Hepatitis A, B, C, D, E, G: An Update

Acute and chronic liver diseases are an assortment of disorders brought to the clinician’s attention by abnormal liver function tests or specific signs and symptoms. The differential diagnosis includes disorders that have primary or secondary liver involvement. This paper will be limited to the epidemiology, clinical manifestations, diagnosis, treatment, and prevention of the different viral liver diseases: A, B, C, D, E and G. (Ethn Dis. 2007;17[suppl 2]:S2-40–S2-45)

Key Words: Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Hepatitis G, Interferon, Ribavirin

INTRODUCTION

The word hepatitis connotes an infection or inflammation of the hepatocytes, as evidenced by abnormal liver function tests (LFTs). This, however, is a nonspecific term since the laboratories combine hepatic enzyme tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and synthetic tests (albumin, bilirubin, and prothrombin time [PT]) into LFTs. These tests can be elevated in a healthy individual.

The differential diagnoses of hepatitis should include, at a minimum: virus infection; drugs or alcohol abuse; hemochromatosis; thyroid, muscle, and autoimmune disorders; celiac disease; alpha-1 antitrypsin deficiency; Wilson’s disease; masses; and fatty liver. This article will be limited to the current appraisal of the epidemiology, clinical manifestations, diagnosis, and treatment of the different viral hepatic disorders: hepatitis A, B, C, D, E, and G.

HEPATITIS A

Epidemiology

Hepatitis A virus (HAV) was first recognized in 1947, but it has been around for centuries. The two distinct forms of the virus were only identified in 1973, consisting of a RNA virus with four genotypes. It occurs worldwide but is highly prevalent in the developing countries and Greenland; however, the global incidence is decreasing because of improved sanitary and living conditions. In the United States, the incidence of hepatitis A has declined dramatically with the institution of the hepatitis A vaccine.

HAV is spread mainly by the fecal-oral route in low-socioeconomic areas, but person-to-person spread has occurred in daycare centers, as have community epidemics from contaminated foods (Mexican green onions). Sexual intercourse, blood, and intravenous drugs are minor routes of transmission of this virus as opposed to the other viral hepatitis disorders.

Clinical Manifestations

HAV infection is usually an acute, self-limiting disease with no sequelae or chronic disease state. Its manifestations vary according to the age of the patient at presentation. Children usually have a silent or subclinical course as opposed to adults, who present with a wide range of symptoms, from an influenza-like illness to fulminant hepatic failure.

Diagnosis

The diagnosis of HAV infection is made by the presence of antibodies against HAV in conjunction with the clinical picture. The incubation period is 30 days, with a range of 15 to 50 days. Hepatitis A virus (HAV) immunoglobulin M (IgM) is the gold standard for making the diagnosis; however HAV IgG appears early and remains positive for decades.

Treatment

Since HAV is usually a self-limiting disease, treatment is generally supportive. Eighty-five percent of patients recover by three months, and nearly 100% will recover by six months. Death can occur in elderly patients or in those concomitantly infected with hepatitis C virus (HCV).

Prevention

Since HAV is predominately spread by the fecal-oral route, the mainstay of prevention is thorough hand washing, heating foods properly, and avoiding water and raw foods in endemic areas. Household bleach (1:100 dilution) will adequately inactivate the virus. Passive immunity

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with intramuscular serum immune globulin—given within two weeks of exposure—will also provide protection against this virus.

**Vaccinations**

The current epidemic of hepatitis A could be avoided though a worldwide viral campaign. The vaccines are safe, efficacious, and relatively inexpensive. The live, attenuated vaccine is no longer in use because of the superiority of the inactivated vaccines. Therefore, the inactivated vaccines are the only Food and Drug Administration (FDA)-approved vaccines that are used in the United States. The inactivated vaccine provides almost a 100% seroconversion rate and a higher antibody response than even serum immune globulin.

**HEPATITIS B**

**Epidemiology**

Hepatitis B virus (HBV) is a global problem, with >350 million carriers worldwide and 1.25 million in the United States. An estimated 100,000 acute infections occur every year in the United States. The mortality is substantial; each year 5000 patients in the United States and >1 million worldwide die. In high-prevalence areas, the predominant mode of transmission is perinatal, while in low-prevalence areas it is by sexual transmission and intravenous drug use. Blood transfusions are another source of spread of HBV, which remains the number one transmitted blood-borne virus in the healthcare environment.

Individuals with HBV are at risk of developing chronic infection, cirrhosis, hepatic decompensation, and hepatocellular carcinoma. After the acute infection, 3%–5% of adults and up to 95% of children fail to produce a sufficient immune response to clear the infection, thus going on to chronic hepatitis B.

