellular membrane, including hepatocytes.[93] Even though it could infect hepatocytes, only around 4% of patients developed hepatitis.[93] It can cause both acute and chronic hepatitis.[93] Parvovirus B19-induced hepatitis could lead to ALF through direct and indirect cytopathogenicity.[93]

Adenovirus (AdV) is a human pathogen that belongs to the family *Adenoviridae*, and it is transmitted through the respiratory route, blood products, and exposure to infected organs. Most AdV infections occur in children and are self-limited. However, in some rare cases, AdV infection has been known to cause hepatitis. AdV-induced hepatitis in immunocompromised individuals carries a higher risk with a fatality rate of 85%. Common symptoms of AdV-induced hepatitis are fever, malaise, diarrhea, and jaundice.[94,95]

Investigating severe acute hepatitis of unknown etiology in children

Between October 2021 and February 2022, nine immunocompetent pediatric hepatitis patients were admitted in Alabama, United States of America.[96] The patients developed severe hepatitis with symptoms of vomiting, fever, diarrhea, and high levels of transaminase. In the first nine cases in Alabama, it was reported that the range of ALT was 603–4,696 U/L, while the range of AST was 447–4,000 U/L.[96] All patients managed to survive, but two patients required liver transplantations. Upon closer examination, the hepatitis was not caused by hepatitis A-E viruses, but of another yet unknown virus.[96] On March 31, 2022, five children in Scotland aged 3–5 years were found to be inflicted with severe hepatitis.[97] It was noticed that the symptoms were similar to the cases in Alabama,[97] including jaundice (74.1%), vomiting (72.8%), pale stools (58%), diarrhea (49.4%), nausea (39.5%), lethargy (55.6%), fever (29.6%), and other gastrointestinal symptoms (19.8%).[98]

As of June 9, 2022, the WHO, in conjunction with the European Centre for Disease Prevention and Control (ECDC), had been notified of 402 cases of unknown severe hepatitis in Europe, including Israel.[99] The WHO/ECDC subsequently issued working case definitions to help identify and report the cases of acute hepatitis of unknown etiology.[1,99] The working case definitions are shown in Table 2.[1,5,99]

As of July 18, 2022, there has been no clue as from where this

illness originated initially. The majority of probable cases came from Europe, specifically the United Kingdom. Cases have also been found in the United States, Singapore, Maldives, Qatar, Brazil, Canada, Argentina, Colombia, Costa Rica, Mexico, Panama, Guatemala, Hong Kong, India, United Arab Emirates, and Japan.[1,98,100] There were 484 probable cases in Europe, of which three were found in Austria, 14 in Belgium, one in Bulgaria, two in Cyprus, eight in Denmark, eight in France, 12 in Greece, 17 in Ireland, five in Israel, 36 in Italy, one in Latvia, one in Luxembourg, 15 in the Netherlands, five in Norway, 11 in Poland, 19 in Portugal, one in the Republic of Moldova, one in Serbia, 40 in Spain, 12 in Sweden, and 272 in United Kingdom.[1,99] In the United States of America, 355 probable cases have been reported nationwide with exceptions in Alaska, Montana, Wyoming, Iowa, Kansas, West Virginia, District of Columbia, South Carolina, New Hampshire, and Vermont.[101] Based on the data from the WHO and ECDC,[1,99,102] most of the children that were being infected were aged 6 years or younger (76%). In European countries, of the 473 cases, 221 patients recovered, 20 needed a liver transplant, and one died.[99]

The main cause of this acute hepatitis is still elusive; thus, there has been no confirmed case so far. In Alabama, all nine cases were reported to be positive when tested against AdV, in which five of them were confirmed to be AdV type 41.[96] Even though these results suggested a probability of AdV type 41 as the cause, reports from European countries indicated that this did not represent the whole picture. Data from 293 patients in Europe had shown that only 53.9% of patients tested positive on AdV. Furthermore, AdV type 41 was only found on 50% of the AdV-positive patients and the remaining 50% were linked to AdV type 40 and other types of AdV equally.[1,99] Interestingly, AdV type 41 has never been reported to cause hepatitis.[98] Thus, it is still not conclusive yet whether AdV is the culprit of the acute hepatitis of unknown etiology.

In the process of writing this review, two preprints were made available that might explain the perpetrator of this unknown hepatitis. Both articles utilized metagenomic and real-time PCR approaches in both the blood sample and liver biopsies. They found adeno-associated virus 2 (AAV2) in all of the liver biopsies.[103,104] AAV2 is known to be able to cause respiratory infection; however, it needs a helper virus to replicate.[103] In both studies, the authors discovered that the main helper viruses were human ADV F41 and human herpes virus (HHV6).[103,104] Interestingly, one of those studies failed to detect viral proteins of AAV2, ADV F41, and HHV6 in their liver biopsies, but found high titer class II human leukocyte antigens (HLA) alleles, which suggested that the hepatic injury was not because of the direct cytopathic effect of the viral infection but rather because of the host immune response.[104] Both studies also described the association of class II HLA alleles with a susceptibility to the unknown hepatitis; namely, DRB1*04:01, DQA1*03:03, and DQB1*03:01.[103,104]

A relationship between several acute hepatitis of unknown etiology with COVID-19 had also been investigated. Data from the WHO/ECDC reported that only 10.9% of the patients were actively infected with SARS-COV-2 and that only 63.9% of the patients showed positive results in the serology test against SARS-COV-2.[99] Moreover, in Alabama, all nine cases were reported to be negative against SARS-COV-2.[96] A relationship with the COVID-19 vaccination had been assessed as well, in which the data showed that most cases (75%) were not yet vaccinated against SARS-COV-2, as the majority of the cases were children under the age of 5 years who had not received a COVID-19 vaccination.[96,99] Taken together, this did not support a causal relationship between SARS-CoV-2 infection or COVID-19 vaccination and severe acute hepatitis of unknown etiology.

