

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2021 May 14; 27(18): 2054-2250



**EVIDENCE REVIEW**

- 2054 Role of microbial dysbiosis in the pathogenesis of esophageal mucosal disease: A paradigm shift from acid to bacteria?  
*D'Souza SM, Houston K, Keenan L, Yoo BS, Parekh PJ, Johnson DA*

**REVIEW**

- 2073 Immune disorders and rheumatologic manifestations of viral hepatitis  
*Maslennikov R, Ivashkin V, Efremova I, Shirokova E*

**MINIREVIEWS**

- 2090 Neurological manifestations of hepatitis E virus infection: An overview  
*Jha AK, Kumar G, Dayal VM, Ranjan A, Suchismita A*
- 2105 Stroma-targeting strategies in pancreatic cancer: Past lessons, challenges and prospects  
*Polani F, Grierson PM, Lim KH*
- 2122 Magnetic resonance imaging-based artificial intelligence model in rectal cancer  
*Wang PP, Deng CL, Wu B*
- 2131 Remaining issues of recommended management in current guidelines for asymptomatic common bile duct stones  
*Saito H, Kadono Y, Shono T, Kamikawa K, Urata A, Nasu J, Imamura H, Matsushita I, Tada S*

**ORIGINAL ARTICLE****Basic Study**

- 2141 Alleviation of acute pancreatitis-associated lung injury by inhibiting the p38 mitogen-activated protein kinase pathway in pulmonary microvascular endothelial cells  
*Zhang XX, Wang HY, Yang XF, Lin ZQ, Shi N, Chen CJ, Yao LB, Yang XM, Guo J, Xia Q, Xue P*
- 2160 Partially hydrolyzed guar gum attenuates non-alcoholic fatty liver disease in mice through the gut-liver axis  
*Takayama S, Katada K, Takagi T, Iida T, Ueda T, Mizushima K, Higashimura Y, Morita M, Okayama T, Kamada K, Uchiyama K, Handa O, Ishikawa T, Yasukawa Z, Okubo T, Itoh Y, Naito Y*

**Retrospective Cohort Study**

- 2177 Factors influencing the failure of interferon-free therapy for chronic hepatitis C: Data from the Polish EpiTer-2 cohort study  
*Janczewska E, Kolek MF, Lorenc B, Klapaczynski J, Tudrujek-Zdunek M, Sitko M, Mazur W, Zarębska-Michaluk D, Buczyńska I, Dybowska D, Czauż-Andrzejuk A, Berak H, Krygier R, Jaroszewicz J, Citko J, Piekarska A, Dobracka B, Socha Ł, Deroń Z, Laurans Ł, Białkowska-Warzecha J, Tronina O, Adamek B, Tomaszewicz K, Simon K, Pawłowska M, Halota W, Flisiak R*

**Retrospective Study**

- 2193 Totally laparoscopic total gastrectomy using the modified overlap method and conventional open total gastrectomy: A comparative study

*Ko CS, Choi NR, Kim BS, Yook JH, Kim MJ, Kim BS*

- 2205 Radiofrequency ablation *vs* surgical resection in elderly patients with hepatocellular carcinoma in Milan criteria

*Conticchio M, Inchingolo R, Delvecchio A, Laera L, Ratti F, Gelli M, Anelli F, Laurent A, Vitali G, Magistri P, Assirati G, Felli E, Wakabayashi T, Pessaux P, Piardi T, di Benedetto F, de'Angelis N, Briceño J, Rampoldi A, Adam R, Cherqui D, Aldrighetti LA, Memeo R*

**Clinical Trials Study**

- 2219 Responses to faecal microbiota transplantation in female and male patients with irritable bowel syndrome

*El-Salhy M, Casen C, Valeur J, Hausken T, Hatlebakk JG*

**Observational Study**

- 2238 Standard *vs* magnifying narrow-band imaging endoscopy for diagnosis of *Helicobacter pylori* infection and gastric precancerous conditions

*Cho JH, Jeon SR, Jin SY, Park S*

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Editorial Board Member of *World Journal of Gastroenterology*, Ferenc Sipos, MD, PhD, Senior Lecturer, Head of Department, Department of Internal Medicine and Haematology, Semmelweis University, Szentkirályi Street 46, Budapest H-1088, Hungary. sipos.ferenc@med.semmelweis-univ.hu

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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Ji-Hong Lin, Production Department Director: Yun-Xiaojuan Wu, Editorial Office Director: Ze-Mao Gong.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Andrzej S Tarnawski, Subrata Ghosh

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

May 14, 2021

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**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Immune disorders and rheumatologic manifestations of viral hepatitis

Roman Maslennikov, Vladimir Ivashkin, Irina Efremova, Elena Shirokova

**ORCID number:** Roman Maslennikov 0000-0001-7513-1636; Vladimir Ivashkin 0000-0002-6815-6015; Irina Efremova 0000-0002-4112-0426; Elena Shirokova 0000-0002-6819-0889.

**Author contributions:** Ivashkin V and Maslennikov R thought idea of the review; all authors searched original publications; Maslennikov R written the draft; all authors made the draft editing.

