Chapter 10
Viral Hepatitis Non: B, C, D and Acute and Acute on Chronic Liver Failure

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Key Concepts
1. Non-B, C, and D viruses that can cause hepatitis can also cause acute liver failure and acute on chronic liver failure.
2. Diagnosis of ALF and ACLF due non-B, C, and D viral hepatidities relies on proper physician awareness, knowledge of each virus’s clinical presentation, and diagnostic capabilities in at-risk populations.
3. HAV and HEV related ALF and ACLF are commonly found in endemic populations while EBV, CMV, and VZV related ALF and ACLF usually only occurs in those who are immunocompromised.
4. Prevention of certain viruses such as HAV and HEV can be effectively done with proper hygiene or vaccination.
5. Management of ALF or ACLF related to non-B, C, and D viral hepatidities includes supportive care for failing organ systems, viral directed medical therapy, and liver transplantation.
Introduction

Acute liver failure (ALF) and acute on chronic liver failure (ACLF) are two distinct clinical syndromes that both carry a substantial mortality risk [1]. ALF is defined as a coagulation abnormality (International Normalized Ratio (INR) ≥1.5), any degree of altered mental status (encephalopathy) in a patient without preexisting cirrhosis with illness lasting less than 26 weeks [2]. On the other hand, acute on chronic liver failure (ACLF) is syndrome of acute clinical worsening of a patient with pre-existing chronic liver disease (CLD). ACLF is present in approximately 30% of patients with cirrhosis admitted to the hospital and is a systemic syndrome that is marked by multi-organ failure and high short-term mortality [3]. Compared to “decompensated cirrhosis”, ACLF carries a significantly worse prognosis with a mortality rate similar to ALF [1]. However, ACLF is a relatively newer term and there is no consensus definition of ACLF but the most commonly used definitions include the American Association for the Study of Liver Diseases (AASLD) /European Association for the Study of Liver (EASL) [4], EASL-chronic liver failure (CLIF) [5], North American Consortium for the Study of the Liver Disease (NACSELD) [6], and Asian Pacific Association for the Study of the Liver (APASL) [7] (See Table 10.1).

The major etiologies of CLD in patients with ACLF include viral hepatitis, alcohol, and non-alcoholic steatohepatitis (NASH) [8]. Meanwhile, the major triggers of decompensation in ACLF include bacterial infections, acute viral hepatitis, and ongoing alcohol use. Among these, viral hepatitis related ACLF is of particular interest because of the availability of effective treatments and prevention strategies for several of the most common hepatotropic viruses such as hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection. Viral hepatitis related ACLF can happen in two manners, the first through the virus itself causing CLD which may decompensate in similar manner to other CLDs, or the second through acute viral hepatitis (AVH) acting as an insult in a patient with pre-existing CLD. In the latter case, the typical causes of AVH that trigger viral related ACLF can be

| EASL-AASLD [4] | APASL [7] | EASL-CLIF [5] | NACSELD [6] |
|----------------|----------|--------------|-------------|
| Acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure. | Acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. | Acute decompensation (i.e. ascites, encephalopathy, gastrointestinal hemorrhage, bacterial infection) followed by the development of one or more organ failures. | Two or more extrahepatic organ failures (brain failure, renal failure, respiratory failure, and/or shock) in a patient with pre-existing cirrhosis. |

EASL European Association for the Study of Liver, AASLD American Association for the Study of Liver Diseases, APASL Asian Pacific Association for the Study of the Liver, CLIF chronic liver failure, NACSELD North American Consortium for the Study of End-stage Liver Disease
comparable to the typical causes of ALF in the same geographical region. For example, in countries where hepatitis A virus (HAV) and hepatitis E virus (HEV) are endemic such as India, HAV and HEV are responsible for a significant number of ALF and ACLF cases. Meanwhile, in non-endemic countries such as the United States, they are considered rare causes of ALF and ACLF [4].

The aim of this review is to discuss in depth how ALF and ACLF relate to non-HBV, hepatitis D virus (HDV), and HCV viral hepatitis. The specific hepatotropic viruses that will primarily be reviewed will include HAV and HEV, as well as non-hepatotropic viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV). For each respective virus, we will proceed to delineate epidemiology, pathophysiology, risk factors, clinical presentation, prognosis and prognostic assessment, and management as it applies to the two syndromes.

Hepatitis A Virus

Hepatitis A is a communicable disease targeting the liver caused by the HAV. HAV belongs to the family Picornaviridae and genus Hepatovirus. HAV is a small, non-enveloped, single-stranded RNA virus [9]. Four of its seven reported genotypes have been associated with human disease and infection with one genotype usually results in lifelong immunity against all strains [9, 10]. HAV is a major cause of AVH throughout the world and although infection in children is often asymptomatic and leads to lifelong immunity, adults and elderly populations are at a higher risk of severe infections that can lead to ALF and ACLF [11–13].

Epidemiology

Prevalence of hepatitis A varies with geographic location and socioeconomic conditions; standards of hygiene and sanitation are strongly associated with its incidence. For example, in areas of high endemicity such as parts of Asia and Africa, most infections occur in children before the age of 10 years leading to high rates of population immunity and low risk of outbreaks [10, 11, 14]. In areas of low or intermediate prevalence areas, childhood transmission is less frequent and more adolescents and adults are infected with certain groups such as international travelers, elderly populations and intravenous drug users, who are at particularly high risk of infection [10, 11, 14, 15].

Globally, an estimated 1.4 million cases of hepatitis A occur each year. Since the introduction of the hepatitis A vaccine in 1995, rates of hepatitis A infection have declined from 6.0 cases/100,000 population in 1999 to 0.4 cases/100,000 in 2011 in the United States [16]. Although the incidence rate of HAV infections have decreased, a large population of susceptible, unvaccinated adults in low to intermediate endemic areas remain vulnerable to infection [17]. In 2017, 649 people in San
Diego, California were infected with hepatitis A leading to 417 hospitalizations and 21 deaths, making it the largest outbreak in the United States over the last 20 years [18]. Overall, from 2016 to 2018 reports of hepatitis A cases in the United States have increased by 294% as compared to 2013–2015 [17].

HAV related ALF is an uncommon manifestation and occurs in less than 1% of cases [13, 19–21]. Certain groups such as those above the age of 50 or those with underlying CLD are at the most risk of ALF and ACLF [19, 22]. Vento et al. prospectively followed 595 patients with chronic HBV and HCV and found 27 cases of superimposed HAV infection. Of the 17 patients that had underlying HCV infection, 7 developed ACLF leading to 6 deaths. A similar study in Thailand compared HAV infections in patients who were asymptomatic HBV carriers or had underlying CLD from HBV and HCV to isolated HAV infections and found high rates of ACLF in HBV carriers (55% of cases) and HBV/HCV CLD (33% of cases) [13]. Patients with CLD were significantly older (age >43 years of age, \( p < 0.02 \)) compared to patients with isolated HAV. Interestingly, there were no differences in mortality rates between asymptomatic HBV carriers and CLD patients.