Indonesia's experience against a potential outbreak of acute hepatitis

It had been reported that three pediatric patients (aged 2, 8 and 11 years) deceased in Jakarta, Indonesia during April 16–30, 2022, presumably due to severe acute hepatitis of unknown etiology. All patients exhibited jaundice, fever, nausea, vomiting, severe diarrhea, convulsion, and loss of consciousness. The Ministry of Health of the Republic of Indonesia subsequently conducted a surveillance of severe acute hepatitis of unknown etiology following the recommendation of the WHO.[1]

The COVID-19 pandemic has provided an important learning for the Indonesia's Ministry of Health on designing and implementing an effective public health policy on early surveillance and emergency response against a potential outbreak of an infectious disease. Pertaining to severe acute hepatitis of unknown etiology, the Indonesia's Ministry of Health is conducting a nationwide surveillance on cases with acute jaundice and is continuously monitoring cases that match the working case definitions as stated by the WHO. Furthermore, the Indonesia's Ministry of Health has issued its decree on April 27, 2022, to four relevant parties (i.e., public health bureau, port health office, public health laboratories, and hospitals) to increase their awareness and participation in screening and monitoring potential cases of acute hepatitis.[105] This joint effort is expected to be able to respond to any probable case and to contain possible pathogen(s) effectively in Indonesia. The decree is summarized in Table 3.

The Ministry of Health also conducted a routine press release on the recorded cases related to the severe acute hepatitis of unknown etiology across 37 provinces of Indonesia since early May 2022.[106] The data transparency was intended to facilitate the raising of the general awareness as well as minimize circulating fake news of this disease.[107] As shown in Table 4,[108–111] there were 28 probable and five pending classification cases by the end of July 2022 in Indonesia. Among those cases, 11 patients were reported as deceased (i.e., 10 from probable and one from pending classification).[108] Furthermore, metagenomic sequencing analysis was already performed in 15 probable cases by end of June 2022.[112] The CMV genome was detected in four probable cases, rendering it to be the most found virus among the cases in Indonesia thus far. It is still elusive, and still unknown whether the CMV infection caused severe acute hepatitis in those Indonesian children.

However, it is difficult to conclude whether the nationwide surveillance and related interventions by the Ministry of Health of the Republic of Indonesia were successful to control the incidence of severe acute hepatitis of unknown etiology. The number of reported cases also did not increase substantially between April and July 2022 and to the best of our knowledge, there was no press release on the cases in Indonesia within August and September 2022. This unfortunate change occurred as well at the international level, as the latest news by the WHO of this disease was publicized on July 12, 2022.[1] This hindered a sufficient comparison on the effectiveness of public health interventions by Indonesia and other countries. In addition, while the public health authority in Indonesia and multiple countries follow the case definitions stipulated by the WHO/ECDC, the United Kingdom Health Security Agency (UKHSA) and the Centers for Disease Control and Prevention

Table 3. Public health policy of Indonesia to anticipate severe acute hepatitis of unknown etiology

Public health bureau	Port health office	Public health laboratories	Hospitals
Monitoring and reporting any case with acute jaundice into the Early Warning and Response System.	Increasing the follow-up on travelers and cabin crew (particularly from countries with related cases), vehicles, luggage, disease vectors, as well as surroundings of seaports and airports.	Coordinating with the public health bureau, reference hospitals, and port health office to perform blood and throat swab tests in individuals with suspected acute hepatitis of unknown etiology.	Increasing the awareness by observing all cases of acute jaundice with unknown causes, managing them according to the guidelines and conducting the laboratory testing.
Providing relevant communication-information-education to the public and related preventive measures of clean and healthy lifestyle.	Increasing health promotional approaches for the border communities.	Conducting an independent assessment on the capabilities and resources of laboratories to perform the required tests.	Conducting a hospital record review on acute hepatitis of unknown etiology cases from January 1, 2022.
Informing the public to immediately visit healthcare facilities if contracting jaundice.	Coordinating health services with the public health bureau and local hospitals.		Notifying the Disease Prevention and Control Bureau immediately through the Public Health Emergency Operation Centre if there is a case matching the operational definition of acute hepatitis of unknown etiology.
Establishing and strengthening the disease surveillance network together with the Education Bureau and the Ministry of Religion.	Coordinating with the Immigration Authority if there is a suspected case among foreign visitors.		
Notifying the Disease Prevention and Control Bureau immediately through the Public Health Emergency Operation Centre if there is an increase in cases with acute jaundice or if there is a case matching the working case definition.	Coordinating with the airlines in detecting travelers with acute jaundice.		
Investigating related reports from healthcare facilities.	Notifying the Disease Prevention and Control Bureau immediately through the Public Health Emergency Operation Centre if there is an increase in cases with acute jaundice or if there is a case matching the working case definition.		

(CDC) of the United States utilize different case definitions. For example, the UKHSA has a working definition of a confirmed case, while the WHO/ECDC does not have this.[107] Next, while the UKHSA and US CDC consider it as a case if the child is aged younger than 10 years, the WHO/ECDC consider it as a case if the child is aged 16 years or younger.[107] These differences could impede a proper calculation of the cases of the severe acute hepatitis of unknown etiology worldwide. Furthermore, an elucidation of the cause of this severe acute hepatitis of unknown etiology would be even more challenging, arguably, as this disease gradually disappears worldwide, and as it is no longer a focus of public health authorities in multiple countries.