**Conflict-of-interest statement:** No conflict of interest for declaration.

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**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology and hepatology

**Roman Maslennikov, Vladimir Ivashkin, Irina Efremova, Elena Shirokova,** Department of Internal Medicine, Gastroenterology and Hepatology, Sechenov University, Moscow 119435, Russia

**Roman Maslennikov,** The Interregional Public Organization “Scientific Community for the Promotion of the Clinical Study of the Human Microbiome”, Moscow 119435, Russia

**Roman Maslennikov,** Department of Internal Medicine 1, Consultative and Diagnostic Center 2 of the Moscow City Health Department, Moscow 107564, Russia

**Corresponding author:** Roman Maslennikov, MD, PhD, Assistant Professor, Professor, Department of Internal Medicine, Gastroenterology and Hepatology, Sechenov University, Pogodinskaya Street, 1, bld. 1, Moscow 119435, Russia. [mmmm00@yandex.ru](mailto:mmmm00@yandex.ru)

### Abstract

Infection with hepatotropic viruses is not limited to the liver and can lead to the development of various immunological disorders (the formation of cryoglobulins, rheumatoid factor, antinuclear antibodies, autoantibodies specific for autoimmune hepatitis and primary biliary cholangitis, and others), which can manifest as glomerulonephritis, arthritis, uveitis, vasculitis (cryoglobulinemic vasculitis, polyarteritis nodosa, Henoch-Schonlein purpura, isolated cutaneous necrotizing vasculitis), and other rheumatologic disorders, and be a trigger for the subsequent development of autoimmune hepatitis and primary biliary cholangitis. A further study of the association between autoimmune liver diseases and hepatotropic virus infection would be useful to assess the results of treatment of these associated diseases with antiviral drugs. The relationship of these immune disorders and their manifestations with hepatotropic viruses is best studied for chronic hepatitis B and C. Only isolated cases of these associations are described for hepatitis A. These links are least studied, and are often controversial for hepatitis E, possibly due to their relatively rare diagnoses. Patients with uveitis, glomerulonephritis, arthritis, vasculitis, autoimmune liver diseases should be tested for biomarkers of viral hepatitis, and if present, these patients should be treated with antiviral drugs.

**Key Words:** Hepatitis A; Hepatitis B; Hepatitis C; Hepatitis E; Vasculitis; Rheumatoid factor

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**Country/Territory of origin:** Russia**Peer-review report's scientific quality classification**Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0**Received:** January 16, 2021**Peer-review started:** January 16, 2021**First decision:** February 28, 2021**Revised:** February 28, 2021**Accepted:** April 22, 2021**Article in press:** April 22, 2021**Published online:** May 14, 2021**P-Reviewer:** Fteiha B, Mohamed GA**S-Editor:** Zhang L**L-Editor:** A**P-Editor:** Liu JH

**Core Tip:** Infection with hepatotropic viruses is not limited to the liver and can lead to the development of various immunological disorders, which can manifest itself as glomerulonephritis, arthritis, uveitis, vasculitis, and other rheumatologic disorders, and be a trigger for the subsequent development of autoimmune hepatitis and primary biliary cholangitis. These associations are best studied for chronic hepatitis B and C. Only isolated cases of these are described for hepatitis A. These links are least studied, and are often controversial for hepatitis E. Patients with uveitis, glomerulonephritis, arthritis, vasculitis, autoimmune liver diseases should be tested for biomarkers of viral hepatitis.

**Citation:** Maslennikov R, Ivashkin V, Efremova I, Shirokova E. Immune disorders and rheumatologic manifestations of viral hepatitis. *World J Gastroenterol* 2021; 27(18): 2073-2089

**URL:** <https://www.wjgnet.com/1007-9327/full/v27/i18/2073.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v27.i18.2073>

## INTRODUCTION

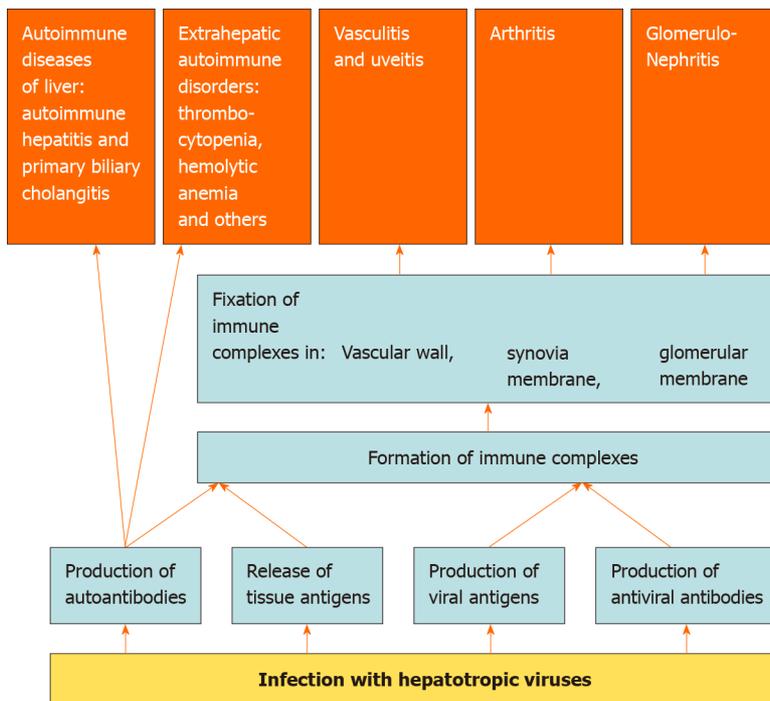
Viruses, unlike bacteria and fungi, cannot reproduce on their own and need the resources of a host cell as they are obligate intracellular parasites[1]. The viral proteins produced by the cell undergo partial proteolysis in the proteosomes, after which their fragments in conjunction with the molecules of the major histocompatibility complex type 1, are exposed on the cell surface to stimulate the immune system[2]. The partial proteolytic products of the cell's own proteins are exposed in a similar way. If these peptides have sufficient similarity to the partial proteolytic peptides of viral proteins, it is possible to develop an autoimmune cross-reaction in response to a viral infection[3]. Antiviral immunity is directed not only and not so much against the virus itself, but against the host cell infected with it, which serves as another predictor for the development of autoimmune aggression[4,5]. Among the autoantibodies produced in response to a viral infection, rheumatoid factor [(RF) an autoantibody against IgG], and cryoglobulins (antibodies that precipitate in the cold), are of utmost importance. The release of viral antigens into the bloodstream also plays a major role. Damage to the tissues, both directly by viruses and as a result of immune aggression against infected cells, also results in the release of a large number of tissue antigens. Tissue and viral antigens interact with antibodies to form immune complexes, which are fixed in the synovial membrane of the joints, glomerular membrane, and vascular wall, including the choroid. This leads to the development of arthritis, glomerulonephritis, vasculitis, and uveitis. Thus, viral infections can be triggers for autoimmune reactions and other immune disorders, which predispose to the development of rheumatologic and immunological complications of viral infections (Figure 1). However, the exact mechanisms of the development of autoimmune reactions in viral infections are yet to be established.