The vast majority of studies studying HAV related ACLF comes from South Asia where HAV related AVH is prevalent [23]. Gupta et al. studied cases of AVH related ACLF as defined by the APASL criteria and found HAV to be the cause of ACLF in 7.8% of cases [12]. Krishna et al. reported that out of 121 cases of ACLF in their series, HAV was the a trigger in 33 (27.2%) cases [24].

**Transmission and Pathophysiology**

Early in the 1900s, physicians recognized that HAV was spread by person to person contact. Although there have been rare reports of vertical transmission or parenteral transmission through contaminated blood product, HAV is mainly spread through the fecal-oral route [9]. Given it’s thermostable and acid resistant properties, HAV is able to survive for extended periods of time in the environment and can be a source of sporadic or epidemic infections [11, 15]. Contaminated foods such as frozen strawberries, ice slush beverages and salad food items have all been reported as sources of outbreaks and in the largest known global epidemic that took place in Shanghai in 1988, 292,301 cases of acute hepatitis A were attributed to eating contaminated seafood [9, 25]. Other sources of infection include waterborne transmission from contaminated sewage, international travelers returning from highly endemic areas and intravenous drug users. However, in nearly 40–47% of cases, no identifiable source can be found [9, 26, 27].

The incubation period is estimated to be between 15 and 50 days with a mean of 30 days. HAV is excreted in the feces for about 1–2 weeks before the onset of illness and up to at least 1 week afterwards [26]. HAV replicates primarily in hepatocytes and although not directly cytopathic, it sparks an immune response that causes liver inflammation [15, 20]. Cell mediated responses from cytotoxic T lymphocytes and
natural killer cells have been implicated and in vitro studies have proposed that interferon gamma production from HAV specific T cells play a central role in the clearance of HAV infected hepatocytes [20, 28]. In an interesting study by Rezende et al., cases of HAV related ALF were reviewed and a lower HAV viral load was found to be significantly associated with ALF; suggesting an excessive host response to the virus [20]. Similarly, although mechanisms are still unclear, ACLF is also associated with marked systemic inflammation, circulatory dysfunction, and pro-inflammatory molecules such as IL-6 or IL-8 [1, 29].

Clinical Manifestations

Clinical manifestations of HAV can vary, but usually present as a mild illness with full recovery or can even be asymptomatic. Ford et al. observed that the rate of clinically apparent disease was much lower in children under 5 years of age [15, 30]. If symptoms do occur, they usually present as a non-specific prodromal illness of fever, malaise, nausea, vomiting, anorexia and abdominal pain [15]. Flu-like symptoms may be present in children [26]. These symptoms typically persist for an average of 5–7 days and tend to decrease with the onset of jaundice which lasts for several weeks followed by a convalescent period [9, 15]. Infected individuals remain contagious during the incubation period for up to about a week after the jaundice appears and full clinical and biochemical recovery is observed within 2–3 months in 85% of patients [31].

Atypical presentations of HAV have been observed and include a prolonged cholestatic pattern, relapsing HAV infection, and extrahepatic manifestations. A study in Korea by Jung et al. followed 595 patients prospectively that were admitted for acute hepatitis A and found 4.7% to have prolonged cholestasis defined as hyperbilirubinemia lasting more than 4 weeks. Patients with prolonged cholestasis were found to be comparatively older and were more likely to be HBV carriers [32]. A biphasic or relapsing form of viral hepatitis A has also been reported in about 6–10% of cases of hepatitis A where after apparent initial clinical and biochemical recovery there is a relapse mimicking the initial episode which can vary in severity from mild to severe [33]. Typically, there is a persistence of anti-HAV IgM antibodies during the entire course and HAV has been recovered in stool during relapses [33, 34]. Cases of leukocytoclastic vasculitis, arthritis and cryoglobulinemia have also been reported with HAV and have been associated with the relapsing form of the infection [35]. Majority cases of either atypical presentation (cholestasis vs relapsing) spontaneously recover without any chronic manifestations [33].

HAV related ALF or ACLF are the two most severe forms of HAV related liver disease. ALF typically presents as hepatic encephalopathy and coagulopathy [13, 21, 22]. In cases of HAV related ACLF, extra-hepatic manifestations such as renal failure, sepsis, ARDS or circulatory disturbances can occur akin to other types of ACLF [1, 23, 24]. Hyponatremia, grade III or IV hepatic encephalopathy and renal failure may be important predictors of mortality in these cases [24]. Shi et al.
compared clinical characteristics of ACLF triggered by hepatic insults such as alcohol, HAV/HEV superimposed infections or HBV flare to extrahepatic insults such as bacterial infections and upper gastrointestinal bleeds and found liver and coagulation failures to be more prevalent in those with hepatic insults as compared to those with extra-hepatic triggers [36]. ACLF has also been reported to be caused by dual insults such as infections of HAV with HEV or HBV or mixed presentations of HAV with extra-hepatic insults. There appears to be a higher rate of mortality with co-infections [23]. Common causes of underlying CLD that have been reported include HBV, alcohol, and cryptogenic causes [24, 37].

**Diagnosis**

Since AVH due to HAV infection is clinically indistinguishable from infection by other hepatotropic viruses, testing for HAV should be pursued in patients at high risk for transmission or those with recent exposure. The diagnosis is established primarily by the presence of anti-HAV IgM antibodies that can be detected from the time of symptom onset to approximately 3–6 months [9, 38] (See Table 10.2). Occasionally, the test is negative at the time of clinical presentation, but repeat testing 1–2 weeks

| Screening test | Comment | Confirmation test | Comment |
|----------------|---------|-------------------|---------|
| HAV Anti-HAV IgM | Can be detected for up to 6 months | HAV RNA PCR | Can be used to detect infection sooner than IgM test |
| HEV Anti-HEV IgM | Can be detected for up to 8 weeks | HEV RNA PCR | Excellent specificity but may be negative if past the acute hepatitis phase |
| CMV Anti-CMV IgM | Can be detected for up to 4 weeks | CMV DNA PCR | More sensitivity than IgM test in early infection |
| EBV Anti-EBV VCA IgM | Can be detected for up to 4 weeks | EBV DNA PCR | More sensitive than IgM test in early infection |
| VZV Anti-VZV IgM | Can be detected for up to 12 months | VZV DNA PCR | More sensitive than IgM test in early infection |

HAV hepatitis A virus, HEV hepatitis E virus, CMV cytomegalovirus, EBV Epstein-Barr virus, VZV varicella zoster virus, VCA viral capsid antigen
later usually demonstrates positivity \cite{9, 32}. Jung et al. reported that 6.7% of symptomatic hepatitis A patients have a delayed IgM conversion. These patients also had more severe symptoms requiring earlier hospital admission, suggesting repeat serologic testing needs be considered for those patients with a high clinical suspicion of hepatitis A who have an undetectable anti-HAV IgM at presentation \cite{32}.