Table 4. Number of putative cases of severe acute hepatitis of unknown etiology in Indonesia

Parameter	End of April 2022[109]	End of May 2022[110]	End of June 2022[111]	End of July 2022[108]
Probable	3	5	16	28
Epidemiologically linked	0	0	0	0
Pending Classification	0	15	18	5

Future directions

The sudden appearance of severe acute hepatitis of unknown etiology during the COVID-19 pandemic has further implied the importance of health security. Several measurements could be done in Indonesia to reduce the risk of this illness becoming endemic. Firstly, increase the numbers of trained personnel who could screen people at entry points. Secondly, expand the testing sites and increase the trained personnel who could perform the testing. Thirdly, initiate research activities in Indonesia on this disease to help the world uncover the mystery and possibly find a cure. Finally, create the transparency of relevant information from the government. As was shown in this article, information regarding the severe acute hepatitis of unknown etiology was sparse and was suddenly stopped in August 2022. This also applied to other diseases, as there was a lack of information regarding them in Indonesia, and it is difficult to investigate them. Nonetheless, the COVID-19 pandemic demonstrated that Indonesia was able to provide continuous and transparent public health data that could be useful for the world. We therefore hope that after experiencing the COVID-19 pandemic and several multinational outbreaks, such as severe acute hepatitis of unknown etiology and monkeypox, Indonesia would invest substantially in the public health and life science sectors in order to increase its national health security.

Conclusions

Thirty-five countries within five WHO Regions (i.e., America, the Eastern Mediterranean, Europe, Southeast Asia, and the Western Pacific) have reported 1,010 probable cases of acute hepatitis of unknown origin among children as from July 8, 2022.[1] The etiology remains unknown and is currently being investigated. Fortunately, there is a declining trajectory in the number of cases globally,[113] thus suggesting that this illness would not be an imminent outbreak. In addition, the current multi-country outbreak of monkeypox has appeared to shift the public health attention from severe acute hepatitis of unknown etiology to the monkeypox disease.[114] Indonesia had followed the WHO's recommendation and modified its early surveillance network and public health emergency responses in anticipating severe acute hepatitis of unknown etiology. However, it remains to be seen whether this effort would be sufficient to screen, monitor, and control the transmission of emerging diseases in Indonesia.

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Conflict of interest

JJ has been an editorial board member of *Exploratory Research and Hypothesis in Medicine* since April 2022. The authors have no other conflict of interest related to this publication.

Author contributions

DH and AS wrote the initial draft of the manuscript. JJ critically reviewed and completed the manuscript. All authors made a significant contribution to this study and approved the final manuscript.

References

[1] World Health Organization. Severe acute hepatitis of unknown aetiology in children - Multi-country. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON400. Accessed July 26, 2022.
[2] Shalimar, Acharya SK, Kumar R, Bharath G, Rout G, Gunjan D, *et al*. Acute Liver Failure of Non-A-E Viral Hepatitis Etiology-Profile, Prognosis, and Predictors of Outcome. J Clin Exp Hepatol 2020;10(5):453–461. doi:10.1016/j.jceh.2019.12.008, PMID:33029054.
[3] Habib S. Autoimmune hepatitis related acute and acute on chronic liver failure: Lost in translation. AME Med J 2019;4:6–6. doi:10.21037/amj.2019.01.03.
[4] Pisano MB, Giadans CG, Flichman DM, Ré VE, Preciado MV, Valva P. Viral hepatitis update: Progress and perspectives. World J Gastroenterol 2021;27(26):4018–4044. doi:10.3748/wjg.v27.i26.4018, PMID:34326611.
[5] Sallam M, Mahafzah A, Şahin GÖ, On Behalf Of Escmid Study Group For Viral Hepatitis-Esgvh. Hepatitis of Unknown Origin and Etiology (Acute Non HepA-E Hepatitis) among Children in 2021/2022: Review of the Current Findings. Healthcare (Basel) 2022;10(6):973. doi:10.3390/healthcare10060973, PMID:35742029.
[6] Williams H. Epidemic Jaundice in New York State, 1921-1922. JAMA 1923;80(8):532. doi:10.1001/JAMA.1923.02640350014007.
[7] de Kleine RH, Lexmond WS, Buescher G, Sturm E, Kelly D, Lohse AW, *et al*. Severe acute hepatitis and acute liver failure of unknown origin in children: a questionnaire-based study within 34 paediatric liver centres in 22 European countries and Israel, April 2022. Euro Surveill 2022;27(19). doi:10.2807/1560-7917.ES.2022.27.19.2200369, PMID:35551705.
[8] Almeida PH, Matielo CEL, Curvelo LA, Rocco RA, Felga G, Della Guardia B, *et al*. Update on the management and treatment of viral hepatitis. World J Gastroenterol 2021;27(23):3249–3261. doi:10.3748/wjg.v27.i23.3249, PMID:34163109.
[9] He Z, Zhuang H, Wang X, Song S, Dong Q, Yan J, *et al*. Retrospective analysis of non-A-E hepatitis: possible role of hepatitis B and C virus infection. J Med Virol 2003;69(1):59–65. doi:10.1002/jmv.10248, PMID:12436478.
[10] Ryder SD, Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system: Acute hepatitis. BMJ 2001;322(7279):151–153. doi:10.1136/bmj.322.7279.151, PMID:11159575.
[11] Gupta SP. Viral Hepatitis: Historical Perspective, Etiology, Epidemiology, and Pathophysiology. Studies on Hepatitis Viruses. Pittsburgh: Academic Press; 2018. doi:10.1016/B978-0-12-813330-9.00001-6.
[12] Migueres M, Lhomme S, Izopet J. Hepatitis A: Epidemiology, High-Risk Groups, Prevention and Research on Antiviral Treatment. Viruses 2021;13(10):1900. doi:10.3390/v13101900, PMID:34696330.
[13] Lemon SM, Ott JJ, Van Damme P, Shouval D. Type A viral hepatitis: A summary and update on the molecular virology, epidemiology, pathogenesis and prevention. J Hepatol 2018;68(1):167–184. doi:10.1016/j.jhep.2017.08.034, PMID:28887164.
[14] Snooks MJ, Bhat P, Mackenzie J, Counihan NA, Vaughan N, Anderson DA. Vectorial entry and release of hepatitis A virus in polarized human hepatocytes. J Virol 2008;82(17):8733–8742. doi:10.1128/JVI.00219-08, PMID:18579610.
[15] Franco E, Meleleo C, Serino L, Sorbara D, Zaratti L. Hepatitis A: Epidemiology and prevention in developing countries. World J Hepatol 2012;4(3):68–73. doi:10.4254/wjh.v4.i3.68, PMID:22489258.
[16] Hu X, Collier MG, Xu F. Hepatitis A Outbreaks in Developed Countries: Detection, Control, and Prevention. Foodborne Pathog Dis 2020;17(3):166–171. doi:10.1089/fpd.2019.2648, PMID:31829731.
[17] Setyowati D, Mubawadi T, Mirasa YA, Purwanto D, Amin M, Utsumi T, *et al*. Molecular epidemiology of hepatitis A outbreaks in two districts in Indonesia in 2018: Same subtype, but different strains. Biomed Rep 2020;12(2):51–58. doi:10.3892/br.2019.1261, PMID:31929874.
[18] Hasil Riskesdas. Basic Health Research. Available from: https://pusdatin.kemkes.go.id/resources/download/general/Hasil%20Riskes-

