

Chapter 19: Management of HBV/HCV coinfection

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Epidemiology of HBV/HCV coinfection

Hepatitis B (HBV) and hepatitis C (HCV) viruses are the most common causes of chronic liver disease world-wide. Due to shared routes of transmission, coinfection with HBV and HCV is not uncommon among individuals in HBV endemic areas who also have a high risk of parenteral infections, such as injection drug users (Pallas 1999), patients on hemodialysis (Reddy 2005), patients undergoing organ transplantation (Aroldi 2005) and HIV-positive individuals (Zhou 2007). Due to a lack of large-scale population-based studies the exact number of HBV/HCV coinfecting patients is unknown. Dual infection with HBV and HCV in the same host ranges from 9% to 30%, depending on the geographic region (Zarski 1998; Liaw 1995). These numbers may underestimate the true number of people with HBV/HCV coinfection as there is a well-known entity of occult HBV infection (i.e., patients with negative hepatitis B surface antigen (HBsAg) but detectable serum HBV DNA) in patients with chronic hepatitis C (Cacciola 1999).

Screening for HBV/HCV coinfection

Persons with a first episode of acute hepatitis should be screened for all viral causes including HBV and HCV (see Chapter 8 on diagnostic tests for hepatitis B and Chapter 12 for hepatitis C). Some patients may be inoculated with both viruses simultaneously and will present with acute hepatitis due to both viruses. In addition, HBV superinfection in patients with chronic hepatitis C, and HCV superinfection in patients with chronic hepatitis B have both been reported (Liaw 2004; Liaw 2000; Liaw 2002). Therefore, episodes of acute hepatitis in patients with known chronic HBV or HCV infection, especially those with ongoing risk behaviour for infection with the other virus such as injection drug users, should prompt screening for superinfection. In addition, in patients with chronic hepatitis C, ruling out occult HBV infection beyond HBsAg testing, i.e., by polymerase chain reaction (PCR), should be done when clinically indicated.

Viral interactions between HBV and HCV

Patients with both HBV and HCV infections may show a large spectrum of virologic profiles. HCV infection can suppress HBV replication and it has been shown that HBV/HCV-coinfecting patients have lower HBV DNA levels, decreased activity of HBV DNA polymerase, and decreased expression of HBsAg and hepatitis B core antigen in the liver (Chu 1998). Moreover, patients with chronic HBV infection who become superinfected with HCV can undergo seroconversion of HBsAg (Liaw 1994; Liaw 1991). Several authors have reported that HBV can reciprocally inhibit HCV replication as well (Sato 1994). Specifically, HBV DNA replication has been shown

to correlate with decreased HCV RNA levels in coinfecting patients (Zarski 1998). Furthermore, coinfecting patients have been shown to have lower levels of both HBV DNA and HCV RNA than corresponding mono-infected controls, indicating that simultaneous suppression of both viruses by the other can also occur (Jardi 2001). Thus, HBV or HCV can play the dominant role, HBV and HCV can inhibit each other simultaneously and they can alternate their dominance (Liaw 1995). Both viruses have the ability to induce seroconversion of the other. The chronology of infection may have a role in determining the dominant virus. However, the overall effect appears to be HCV suppression of HBV (Liaw 2001).

Clinical scenarios of HBV and HCV infection

Different scenarios of infection have been described with HBV/HCV coinfection including acute hepatitis with HBV and HCV (Alberti 1995), occult HBV coinfection of chronic hepatitis C (Sagnelli 2001), and superinfection by either virus in patients with pre-existing chronic hepatitis due to the other virus (Figure 1).

Acute hepatitis by simultaneous infection of HBV and HCV

Simultaneous coinfection with HBV and HCV is rarely seen, but the interaction of HBV and HCV appears to be similar to chronic infection. In acute infection with HBV and HCV, patients show delayed HBsAg appearance and a shorter hepatitis B surface antigenemia compared to those with acute HBV alone (Mimms 1993). Biphasic alanine aminotransferase (ALT) elevation was found in some patients (Alberti 1995).

HCV superinfection

HCV superinfection is frequent in endemic areas of HBV infection, such as in Asian countries (Liaw 2002; Liaw 2004), which can result in the suppression of HBV replication and termination of HBsAg carriage. However, long-term follow-up analyses have described a higher rate of liver cirrhosis and hepatocellular carcinoma. Fulminant hepatic failure was significantly higher among patients with underlying HBV infection than those without (23% vs. 3%) (Chu 1999; Chu 1994).