Viremia is present 3–4 weeks before the onset of jaundice and high blood viral concentrations are present prior to the onset of liver test abnormalities. Viremia is thought to persist through the clinical and biochemical disease phase with a gradual decline in the convalescent phase \cite{38, 39}. In a study on the outbreaks of HAV in Rio De Janeiro, Brazil, out of 195 patients who tested negative for anti-HAV antibodies, about 12–13% tested positive for HAV RNA, suggesting that RNA testing could be used for earlier detection \cite{40}. Serum anti-HAV IgG antibodies appear early in the convalescent phase and persists for years to decades after the infection conferring immunity to HAV \cite{26}. Individuals with detectable anti-HAV IgG in the absence of anti-HAV IgM reflect either past infection or vaccination.

\textit{Prognosis}

Mortality from HAV usually occurs after the development of ALF or ACLF however direct literature that enables true characterization of prognosis are lacking. A study by Gupta et al. showed that mortality in with HAV related ACLF is significantly higher than those presenting with simple AVH (28% vs 1.94\%) \cite{12}. 3-month mortality with HAV related ACLF have been reported to be as high as 51.5\% \cite{24}. In addition, other studies on HAV related ACLF have reported high rates of mortality of up to and exceeding 50\% listing clinical factors such as old age, high white blood cell count, elevated international normalized ratio and creatinine, hyponatremia and the presence of hepatic encephalopathy as independent predictors of worse outcomes \cite{23, 24, 36, 41}. The number of organ systems failing is expected to positively correlate with mortality rates as in typical ACLF with mortality rates ranging from 26\% in patients with only one organ failure to > 90\% in patients with four or more organ systems affected \cite{37, 41}. However, further studies are needed to elucidate the optimal prognostic models for HAV related ALF and ACLF.

\textit{Management}

Uncomplicated HAV AVH is typically conservatively managed \cite{9}. Most patients can be treated at home unless persistent vomiting or severe anorexia is present. Prohibition of alcohol and medications that might cause liver damage is recommended \cite{26}. Post-exposure prophylaxis with immunoglobulin is advised for those <12 months or >40 years of age and for those who are immunocompromised or have CLD \cite{42}. Use of oral corticosteroids in cases of severe cholestatic hepatitis A have
been reported with favorable results but the majority will show full clinical and biochemical recovery with conservative management within 3–6 months [9, 43].

When HAV is complicated by ALF or ACLF, management is determined by the complications that develop and the availability of transplantation. Extra-hepatic manifestations such as renal failure, circulatory disturbances or sepsis require supportive care including intensive care services [1]. Patients with ALF or ACLF from HAV should be evaluated for liver transplantation however HAV related ALF resolves more frequently than other causes of ALF making the decision for transplant particularly difficult [20]. Data on liver transplant and outcomes in patients with HAV related ACLF are lacking but expectations can be extrapolated from studies that have shown acceptable one year post-transplant survival rates ranging from 75 to 84% in all-cause ACLF [44, 45].

The most effective strategy for HAV related ALF or ACLF is prevention. Basic approaches such as handwashing, avoiding tap water in endemic areas, and heating foods appropriately can help limit disease transmission [9]. Although the development of the HAV vaccine has led to a substantial decrease in hepatitis A outbreaks, many developing countries are experiencing an epidemiological shift of HAV exposure leading to more adults being at risk [16, 46]. Targeting high risk groups for vaccination such as those with CLD or those who are immunocompromised would be beneficial in reducing chances of developing ALF or ACLF and is safe and cost-effective strategy [47]. Groups for whom HAV vaccine is recommended from the Advisory Committee on Immunization Practices of the United States Centers for Disease Control and Prevention are shown in Table 10.3.

### Table 10.3 Groups for hepatitis A vaccination is recommended

| Persons at Increased Risk for Infection |
|----------------------------------------|
| • Travelers to countries with high endemicity for hepatitis A virus infection; |
| • Men who have sex with men; |
| • Users of injection and non-injection illegal drugs; |
| • Persons who receive blood product replacement therapy for clotting factors; |
| • Children and adolescents living in states with historically elevated rates of hepatitis A. |a |

| Persons at Increased Risk for Adverse Consequences of Hepatitis A |
|---------------------------------------------------------------|
| • Persons with chronic liver disease of any etiology. |

Source: CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practice (ACIP). MMWR 1999;48(RR-12):1–37

aRoutine vaccination recommended: Alaska, Arizona, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Utah and Washington; routine vaccination should be considered: Arkansas, Colorado, Missouri, Montana, Texas and Wyoming

Hepatitis E Virus

HEV is a non-enveloped virus measuring approximately 24–37 nm in size and is the sole member of the *Hepevirus* genus belonging to the *Hepeviridae* family [48]. HEV was first identified in 1983 by the Russian virologist Mikhail Balayan and thus
far, eight genotypes have been identified with four genotypes predominately affecting humans [49, 50]. HEV may be the most common cause of AVH in the world and is an important cause of ALF and ACLF in endemic areas [51].

**Epidemiology**

HEV is endemic to Asia, Africa, and Central America and is an especially common cause of AVH, ALF, and viral hepatitis related ACLF in those countries but rarely found elsewhere [12, 52]. Studies regarding HEV related ALF and ACLF have been published primarily from developing countries in Asia and Africa with the vast majority of studies coming from India [24, 53–56]. HEV in these regions is caused primarily by genotypes 1 and 2 [51].

HEV related ACLF is responsible for nearly 50% of ACLF cases in endemic countries [23]. Gupta et al. reported in a study from India that 60 of 89 cases of viral hepatitis related ACLF was solely due to acute hepatitis E [12]. Jha et al. found in a prospective study of consecutive cases of ACLF from any etiology that 13.5% of cases were HEV related [23]. A collective review reported a median of 21% (range 4–72%) of ACLF cases in endemic countries were from HEV. Although HEV and HAV related ACLF are both endemic to India, the prevalence of HEV related ACLF occurs more often. Krishna et al. found that HEV related ACLF occurred about twice as often as HAV related ACLF although 6.1% of their cases had evidence of acute HEV and HAV [24]. Meanwhile, Shalimar et al. showed 67 of 368 (18.2%) of ACLF cases were HEV related compared to only 2 of 368 (0.5%) that were HAV related [57].

Interestingly, despite a high seroprevalence of HEV IgG in non-endemic countries, sporadic outbreaks of HEV ALF and ACLF outside of endemic regions including developed countries of Asia, Europe, and the United States is thought to be rare but conflicting data exists [58, 59]. Genotypes 3 and 4 are the predominant HEV pathologic genotypes in these regions [51]. Fontana et al. reported that only 3 of a cohort of 681 ALF patients were positive for HEV IgM [58]. In addition, 294 patients or 43.4% of the cohort were positive for anti-HEV IgG. In contrary, Manka et al. reported from Germany that 8 of 80 patients or 10% with ALF had detectable HEV viremia [60].