das%202013.pdf. Accessed May 26, 2022.
[19] Chakravarti A, Bharara T. Epidemiology of Hepatitis A: Past and Current Trends. In: Teodor Streba C, Constantin Vere C, Rogoveanu I, Tripodi V, Lucangioli S (eds). Hepatitis A and Other Associated Hepatobiliary Diseases. London: IntechOpen; 2020.
[20] Webb GW, Kelly S, Dalton HR. Hepatitis A and Hepatitis E: Clinical and Epidemiological Features, Diagnosis, Treatment, and Prevention. Clin Microbiol Newsl 2020;42(21):171–179. doi:10.1016/j.clinmicnews.2020.10.001, PMID:33110280.
[21] Misumi I, Mitchell JE, Lund MM, Cullen JM, Lemon SM, Whitmire JK. T cells protect against hepatitis A virus infection and limit infection-induced liver injury. J Hepatol 2021;75(6):1323–34. doi:10.1016/j.jhep.2021.07.019, PMID:34331968.
[22] Wang M, Feng Z. Mechanisms of Hepatocellular Injury in Hepatitis A. Viruses. 2021;13(5):861. doi:10.3390/v13050861, PMID:34066709.
[23] Nelson NP, Weng MK, Hofmeister MG, Moore KL, Doshani M, Kamili S, *et al*. Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep 2020;69(5):1–38. doi:10.15585/mmwr.rr6905a1, PMID:32614811.
[24] Nainan OV, Xia G, Vaughan G, Margolis HS. Diagnosis of hepatitis a virus infection: a molecular approach. Clin Microbiol Rev 2006;19(1):63–79. doi:10.1128/CMR.19.1.63-79.2006, PMID:16418523.
[25] Koenig KL, Shastry S, Burns MJ. Hepatitis A Virus: Essential Knowledge and a Novel Identify-Isolate-Inform Tool for Frontline Healthcare Providers. West J Emerg Med 2017;18(6):1000–1007. doi:10.5811/westjem.2017.10.35983, PMID:29085529.
[26] Pintó RM, Bosch A, Kaplan G. Hepatitis A: Immune Response and Virus Evolution. In: Gershwin ME, Vierling JM, Manns MP (eds). Liver Immunology. Cham: Springer International Publishing; 2014.
[27] D'souza S, Lau KC, Coffin CS, Patel TR. Molecular mechanisms of viral hepatitis induced hepatocellular carcinoma. World J Gastroenterol 2020;26(38):5759–5783. doi:10.3748/wjg.v26.i38.5759, PMID:33132633.
[28] Van Damme E, Vanhove J, Severyn B, Verschueren L, Pauwels F. The Hepatitis B Virus Interactome: A Comprehensive Overview. Front Microbiol 2021;12:724877. doi:10.3389/fmicb.2021.724877, PMID:34603251.
[29] Suhail M, Abdel-Hafiz H, Ali A, Fatima K, Damanhouri GA, Azhar E, *et al*. Potential mechanisms of hepatitis B virus induced liver injury. World J Gastroenterol 2014;20(35):12462–12472. doi:10.3748/wjg.v20.i35.12462, PMID:25253946.
[30] Gnyawali B, Pusateri A, Nickerson A, Jalil S, Mumtaz K. Epidemiologic and socioeconomic factors impacting hepatitis B virus and related hepatocellular carcinoma. World J Gastroenterol 2022;28(29):3793–3802. doi:10.3748/wjg.v28.i29.3793, PMID:36157533.
[31] Holmes KK, Bertozzi S, Bloom BR, Jha P. Disease Control Priorities, Third Edition (Volume 6): Major Infectious Diseases. The World Bank eLibrary; 2017.
[32] Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, *et al*. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(1):1–31. doi:10.15585/mmwr.rr6701a1, PMID:29939980.
[33] Komatsu H, Inui A, Sogo T, Tateno A, Shimokawa R, Fujisawa T. Tears from children with chronic hepatitis B virus (HBV) infection are infectious vehicles of HBV transmission: experimental transmission of HBV by tears, using mice with chimeric human livers. J Infect Dis 2012;206(4):478–485. doi:10.1093/infdis/jis293, PMID:22508939.
[34] Drazilova S, Kristian P, Janicko M, Halanova M, Safcak D, Dorcakova PD, *et al*. What is the Role of the Horizontal Transmission of Hepatitis B Virus Infection in Young Adult and Middle-Aged Roma Population Living in the Settlements in East Slovakia? Int J Environ Res Public Health 2020;17(9):E3293. doi:10.3390/ijerph17093293, PMID:32397342.
[35] Nguyen MH, Wong G, Gane E, Kao JH, Dusheiko G. Hepatitis B Virus: Advances in Prevention, Diagnosis, and Therapy. Clin Microbiol Rev 2020;33(2):e00046–19. doi:10.1128/CMR.00046-19, PMID:32102898.