HBV superinfection

HBV superinfection is less common in HCV-infected patients and very limited data is available. In one report a patient became seronegative for HCV RNA after HBV superinfection, indicating that superinfection of HBV may lead to suppression of HCV (Liaw 2000; Wietzke 1999). Other reports have shown that HBV superinfection may be associated with acute deterioration of liver function among patients with chronic HCV infection, and the risk of fulminant hepatitis may be increased (Sagnelli 2002).

Occult HBV infection in patients with HCV infection

Occult HBV infection has been identified in up to 50% of patients with chronic HCV. Importantly, a relation to HCV treatment outcomes has been described (Zignego 1997; Fukuda 2001; Sagnelli 2001). HCV infection with occult HBV infection has been associated with higher ALT levels, greater histological activity index and liver disease more often progressing to liver cirrhosis (Fukuda 1999; Cacciola 1999; Sagnelli 2001).

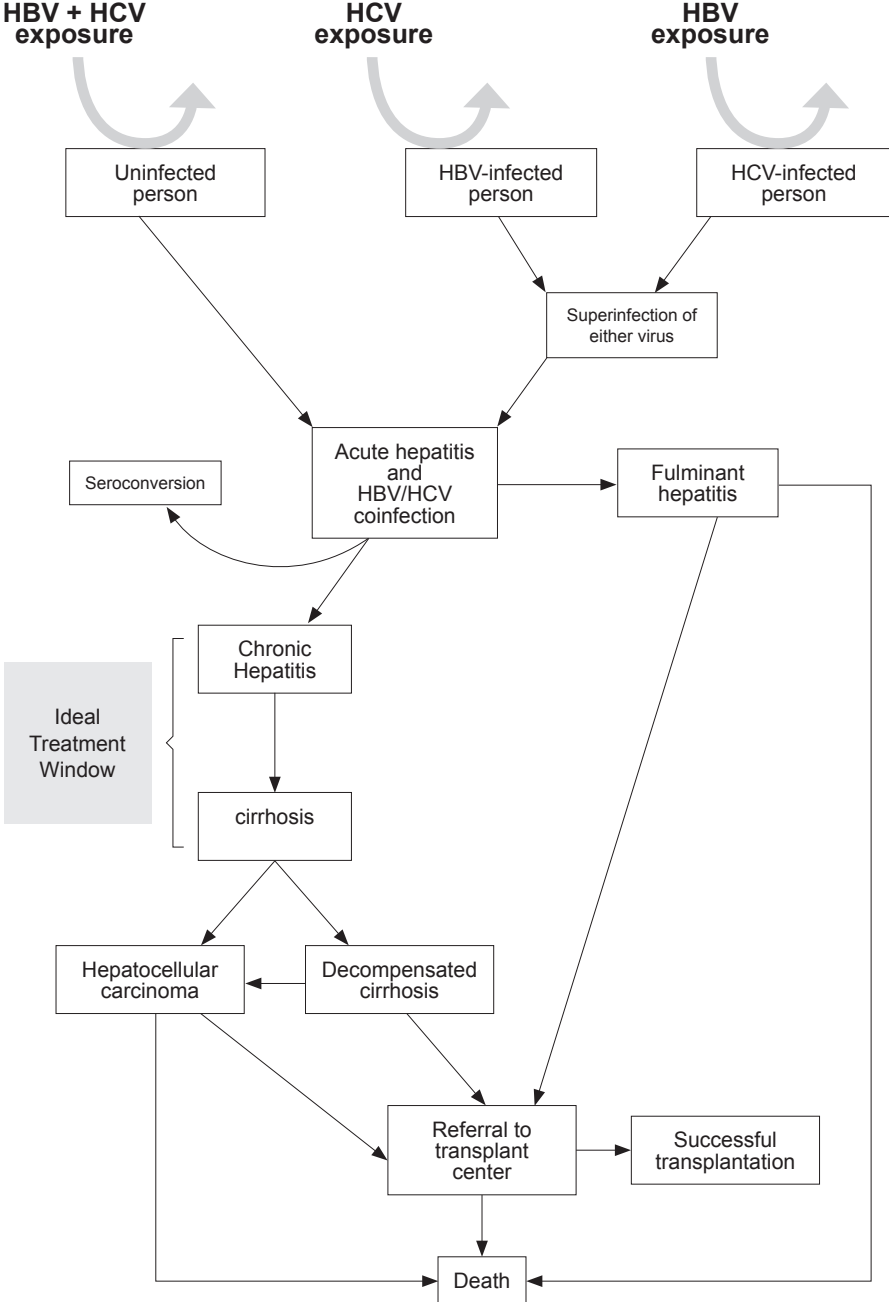


Figure 1. Clinical scenarios of HBV/HCV coinfection (modified after Crockett & Keeffe 2005).