Many viruses can infect the liver, but only for five of them it is the main target organ: hepatitis A viruses (HAV), hepatitis B viruses (HBV), hepatitis C viruses (HCV), hepatitis D viruses (HDV) and hepatitis E viruses (HEV)[6]. HDV is a defective virus and can only replicate when co-infected with HBV[7].

Our review is devoted to describe the development of the aforementioned immunological disorders and caused by them rheumatologic and other extrahepatic manifestations in viral hepatitis. Knowing these complications is very important as infection with hepatotropic viruses can manifest only in the form of these disorders, leading to misdiagnosis and inadequate treatment.

## HEPATITIS A

Hepatitis A occurs only in an acute form[8]. Perhaps due to the short-term contact of the macroorganism with the virus, immune and rheumatologic disorders rarely develop.



**Figure 1** Scheme of the development of immunological disorders and caused by them rheumatologic and other extrahepatic manifestations of viral hepatitis.

Joint pain without arthritis occurs on average in 10%-20% of patients with hepatitis A[9-11]. True arthritis in hepatitis A develops within vasculitis (see below).

RF was found in only two patients with hepatitis A who had cryoglobulinemic vasculitis[12].

Cryoglobulinemia is observed in 95% of patients with hepatitis A in one study. Cryoprecipitate was represented by IgM, including antibodies against HAV. IgA and/or IgG were also represented in the cryoprecipitate of 15% of patients. After recovery, the cryoglobulin content decreased to normal. Interestingly, the cryoglobulin level in hepatitis A was higher than in acute hepatitis B[13].

Mesangioproliferative glomerulonephritis with deposits of IgM and complement components was found in a 7-year-old boy with hepatitis A. This was accompanied by the development of severe nephrotic syndrome, neutrophilic leukocytosis, and a decrease in the blood complement (components C3 and C4) levels. The disease ended in complete recovery[14].

In another case, mesangioproliferative glomerulonephritis in a young woman led to deposits of all three types of immunoglobulins and complement component C1q, and was accompanied by the development of acute renal failure, but not nephrotic syndrome; blood complement levels were normal. Complete recovery was observed here also[15].

The development of IgA nephropathy in hepatitis A has also been reported[16,17].

Polymyositis with myoglobinuria, increased creatine kinase activity and electromyographic changes was verified by muscle biopsy in a patient with hepatitis A[18].

A 23-year-old man with hepatitis A developed adult-onset Still's syndrome: Fever, maculopapular rash on the trunk and legs, generalized arthralgia, severe neutrophilic leukocytosis, and hyperferritinemia. The disease was successfully controlled by glucocorticoids[19].

A case of unilateral autoimmune parotitis with left-sided pain and swelling in the face, generalized arthralgia, and rash was reported. Biopsy revealed mononuclear infiltration of the affected parotid gland. The disease was resistant to antibiotics, but was quickly treated with prednisolone[20].

We found 13 published cases of hepatitis A-associated vasculitis (Tables 1 and 2) [12,21-30]. These were Henoch-Schonlein purpura (HSP) (53.8%), cryoglobulinemic vasculitis (CGV) (30.8%), and isolated cutaneous necrotizing vasculitis (15.4%). Most of them (76.9%) occurred in children. The pathological process involved the skin (92.3%), joints (69.2%), intestines (46.2%) and kidneys (7.7%). Arthralgia without synovitis was observed in 15.4% of cases and arthritis in 54.8% of cases (mainly in the knees and

**Table 1** Cases of vasculitis in hepatitis A

Case	Dan <i>et al</i> [21]	Press <i>et al</i> [22]	Nassih <i>et al</i> [23]	Chemli <i>et al</i> [24]	Mohan <i>et al</i> [25]	Altinkaynak <i>et al</i> [26]
Age, yr	30	2	8	10	< 1	10
Sex	Female	Female	Female	Male	Female	Male
Diagnosis	CNV	CNV	CGV	HSP	HSP	HSP
Body temperature	N	N/A	N	N/A	Mild fever	N
Time of the onset after the onset of hepatitis	2 wk	N/A	8 wk	3 d after admission to hospital	During the first month of illness	2 wk
Second wave of hepatitis	-	N/A	-	-	-	-
Pruritus	+	N/A	+	+	-	-
Jaundice	+	N/A	+	N/A	+	+
Rash	EPR over the hips, but also involving the buttocks and arms, and rare petechiae	Echymotic lesions	PP on the legs, forearms, and the back	PP on the declivous regions	Bluish PP on both lower limbs, swelling over dorsum of hands and feet	PP on the legs and on the gluteal regions.
Joints	N	N/A	Arthritis in the knees	Arthralgia	Arthritis in the right knee	Arthralgia
GN	No	N/A	Dipstick test was positive to proteins (2+) and blood (3+)	No	No	No
Gut	N	N/A	N	Abdominal pain	Small amount of blood in stool	Abdominal pain
RF	N/A	N/A	Negative	N/A	Negative	Negative
ANA	N/A	N/A	Negative	N/A	Negative	Negative
WBC, 10 <sup>9</sup> /L	6.3	N/A	7.2	N/A	↑	9.9
CRP, mg/L	N/A	N/A	38	N/A	N/A	N
Platelets, 10 <sup>9</sup> /L	408	N/A	N/A	N/A	N	416
ESR, mm/h	80	N/A	80	N/A	N/A	N/A
Cryoglobulins	N/A	N/A	IgM, IgA, and IgG	N/A	N/A	N/A
Transaminases	↑	N/A	↑	↑	↑	↑
Complement	N	N/A	N/A	N/A	N/A	N
Skin biopsy	LCV with deposition of IgM and C3	Necrotizing vasculitis with fibrin thrombi	LCV	N/A	LCV	N/A
Treatment	N/A	GC	GC	N/A	Analgetics	N/A