[36] Zage AU, Ali M, Diso SU. Epidemiology, virology, transmission, clinical manifestation and vaccine for hepatitis virus B: A review. Int J Vaccines Vaccin 2018;5(3):48–52. doi:10.15406/ijvv.2018.05.00103.
[37] Wilkins T, Sams R, Carpenter M. Hepatitis B: Screening, Prevention, Diagnosis, and Treatment. Hepat B 2019;99(5):314–323. PMID:30811163.
[38] Song JE, Kim DY. Diagnosis of hepatitis B. Ann Transl Med. 2016;4(18):338. doi:10.21037/atm.2016.09.11, PMID:27761442.
[39] Lee JH, Kim HS. Current laboratory tests for diagnosis of hepatitis B virus infection. Int J Clin Pract 2021;75(12):e14812. doi:10.1111/ijcp.14812, PMID:34487586.
[40] Guidotti LG, Chisari FV. Immunobiology and pathogenesis of viral hepatitis. Annu Rev Pathol 2006;1:23–61. doi:10.1146/annurev.pathol.1.110304.100230, PMID:18039107.
[41] Tang LSY, Covert E, Wilson E, Kottilil S. Chronic Hepatitis B Infection: A Review. JAMA 2018;319(17):1802–1813. doi:10.1001/jama.2018.3795, PMID:29715359.
[42] Khanam A, Chua JV, Kottilil S. Immunopathology of Chronic Hepatitis B Infection: Role of Innate and Adaptive Immune Response in Disease Progression. Int J Mol Sci 2021;22(11):5497. doi:10.3390/ijms22115497, PMID:34071064.
[43] Parikh P, Ryan JD, Tsochatzis EA. Fibrosis assessment in patients with chronic hepatitis B virus (HBV) infection. Ann Transl Med 2017;5(3):40. doi:10.21037/atm.2017.01.28, PMID:28251119.
[44] Petruzziello A. Epidemiology of Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Related Hepatocellular Carcinoma. Open Virol J 2018;12:26–32. doi:10.2174/1874357901812010026, PMID:29541276.
[45] Shi G, Suzuki T. Molecular Basis of Encapsidation of Hepatitis C Virus Genome. Front Microbiol 2018;9:396. doi:10.3389/fmicb.2018.00396, PMID:29563905.
[46] Moriishi K, Matsuura Y. Structural Proteins of HCV and Biological Functions. In: Miyamura T, Lemon SM, Walker CM, Wakita T (eds). Hepatitis C Virus I. Tokyo: Springer; 2016.
[47] Roudot-Thoraval F. Epidemiology of hepatitis C virus infection. Clin Res Hepatol Gastroenterol 2021;45(3):101596. doi:10.1016/j.clinre.2020.101596, PMID:33610022.
[48] H Muljono D. Epidemiology of Hepatitis B and C in Republic of Indonesia. Euroasian J Hepatogastroenterol 2017;7(1):55–59. doi:10.5005/jp-journals-l0018-1212, PMID:29201773.
[49] Millman AJ, Nelson NP, Vellozzi C. Hepatitis C: Review of the Epidemiology, Clinical Care, and Continued Challenges in the Direct Acting Antiviral Era. Curr Epidemiol Rep 2017;4(2):174–185. doi:10.1007/s40471-017-0108-x, PMID:28785531.
[50] Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014;61(1):S58–68. doi:10.1016/j.jhep.2014.07.012, PMID:25443346.
[51] Irshad M, Gupta P, Irshad K. Immunopathogenesis of Liver Injury During Hepatitis C Virus Infection. Viral Immunol 2019;32(3):112–120. doi:10.1089/vim.2018.0124, PMID:30817236.
[52] Rosu AF, Freitas C, Marinho RT, Velosa J. Spontaneous Cure of Acute Hepatitis C. Curr Health Sci J. 2015;41(4):375–378. doi:10.12865/CHSJ.41.04.13, PMID:30538845.
[53] Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48(2):418–431. doi:10.1002/hep.22375, PMID:18563841.
[54] Khudur Al-Nassary MS, Mahdi BM. Study of Hepatitis C Virus Detection Assays. Ann Med Surg (Lond) 2018;36:47–50. doi:10.1016/j.amsu.2018.10.002, PMID:30377525.
[55] Gupta E, Bajpai M, Choudhary A. Hepatitis C virus: Screening, diagnosis, and interpretation of laboratory assays. Asian J Transfus Sci 2014;8(1):19–25. doi:10.4103/0973-6247.126683, PMID:24678168.
[56] Michalak TI. HCV Lymphotropism and Its Pathogenic Significance. In: Shahid I (ed). Hepatitis C - From Infection to Cure. London: IntechOpen; 2018.
[57] Jo J, Lohmann V, Bartenschlager R, Thimme R. Experimental models to study the immunobiology of hepatitis C virus. J Gen Virol 2011;92(3):477–493. doi:10.1099/vir.0.027987-0, PMID:21148278.
[58] Golden-Mason L, Rosen HR. Natural killer cells: primary target for hepatitis C virus immune evasion strategies? Liver Transpl 2006;12(3):363–372. doi:10.1002/lt.20708, PMID:16498647.

