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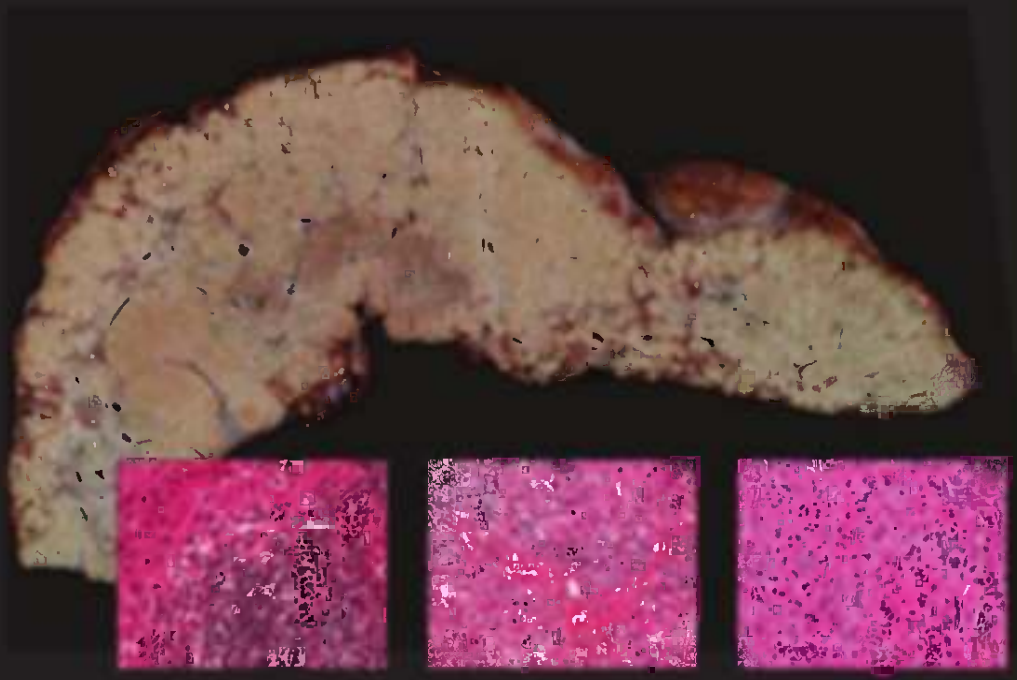
Comparative Hepatitis

Olaf Weber
Ulrike Protzer

Editors



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BAID

Comparative Hepatitis

Olaf Weber
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Birkhäuser
Basel · Boston · Berlin

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Cover illustration: Section through a cirrhotic human liver. Small pictures: left, portal lymphoid follicle in HCV infection (H&E, original magnification 200×); middle, zonal pattern with perivenular necrosis in drug-induced hepatitis (H&E, original magnification 100×); right, ground glass hepatocytes in chronic hepatitis B (H&E, original magnification 200×). With kind permission of Thomas Longerich and Peter Schirmacher.
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Preface

Hepatitis is an inflammation of the liver tissue causing hepatocellular injury which may have different aetiologies. In humans, acute and chronic hepatitis and hepatitis-related diseases such as liver failure, liver cirrhosis and hepatocellular carcinoma are among the most important causes for disabilities and death. Whereas the reaction of the liver tissue is relatively uniform, the causes for hepatocellular injury are heterogeneous and include viruses, toxins, radiation, injury and drugs but also bacteria, parasites and autoimmune reactions.

In this volume of *Birkhäuser Advances in Infectious Diseases* we review today's knowledge about hepatitis with emphasis on comparative aspects between hepatitis in humans and animals, but also between different etiological agents.

This book is dedicated to Heinz Schaller who dedicated most of his life as a scientist to the understanding of the interaction between hepatitis B viruses and their hosts.

Heinz is a personality who managed a difficult thing to do: he successfully crossed barriers. He worked as an enthusiastic scientist crossing classical barriers between chemistry, biology and medicine. He guided scientists and students and helped to form new ways of thinking and organizing academic research in Germany. A remarkable number of his fellows made outstanding carriers in different scientific areas.