ANA: Antinuclear antibodies; CNV: Cutaneous necrotizing vasculitis; CRP: C-reactive protein; CGV: Cryoglobulinemic vasculitis; EPR: Erythematous papular rash; ESR: Erythrocyte sedimentation rate; GN: Glomerulonephritis; GC: Glucocorticoids; HSP: Henoch-Schonlein purpura; LCV: Leukocytoclastic vasculitis; N: Normal; N/A: No available; PP: Palpable purpura; RF: Rheumatoid factor.

ankles). Vasculitis developed about 5wk after the onset of the disease, and was accompanied by a second wave of hepatitis in 30.8% of cases and a protracted course (more than one month) of hepatitis in 23.1% of cases. All patients experienced complete recovery.

Experimental infection of monkeys marmosets with HAV led to the development of proliferative glomerulonephritis with deposits of IgM, component C3 (less often other immunoglobulins), and vasculitis[31].

Isolated cases of uveitis associated with hepatitis A have also been described[32,33]. Moreover, uveitis appeared before the symptoms of hepatitis[32].

One patient with hepatitis A developed lupus-like syndrome: symmetrical arthralgia in the wrists, metacarpophalangeal and proximal interphalangeal joints, left-sided pleurisy, Lupus cells, and antinuclear antibodies (ANA), antibodies against

Table 2 Cases of vasculitis in hepatitis A

Case	Garty <i>et al</i> [27]	Sasan <i>et al</i> [28]	Islek <i>et al</i> [29]	Islek <i>et al</i> [29]	Bozaykut <i>et al</i> [30]	Inman <i>et al</i> [12]	Inman <i>et al</i> [12]
Age, yr	8	8	13	11	< 1	26	26
Sex	Male	Male	Male	Female	Female	Female	Female
Diagnosis	HSP	HSP	HSP	HSP	CGV	CGV	CGV
Body temperature	N/A	37.2	N	N	N	N	N
Time of the onset after the onset of hepatitis	5 wk	5 wk	13 wk	5 wk	N/A	20 wk	19 wk
Second wave of hepatitis	-	-	+	+	N/A	+	+
Pruritus	-	-	-	+	-	-	-
Jaundice	-	-	-	+	-	+	-
Rash	PP on on the buttocks, penis and legs, which began with darkening of the right half of the scrotum	Non blanching red-brown papules over both thighs and legs	PP on the legs	PP on the legs	Oedema and ecchymosis on the dorsum of the hands and from feet to the knees	PP on on the legs, buttocks, arms, which began with ankles	No rash
Joint	N	Arthritis in the knees and ankles	Arthritis in the right knee and ankle	Arthritis in unspecified joints	N	Arthritis in the knees and ankles	Arthritis in the ankles, right fourth and fifth right metatarsophalangeal joints
GN	No	No	No	No	No	No	No
Gut	N	Abdominal pain	Abdominal pain	Abdominal pain	N	N	N
RF	N/A	N/A	Negative	Negative	N/A	1:160	1:320
ANA	N/A	N/A	Negative	Negative	N/A	N/A	N/A
WBC, 10 <sup>9</sup> /L	N/A	10.1	4.6	7.2	12	N/A	N/A
CRP, mg/L	N/A	N/A	N	N/A	N/A	N/A	N/A
Platelets, 10 <sup>9</sup> /L	N/A	516	250	407	300	N/A	N/A
ESR, mm/h	N/A	34	22	42	N/A	N/A	N/A
Cryoglobulins	N/A	N/A	N/A	N/A	Positive	Anti-HAV IgG	Anti-HAV IgG
Transaminases	↑	N	↑	↑	N	↑	↑
Complement	N/A	N/A	N	C3↑, C4 - N	N	N/A	N/A
Skin biopsy	N/A	N/A	LCV with deposition of IgM in the dermo-epidermal junction	LCV	LCV	LCV	N/A
Treatment	N/A	GC	Symptomatically	N/A	No	No	NSAID

ANA: Antinuclear antibodies; CRP: C-reactive protein; CGV: Cryoglobulinemic vasculitis; ESR: Erythrocyte sedimentation rate; GN: Glomerulonephritis; GC: Glucocorticoids; HSP: Henoch-schonlein purpura; LCV: Leukocytoclastic vasculitis; N: Normal; N/A: No available; NSAID: Nonsteroidal anti-inflammatory drugs; PP: Palpable purpura; RF: Rheumatoid factor.

double-stranded deoxyribonucleic acid (DNA) and cardiolipin, which disappeared within a few months[34].

Autoimmune hepatitis (AIH) was triggered by hepatitis A in 11 published cases[35-44]. In some of these patients, this was accompanied by the appearance of ANA. A case of a 24-year-old woman with an autoimmune hepatitis/primary biliary cirrhosis overlap syndrome triggered by an acute hepatitis A infection was

reported[45]. No case of isolated primary biliary cholangitis (PBC) associated with HAV was found.