[59] Rizzetto M, Canese MG, Aricò S, Crivelli O, Trepo C, Bonino F, *et al*. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. Gut 1977;18(12):997–1003. doi:10.1136/gut.18.12.997, PMID:75123.
[60] Rizzetto M, Hoyer B, Canese MG, Shih JW, Purcell RH, Gerin JL. delta Agent: association of delta antigen with hepatitis B surface antigen and RNA in serum of delta-infected chimpanzees. Proc Natl Acad Sci U S A 1980;77(10):6124–6128. doi:10.1073/pnas.77.10.6124, PMID:6934539.
[61] Wedemeyer H, Manns MP. Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. Nat Rev Gastroenterol Hepatol 2010;7(1):31–40. doi:10.1038/nrgastro.2009.205, PMID:20051970.
[62] Farci P, Niro GA, Zamboni F, Diaz G. Hepatitis D Virus and Hepatocellular Carcinoma. Viruses 2021;13(5):830. doi:10.3390/v13050830, PMID:34064419.
[63] Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, *et al*. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol 2020;73(3):523–532. doi:10.1016/j.jhep.2020.04.008, PMID:32335166.
[64] Pascarella S, Negro F. Hepatitis D virus: an update. Liver Int 2011;31(1):7–21.doi:10.1111/j.1478-3231.2010.02320.x,PMID:20880077.
[65] Muhammad H, Tehreem A, Hammami MB, Ting PS, Idilman R, Gurakar A. Hepatitis D virus and liver transplantation: Indications and outcomes. World J Hepatol 2021;13(3):291–299. doi:10.4254/wjh.v13.i3.291, PMID:33815673.
[66] Goyal A, Murray JM. The impact of vaccination and antiviral therapy on hepatitis B and hepatitis D epidemiology. PLoS One 2014;9(10):e110143. doi:10.1371/journal.pone.0110143, PMID:25313681.
[67] Cole SM, Gowans EJ, Macnaughton TB, De La M. Hall P, Burrell CJ. Direct evidence for cytotoxicity associated with expression of hepatitis delta virus antigen. Hepatology 1991;13(5):845–851. PMID:1709411.
[68] Davies SE, Lau JYN, O'Grady JG, Portmann BC, Alexander GJM, Williams R. Evidence that Hepatitis D Virus Needs Hepatitis B Virus to Cause Hepatocellular Damage. Am J Clin Pathol 1992;98(6):554–558. doi:10.1093/ajcp/98.6.554, PMID:1462952.
[69] Niro GA, Smedile A. Current concept in the pathophysiology of hepatitis delta infection. Curr Infect Dis Rep 2012;14(1):9–14. doi:10.1007/s11908-011-0233-5, PMID:22161240.
[70] Holla RP, Ahmad I, Ahmad Z, Jameel S. Molecular virology of hepatitis E virus. Semin Liver Dis 2013;33(1):3–14. doi:10.1055/s-0033-1338110, PMID:23564385.
[71] Wang B, Meng XJ. Structural and molecular biology of hepatitis E virus. Comput Struct Biotechnol J 2021;19:1907–1916. doi:10.1016/j.csbj.2021.03.038, PMID:33995894.
[72] Yadav KK, Kenney SP. Hepatitis E Virus Immunopathogenesis. Pathogens 2021;10(9):1180. doi:10.3390/pathogens10091180, PMID:34578211.
[73] Nair VP, Anang S, Subramani C, Madhvi A, Bakshi K, Srivastava A, *et al*. Endoplasmic Reticulum Stress Induced Synthesis of a Novel Viral Factor Mediates Efficient Replication of Genotype-1 Hepatitis E Virus. PLoS Pathog 2016;12(4):e1005521. doi:10.1371/journal.ppat.1005521, PMID:27035822.
[74] Yadav KK, Boley PA, Fritts Z, Kenney SP. Ectopic Expression of Genotype 1 Hepatitis E Virus ORF4 Increases Genotype 3 HEV Viral Replication in Cell Culture. Viruses 2021;13(1):75. doi:10.3390/v13010075, PMID:33430442.
[75] Pallerla SR, Harms D, Johne R, Todt D, Steinmann E, Schemmerer M, *et al*. Hepatitis E Virus Infection: Circulation, Molecular Epidemiology, and Impact on Global Health. Pathogens 2020;9(10):856. doi:10.3390/pathogens9100856, PMID:33092306.
[76] Velavan TP, Pallerla SR, Johne R, Todt D, Steinmann E, Schemmerer M, *et al*. Hepatitis E: An update on One Health and clinical medicine. Liver Int 2021;41(7):1462–1473. doi:10.1111/liv.14912, PMID:33960603.
[77] Corwin A, Jarot K, Lubis I, Nasution K, Suparmawo S, Sumardiati A, *et al*. Two years' investigation of epidemic hepatitis E virus transmission in West Kalimantan (Borneo), Indonesia. Trans R Soc Trop Med Hyg 1995;89(3):262–265. doi:10.1016/0035-9203(95)90529-4, PMID:7660427.