Furthermore, he has in significant ways enhanced our understanding of the pathogenesis of hepatitis B virus infections, has contributed to the development of the current vaccine, has improved the care of patients infected with the virus, and has trained some of the most distinguished members of the current generation of hepatologists and virologists.

But he also crossed borders by searching for applications of his research. He is one of the few who, in addition to a successful academic career, have set the stage for a commercial success story – Heinz was a co-founder of one of the first companies dedicated to biotechnology: Biogen Idec. Thanks to his major input and intervention, the Center for Molecular Biology Heidelberg (ZMBH) as a biomedical research center with world-wide reputation was founded. Last not least, Heinz has used this success for a sustained support of biomedical research in academics with the "Chica and Heinz Schaller Stiftung".

Heinz's work has been catalytic for our understanding of hepatitis B – one of the most prevalent forms of chronic hepatitis. Crossing borders – are there that many?

Here, we would like to take the opportunity to thank Heinz for his dedication to science and wish him all the best for the years to come.

January 2008

Olaf Weber
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Comparative Hepatitis
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Hepatitis in the clinics – Treatment options

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Abstract

Hepatitis is an inflammation of the liver based on different aetiologies. Clinicians distinguish acute from chronic hepatitis. Pathophysiological changes lead to damage and hepatocellular degeneration. The causes for hepatocellular injury are heterogeneous, such as viruses, toxins, drugs, autoimmunity, cryptogenic. The latest official classification of chronic hepatitis by the International Association the Study of the Liver (IASL) [1] is still valid and is based on:

1. Aetiology
2. Inflammatory activity (Grading)
3. Fibrosis stage (Staging)

This classification has become very relevant since we nowadays not only diagnose the different liver diseases according to their aetiology but also have developed specific treatments that are targeting specific aetiologies of chronic liver disease. Overlap syndromes with primary biliary cirrhosis and primary sclerosing cholangitis and genetic liver diseases add to the clinical spectrum of this syndrome.

In this chapter we will describe the different causes of hepatitis, their treatment options and differential diagnosis.

Introduction

Hepatitis is an inflammation of the liver due to various reasons. Pathophysiological changes lead to hepatocellular damage. Causes of this hepatocellular degeneration are heterogenous such as toxins, drugs, viruses and autoimmunity. The pathologic changes due to different aetiologies share similarities; these include lobular disarray, inflammation involving portal tracts and lobules and hepatocellular degeneration in the form of ballooning and apoptosis. Microorganisms such as bacteria, viruses, fungi or parasites induce the secretion of biologically active molecules by macrophages after penetrating the epithelial surfaces of the body. Activated macrophages secrete cytokines which are defined as proteins released

Table 1. Classification of chronic hepatitis on the basis of pathogenesis [1]

Hepatitis type	HBsAg	HBV-DNA	HDV antibody (HDV-RNA)	HCV antibody (HCV-RNA)	Autoantibodies
B	+	+/–	–	–	–
D	+	–	+	–	~10% anti-LKM-3
C	–	–	–	+	~2% anti-LKM-1
Autoimmune					
type 1	–	–	–	–	ANA
type 2	–	–	–	–	LKM-1
type 3	–	–	–	–	SLA/LP
Drug-induced	–	–	–	–	Some: ANA, LKM; LM
Cryptogenic	–	–	–	–	–

SLA, soluble liver antigen antibody; LP, liver-pancreas antigen antibody; LM, liver cell membrane antibody

by cells that affect their behaviour, or other cells that bear receptors for them. The cytokines and chemokines initiate the process known as inflammation. Later inflammatory responses also involve lymphocytes, which in the meanwhile have been activated by microbial antigens. Infection with microorganisms, physical or chemical injury leads to cell disintegration or necrosis which is associated with the release of proteins and enzymes from the injured cells. These pathophysiologic changes may not only result in an increase of transaminases, but also in liver dysfunction, e.g., impaired bilirubin metabolism or coagulation factor synthesis. Chronic hepatitis is a progressive disease of heterogeneous multifactorial aetiology defined as continuous inflammation of the liver without improvement for six months or longer [1] (Tabs 1 and 2).