Thus, immunological disorders and rheumatologic manifestations in hepatitis A are rare, have a favorable prognosis, and run their course without treatment or after treatment with glucocorticoids or non-steroidal anti-inflammatory drugs.

## HEPATITIS B

Hepatitis B is characterized by lifelong infection, which predisposes to more frequent immunological disorders and caused by them rheumatologic and other extrahepatic manifestations.

Among patients with chronic hepatitis B, Raynaud's phenomenon occurs in 2%, arthralgia or arthritis in 3%, myalgia in 3%, Sjogren's syndrome in 3%, glomerulonephritis in 3%, uveitis in 2%, cryoglobulins in 2%[46].

RF is detected more often in asymptomatic carriers of HBV surface antigen (HBsAg) than in healthy individuals (11.8% *vs* 3.4%). RF positive rate was not significantly associated with the level of alanine aminotransferase or C-reactive protein in individuals with HBsAg[47]. HBV DNA levels significantly correlated with the titers of RF[48]. Antibodies against cyclic citrullated peptide (anti-CCP), a more specific marker of rheumatoid arthritis, were detected in individuals with HBsAg less often than was RF (4.6% *vs* 11.8%). Among patients with HBsAg, RF is found in 46% of patients with arthritis, 5% of patients with arthralgia, and in 8% of patients without rheumatologic complaints. Anti-CCP is found in 36%, 0% and less than 1% of these patients, respectively. Joint disorders and biochemical changes classified as rheumatoid arthritis were observed in 4.1% of patients with HBsAg. These patients accounted for 32.1% of HBV infected individuals with RF, 81.8% of those with anti-CCP and 90% of them have both RF and anti-CCP[49].

Patients with HBV infection accounted for 6.3% of patients with complaints of pain in joints and/or muscles. Moreover, only 26.3% of them had true arthritis[50].

HBV-associate non-rheumatoid arthritis can develop simultaneously in all affected joints, be migratory, or have an additive pattern. Synovitis develops abruptly and is severe. Arthritis develops within 12 wk after the onset of the disease, but in some cases, it is the first manifestation of hepatitis B. The age of patients with arthritis is 14-35 years in 82.8% of cases. Monoarthritis of a large joint is observed in about 40% of cases, polyarthritis of the small joints of the fingers in 10%, and a combined lesion of large and small joints in 50%. Among the large joints, the knee joints are most often affected, followed by the wrist, ankle, elbow, shoulder and hip joints. The metacarpophalangeal and proximal interphalangeal joints of the hands are affected as often as the knee joints, whereas the small joints of the feet are less frequently affected. Synovitis is usually symmetrical. The cervical and lumbar intervertebral joints are involved in about 10% of cases, usually together with other joints. ANA is determined in approximately 10% of such patients, and RF in approximately 25%, anti-CCP in approximately 5%. Complement is reduced in almost half of these patients. In all cases, arthritis resolved spontaneously or after treatment with non-steroidal anti-inflammatory drugs within 3-7 d. No development of chronic arthritis or recurrence of arthritis has been observed[49,51].

On average, 3% of glomerulonephritis is associated with the presence of HBsAg. It is membranous glomerulonephritis in 40% of cases, membranoproliferative glomerulonephritis in 20%, focal segmental glomerulosclerosis in 20%, IgA nephropathy in 10%; the remaining 10% account for the other forms. There are nephrotic syndrome in 60% of cases of HBV-associated glomerulonephritis, and nephritic syndrome or isolated changes in urine analysis in other cases[52].

Fibromyalgia is more often detected in patients with hepatitis B than in those without infection (32% *vs* 5%). Moreover, there was no difference in the incidence of this disease between patients with untreated active chronic hepatitis B, an inactive hepatitis B virus infection, and patients receiving treatment for this infection[53].

Autoantibodies are detected on average in 60% of patients with chronic hepatitis B. Most often, these are ANA (approximately 25%), anti-Ro52 (approximately 30%), anti-gp210 and anti-PML (approximately 10%), AMA-M2 (approximately 7%), anti-Sp100, anti-SMA, anti-LC-1 and anti-SLA/LP (all constituting approximately 3%), and anti-LKM-1 (< 1%). The frequency of detection of ANA was higher in the pre-cirrhotic stage than in cirrhosis (30% *vs* 20%). The frequency of detection of other autoantibodies did not differ significantly between these stages of the disease[54].

The high percentage of autoantibodies that are specific for PBC (anti-gp210, anti-PML, and AMA-M2) in HBV infection may indicate that HBV could be trigger for the development of this disease. Thus, in one study, signs of silent HBV infection (anti-HBc without HBsAg) were found in 40% of patients with PBC. Bilirubin level is higher and the degree of fibrosis is greater in these patients than in those with idiopathic PBC[55]. PBC will be diagnosed in 2%-3% of patients with hepatitis B over the next 15 years[56].

Specific biomarkers of AIH (anti-SMA, anti-LC-1, anti-SLA/LP, and anti-LKM-1) have been identified in 1%-3% of patients with hepatitis B[54]. Among patients with AIH, HBV DNA was detected in almost 25%, and serological biomarkers of HBV infection without signs of viral replication were found in another 30%[57].

About 35% of polyarteritis nodosa (PAN) cases are associated with hepatitis B. For this variant of the disease, neuropathies (approximately 85% *vs* 65%), arterial hypertension (49% *vs* 27%), abdominal pain (50% *vs* 28%), testicular involvement (24% *vs* 13%), cardiomyopathy (13% *vs* 4%) were more characteristic than for idiopathic PAN unlike livedo (10% *vs* 20%). The prognosis in patients with HBV-associated PAN was worse than in idiopathic PAN: 60% of patients from the first group and 74% from the second were alive after 10 years[58]. Hepatitis B was diagnosed before the development of PAN in approximately 30% of these patients. Vasculitis developed before the end of the clinical manifestations of hepatitis or in the next few days after this in half of these cases, and within the first 6 mo after this in the others. Transaminases are normal in 33%-50% of patients at the time of the onset of PAN[59,60].