**Transmission, Pathophysiology, and Risk Factors**

HEV is transmitted predominately via the fecal oral route akin to HAV. Transmission of HEV is different in endemic compared to non-endemic areas [61]. In endemic areas, transmission usually occurs through contaminated water. In non-endemic countries, transmission is primarily through animal vectors such as swine from unclean food consumption. HEV induced liver injury results from the patient’s
immune response rather than direct viral injury to the hepatocytes [62]. Chandra et al. showed HEV viremia can be present despite normalization of liver chemistries further suggesting that liver injury is independent of viral replication [63]. This immune-mediated inflammatory response is excessive, systemic, and subsequently leads to decompensation in a patient with already pre-existing CLD resulting in multi organ failure and ACLF. Interestingly, although HEV results in significantly mortality in pregnant patients, pathogenesis remains unknown [64].

Pregnancy appears to be the biggest risk factor of HEV ALF which is likely related to a dramatic increase in viral replication [65]. Kar et al. reported that 38/50 or 76% of pregnant ALF patients were infected with HEV compared to only 17/50 or 34% of non-pregnant ALF patients [65]. Jilani et al. showed that 38/50 or 76% of pregnant ALF patients had HEV compared to only 15/50 or 30% of non-pregnant ALF patients [66]. These findings are hypothesized to be due to diminished cellular immunity and alteration in sex steroid hormones that can influence viral replication [67]. Risk factors for HEV related ACLF includes males, age less than 45 years, and albumin level < 3.5 g/dl [12, 24, 54]. HEV genotype 3 is the only genotype that has been reported to cause CLD [68].

Clinical Presentation

HEV usually causes a mild, self-limiting infection that lasts a few weeks in most patients or can even be even asymptomatic [51]. Symptoms may include malaise, abdominal discomfort, jaundice, nausea, vomiting, and fevers after a viral incubation period of approximately 4–10 weeks [61]. However, HEV can also cause two other types of life-threatening syndrome. First, in certain patients, particularly pregnant women, HEV can result in an AVH that may progress to ALF. Second, a syndrome of HEV related ACLF can occur from either acute HEV occurring in a patient with pre-existing CLD leading ACLF or rarely from HEV infecting a patient (usually post-transplant) leading to CLD that may become ACLF with viral or non-viral associated ACLF insults. Kamar et al. showed that 66% of post solid organ transplant patients who were found to have AVH from HEV developed chronic hepatitis and 9.4% developed cirrhosis [69]. These insults can include bacterial sepsis such as spontaneous bacterial peritonitis, hepatic and portal vein thrombosis, hepatocellular carcinoma, and gastrointestinal bleed [70]. HEV resulting in CLD is primarily an issue in patients in the post-transplant setting, those receiving chemotherapy, and those with HIV.

Presenting symptoms of HEV ALF or ACLF can include jaundice, hepatic encephalopathy, and ascites [24, 52]. Most patients with HEV related ACLF will present with all three findings however a small subset may present with only encephalopathy and jaundice [41]. It is important to note that patients with acute hepatitis E may present with a variety of extrahepatic manifestations including neurologic syndromes, pancreatitis, thrombocytopenia, and aplastic anemia [51]. On laboratory, leukocytosis, elevated alanine aminotransferase (ALT) levels around
1000–3000 IU/L, and hyperbilirubinemia are common [51]. The underlying chronic disease in HEV related ACLF can significantly vary and will depend on the patient population and geographical region. Based on available data regarding where HEV related ACLF is the most common, HBV and cryptogenic cirrhosis appears to be the two most common underlying chronic liver diseases [24]. In addition, patient’s with Wilson’s disease may be at increased risk of HEV related ACLF for unclear reasons [70].

It is important to keep in mind that patients with HEV related ACLF may rarely be co-infected with another acute or chronic viral hepatitis such as HAV or HBV. Gupta et al. reported that 2 of their 89 cases of viral hepatitis related ACLF were co-infected with acute HEV plus HBV [12]. HEV super-infection may be especially common in patients with HBeAg (+) patients from endemic countries accounting for 36.2% of acute exacerbations in one study [71]. Jha et al. found that 2 of their 52 cases of all cause ACLF were co-infected with acute HEV plus HAV [23]. It is also important to note that patients may also present with dual acute insults such as HEV/HAV, HEV/sepsis, or HEV/drug toxicity triggered ACLF. Thus, in patients with HEV related ACLF, a healthy amount of awareness needs to be paid to other etiologies of ACLF especially in patients with systemic inflammatory response syndrome (SIRS). HEV with *P. falciparum* have also been reported to be a cause of ACLF [23].

**Diagnosis**

The diagnosis of HEV related ACLF requires special awareness especially in patients from high endemic areas and those who are immunocompromised (i.e. post-transplant). Initial testing in a patient suspected to have HEV ALF or ACLF include testing for anti-HEV IgM via ELISA or immunochromatographic assays that are based on ORF2/ORF3 peptides or recombinant HEV antigens [72]. Anti-HEV IgM is a marker of acute infection and may remain significantly elevated for up to 8 weeks [51] (See Table 10.2). However, false positive and negative anti-HEV IgM can occur depending on the timing of the testing in respect to the infection. Thus, if the suspicion is high then a serum HEV RNA PCR should be sent [60]. The anti-HEV IgM ELISA reads out within days but the performance of available anti-HEV IgM ELISA assays ranges significantly. One study comparing five different assays showed that the sensitivities ranged from 42 to 96%, respectively [73]. Lower performance of these assays typical occurs due to a lesser ability to detect a particular genotype. Immunochromatographic assays have been shown to have higher sensitivity and specificity compared to the ELISA and can read out results within minutes [74]. Both types of assay will detect antibodies induced by any of the major genotypes of HEV such that there is no genotype specific assay [75].

After a patient is found to be anti-HEV IgM positive, confirmation should be done via the serum HEV RNA PCR test. HEV RNA PCR has high specificity and accuracy for anti-HEV IgM [54]. Zaki et al. showed that all HEV related ACLF
patients in their cohort that had a positive anti-HEV IgM had a positive HEV RNA PCR. HEV viremia only lasts a few weeks in AVH so if a HEV RNA PCR is checked too late, negative results does not rule out HEV related ALF or ACLF. Fontana et al. reported three possible HEV ALF cases with positive anti-HEV IgM but negative HEV RNA PCR [58]. Davern et al. showed that only 4 of 9 patients with severe liver injury and positive anti-HEV IgM had a positive HEV RNA PCR [76]. However, commercial HEV RNA PCR assays have recently been shown to have excellent performance and are now available for order [77]. Interestingly, stool shedding of the virus can last for weeks after a patient stops being viremic [52].