**Clinical Manifestations**

The clinical manifestations encompass a wide spectrum in the acute as well as the chronic state. The virus has an incubation period of two to six weeks. Up to 70% of the acute cases present as a subclinical anicteric state, and the remainder present with jaundice, nausea and vomiting, fevers, right upper quadrant pain, and hepatomegaly or fulminating hepatic failure. Some of these can also present with extra hepatic manifestations.

If the LFTs are still elevated after six months, then the individual is considered to have a chronic HBV infection, but most patients with chronic hepatitis B are asymptomatic.

**Diagnostic Markers**

The diagnosis of HBV is based on the clinical presentation (complete history and physical); serologic, virologic, and biochemical markers; and occasionally histologic markers. Hepatitis B surface antigen (HBsAg) is the first serologic marker to appear after infection. Hepatitis B "e" antigen (HBeAg) indicates active viral replication, which makes a patient highly contagious. Hepatitis B core antibody (HBcAb) appears next and implies an acute or chronic state or early recovery period. Hepatitis B surface antibody (HBsAb) is the last to appear and implies recovery, immunity, or the post-vaccine state.

Hepatitis B virus (HBV) DNA is a virologic marker that measures the level of viral replication. In the past, this was measured by nonamplified hybridization assays, which have been replaced by the current target amplification assays, such as polymerase chain reaction (PCR). Hepatitis B virus (HBV) has eight genotypes (A–H) based on DNA sequencing and geographic distribution. However, genotype testing is not used in clinical practice because its relevance remains uncertain and controversial.

Elevated LFTs are an indication of necroinflammation and represent the biochemical markers. An elevated PT, in conjunction with a low albumin, usually indicates a poor prognosis or chronicity.

Histologic examination by liver biopsy is the most specific and accurate indicator of liver disease. Most individuals do not need a biopsy for diagnosis or prognosis. However, some individual with normal LFTs, and elevated HBV DNA levels have substantial fibrosis on biopsy.

**Treatment of HBV**

The goals of HBV treatment are to 1) prevent cirrhosis and its complications; 2) prevent hepatocellular carcinoma; 3) obtain undetectable HBV DNA levels; 4) normalize LFTs; 5) eradicate HBsAg; and 6) improve histology. The dilemma is that the above aims are difficult to achieve because no standard treatment algorithms, guidelines, or treatment endpoints exist and because, patients usually present with conflicting data. Treatment should be considered for individuals who are HBsAg-positive or DNA-positive by PCR.

The care of the patient with normal ALT adds a further dilemma to the treatment options. With or without treatment, circulating HBsAg can disappear but HBV DNA can be found by PCR in the liver of many individuals. Regardless of the treatment, many experts believe that chronic HBV infection can be controlled but not cured.

Agents used to treat HBV include interferon, lamivudine, adefovir, entecavir, and telbivudine. Tenofovir is approved to treat HIV and HBV co-infection only. The Asian-Pacific guidelines also include thymosin alpha, which is not an FDA-approved drug.

Interferon was the first drug used to treat HBV in most countries and has antiviral, antiproliferative, and immunomodulatory effects; in addition, it can achieve a durable response after a finite course of treatment (24–52 weeks).
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general, elevated LFTs and low HBV DNA are the best predictors of treatment response.12 Interferon therapy, however, is costly, must be given by injection, and has many side effects. The nucleoside/nucleotide analogues are more potent than interferon in suppressing the HBV DNA levels and can lead to undetectable levels by PCR; however, interferon has immunomodulatory effects and is the only drug associated with HBVsAg conversion.13,14

Interferon usually causes a flare in the ALT level because of immunemediated lyses of the hepatocytes. This response, coupled with a later normalization of LFTs and a decrease in inflammation, heralds a good prognosis.

Polyethylene glycol (PEG) is attached to the interferon molecule to decrease its rate of absorption and renal and cellular clearance, which increases its half-life. This characteristic has propelled PEG-interferon as the drug of choice over standard interferon.14 PEG-interferon is safe in compensated but not decompensated cirrhosis.

Lamivudine, a nucleoside analog, was originally used to treat HIV disease. For HBV, it is well tolerated, is given orally (100 mg/day), is relatively inexpensive ($7/day), has minimal side effects, and can be used in decompensated cirrhosis; however, it is associated with a high rate of drug resistance.