Biomarkers of hepatitis B are detected in 2%-6% of cases with mixed cryoglobulinemia[61-63] and in almost 10% of cases with non-HCV CGV[64]. Manifestations of HBV-associated CGV are: Purpura (100%), arthralgias (71%), peripheral neuropathy (29%), glomerulonephritis (18%), Raynaud phenomenon (18%), and leg ulcer (6%)[65]. Cryoglobulins disappear in the serum leading to the regression of vasculitis in the majority of patients treated with entecavir, adefovir, and lamivudine. Corticosteroid therapy is effective for clinical symptoms of vasculitis, but ineffective for suppression of HBV and immunological features. Immunosuppressive agents are not recommended because of possible flare-up of viral replication. The use of interferons in these cases does not always lead to a positive effect[66].

There are only a few published cases of the association of HSP with hepatitis B[67-71].

Interestingly, according to a meta-analysis, biomarkers of hepatitis B are less common in systemic lupus erythematosus than in the general population: Odds ratio of HBsAg was 0.24 [95% confidence interval (CI): 0.17-0.33] and odds ratio of anti-HBc was 0.4 (95%CI: 0.31 - 0.50)[72].

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## HEPATITIS C

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HCV (like HBV) persists for a long time in the body; therefore, the frequency of immunological disorders and rheumatologic manifestations is also quite high[73].

Patients with HCV infection accounted for 5.3% of patients with complaints of pain in the joints and/or muscles. Moreover, 40% of them had true arthritis, 50% had arthralgia, and 10% had no joint disorders[50].

Pain in the joints and/or muscles are noted in 70% of patients with chronic hepatitis C if the medical history was collected carefully. Backache is the most common complaint (54%), followed by early morning stiffness (45%), arthralgia (42%), myalgia (38%), neck pain (33%), generalized pain (21%), and subjective joint swelling (20%). Diffuse pain was present in 23% of patients, non-diffuse regional plus axial pain in 18%, axial pain in 17%, and regional pain in 12%[74].

Among patients with HCV having no rheumatologic complaints, RF is detected more than in the general population (15% *vs* 5%), unlike anti-CCP with the same incidence (about 5%)[75]. Patients with HCV and joint involvement have RF in 60% of cases, cryoglobulins in almost 50%, and both in 40%. Anti-CCP was detected only in patients without RF and cryoglobulins[76].

Cryoglobulins are found in almost 65% of a general population of HCV patients, but they clinically manifest only in 5% of them. The achievement of a stable viral response leads to a decrease in the detection rate of cryoglobulins from 57% to 33%, whereas the detection rate remains unchanged among those in whom it was not achieved. In approximately 20% of patients with cryoglobulinemia, it persists for 8 years after achieving a stable viral response. Moreover, 80% of these patients with persisted cryoglobulinemia have its clinical manifestations during this time[77]. The high

incidence of cryoglobulinemia in chronic hepatitis C can be explained by the fact that HCV can replicate in lymphocytes, protecting them from apoptosis and resulting in polyclonal proliferation, including clones that produce cryoglobulins[78].

Anti-HCV antibodies are detected in 92%-95% of patients with mixed cryoglobulinemia, and HCV RNA in 90%[61,63].

Arthritis in HCV infection develops in 5%-10% of cases[79]: Symmetric polyarthritis in 2/3 of cases, and oligo- or monoarthritis in the rest 1/3 of cases. Morning stiffness for more than 1 h occurs in 70% of HCV infected patients with arthritis, whereas erosion in the joints and subcutaneous nodules are not observed. Cryoglobulins, RF and ANA are detected in 43%, 60% and 20% of these cases, respectively. The level of complement C3 is reduced in 15% of these patients, and C4 in 30% of these patients. In addition, 86% of them had elevated transaminases. The use of anti-inflammatory or disease-modifying drugs is not effective[80], but the use of direct-acting antivirals (DAA) drugs is the most promising[81]. This arthritis is very similar to rheumatoid arthritis, and anti-CCP (unlike RF) should be used to differentiate between these diseases[82,83].

Autoantibodies are detected in 66% of patients with chronic hepatitis C. These are ANA (20%-32%), anti-LKM-1 (1%-22%), anti-Ro52 (about 15%), anti-SMA (3%-8%), AMA-M2 (approximately 3%), and anti-LC-1 (approximately 1%)[54,84].

Furthermore, 8%-12% of patients with PBC had biomarkers of HCV-infection (anti-HCV antibodies or RNA HCV)[85-87]. Despite the frequent detection of AIH-specific antibodies, it is very rarely diagnosed in HCV-infection[88]. HCV biomarkers are also rarely detected in AIH[89]. However, AIH was successfully treated with DAA in a patient with concomitant HCV infection[90].

Antibodies against HCV are detected in 40% of patients with glomerulonephritis[91]. Occult HCV infection (presence of HCV RNA by an ultrasensitive method in the absence of antibodies against HCV) is detected in 40% of the rest part of these patients: in 40% with membranous glomerulonephritis, 30% with membranoproliferative glomerulonephritis, 50% with IgA nephropathy, 30% with idiopathic nephrotic syndrome (including minimal change disease, focal segmental glomerulosclerosis, and IgM nephropathy), 50% with lupus nephropathy, and 40% with anti-neutrophil cytoplasmic antibody (ANCA) positive glomerulonephritis and 4% in the control group (hereditary glomerular nephropathy)[92]. The most common form of HCV-nephropathy is membranoproliferative glomerulonephritis, followed by focal segmental glomerulosclerosis, mesangioproliferative, and membranous glomerulonephritis[91]. Anti-HCV is detected in 98% of cases of glomerulonephritis with mixed cryoglobulinemia and in 2% glomerulonephritis without cryoglobulinemia[93]. Autopsies of patients with hepatitis C revealed glomerulopathies: Mesangioproliferative glomerulonephritis (18%), membranoproliferative glomerulonephritis (11%), membranous glomerulonephritis (3%), and mesangial expansion without hypercellularity (23%). No glomerular pathology was observed in 45% of autopsies in hepatitis C[94].