[78] Corwin A, Putri MP, Winarno J, Lubis I, Suparmanto S, Sumardiati A, *et al*. Epidemic and sporadic hepatitis E virus transmission in West Kalimantan (Borneo), Indonesia. Am J Trop Med Hyg 1997;57(1):62–65. doi:10.4269/ajtmh.1997.57.62, PMID:9242320.
[79] Sedyaningsih-Mamahit ER, Larasati RP, Laras K, Sidemen A, Sukri N, Sabaruddin N, *et al*. First documented outbreak of hepatitis E virus transmission in Java, Indonesia. Trans R Soc Trop Med Hyg 2002;96(4):398–404. doi:10.1016/s0035-9203(02)90373-1, PMID:12497976.
[80] Widasari DI, Yano Y, Utsumi T, Heriyanto DS, Anggorowati N, Rinonce HT, *et al*. Hepatitis E virus infection in two different regions of Indonesia with identification of swine HEV genotype 3: HEV from different Indonesian regions. Microbiol Immunol 2013;57(10):692–703. doi:10.1111/1348-0421.12083, PMID:23865729.
[81] Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. N Engl J Med. 2012;367(13):1237–1244. doi:10.1056/NEJMra1204512, PMID:23013075.
[82] Murali AR, Kotwal V, Chawla S. Chronic hepatitis E: A brief review. World J Hepatol 2015;7(19):2194–2201. doi:10.4254/wjh.v7.i19.2194, PMID:26380044.
[83] Wu J, Ling B, Guo N, Zhai G, Li M, Guo Y. Immunological Manifestations of Hepatitis E-Associated Acute and Chronic Liver Failure and Its Regulatory Mechanisms. Front Med (Lausanne) 2021;8:725993. doi:10.3389/fmed.2021.725993, PMID:34434948.
[84] Surjit M, Varshney B, Lal SK. The ORF2 glycoprotein of hepatitis E virus inhibits cellular NF-κB activity by blocking ubiquitination mediated proteasomal degradation of IκBα in human hepatoma cells. BMC Biochem 2012;13:7. doi:10.1186/1471-2091-13-7, PMID:22590978.
[85] Luedde T, Schwabe RF. NF-κB in the liver—linking injury, fibrosis and hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2011;8(2):108–118. doi:10.1038/nrgastro.2010.213, PMID:21293511.
[86] Luedde T, Beraza N, Kotsikoris V, van Loo G, Nenci A, De Vos R, *et al*. Deletion of NEMO/IKKgamma in liver parenchymal cells causes steatohepatitis and hepatocellular carcinoma. Cancer Cell 2007;11(2):119–132. doi:10.1016/j.ccr.2006.12.016, PMID:17292824.
[87] Beg AA, Baltimore D. An essential role for NF-kappaB in preventing TNF-alpha-induced cell death. Science 1996;274(5288):782–784. doi:10.1126/science.274.5288.782, PMID:8864118.
[88] Brennan PN, Donnelly MC, Simpson KJ. Systematic review: Non A-E, seronegative or indeterminate hepatitis; what is this deadly disease? Aliment Pharmacol Ther 2018;47(8):1079–1091. doi:10.1111/apt.14566, PMID:29468698.
[89] Crum NF. Epstein Barr virus hepatitis: case series and review. South Med J 2006;99(5):544–547. doi:10.1097/01.smj.0000216469.04854.2a, PMID:16711324.
[90] Kimura H, Nagasaka T, Hoshino Y, Hayashi N, Tanaka N, Lan Xu J, *et al*. Severe hepatitis caused by Epstein-Barr virus without infection of hepatocytes. Hum Pathol 2001;32(7):757–762. doi:10.1053/hupa.2001.25597, PMID:11486177.
[91] Drebber U, Kasper HU, Krupacz J, Haferkamp K, Kern MA, Steffen HM, *et al*. The role of Epstein–Barr virus in acute and chronic hepatitis. J Hepatol 2006;44(5):879–885. doi:10.1016/j.jhep.2006.02.006, PMID:16554102.
[92] Da Cunha T, Wu GY. Cytomegalovirus Hepatitis in Immunocompetent and Immunocompromised Hosts. J Clin Transl Hepatol 2021;9(1):106–115. doi:10.14218/JCTH.2020.00088, PMID:33604261.
[93] Bihari C, Rastogi A, Saxena P, Rangegowda D, Chowdhury A, Gupta N, *et al*. Parvovirus b19 associated hepatitis. Hepat Res Treat 2013;2013:472027. doi:10.1155/2013/472027, PMID:24232179.
[94] Ronan BA, Agrwal N, Carey EJ, De Petris G, Kusne S, Seville MT, *et al*. Fulminant hepatitis due to human adenovirus. Infection 2014;42(1):105–111. doi:10.1007/s15010-013-0527-7, PMID:23979854.
[95] Ali S, Prakash S, Murali AR. Hepatic Manifestations of Nonhepatotropic Infectious Agents Including Severe Acute Respiratory Syndrome Coronavirus-2, Adenovirus, Herpes Simplex Virus, and Coxiella burnetii. Gastroenterol Clin North Am 2021;50(2):383–402.