Adefovir, a nucleotide analogue of adenosine, can be used in HBeAg-positive or HBeAg-negative patients and with compensated or decompensated cirrhosis. Its route of administration is oral (10 mg/day) at a cost of $15–$20/day. It has a low rate of drug resistance, but its duration of therapy is greater than one year, and the dose needs to be adjusted in renal insufficiency. Adefovir can be added to lamivudine in case of lamivudine resistance; therefore, most physicians prefer adefovir.15

Entecavir is a nucleoside analog that is given orally at 0.51 mg/day that suppresses HBV DNA levels to a greater extent than lamivudine and adefovir. It is associated with a low rate of drug resistance, and the duration of therapy is greater than one year. Entecavir has few side effects, but like lamivudine, it has a black box warning as a potential cause of lactic acidosis, hepatomegaly, and steatosis.

Tenofovir is a nucleotide analog similar to adefovir, but it is more potent. It is effective against HIV and HBV and should only be used in co-infection with both diseases.

Telbivudine is a nucleoside analogue that was recently approved by the FDA. It is administered orally (600 mg/day) and might suppress HBV DNA levels to a greater extent than the previous medications.

HBV Prevention

There are more than 350 million carriers worldwide with HBV and almost one million deaths per year. The greatest hope to prevent this disease is through primary prevention: safe sexual practices, intravenous drug avoidance, and vaccination to increase herd immunity. The HBV vaccine is safe, is relatively inexpensive, has a high seroconversion rate, and is given in three doses intramuscularly.

Hepatitis C

Epidemiology

Hepatitis C infection affects >170 million people worldwide and >4 million Americans, but most are asymptomatic and unaware of their disease.16 Most patients acquired HCV by injection drug use or through pre-1990 blood transfusions. In the 1980s, 230,000 new cases were diagnosed each year in the United States, but now only 36,000 cases are diagnosed year because of decreased injection drug use and increased awareness. The risk of transmission between monogamous partners is low but rises with multiple sexual partners. Rare forms of percutaneous transmissions are tattoos, body piercing, and intranasal cocaine use.

HCV is a small RNA virus with six genotypes and was first identified in 1989. Genotype 1 accounts for 70%–75% of all HCV infections in the United States. It is the most common blood-borne infection in the United States, and the highest prevalence is in persons aged 30–49 years old. In this age group, the highest prevalence occurs in African Americans.17

Most acutely infected patients are asymptomatic or have a subclinical infection without jaundice. Chronic HCV infection develops in 60%–80% of infected persons, probably secondary to rapid mutations that cause a failure in T-cell immune recognition. Hepatitis C virus (HCV) is the number one cause of chronic liver disease, cirrhosis, and liver transplantation in the United States.

Diagnostic Tests

Hepatitis C virus (HCV) DNA in the serum or liver is the first sign of infection. The virus becomes positive in tests days to weeks after exposure. This test detects, quantifies, and characterizes the viral particle components. This test is further broken down into a qualitative and a quantitative test. The qualitative test is more sensitive, 98%–99% specific, and is done by either PCR or by transcription-mediated amplification (TMA). The quantitative test can detect <50 copies of the virus and is done by either PCR, TMA, or branched chain DNA (bDNA).

The indirect tests (HCV and genotyping) detect antibodies. The third-generation enzyme assay detects HCV proteins. It becomes positive eight weeks after exposure and detects 99% of immunocompetent individuals. The recombinant immunoblot assay now has limited utility thanks to this third generation test. HCV genotyping detects type-specific antibodies and predicts treatment response.
Liver function tests (LFTs) start to rise 6–12 weeks after exposure, with a range of 20–26 weeks. However, ALT level correlates poorly with disease activity and many individuals have normal levels despite having chronic HCV.

The National Institutes of Health (NIH) Consensus Development Conference in 1997 endorsed pretreatment liver biopsy as the gold standard for assessing inflammation (grade) and extent of fibrosis (stage) in anticipation of instituting antiviral therapy. It is also used to determine the urgency of treatment and prognosis, and it can rule out other diseases, such as fatty liver, alcoholic liver disease, and hemochromatosis. A liver biopsy is not necessarily needed with genotypes 2 and 3, since these are associated with an excellent prognosis. In untreated patients, a repeat liver biopsy — the only reliable means of assessing the progression of fibrosis — is recommended every three to five years.

Several histologic classifications are used to standardize results and comparisons when assessing results in different clinical trials. The three common scoring systems are Knodell, Metavir, and Ishak systems. The Knodell score, also known as the histologic activity index, and the Metavir score have four scores, from normal to cirrhosis. The Metavir score was designed to address some of the shortcomings of the Knodell system; in addition, it was designed specifically to stage hepatitis C. The Ishak system goes from normal (zero) to cirrhosis (six).