Infection

The most common causes for acute and chronic hepatitis are viral infections. Five viruses have been identified that can primarily manifest clinically as acute hepatitis: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV). While HAV and HEV are transmitted by the faecal-oral route and are often associated with acute icteric hepatitis, they do not lead to chronic infection. By contrast, HCV, HBV and HDV are transmitted parenterally and sexually. They are the most common cause of human viral infections leading to chronic hepatitis [2]. HBV, HCV and HDV infections can lead to viral persistence that may lead to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC).

Table 2. Causes of hepatitis

1. Infection	Hepatitis viruses	Hepatitis A Hepatitis B Hepatitis C Hepatitis D Hepatitis E
	Primary non-hepatotropic virus infections	Epstein-Barr-virus Cytomegalovirus Herpes simplex virus
2. Autoimmune hepatitis		
3. Differential diagnosis	Alcohol induced liver disease Drug-induced liver disease Chemical intoxication Primary biliary cirrhosis Primary sclerosing cholangitis	
	Metabolic liver disease	Non-alcoholic steatohepatitis (NASH)
	Genetic liver diseases	Haemochromatosis Alpha1-antitrypsin deficiency Wilson disease

Hepatitis A

Hepatitis A is considered the most common cause of acute viral hepatitis with seroprevalences from less than 30% in western European countries and up to 90% in developing countries [3, 4]. The major form of transmission is person to person *via* the faecal-oral route. The incubation period is approximately 15–45 days [4]. The onset of symptoms is abrupt with prodromal symptoms such as fatigue, weakness, nausea, abdominal pain and vomiting [5]. Diarrhoea is not typical for adults but is in the case of children with acute hepatitis A [5]. A fulminant course of hepatitis A is a rare event in young patients; however, mortality due to a fulminant course increases with age. Approximately only 4% of fulminant hepatitis cases are due to acute hepatitis A in the Western world [6]. Supportive measures are the only treatment for acute HAV infection. Prevention of HAV infection requires maintenance of high hygienic standards and strategies for active immunisation. Chronic hepatitis has not been reported to develop after hepatitis A infection.

Hepatitis B

Acute hepatitis B varies from an asymptomatic infection to cholestatic hepatitis and acute liver failure. There is no established treatment for acute HBV infection. Severe acute hepatitis B is now being treated with lamivudine within a German national multicentre study (GAHAB) sponsored by BMBF, DFG and Hep-Net, our National Network of excellence on viral

hepatitis. Acute hepatitis B resolves in most symptomatic patients. Rarely, however, the disease takes a fulminant course with a mortality rate of 65% [7, 8]. The best way to avoid a HBV infection is active immunisation with a recombinant hepatitis B vaccine. Usually the acute hepatitis B is self-limiting, but in some cases, particularly in patients with an asymptomatic course of disease, hepatitis B develops a chronic course. This occurs in 5–10% of adults with an intact immune system but in more that 90% of adult patients with immunodeficiency states such as HIV coinfection, post organ transplantation and following antitumour chemotherapy as well as neonates with a still underdeveloped immune system.