The HCV antigen is detected in the glomeruli in almost 30% glomerulonephritis with antibodies against HCV in the blood and in almost 60% in glomerulonephritis with HCV RNA in the blood[95].

Extrarenal manifestations of HCV-glomerulopathy were absent in 80% of patients even though 54% had cryoglobulinemia. Electron microscopy revealed virus-like particles in 50% of renal biopsies[91].

There are publications showing the effectiveness of DAA in the treatment of HCV-nephropathy[96-98].

Among rheumatologic diseases in patients with HCV infection, Sjogren's syndrome is most often detected (almost 50% of cases) followed by rheumatoid arthritis (15%), systemic lupus erythematosus (11%), PAN (8%), antiphospholipid syndrome (6%), inflammatory myopathies (4%), systemic sclerosis (1%). The rest of rheumatic diseases, including HSP, accounted for less than 1%[99]. A meta-analysis showed that in patients with HCV infection, cryoglobulinemia [30% *vs* 2%, odd ratio (OR) is 11.5], CGV (5%), Sjogren's syndrome (12% *vs* 0.7%, odd ratio is 2.3) and arthritis (1% *vs* 0.1%, OR is 2.4) are significantly more often detected than in the general population[100]. Raynaud phenomenon was found in 8% of patients with HCV[101].

Vasculitis associated with HCV-infection are CGV in approximately 80% of cases and PAN in approximately 20% of cases[102]. Other vasculitis, including HSP, are rare[99].

Among patients with PAN, antibodies against HCV were detected in 20%, and HCV RNA in 5%[103]. PAN was diagnosed on average 2 years after the diagnosis of HCV infection. These patients had purpura (68%), livedo reticularis (20%-60%), arthralgia (61%), weight loss (60%), multiplex mononeuritis (70%), myalgias or weakness (58%),

altered arteriography (49%), hypertension (37%-55%), abdominal pain (30%), raised creatinine (26%), fever (20%), polyneuropathy (16%), proteinuria (16%), hematuria (16%), intestinal bleeding (16%), diarrhea (13%), orchitis (0%-7%)[99,102].

CGV was also diagnosed on average 2 years after the diagnosis of HCV infection. The most common manifestations of HCV-associated CGV are purpura (67%), polyneuropathy (65%), arthralgia (50%), proteinuria (30%), hematuria (22%), and arterial hypertension (22%). Myalgia (9%), multiplex mononeuritis (9%), livedo reticularis (3%), weight loss (4%), and abdominal pain (1.5%) are less common. Fever, intestinal bleeding, diarrhea, and orchitis are usually absent[102].

The differential diagnoses of vasculitis in HCV infection are presented in Table 3.

Rituximab allows to achieve remission in HCV-associated CGV in 87% of cases[104]. The effectiveness of DAA in the treatment of CGV in HCV-infection is under study. Experts currently recommend DAAs as first line treatment for mild to moderate CGV and rituximab with or without apheresis for severe cases[105].

Patients with HCV-associated Sjogren's syndrome present with xerophthalmia (97%), xerostomia (97%), positive Schirmer test (98%), altered salivary flow (81%), ANA (68%), RF (53%), and anti-Ro/La (25%)[99].

Very few cases of uveitis in HCV-infection were noted[106].

## HEPATITIS E

Hepatitis E, as a rule, is an acute infection but it can become chronic in persons with immunodeficiency[107].

Joint or/and muscle pain without arthritis and myositis is present in approximately 60% of patients with acute hepatitis E[108]. Arthralgias were observed in 5% of patients with chronic hepatitis E[109].

Two cases of arthritis development in acute hepatitis E have been described (Table 4)[110,111].

ANA were found in 9% of patients with acute hepatitis E and in 24% of patients with chronic hepatitis E. Cryoglobulins were found in 7% and 27%, respectively. Cryoglobulinemia persisted for a median of 4 mo (range 3–15 mo). Patients with cryoglobulins had higher levels of creatinine, IgM, and HEV RNA in the blood. There were no clinical manifestations of cryoglobulinemia in all patients in this study except for a patient with neuralgic amyotrophy[112]. In another study, ANA was detected in 37% of patients with acute hepatitis E, and anti-SMA test was positive in 23% of them. These antibodies remained in the blood for more than 1 year in 37% of these cases. Moreover, no patients developed AIH during this follow-up period[113]. Similar results were published in the third study[114]. Seroprevalence of HEV in patients with AIH did not differ from that of the general population[115,116]. Another study showed that antibodies against HEV were detected slightly more often in AIH than the average for the population, but the detection rate was significantly lower than in the previous study[117]. In general, the relationship between HEV and AIH remains unclear.

Antibodies against HEV were not found in any of the 25 patients with PBC; thus, the relationship between these diseases is extremely unlikely[118].

ANCA was positive in 15% of patients with acute hepatitis E[114].

Most cases of glomerulonephritis and manifested cryoglobulinemia in hepatitis E have been described after transplantation[119,120]. Therefore, the exact cause of their development is unclear: HEV infection, the consequences of transplantation, or their combination. In any case, testing for HEV biomarkers should be performed in these patients. A cure for cryoglobulinemic membranoproliferative glomerulonephritis has been described in such a patient after treatment with ribavirin[121].