<table>
<thead>
<tr>
<th>Table 1. Factors Associated with SVR</th>
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<tr>
<td><strong>Viral</strong></td>
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<tr>
<td>- Genotype (2 or 3)</td>
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<tr>
<td>- Lower HCV RNA level</td>
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<tr>
<td>- Early virologic response</td>
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<tr>
<td><strong>Disease-related</strong></td>
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<tr>
<td>- Absence of advanced fibrosis</td>
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<tr>
<td>- Lack of steatosis</td>
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<tr>
<td>- Higher ribavirin dose</td>
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**Factors Affecting Prognosis**

The factors that affect the progression of fibrosis with a detrimental effect are external or host related. External factors are alcohol consumption, drug use, and cigarette smoking. The host-related factors are advanced age at infection, being African American, male sex, immunosuppression or co-infection (HIV, HBV, HAV), and comorbidities (hemochromatosis, obesity).

**Therapy for Hepatitis C**

The 2002 NIH consensus conference recommended that all patients with hepatitis C should be considered potential candidates for therapy. Once a patient is treated, the optimal endpoint of therapy is sustained virologic response (SVR). The factors associated with a SVR are: genotype, absence of fibrosis, etc (Table 1).

Hepatitis C virus (HCV) RNA testing is done before therapy, 12 weeks into therapy, and 24 weeks after the end of therapy, and its absence is a surrogate marker for resolution of liver injury, reduction in fibrosis, and a low likelihood of recurrent HCV infection.

The guidelines for therapy can be broken down into three areas: those in whom therapy is widely accepted, those whose therapy should be individualized, and those in whom therapy is contraindicated. Indications for therapy are age >18 years, abnormal LFTs, HCV RNA level elevation, and acceptable hematologic and biochemical values (hemoglobin >13 g/dL, lack of significant thrombocytopenia, creatinine <1.5 mg/gL, and liver biopsy without significant fibrosis).

Therapy needs to be individualized in those with normal LFTs, continuous alcohol or drug use, prior treatment failures with the older regimens, age <18 years, minimal liver involvement, decompensated cirrhosis, and HIV co-infection. Absolute contraindications to therapy are pregnancy, major uncontrolled psychiatric disorders, autoimmune disorders, hemoglobinopathies, transplant recipients, severe co-morbid conditions (coronary artery disease, cerebrovascular accident, end-stage renal disease, and chronic obstructive pulmonary disease) and hypersensitivity to the components of therapy.

The use of PEG rather than standard interferon with ribavirin increases SVR to 54%–56% with genotype 1 and 82% with genotype 2 or 3. Two different formulations of PEG-interferon are available: interferon alfa-2a is dosed at 180 ug subcutaneously every week, and interferon alfa-2b is dosed at 1.5 ug/kg subcutaneously every week. Either drug plus oral ribavirin 800–1200 mg (weight-based dosing) once a day is given for 48 weeks with genotype 1. The NIH consensus conference recommended that with genotypes 2 or 3, PEG-interferon plus ribavirin 800 mg be used for 24 weeks. Regardless of the regimen, therapy should be discontinued if HCV RNA has not decreased by >2 logs at 12 weeks.

Treatment is associated with many side effects (Table 2), and ~20% of patients experience severe side effects that result in discontinuation of their therapy. Before starting therapy, patients should be thoroughly educated about the side effects and self-management techniques to help them get through their therapy. Many of the side effects can be easily managed with proper dose reductions, growth factors, epoetin for anemia, increased fluids and exercise, acetaminophen, dosing the medications at night, diphenhydramine,
serotonin reuptake inhibitors for depression, and thyroid medications.

Milk thistle has been advocated by some to be beneficial in the treatment of HCV. It lowers LFTs but does not affect the virus itself. Viramidine, a ribavirin prodrug, produces less hemolysis, lasts longer in the liver, is less concentrated in peripheral blood, and has fewer overall side effects but is not FDA approved. The protease inhibitor VX-950 has shown promise in early clinical trials.

**Hepatocellular Carcinoma**

Patients with hepatitis B, hemochromatosis, environmental toxins and cirrhosis due to any cause are at increased risk for developing hepatocellular carcinoma (HCC). Hepatitis C in many parts of the world is the number one cause though. Screening for HCC should include: upper endoscopy in those with cirrhosis, ultrasound and serum alpha fetoprotein every six months.

**Vaccines**

Individuals with chronic liver disease should receive vaccines for hepatitis A and B, pneumococcus, and influenza.