Patients with a chronic HBV infection and liver cirrhosis should receive antiviral therapy if there is viremia independent of the level of viral replication. In patients without liver cirrhosis viremia, inflammation, fibrosis score and the level of transaminases should be taken into consideration when considering treatment. The new German guidelines for the diagnosis and treatment of hepatitis B [9] are a joined effort of Hep-Net, the German national excellence network on viral hepatitis, the German societies for Gastroenterology (DGVS), Pathology (DGP), Virology (GfV) and Pediatric Gastroenterology and Nutrition (GPGE). The treatment goal in hepatitis B is to decrease HBV replication in order to decrease liver inflammation, thereby preventing the progression of fibrosis and the development of cirrhosis and its complications, including HCC [10]. Currently, Interferon-alpha, nucleotides and nucleosides are available for antiviral therapy of chronic HBV patients. In contrast to the oral nucleoside analogues, interferon has direct immunomodulatory properties and treatment response is sustained in a significant proportion of patients. Pegylated interferon alpha 2a has been found to be more effective than conventional interferon in the treatment of HBV infection in a Phase II study [11]. A number of factors are predictive in the response to Interferon-alpha, e.g., low serum HBV DNA levels, high serum alanine aminotransferase (ALT) levels and certain HBV-genotypes, in particular genotype A.

Nucleoside and nucleotide analogues have a good safety record and show less adverse effects than interferon. However, they often lead to drug resistance and viral rebound after the termination of treatment is usual. Therefore, knowledge of the pros and cons of the various treatment options nowadays available is important to allow the best choice of treatment for the individual patient based on an individual judgement of the appropriate benefit risk ratio [9] (Tab. 3).

Hepatitis C

The rate of chronicity in patients with acute hepatitis C is 50–90%. Patients with asymptomatic acute hepatitis C are more likely to develop chronic hepatitis. Therefore, the main aim of optimal patient management in acute

Table 3. Efficacy of oral antiviral agents in naïve hepatitis B patients ADDIN [9]

		Nucleoside analogues			Nucleotide analogues
		Lamivudine (Zeffix®)	Telbivudine (Sebivo®)	Entecavir (Baraclude®)	Adefovir (Hepsera®)
Dose (once a day)		100 mg	600 mg	0.5 mg (1.0 mg in patients with Lamivudine resistance)	10 mg
HBeAg-positive patients week 48/52	HBV-DNA <300 cop/ml	36%	60%	67%	21% <400 cop./ml
	HBeAg Seroconversion	18%	23%	21%	12%
	ALT normalisation*	60%	77%	68%	48%
HBeAg-negative patients week 48/52	HBV-DNA <300 cop/ml	72%	88%	90%	51% <400 cop./ml
	ALT normalisation*	71%	74%	78%	72%
Resistence development (virological breakthrough)	Week 48/52	10–32%	3–5%	<0,5%**	0%
	Week 96/104	22–42%	9–22%	<0,5%**	3–20%
	3 years	–53%		<0,5%**	11%
	4 years	–70%			18%
	5 years				29%

*The biochemical response was variable defined in different studies (normalisation of transaminases or ALT decrease <1,25 (Entecavir) or 1,3 (Telbivudine) upper limit of normal
**In lamivudine resistant patients virological breakthrough developed in 7% of patients after 1 year, in 16% after 2 years and 27% after 3 years treated with Entecavir. Treatment was stopped in patients with a viral replication $>7\times10^5$ copies/ml after treatment week 48 (about 5% of patients)

hepatitis C patients lies in avoiding chronicity, and subsequently in preventing cirrhosis associated complications. Fulminant acute hepatitis C is almost unknown in the Western world. Fortunately, it has been shown that the initiation of interferon monotherapy during the acute phase of hepatitis C virus infection significantly reduces the evolution of chronic hepatitis C [12]. Immediate treatment of acute HCV infection within 2–3 months after infection led to 98% of sustained virological response rates between 84–89% using PEG-interferon-alpha-2b for 6 months in subsequent trials [13]. At present a nationwide Hep-Net study compares immediate antiviral treatment of PEG-interferon alpha 2b monotherapy with a delayed start of treatment after 12 weeks with combination of PEG-interferon alpha 2b plus weight based dosing of ribavirin. Chronicity is associated with the risk of developing liver cirrhosis and subsequently to develop hepatic decompensation and hepatocellular carcinoma.