After the initial anti-HEV IgM response during HEV AVH, patients will usually develop anti-HEV IgG antibodies. However, a positive anti-HEV IgG is not helpful in diagnosing HEV ALF or ACLF. Positive anti-HEV IgG can suggest either past HEV exposure in which the protective role of anti-HEV IgG from past exposure is not fully understood or it can suggest chronic HEV infection. Either way, it does not guarantee protection against HEV ALF or ACLF. Positivity to anti-HEV IgG may be linked to patient qualities such as being a farmer, drinking water from wells, and handling pig and eating pork [55]. In fact, one study showed that anti-HEV IgG had only 13% sensitivity and 63% accuracy for detecting HEV related ACLF patients who were HEV viremic by PCR [54].

Since HEV can be a cause of ALF and ACLF regardless of geographical region, it is important for the diagnosing physician to be aware of that possibility [78]. This is especially true in cases that are suspected to be drug-induced liver injury (DILI) related ALF or ACLF since they can mimic HEV ALF or ACLF [60, 76, 78]. Davern et al. reported that 3% of 318 patients with DILI were positive for anti-HEV IgM [76]. Thus, anti-HEV IgM should be checked in patients with DILI who are at high risk of HEV.

**Prognosis and Prognostic Assessment**

When HEV outbreaks occur, mortality rates of 0.5–4% are seen in hospitalized patients [79]. Mortality typically occurs either from HEV ALF or ACLF. When HEV ALF is associated with pregnancy, particularly high mortality rates (20–65.8%) to the mother and fetus are encountered [65, 80].

HEV ACLF appears to have a worse prognosis compared to HEV ALF when it does not occur in pregnant woman. This mortality risk is comparable to that of other causes of ACLF [81]. However, this risk may be somewhat less than that of alcohol-related ACLF [82]. The mortality risk in HEV related ACLF is significantly higher than that of HAV related ACLF [83]. In a cohort of primarily HEV related ACLF, a mortality rate of 28% has been reported [12]. Acharya et al. reported in a large cohort of cirrhotic patients that HEV infection was independently associated with rapid decompensation and death. The mortality rate of HEV related ACLF was
nearly double that of non-HEV infected patients with cirrhosis (43% vs. 22%, \( p = 0.001 \)) [84]. Similarly, Krishna et al. described a 3-month mortality rate of 44.6% in a cohort made up of 61% HEV related ACLF. A collective review published by Kumar et al. summarized the findings of 12 studies totaling 464 subjects with HEV related ACLF and found a 34% median short-term mortality [56]. Interestingly, mortality may be increased when patient is co-infected with HEV and another viral hepatitis [23].

Prognostic models such as the MELD score that have been validated in ACLF can be applied to HEV related ACLF [85]. In a study by Krishna et al., MELD was found to have an area under the receiver operating characteristic (ROC) curve of 0.941 in predicting mortality [24]. A MELD score of 27 was 91% sensitive and 85% specific. Meanwhile, Child-Turcotte-Pugh score is not an adequate prognostic model with an area under the ROC (AUROC) curve of 0.631. Such as the case as other causes of ACLF, hyponatremia can also be an important prognostic marker in HEV related ACLF. Krishna et al. found that a hyponatremia carried an adjusted odds ratio of 9.2 in predicting mortality within 3 months [24].

**Management**

The most critical step in the management of HEV related ACLF is to prevent the initial infection. Healthy practices that can prevent HEV infection includes drinking clean water, practicing hygienic sanitation practices, and avoiding undercooked meats especially pork [51]. HEV vaccination is on the horizon and would be an ideal way to prevent HEV related ACLF in those who are anti-HEV IgG negative and perhaps even in patients with low anti-HEV IgG titers. A significant percentage of CLD patients in endemic areas (44–82%) are negative for anti-HEV IgG and thus would benefit. This rate is similar to, if not higher than the general population creating a large need for vaccination [70, 86]. A recombinant hepatitis E vaccine given as a 3-shot series has shown 100% efficacy in preventing HEV infection within a year in a randomized, double-blinded placebo-controlled, phase 3 trial conducted in China [87]. However, data on the efficacy of this vaccine elsewhere in the world is lacking and availability of this vaccine is limited.

Once HEV related ACLF develops, the primary goals are supportive such as preventing further decompensation of liver function, treating other insults such as sepsis and gastrointestinal bleed, and support failing organs. Medical care to support failing organs may include blood pressure support with vasopressors, hepatorenal syndrome treatment with medications such as albumin, terlipressin, and norepinephrine, intubation for a Glasgow coma score <8, and lactulose/rifaximin for hepatic encephalopathy [56].

Ribavirin is the treatment of choice in chronic HEV with sustained viral clearance rates of approximately 78% after a 3-month course of therapy [88]. In vitro and
in vivo studies have shown that ribavirin inhibits HEV replication through the depletion of cellular guanosine triphosphate (GTP) pools [89, 90]. Studies in HEV related ACLF are lacking however. A pilot study exploring the use of ribavirin in 4 patients with HEV related ACLF suggested that the medication is safe and effective [91]. Treated with a dose ranging from 200 to 600 mg/day for a median of 12 (range 3–14) weeks, HEV RNA became undetectable in all four patients and survival was 100%. There were no serious adverse events reported.

Literature regarding alternative HEV therapies is lacking. Interferon alpha has been shown to have synergism with ribavirin in in vitro studies and may be a potential alternative method of treatment [89]. Kamar et al. showed that a 3-month course of pegylated interferon-alpha-2a can clear chronic HEV [92]. Additionally, sofosbuvir has demonstrated anti-viral effect in chronic HEV and can be used in conjunction with ribavirin. However, results have been mixed with some patients achieving sustained virologic response but others only having temporary viral suppression [93, 94]. Finally, immunosuppression via steroids ± azathioprine has also been reported to be of possible benefit in the setting of autoimmunity associated with HEV AVH [95]. Liver transplantation for the treatment of HEV related ACLF has not been well studied. Moreover, expertise and organ availability are often limited in regions where HEV is endemic.

**Epstein-Barr Virus**

**Epidemiology**

EBV is a double-stranded DNA γ human herpes virus that has a seroprevalence of over 95% worldwide. It infects the B lymphoid system typically during childhood, affecting 345–671/100,000 people aged 15–19 years per year [96, 97]. In contrast, the incidence decreases to 2–4/100,000 per year in patients over the age of 34 years [97]. Once infected, EBV cannot be eradicated as it remains latent in B cells throughout the lifespan of the host. As such, EBV has been associated with both acute primary and acute reactivation, as well as chronic active EBV infection [98].

EBV infection is commonly self-limited, however, in rare cases, it has been associated with ALF and ACLF. EBV ALF has been reported to occur in up to 0.21% of patients with ALF [99]. Of these cases, the median age was 30 and it occurred primarily in males [99]. However, there have also been cases reported in patients over the age of 60 resulting in increased mortality risk. EBV ALF can occur in both immunocompromised and immunocompetent patients with primary infection and reactivation [100]. Unfortunately, data regarding EBV related ACLF is limited. In one study, EBV viremia was present in 8.24% of patients and the presence of EBV was associated with a higher rate of ACLF in comparison to those patients without EBV [101].
Transmission, Pathophysiology, and Risk Factors

EBV is commonly transmitted via saliva, however, it can also spread through blood and semen. EBV can present as either a primary infection or as reactivation of latent infection. During the primary EBV infection, B cells are infected with EBV and polyclonal B cell expansion is followed by an oligoclonal or monoclonal proliferation of CD8-positive cytotoxic T cells [102]. After primary infection, EBV develop a lifelong latency in B cells [96]. EBV can be reactivated from these latent B cells by chemicals, antibodies, or immunoglobulins which stimulate the expression of the EBV BZLF1 gene product, triggering viral replication [103].