Chronic hepatitis in HBV/HCV coinfection

Various immune profiles are found in patients with chronic HBV/HCV hepatitis (Table 1). Patients with detectable serum HBV DNA and HCV RNA are at highest risk of progression to cirrhosis and liver decompensation and therefore should be considered for treatment. Active HCV infection (HCV RNA+) in the setting of inactive HBsAg (HBsAg+/HBV DNA-) behaves similarly to patients with HCV mono-infection. Another possibility is active HBV infection in patients with inactive or prior HCV infection (HBV DNA +/HCV RNA-/anti-HCV+). This immune profile is less common, and may indicate HBV suppression of HCV.

	HBV and HCV active	Occult HBV in chronic active HCV	HCV active in HBsAg carrier
HBsAg	+	-	+
HBV DNA	+	+	-
Anti-HCV	+	+	+
HCV RNA	+	+	+

Table 1. Immune profiles in HBV/HCV coinfecting patients with chronic hepatitis.

Cirrhosis

Higher rates of cirrhosis have been demonstrated in HBV/HCV-coinfecting patients. In comparison to patients with HBV mono-infection higher rates of cirrhosis (44% vs. 21%) and decompensated liver disease (24% vs. 6%) were demonstrated in coinfecting patients (Fong 1991). Compared to HCV mono-infected patients a higher rate of cirrhosis (95% vs. 49%) and more decompensated liver disease (Child-Pugh class C 37% vs. 0%) were found in HBV/HCV-coinfecting patients (Mohamed Ael 1997).

Hepatocellular carcinoma

In many studies coinfection with HBV and HCV has been shown to be associated with an increased risk of HCC development (Kaklamani 1991; Mohamed Ael 1997).

In one longitudinal study incidence of HCC was 6.4 per person years in HCV/HBV-coinfecting patients compared to 2.0 in HBV and 3.7 in patients with HCV mono-infection. The cumulative risk of developing HCC after 10 years was 45% in HBV/HCV-coinfecting patients compared with 16% in HBV and 28% in HCV mono-infected patients (Chiaromonte 1999). HBV/HCV-coinfecting patients should undergo a screening routine for HCC with liver ultrasound and alpha-fetoprotein levels in serum at least every 6 months.

Treatment of HBV and HCV coinfection

Currently there are no well-established treatment guidelines for HBV/HCV-coinfecting patients. Generally, treatment guidelines for mono-infected patients should be applied to coinfecting patients. As with HBV and HCV mono-infection, treatment of coinfecting

patients should be started in patients with active chronic hepatitis or cirrhosis before liver decompensation. Due to the variety of virological profiles in HBV/HCV coinfection it is important to assess the dominant virus prior to initiating therapy. Treatment studies for HBV/HCV coinfection are reviewed in (Crockett 2005) and (Chu 2008). In patients with HBV/HCV coinfection treatment should be initiated when inclusion criteria for standard treatment guidelines of HBV or HCV mono-infection are met (see Chapter 9 for HBV Therapy and Chapter 13 for HCV Therapy).

In coinfecting patients with dominance of HCV infection, IFN plus ribavirin has been well-studied and proven efficient. However, pegylated IFN is the standard of care for HCV mono-infected patients and future studies in HBV/HCV-coinfecting patients will be carried out using pegylated IFN. A recent prospective multicenter study including 19 coinfecting patients found the combination of PEG-IFN α -2b plus ribavirin to be effective to induce a sustained HCV RNA response in 93% (88% in HCV genotype 1 and 100% in genotype 2 and 3) of coinfecting patients (Potthoff 2008).

In patients with dominance of HBV disease IFN +/- HBV polymerase inhibitor is a possible option. Until now most data available are for lamivudine. There is very little experience with the newer anti-HBV agents. Future studies are needed to assess the safety and effectiveness of antiviral therapy with pegylated interferon, ribavirin and a combination of the newer nucleos(t)ide analogues. Due to loss of viral suppression from the successfully treated dominant virus, deterioration of liver disease has been reported (Yalcin 2003), thus caution must be exercised upon initiation of therapy.

Conclusion

Coinfection with HBV and HCV is not uncommon, especially within areas of high hepatitis B prevalence. HBV/HCV coinfection is a challenge for clinicians due to the complex interaction of HBV and HCV, and the propensity for developing severe liver disease. No treatment standard has been established for HBV/HCV-coinfecting patients. Treatment decisions must be made based upon identification of the dominant virus. Standard IFN, ribavirin and lamivudine are the best-studied treatment agents. However, larger randomized, controlled trials are needed to establish the role of PEG-IFN in combination with ribavirin and nucleos(t)ide analogues for treatment of HBV/HCV coinfection. Finally, caution must be exercised in treating coinfecting patients, as flares of the untreated virus may occur.

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