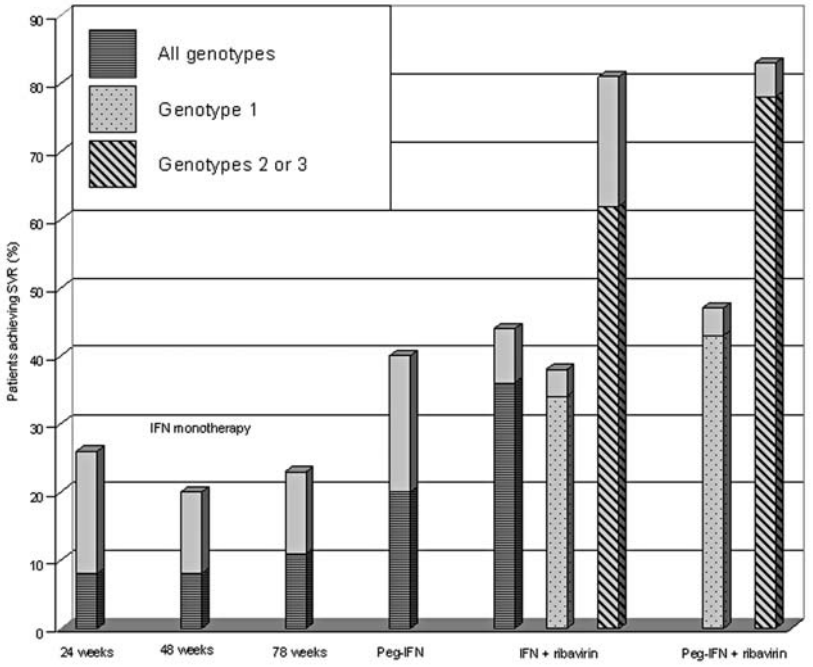

Figure 1. Development of antiviral treatment in chronic hepatitis C in the recent 20 years. Modified according to Manns et al. [18]

Worldwide more than 150 million people are considered to be chronically infected with the hepatitis C (HCV) virus. Combination therapy of chronic hepatitis C with pegylated interferon-alpha plus ribavirin is still the standard of care since 2001 [14]. However, this treatment is only successful in approximately half of the patients chronically infected with hepatitis C, genotype 1. This therapy can be associated with significant side effects and costs [15]. The standard of care for the treatment of chronic hepatitis C patients PEG-interferon alpha plus ribavirin has been optimised over the recent years after 2001, which led to further improvements in response with sustained virological response rates (SVR) up to 60% for the difficult to treat genotypes 1, and more that 80% for the so-called easy to treat genotype 2 and 3 patients [14, 16–18] (Fig. 1). Both interferon and ribavirin induce side effects that have to be considered in the management of patients with chronic hepatitis C. The interferon related side effects can be divided into interferon induced bone marrow depression, flu-like symptoms, neuropsychiatric disorders and autoimmune syndromes. The main problem of ribavirin is haemolytic anaemia. Overall, side effects result in 10–20% premature withdrawals from therapy and an additional 20–30% of patients

require dose modifications [19]. The big unmet need in the treatment of chronic hepatitis C is the therapy of non-responders to previous PEG-interferon and ribavirin treatment. Here only the new small direct antiviral drugs, the so-called STAT-C drugs, will lead to further improvements [18].

Hepatitis D

The hepatitis delta virus (HDV) is an RNA viroid dependent for infection on obligatory helper functions provided by the HBV; it therefore can only infect individuals with simultaneous HBV infection. Acute infection with HDV can be simultaneous with acute HBV infection (coinfection) or can occur in patients chronically infected with HBV as a super-infection. While super-infection usually is associated with chronicity and a higher rate of cirrhosis development compared to monoinfected patients [20–22], acute HBV/HDV coinfection usually leads to spontaneous clearance and chronicity is less than 10%. A recent study has shown that PEG-interferon-alpha-2a displays a significant antiviral efficacy in more than 40% of HDV/HBV coinfected patients alone or in combination with adefovir. Adefovir does not alter HDV-replication, but may be considered for patients with high HBV-levels. Combination therapy of PEG-interferon-alpha-2a plus adefovir has no advantages for HDV-RNA reduction, but is superior in reduction of quantitative HbsAg levels [23]. HBsAg loss was only seen in the group of patients treated with a combination of PEG-interferon alpha 2a plus adefovir.