Age, especially those who are 60 years or older, are at a significantly increased risk of EBV AVH [104]. Unfortunately, there is a paucity of data assessing risk factors for EBV related ALF and ACLF. Malignancy, CMV, HIV, and use of immunosuppressant drugs has been implicated in EBV ALF. However, cases of EBV ALF have been described in immunocompetent patients as well [100].

Clinical Presentation

Acute EBV infection typically presents in childhood and can be subclinical in 80–90% of cases [105]. However, patients may develop symptoms of mononucleosis including fever, tonsillitis, and lymphadenopathy. Interestingly, only 50% of patients with EBV AVH will have all three symptoms at presentation [106]. Approximately 80–90% of infectious mononucleosis cases will have a moderate and transient elevation in liver enzymes, however, clinical symptoms are rare. Serum aminotransferases are commonly elevated in a hepatocellular pattern and are typically less than five-fold normal [105]. Transaminase abnormalities occur within the first week after onset of illness, peak during the second, and return to normal during the third week [107]. Hyperbilirubinemia is present in 45% of patients, however, clinical jaundice occurs in less than 5% of patients [108]. Cholestatic liver disease is uncommon, however, but jaundice can occur during EBV infection due to autoimmune hemolytic anemia, cholestasis due to acalculous cholecystitis or biliary obstruction, or rarely cholestatic hepatitis [109–112]. Jaundice occurs more frequently in people aged 35 years or older [113]. In a case series of those with ALF due to EBV. The median AST was 654 Iu/L (range 192–2690) and median serum ALT was 504 (range 156–4920). The median total bilirubin was 17.5 mg/dL (range 11.1–27) with a median INR of 2.3 (range 1.6–3.6). The pattern of liver injury was variable, including both hepatocellular injury and cholestatic injury [99].

While there is little data on EBV related ACLF and its clinical presentation, there is one case report of an elderly male who presented with fever and general malaise for 2 months and developed shock, multi-organ failure, and death. Post-mortem, he was found to have severe chronic active EBV with the presence of EBV DNA in the
liver and lymphatic tissue [114]. In addition, there is one study that showed that patients with ACLF associated with presence of EBV had no difference in the rate of complications such as ascites, hepatic encephalopathy, gastrointestinal bleeding, hepatorenal syndrome, infections, and hepatocellular carcinoma compared to those without EBV [101].

**Diagnosis**

EBV infection can be diagnosed via serology, PCR, and/or by evidence of EBV infection in liver tissue by light microscopy or EBV-encoded RNA positive staining. Typically, the heterophile antibody will be negative. If serology is performed, an acute EBV infection is defined by positive anti-EBV viral capsid antigen (VCA) IgM with or without positive anti-EBV VCA IgG titers [99]. Anti-EBV VCA IgG are produced concurrently during early infection and in an immunocompetent person lasts a lifetime, thus it is not a good marker for acute infection [115]. During early EBV infection, EBV DNA PCR is more sensitive [116].

Although there is not a set diagnostic criteria of EBV ALF pathologically, one study of patients who underwent liver transplant found that in the explanted liver there was more than 90% hepatocellular necrosis with extensive lymphohistiocytic infiltrate in both the portal and lobular distributions, presence of ductular reaction, cholestasis and central venulitis, and numerous parenchymal macrophages. Hepatic lymphocytes stained positive for cytoplasmic CD3, CD8, granzyme B, perforin, and EBERS, but they were negative for CD4, CD20, and CD56. EBER-positive lymphocytes were positive for CD45RO but negative for CD20 [117].

**Prognosis and Prognostic Assessment**

The data on prognosis of EBV ALF and ACLF is limited to case reports and case reviews. From the limited data, the mortality rate of EBV associated ALF is approximately 68–87% [117, 118]. While the MELD, Child-Pugh score and King’s College Criteria can be applied as a prognostic score, there is little data to suggest benefit of one over the other. Kumar et al. used the Acute Liver Failure Early Dynamic (ALFED) model which is based on arterial ammonia, serum bilirubin, INR, and hepatic encephalopathy and whether these variables remain high or increases over 3 days. The ALFED model has been shown to accurately predict outcomes in patients with ALF [119]. Serial assessment of the severity of ALF based on the ALFED model during the first 5 days after initiation of artificial liver support assisted in determining the need for LT in patients with EBV ALF [117].
Management

The overall benefit of anti-viral treatment in EBV is unclear as controlled trials have shown that anti-virals neither reduce the severity or duration of clinical symptoms. However, in severe EBV AVH, the use of anti-viral drugs such as ganciclovir, valganciclovir, acyclovir, and steroids are supported. Still, there are no specific guidelines or randomized controlled trials that support a specific treatment or recommended dose, or duration of therapy [120]. Definitive treatment for EBV ALF is liver transplantation [117]. Although there is a paucity of information, successful liver transplantation for EBV ALF have been reported [99, 100, 121]. Five-year survival rate post liver transplantation is excellent at approximately 80% [122]. In the post-transplant setting, consideration of treatment with acyclovir is important as it can assist preventing infection of the graft liver as immunosuppression may increase the replication of EBV [100].

Cytomegalovirus

Epidemiology

CMV is a double-stranded DNA β human herpes virus with a seroprevalence of 30–100% [123–125]. It can cause infection either via primary infection or reactivation in both immunocompetent and immunocompromised hosts. Immunocompetent individuals usually develop primary CMV infection, in contrast to immunocompromised individuals who typically develop infection via reactivation. CMV can cause clinically apparent liver disease ranging from mild elevation in transaminases, to CMV hepatitis, and rarely ALF or ACLF. The incidence of CMV AVH ranges from 2 to 34% [126]. The cases of CMV related ALF and ACLF are only limited to case reports and case reviews [127, 128].

Transmission, Pathophysiology, and Risk Factors

CMV is transmitted via secretions such as tears, saliva, urine, genital secretions, breast milk or blood. Incubation of the virus is for 4–6 weeks and often may be asymptomatic. However, CMV can present with mononucleosis like symptoms with fever, cough, and fatigue.

The key to CMV infection is viremia as CMV requires a high viral load to cause end-organ disease. Thus, an intact immune system with humoral immunity and innate immunity involving a complex role of natural killer cells and T-cell mediated response is important in controlling viral replication [129]. After primary infection, CMV causes a lifelong latent infection.
CMV reactivation occurs via three main pathways which require TNF-α, inflammatory prostaglandins, and catecholamines. Release of TNF-α binds to TNF-α receptors on latently infected cells and activates nuclear factor κB and allows for initiation of viral replication. In addition, inflammatory prostaglandins and catecholamines assist in activation and production of cAMP, respectively.