### Hepatitis D

Hepatitis D virus, also known as delta virus, is a defective RNA virus that can replicate on its own, but it requires concurrent HBV for assembly and secretion; as a result, patients with HDV are always dually infected with HBV. There are three genotypes; all are spread percutaneously, through injection drug use, and through unprotected intercourse. The virus is endemic in the Mediterranean region and Asia. Hepatitis D virus (HDV) presents as either a co-infection—like an acute hepatitis B infection with its manifestations—or as a super infection—a severe, acute infection in a previously stable chronic hepatitis B patient.

**Diagnosis**

Since HDV is dependent on HBV, HBsAg is a requirement for the diagnosis of HDV infection. In addition, antibodies to HDV (IgM and IgG) are required for the diagnosis. Serum assays for HDAg are short-lived and are not clinically available in the United States. HDV RNA can be detected by molecular hybridization or by PCR.

**Treatment**

The primary aim and endpoint of treatment are undetectable HDV RNA levels, normalization of LFTs, and a decrease of inflammation on liver biopsy. A secondary aim is suppression of HBV DNA levels and seroconversion of HBsAg to HBsAb. Interferon alfa is the only FDA-approved drug against HDV. Ribavirin, lamivudine, and other drugs are ineffective against HDV infection.

**Prevention**

Hepatitis B affects >350 million people worldwide. Thus, the only way to prevent HDV is through primary education about its risk factors or through vaccination against HBV.

### Hepatitis E

**Epidemiology**

The hepatitis E virus (HEV) is an RNA virus with four genotypes that was first described in India in 1955. It is a self-limiting, enterically transmitted disease like hepatitis A but is more severe, easily transmitted, and distributed worldwide. Its highest incidence is in developing countries, and it is the second most common cause of sporadic hepatitis in northern Africa and the Middle East. It is usually spread by fecally contaminated water, but it can also be spread by blood and blood products. There is a low incidence of person-to-person transmission.

**Manifestations**

Hepatitis E virus (HEV) infection has an incubation period of 15–60 days. It presents like other acute hepatitis illnesses but with prolonged cholestasis. There is a low rate of fulminant hepatic failure, except in pregnant women, who have a mortality of 15%–25%. The acute state usually lasts for up to six weeks, and for those that recover there is no chronic state.

**Diagnosis, Treatment, and Prevention**

Hepatitis E virus (HEV) infection is diagnosed by detecting HEV in the serum or feces by PCR or by detecting IgM antibodies. A March 1, 2007 NEJM article featured a new recombinant HEV vaccine that showed promise in a phase two trial from Nepal. Heretofore, treatment is generally supportive since there is no FDA approved vaccine. Therefore, prevention entails avoiding contaminated water and uncooked foods in endemic areas.

### Hepatitis G

**Epidemiology**

The hepatitis G virus (HGV) is a blood-borne virus that is spread by

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**Table 2. Side effects of therapy**

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<tr>
<th>Common</th>
<th>Interferon</th>
<th>Ribavirin</th>
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<tr>
<td>Flu-like symptoms</td>
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<td>Cough, shortness of breath</td>
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<tr>
<td>Irritability</td>
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<td>Insomnia</td>
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<td>Diarrhea, gastrointestinal intolerance</td>
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<td>Rash, pruritus</td>
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<tr>
<td>Alopecia</td>
<td></td>
<td>Elevated uric acid</td>
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<tr>
<td>Leukopenia, thrombocytopenia</td>
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<td>Hemolytic anemia</td>
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<table>
<thead>
<tr>
<th>More serious</th>
<th>Interferon</th>
<th>Ribavirin</th>
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<tbody>
<tr>
<td>Retinopathy</td>
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<td>Induction autoimmune diseases</td>
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<td>Thyroid dysfunction</td>
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<tr>
<td>Neuropsychiatric disturbances</td>
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contaminated blood and blood products. It has a worldwide distribution and is especially common in blood donors in the United States. Because this virus may not produce disease in humans, blood is not routinely screened for HGV.

Studies have found that in the United States, 10%–20% of HGV patients are also co-infected with HCV. Mounting evidence has also shown a protective role of HGV in HIV patients.24,25

CONCLUSION

The viral hepatic disorders are divided into the acute disorders (hepatitis A, E, G) and those with acute and chronic states (hepatitis B, C, D). They are spread by the fecal-oral route, perinatally, percutaneously, through blood or blood products, or by unprotected intercourse. Treatment is mostly supportive, although several medications are available, depending on the individual disorder. Prevention is through proper sanitary conditions, vaccination, and education on risk factors.

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REFERENCES


AUTHOR CONTRIBUTIONS

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Manuscript draft: Hall
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Supervision: Hall