Hepatitis E

Hepatitis E is transmitted by the faecal-oral route. The symptoms are unspecific and similar to hepatitis A, i.e., flu-like symptoms, including fever, abdominal pain, anorexia, nausea, diarrhoea and vomiting [24, 25]. Like other forms of acute hepatitis, the mainstay of therapy is in monitoring the complications and in treating the symptoms. The HEV infection is usually self-limited. However, fulminant hepatitis may occur. Acute hepatitis E is almost absent in the developed world but is the most prevalent cause of acute hepatic in some parts of the developing world like Kashmir, parts of India, Taschkent and at the horn of Africa like parts of Ethiopia. So far chronic hepatitis has not been reported to develop after hepatitis E infection.

Primary non-hepatotropic virus infections

Several other viral infections may damage the liver, but are not primarily regarded as hepatotropic. These infections include Ebstein Barr virus, cytomegalovirus and herpes simplex virus (Tab. 1).

Autoimmunity hepatitis

Autoimmune hepatitis (AIH) is another entity of chronic hepatitis. AIH is characterised by a loss of tolerance against hepatic tissue which leads to a chronic, mainly periportal hepatitis and destruction of hepatic parenchyma. AIH may also start as acute hepatitis and may even manifest as fulminant hepatitis. The estimated prevalence in Northern Europe is 170 cases per million [26]. There is no single sensitive and specific diagnostic marker of AIH. Diagnosis is made from a combination of clinical, biochemical, serological and histological features [27]. AIH is most prevalent in females and is often found clustered in families. Serologic detection of autoantibodies is one of the distinguishing features [28] that has lead to the sub classification of AIH in three groups. AIH type 1 is characterised by the presence of antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA) directed predominantly against smooth muscle actin. AIH type 2 is characterised by anti-liver-kidney microsomal autoantibodies (LKM-1) directed against cytochrome P450 (CYP) 2D6 and with lower frequency against UDP-glucuronosyltransferases (UGT) [29, 30]. AIH type 3 is characterised by autoantibodies against soluble liver antigens (SLA/LP) [31, 32]. Seropositivity in fluorescence tests is considered at titres greater than 1:80 [33].

The clinical presentation ranges from a spectrum of benign asymptomatic disease to fulminant hepatitis [1, 34]. In half of the patients the onset is insidious and half show features of chronic liver disease. AIH is therefore characterised by non-specific features such as right upper abdominal pain, fatigue, arthralgias, myalgia, jaundice and pruritus. About 25% of patients show an acute onset of AIH and rare cases of fulminant progression of AIH leading to acute liver failure have also been reported [34]. Next to the autoantibodies, the diagnosis of AIH is established by the exclusion of other aetiologies of chronic hepatitis.

The liver histology in AIH is characterised by the presence of interface hepatitis in which several mononuclear cells infiltrate the portal tract, invade the adjacent liver parenchyma and surround dying hepatocytes [1]. Studies have shown that untreated AIH had a very poor prognosis with 5–10 year survival rates of 50 and 10% and furthermore demonstrated that immunosuppressive treatment significantly improved survival [35, 36]. The goal of treatment is a complete biochemical and histological resolution of inflammation as well as clinical remission of symptoms. The standard treatment of AIH is either prednisolone monotherapy or combination therapy with prednisolone and azathioprine. Combination therapy is preferred on the whole, because it allows the reduction of prednisolone and thereby the reduction of steroid-associated side effects.

Overlap syndromes of AIH and PBC and of AIH and PSC both appear to be present in about 8% of AIH patients [37, 38]. Overlap syndromes are conditions in which patients have clinical, histological and also immunologi-