As a result of the physiology of CMV infection, those who are immunosuppressed are at the highest risk; this includes immunosuppression or high dose corticosteroid use, T-cell depletion, acute and chronic GVHD, rejection, and viral co-infection [130–133]. In addition, patients who have received bone marrow and solid organ transplant are frequently at risk post-transplantation. However, this risk is dependent on the serostatus of the donor and the recipient with the greatest risk in a positive donor/negative recipient (D+/R-) [134]. Recipients who are CMV seropositive can also develop a CMV infection via reactivation of latent CMV infection or by de novo infection with a different strain. CMV replication is increased after transplantation with peak viremia occurring at 35–40 days post-transplantation, thus providing an opportune time to develop an acute or reactivation infection [135].

In regard to ACLF, patients who have chronic alcohol consumption and cirrhosis may be at risk of latent CMV reactivation as control of viral replication is dependent on CD4+ and CD8+ T cell function, which is impaired in this population [136, 137]. Furthermore, HBV infection has also been found to be a risk factor for CMV related ACLF, especially if the HBV DNA is <1000 IU/mL, increasing risk to 34-fold [138]. Studies have shown that 5–10% of patients with HBV infection may be co-infected with CMV [138, 139]. This may be due to inhibition of HBV replication and gene expression or increase in HBV viral clearance [140, 141].

**Clinical Presentation**

In the immunocompetent population, most infections with CMV are asymptomatic, however, 10% of affected individuals may have clinical symptoms [142]. Symptoms on presentation can include a mononucleosis-like syndrome such as fever, pharyngitis, lymphadenopathy, arthralgia, lymphocytosis, and splenomegaly [143]. During clinically evident primary CMV infection, liver test abnormalities can occur in up to 90% of cases, with a mild to moderate transaminitis, but rarely exceeds five-fold above normal [144]. ALT tends to be higher than AST level, while alkaline phosphatase and bilirubin levels are within normal ranges. These laboratory abnormalities generally normalize within a few weeks [145]. In patients with CMV hepatitis, the most common symptoms include fever, tonsillitis, abdominal pain, vomiting, and anorexia [106]. Peripheral adenopathy, neutropenia, and monocytosis may also be seen. On histology, there may be findings of focal lobular hepatocyte necrosis with the presence of macrophages or CMV nuclear inclusions.

Data on the clinical presentation of CMV related ALF and ACLF is limited to case reports. Shusterman et al. reported the first case of CMV ALF in 1978 in a 33-year-old with general malaise, fever, and night sweats for 2 weeks [146]. Since then, there have been numerous other case reports in which patients presented with
a range of symptoms including fever, general malaise, jaundice, headache, plantar rash, and associated Q fever [128, 145, 147].

**Diagnosis**

Diagnosis of CMV infection is achieved through serology or detection of CMV DNA. CMV induces the production of IgM and IgG. Anti-CMV IgM is the first to appear in serum and can last up to 4 weeks. Determination of the IgG avidity index allows the confirmation of recent infection if both IgG and IgM are positive; avidity is weaker in a recent infection [148]. Thus, diagnosis of CMV infection can be confirmed with the presence of anti-CMV IgM antibodies. In addition, a four-fold increase over the upper limit of normal of anti-CMV IgG titers is also diagnostic of infection [149]. In contrast to serology, during early infection, quantitative PCR is the standard method for diagnosis. CMV DNA viral load of 1000–100,000 copies/mL suggests active infection, reactivated infection, or latent infection without disease [126]. In the post-transplant period, the pp65 antigenemia assay can be used to differentiate CMV reactivation from acute CMV infection [150].

Histologic features on biopsy of CMV hepatitis include sinusoidal infiltration by mononuclear cells and mild hepatocellular necrosis along with granuloma formation. Intranuclear inclusions also known as “Owl’s eye” may be present but are not specific. In immunocompetent individuals with CMV hepatitis, intranuclear inclusions and immunohistochemical staining may not be seen because a strong immune response may destroy the infected cells [151]. CMV ALF on explant can show massive hepatic necrosis with positive immunohistochemical staining for CMV protein [145].

**Prognosis and Prognostic Assessment**

Unfortunately, the data for CMV related ALF and ACLF is limited. However, case reports have shown good outcomes with early detection and treatment with antivirals or liver transplantation.

**Management**

CMV infection is typically self-limited and does not require treatment. This is especially true in the immunocompetent patient. Treatment is recommended in severe CMV infection in immunocompromised individuals [152]. However, as there is no data to support for or against anti-viral treatment of immunocompetent patients with ALF, we would suggest the use of anti-virals in these patients as they are at high risk of morbidity and use of anti-virals have shown success [128].
The end point of treatment is clearance of the virus from the blood. Valganciclovir can be used 2–3 months after completion of treatment to avoid CMV recurrence in high risk individuals [153]. However, the treatment of CMV with valganciclovir and ganciclovir is not a benign treatment. Potential side effects include myelosuppression, central nervous system disorders, hepatotoxicity, irreversible infertility, and teratogenesis [154].

In addition, when discussing the management of CMV, it is also important to discuss prophylaxis, especially in the post-transplant period. Prophylaxis with ganciclovir or valganciclovir is commonly used in the post-transplant period. The risk of CMV infection post liver transplant ranges between 25 and 80%, however, the mortality rate is only 0.9%, thus one study suggests that CMV prophylaxis may not be mandatory [155].

Varicella Zoster Virus

Epidemiology

VZV is a double-stranded DNA α herpes virus that only naturally infects humans [156]. The incidence of VZV ranges from 13 to 16 cases per 1000 persons per year, with the greatest incidence of disease during childhood and adolescence [156]. Primary infection of VZV, which is also known as chickenpox, infects 1–2% of adults, among whom complications and mortality are 10–20 times more frequent [157].

After primary infection, VZV remains latent in ganglionic neurons and can develop as a secondary reactivation infection later in life. This is also known as zoster. As age increases, the severity and incidence of zoster also increases [156]. The incidence of zoster goes from ~1 per 1000 patients per year in children <10 years to >10 per 1000 patients per year in adults ≥60 years [158].

In addition to its characteristic cutaneous manifestations, VZV is also associated with neurologic disorders, ocular disorders, and gastrointestinal disorders including hepatitis, pancreatitis, and ulcers. VZV-associated hepatitis is rare, and cases of VZV ALF are only limited to case reports [159–168]. There have been no reported cases of VZV related ACLF.