Thus far, only one case of HEV-associated cryoglobulinemic membranoproliferative glomerulonephritis in a non-transplanted person has been published. The condition appeared a month after the onset of acute hepatitis E. The activity of the inflammatory process in the liver remained elevated. This patient had RF in the blood and was successfully treated with plasmapheresis and pulse glucocorticoids[122].

The only case of HSP triggered by acute hepatitis E virus infection has been described[123].

There are no published studies on the frequency of detection of HEV biomarkers in patients with uveitis or PAN.

**Table 3 Differential diagnosis of vasculitis in hepatitis C viruses-infection (modification from[102])**

	Cryoglobulinemic vasculitis	Polyarteritis nodosa
Weight loss	+/-	+++
Fever	-	++
Myalgia	+	++
Polyneuropathy	+++	++
Mononeuritis multiplex	+	+++
Livedo	+/-	++
Arterial hypertension	++	+++
Orchitis	-	+
Abdominal pain	+/-	++
Diarrhea	-	+
Intestinal bleeding	-	+
Microaneurysms or stenosis	-	+++
C-reactive protein level	Normal	↑

**Table 4 Cases of arthritis in hepatitis E**

Case	Al-Shukri <i>et al</i> [110]	Serratrice <i>et al</i> [111]
Age	52	51
Sex	Female	Female
Joints	Shoulders, elbows, hips, knees, ankles, left second and third metacarpophalangeal	Ankles and knees followed by the wrists and fingers
Duration of arthritis	No data	3 mo
Rash	Maculopapular, non-itchy rash all over her body	No
Fever	No	No
Jaundice	No	No
Pruritus	No	No
Other symptoms and signs	Retroorbital pain, eye discharge, headache, and loss of appetite	No
Rheumatoid factor	No	No
Antinuclear antibodies	No	No
White blood cells, 10 <sup>9</sup> /L	Normal	2.8
Erythrocyte sedimentation rate, mm/h	35	24
C-reactive protein, mg/L	25	3
Transaminases	↑	↑
Complement	C3 - ↑; C4 -Normal	No data
Treatment	No data	No specific treatment

## CONCLUSION

There is a wide array of extrahepatic manifestations potentially associated with hepatitis viruses. These viruses can lead to the development of various immunological disorders (the formation of autoantibodies and cryoglobulins), which can manifest as glomerulonephritis, arthritis, uveitis, vasculitis, and other rheumatologic disorders. In addition, it is quite possible that this infection could be a trigger for the subsequent development of AIH and PBC.

**Table 5 A summary of the main immunological and rheumatologic manifestation in viral hepatitis**

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis E
Rheumatoid factor	Only 2 cases	Approximately 12% of patients	15% of patients	1 case in a patient without transplant
Antinuclear antibodies	In a case of lupus-like reaction and some cases of AIH triggered by HAV infection	Approximately 25% of patients	20%-30% of patients	9%-37% (acute) and 24% (chronic) of patients
Cryoglobulins	95% of patients in 1 study	2% of patients	65% of patients	7% (acute) and 27% (chronic) of patients
Arthralgia	10%-20% of patients	3% of patients	42% of patients	Approximately 60% of patients
Arthritis	Only in patients with vasculitis (7 cases)	About a quarter of patients with pain in joints	5%-10% of patients	2 cases
GN	4 cases of mesangio-proliferative GN	3% of GN: membranous GN (40%); membrano-proliferative GN (20%); focal segmental glomerulo-sclerosis (20%); mesangio-proliferative GN (10%), others (10%)	Approximately 50% of GN: membranous GN (5%); membrano-proliferative GN (55%); focal segmental glomerulo-sclerosis (25%); mesangio-proliferative GN (20%), others (5%)	1 case of membrano-proliferative GN; some cases of GN after transplantation
Henoch-Schonlein purpura	7 cases	Some cases	Some cases	1 case
CGV	4 cases	10% of non-HCV CGV cases	90%-95% of CGV cases	Some cases
PAN	No cases	35% of PAN cases	20% of PAN cases	No cases
Uveitis	Some cases	2% of patients	Some cases	No cases
AIH	11 cases	55% of AIH cases	Very rare	No cases
PBC	1 case of overlap syndrome	40% of PBC cases	Approximately 10% of PBC cases	No cases

AIH: Autoimmune hepatitis; CGV: Cryoglobulinemic vasculitis; GN: Glomerulonephritis; HCV: Hepatitis C viruses; PAN: Polyarteritis nodosa; PBC: Primary biliary cholangitis.

The relationship between autoimmune liver diseases and hepatotropic virus infection is very interesting, especially when treated with antiviral drugs. A further study of this field would be useful to test for biomarkers of hepatotropic viruses in these diseases and to analyze the results of their treatment with antiviral drugs.

In addition to the manifestations described above, immunological disorders due to infection with hepatotropic viruses can lead to the development of many other autoimmune diseases (autoimmune thyroiditis, thrombocytopenia, hemolytic anemia, diabetes mellitus, pulmonary fibrosis, and others), the consideration of which is beyond the scope of this review.

These associations are best shown for chronic viral hepatitis B and C. Only isolated cases of these are described for hepatitis A. These links are least studied, and often controversial for hepatitis E, possibly due to its relatively rare diagnoses.

We have summarized the data presented in the review in [Table 5](#).

To date, few studies have been published on the effectiveness of modern DAA in the treatment of patients with rheumatologic and autoimmune manifestations of hepatotropic virus infection, which represents a large field for future research.

Nevertheless, patients with uveitis, glomerulonephritis, arthritis, vasculitis, autoimmune liver diseases should be tested for biomarkers of viral hepatitis, and if these infections are present, they should be treated.

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