doi:10.1016/j.gtc.2021.02.012, PMID:34024447.
[96] Baker JM, Buchfellner M, Britt W, Sanchez V, Potter JL, Ingram LA, *et al*. Acute Hepatitis and Adenovirus Infection Among Children - Alabama, October 2021-February 2022. MMWR Morb Mortal Wkly Rep 2022;71(18):638–640. doi:10.15585/mmwr.mm7118e1, PMID:35511732.
[97] Aricò M, Caselli D. Acute, Severe Hepatitis of Unknown Origin: Should We Really Be Afraid of Another Obscure Enemy of Our Children? Pediatr Rep 2022;14(2):217–219. doi:10.3390/pediatric14020029, PMID:35645366.
[98] Mücke MM, Zeuzem S. The recent outbreak of acute severe hepatitis in children of unknown origin – what is known so far. J Hepatol 2022;77(1):237–242. doi:10.1016/j.jhep.2022.05.001, PMID:35533802.
[99] Joint ECDC-WHO Regional Office for Europe Hepatitis of Unknown Origin in Children Surveillance Bulletin. Available from: https://cdn.ecdc.europa.eu/novhep-surveillance/. Accessed June 13, 2022.
[100] van Beek J, Fraaij PL, Giaquinto C, Shingadia D, Horby P, Indolfi G, *et al*. Case numbers of acute hepatitis of unknown aetiology among children in 24 countries up to 18 April 2022 compared to the previous 5 years. Euro Surveill 2022;27(19):2200370. doi:10.2807/1560-7917.ES.2022.27.19.2200370, PMID:35551703.
[101] Centers for Disease Control and Prevention. Updates - Pediatric Hepatitis of Unknown Cause Available from: https://www.cdc.gov/ncird/investigation/hepatitis-unknown-cause/updates.html. Accessed June 14, 2022.
[102] Pérez-Gracia MT, Tarín-Pelló A, Suay-García B. Severe Acute Hepatitis of Unknown Origin in Children: What Do We Know Today? J Clin Transl Hepatol 2022;10(4):711–717. doi:10.14218/JCTH.2022.00244, PMID:36062273.
[103] Ho A, Orton R, Tayler R, Asamaphan P, Tong L, Smollett K, *et al*. Adeno-associated virus 2 infection in children with non-A-E hepatitis. medRxiv [preprint] 2022. doi:10.1101/2022.07.19.22277425.
[104] Morfopoulou S, Buddle S, Montaguth OET, Atkinson L, Guerra-Assunção JA, Storey N, *et al*. Genomic investigations of acute hepatitis of unknown aetiology in children. medRxiv [preprint] 2022. doi:10.1101/2022.07.28.22277963.
[105] Ministry of Health. Surat Edaran Nomor: HK.02.02/C/2515/2022. Available from: https://infeksiemerging.kemkes.go.id/document/download/wB5rQb9O2a. Accessed July 26, 2022.
[106] Sehat Negeriku. The Ministry of Health's Efforts to Anticipate the Spread of Acute Hepatitis in Indonesia. Available from: https://sehatnegeriku.kemkes.go.id/baca/umum/20220513/5039824/upaya-kemenkes-antisipasi-penyebaran-hepatitis-akut-di-indonesia/. Accessed September 13, 2022.
[107] Khader S, Foster I, Dagens A, Norton A, Sigfrid L. Severe acute hepatitis of unknown aetiology in children-what is known? BMC Med 2022;20(1):280. doi:10.1186/s12916-022-02471-5, PMID:35906650.
[108] celebrities.id. Update on Acute Hepatitis Cases in Indonesia, 11 People with Probable Status and Pending Classification Dies. Available from: https://www.celebrities.id/read/update-kasus-hepatitis-akut-di-indonesia-11-orang-berstatus-probable-dan-pending-classification-meninggal-dunia-Nn0V87. Accessed September 13, 2022.
[109] Sehat Negeriku. The public to be alert after 3 pediatric patients with acute hepatitis died. Available from: https://sehatnegeriku.kemkes.go.id/baca/rilis-media/20220501/3939769/masyarakat-agar-waspada-setelah-3-pasien-anak-dengan-hepatitis-akut-meninggal-dunia/. Accessed September 13, 2022.
[110] Indonesia CNN. Cases of Suspected Mysterious Acute Hepatitis in Indonesia Increase to 20. Available from: https://www.cnnindonesia.com/nasional/20220531094205-20-803035/kasus-dugaan-hepatitis-akut-misterius-di-ri-bertambah-jadi-20. Accessed September 13, 2022.
[111] Indonesia CNN. Cases of Suspected Acute Hepatitis in Indonesia Increase to 75. Available from: https://www.cnnindonesia.com/nasional/20220630122426-20-815483/kasus-dugaan-hepatitis-akut-di-ri-bertambah-jadi-75. Accessed September 13, 2022.
[112] Ministry of Health Republic of Indonesia. This Pathogen is Most Found in Hepatitis Patients. Available from: https://www.kemkes.go.id/article/view/22062500005/patogen-ini-paling-banyak-ditemukan-pada-pasien-hepatitis.html. Accessed September 13, 2022.
[113] Becky Mccall. Acute Hepatitis Cases in Children Show Declining Trend. Available from: https://www.medscape.com/viewarticle/976174. Accessed August 4, 2022.
[114] Isidro J, Borges V, Pinto M, Sobral D, Santos JD, Nunes A, *et al*. Phylogenomic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus. Nat Med 2022;28(8):1569–1572. doi:10.1038/s41591-022-01907-y, PMID:35750157.