Transmission, Pathophysiology, and Risk Factors

VZV is transmitted via the respiratory route and by direct contact. The incubation period averages 14 days with a range of 10–23 days. During primary infection, VZV infects T cells and the virus disseminates to the skin and potentially other organs. At first, viral replication in the skin is delayed by innate immunity, however, after time, this cutaneous innate immune response is overcome by virus and there is substantial viral replication resulting in a characteristic rash [156]. Latency then develops in the ganglionic neurons, however, its transference to neurons is unclear. As cellular
immunity declines with advancing age or an immunocompromised state, VZV reactivates causing a secondary infection, although the direct mechanism is also unclear. Rarely does VZV cause ALF, but when it occurs, it is usually due to primary VZV infection [160, 169]. Immunosuppressed patients including those with either iatrogenic or acquired immunosuppression (i.e. status post organ transplantation or splenectomy, patients on steroids or other immunosuppressive agents, and patients with AIDS) are at the greatest risk [167]. However, there have been 2 reported cases of VZV ALF in immunocompetent patients [162, 170].

**Clinical Presentation**

VZV can cause primary infection, chickenpox, and secondary infection, herpes zoster. Primary infection typically presents in childhood with a generalized rash. The virus then remains latent in the dorsal root ganglia and can later reactivate as shingles or herpes zoster with a localized dermatomal vesicular eruption. This rash is characterized by a pruritic, vesicular lesion in successive crops, with various stages of development noted simultaneously including papules, vesicles, pustules, and crusts. Patients with VZV hepatitis are often asymptomatic with mild and limited elevation in transaminases. However, if symptomatic, they may initially present with severe abdominal or back pain, fever, chills, malaise, or fatigue. During early presentation, there may be few or no cutaneous lesions [171, 172]. However, the rash can precede, occur concurrently, or develop after the onset of abdominal pain [167]. Patients are moderately ill for a few days with only mild elevations of liver enzymes, however, a small subset can develop ALF with coagulopathy and encephalopathy, followed by multi-organ failure [167]. In these patients, liver tests can reach levels in the thousands secondary to hepatic necrosis from VZV [169, 173].

**Diagnosis**

Diagnosis is confirmed with additional presence of VZV DNA, VZV antigens in infected tissue, or positive viral culture in the appropriate clinical setting. VZV DNA can be detected by PCR in the serum or in tissue samples of the liver [174, 175]. Skin biopsy is diagnostic for varicella infection when immunofluorescent staining identifies VZV antigen [166]. VZV cultures can also be done on skin lesions, blood, or other infected tissue. Liver biopsy is rarely done for diagnostic purposes because of severe coagulopathy. However, biopsy generally reveals hemorrhagic necrosis and eosinophilic Cowdry type A intranuclear inclusions [165, 174]. Occasionally intracellular virions and multinucleated giant cells can be identified. Immunofluorescence for VZV antigen and PCR of VZV DNA on liver tissue are also diagnostic [166, 174]. In addition, pANCA may be positive in some cases.

Tzanck smear of skin lesions can also be helpful but a positive smear does not differentiate HSV from VZV. Serology can support the diagnosis with positive IgG
antibodies in reactivation and positive IgM antibodies in primary infection. However, there is one reported case of VZV ALF that did not develop VZV antibodies and diagnosis was confirmed with detection of VZV DNA by PCR in the serum and liver [174].

**Prognosis and Prognostic Assessment**

Unfortunately, the data on prognostic measurements of VZV ALF are limited. However, VZV ALF has a poor prognosis with a fatal outcome in the majority of cases (~75%) within 3–13 days of initial presentation despite early therapy with acyclovir [168].

**Management**

Early diagnosis and IV acyclovir is critical in the management of VZV ALF. Treatment with IV acyclovir at a dosage of 10 mg/kg every 8 h should be initiated if the diagnosis is considered and the patient should be evaluated for emergent liver transplantation as there have been a few cases of successful transplantation for VZV ALF [160, 176, 177].

Furthermore, in immunocompromised patients who have been exposed to an individual with chickenpox, despite the patients’ previous exposure, consideration should be given to the administration of VZIG within 72–96 h [178, 179]. As a result of varicella’s high mortality rate when associated with ALF, attention should also be focused on prevention with vaccination.

**Conclusion**

ALF and ACLF are two unique clinical syndromes associated with a high risk of mortality. Non-HBV/HCV/HDV viruses including the hepatotrophic viruses (HAV and HEV) and non-hepatotrophic viruses (EBV/CMV/VZV) are important causes of ALF and ACLF. HAV and HEV infection are especially common in endemic countries and needs to be on the differential for a patient presenting with ALF or ACLF. In those who are immunosuppressed, EBV, CMV, and VZV needs to be considered. However, early diagnosis based on awareness is critical and relies primarily on the detection of IgM antibodies and/or viremia in the correct clinical context. Studies on the presentation, prognosis, and management of ALF and ACLF associated with these viruses are lacking. Correct management includes supportive care for failing organ systems, virus directed treatment such as ribavirin for HEV, and liver transplantation.
Questions
1. What is the typical serologic pattern of HAV related ALF and ACLF?
   (a) HAV IgM negative, HAV IgG negative
   (b) HAV IgM positive, HAV IgG negative
   (c) HAV IgM negative, HAV IgG positive

2. Which of the following appears to be the biggest risk factor for HEV related ALF?
   (a) Smoking
   (b) Alcohol use
   (c) Pregnancy
   (d) Tylenol

3. What are some of the risk for HEV related ALF?
   (a) Being from a HEV endemic country
   (b) Pregnancy
   (c) Post-transplant
   (d) All of the above

4. How can EBV related ALF or ACLF be diagnosed?
   (a) Anti-EBV viral capsid IgM
   (b) EBV DNA PCR
   (c) Liver biopsy
   (d) All of the above

5. The risk of CMV hepatitis is highest in which post-transplantation donor-recipient combination?
   (a) Donor CMV negative/Recipient CMV negative
   (b) Donor CMV positive/Recipient CMV negative
   (c) Donor CMV positive/Recipient CMV positive
   (d) Donor CMV negative/Recipient CMV positive

Answers and Explanations
1. Answer—B. HAV IgM will usually become positive at time of symptom onset. If HAV IgM is negative but high clinical suspicion remains, repeat testing can be performed in 1–2 weeks. Conversion to HAV IgG positivity occurs later and confers immunity to HAV.

2. Answer—C. Pregnancy appears to be the biggest risk factor for ALF from HEV due a dramatic increase in viral replication due to diminished cellular immunity and alterations in sex steroid hormones.
3. **Answer—D.** Risk factors for HEV ALF includes being from a HEV endemic country, being immunocompromised (i.e. post-transplant state), and pregnancy.

4. Answer—D. The diagnosis of EBV ALF can be made via positive anti-EBV viral capsid antigen IgM with or without anti-EBV viral capsid antigen IgG, detectable serum EBV PCR, and/or evidence of EBV infection in liver tissue by light microscopy or EBV-encoded RNA positive staining.

5. Answer—B. The risk of CMV hepatitis in highest when the donor is CMV seropositive and the recipient is CMV seronegative. These patients commonly receive prophylaxis for at least 3–6 months post-transplantation.

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