

# Extrahepatic Conditions Related to HCV infection

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Module 2: [Evaluation, Staging, and Monitoring of Chronic Hepatitis C](#)  
Lesson 7: [Extrahepatic Conditions Related to HCV infection](#)

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## Overview of Extrahepatic Manifestations

### Background and Prevalence

Although hepatitis C virus (HCV) infection primarily affects the liver, other organ systems can become involved, which may result in a variety of clinical complications, including cryoglobulinemia, renal disease, dermatologic disorders, diabetes, and lymphomas ([Figure 1](#)).[\[1,2,3,4,5\]](#) The HCV-associated extrahepatic manifestations can have a major impact on morbidity, mortality, and medical costs.[\[6,7,8,9\]](#) The percentage of persons with chronic HCV infection who develop some extrahepatic manifestation remains poorly defined. Nevertheless, some experts have estimated that approximately 40 to 70% of persons with HCV will develop at least one extrahepatic manifestation at some point.[\[10\]](#)

### Need for Recognition

It is extremely important that clinicians consider the potential for HCV to cause extrahepatic manifestations in persons with chronic HCV infection ([Figure 2](#)). It is unclear how well clinicians recognize, diagnose, and treat such extrahepatic conditions, especially since many individuals with HCV infection may not have obvious manifestations of chronic liver disease and often have undiagnosed HCV infection. An awareness of the range of potential extrahepatic manifestations could facilitate earlier diagnosis and more appropriate and timely treatment of these disorders.

### Quality of Evidence

Most of the literature on HCV-related extrahepatic manifestations consists of observational studies that have shown an association between a specific extrahepatic condition and the presence of HCV antibody and/or detection of HCV RNA. Most of these studies are prone to selection bias. A few studies have used large datasets, such as the Veterans Administration medical database, and these studies are most useful when the extrahepatic condition in question can be easily defined and the data is easily accessible (e.g. renal disease as determined by a creatinine level or glomerular filtration rate [GFR]).[\[11,12,13\]](#) For extrahepatic conditions that require a clinical diagnosis, such as lichen planus, identifying the specific condition is much more difficult when utilizing larger datasets.[\[14,15\]](#) Thus, it is important to keep in mind the original source and type of data when estimating prevalence of these extrahepatic conditions and considering the need for screening.

### Relevance to Initiating DAA Therapy

Extrahepatic manifestations of HCV are usually considered by health insurance plans to be a justification for coverage of direct-acting antiviral (DAA) therapy. It is extremely important to realize that the existence of any

of the extrahepatic HCV conditions described in this lesson usually makes the need for DAA treatment of HCV considered urgent. Although both public plans and commercial policies regarding approval for HCV treatment are constantly changing, these payers typically cover DAA therapies when any extrahepatic manifestation exists, despite level of hepatic fibrosis.

# Cryoglobulinemia

## Definition of Cryoglobulinemia

Cryoglobulinemia refers to the presence of one (monoclonal) or more (mixed or polyclonal) blood proteins in the serum, which reversibly precipitate *in vitro* at temperatures below normal body temperature (less than 37°C).[16] The blood proteins that precipitate are referred to as cryoglobulins, and they dissolve again when reheating the serum. Cryoglobulins are composed of either pure immunoglobulins or a mixture of immunoglobulins and complement.[16]

## Mechanism of Disease

In HCV-related mixed cryoglobulinemia, end-organ disease is caused by an immune-mediated mechanism.[16] Specifically, immune complexes that contain HCV particles deposit in the walls of capillaries, venules, or arterioles, leading to endothelial activation, stimulation of chemotactic peptides, and an inflammatory response; the end result is leukocytoclastic vasculitis.[17,18] Among persons who develop cryoglobulinemia, HCV antigens drive chronic stimulation of B-lymphocytes, which is thought to induce B-cell clonal expansion and production of antibodies, with the potential for development of a B-cell non-Hodgkin's lymphoma.[17]

## Clinical Manifestations Associated with Cryoglobulinemia

Most persons with chronic HCV infection and cryoglobulinemia have either no symptoms or nonspecific clinical manifestations. A triad of purpura, myalgia, and arthralgia (Meltzer's triad) is the most common presentation in persons with HCV-related mixed cryoglobulinemia.[16,19] Approximately 30% of persons with mixed cryoglobulinemia develop renal disease.[19] Additional clinical features that may develop with mixed cryoglobulinemia include peripheral neuropathy, skin ulcers, and lymphoproliferative disorders.[20] A variety of clinical syndromes can be associated with cryoglobulinemia. The most common manifestations of HCV-associated mixed cryoglobulinemia are shown in the following list:[16,18,19]

- Palpable purpura
- Chronic leg ulcers
- Arthralgias
- Weakness
- Myalgias
- Renal disease
- Peripheral neuropathy

## Classification of Cryoglobulinemia

Cryoglobulinemia is classically grouped into three types according to the 1974 Brouet classification system; note that type I is considered monoclonal cryoglobulinemia and types II and III are classified as mixed cryoglobulinemia.[16,21]

- **Type I Cryoglobulinemia:** This disorder consists of isolated monoclonal immunoglobulin (IgM or IgG) and most commonly occurs in association with lymphoproliferative disorders; type I cryoglobulinemia represents only 10 to 15% of cases of cryoglobulinemia.
- **Type II Cryoglobulinemia:** This type of cryoglobulinemia consists of mixed immune complexes, typically monoclonal IgM and polyclonal IgG. This type of cryoglobulinemia most often develops in persons who have chronic viral infections, such as HCV, hepatitis B virus, and cytomegalovirus (CMV), but also occurs in persons with chronic inflammatory states, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome. Type 2 cryoglobulinemia is the most common type of cryoglobulinemia seen in persons with HCV infection. The type 2 cryoglobulins have rheumatoid factor

activity, which means these immunoglobulins bind to the Fc portion of IgG.

- **Type III Cryoglobulinemia:** This disorder consists of mixed immune complexes, typically formed by polyclonal IgM and IgG, and it represents 25 to 30% of cases of cryoglobulinemia.

## Association between HCV and Mixed Cryoglobulinemia

Multiple reports have shown a close association of HCV and mixed cryoglobulinemia, most often type II cryoglobulinemia—more than 90% of persons with mixed cryoglobulinemia have evidence of active HCV infection.[17,22,23] With HCV-related mixed cryoglobulinemia, immune complexes comprised of immunoglobulin and HCV particles precipitate in many organs, including the skin, kidneys, and peripheral nerve fibers.[16,18] Investigators have postulated that expansion of rheumatoid factor activity and cryoprecipitability is responsible for the vasculitis. Most individuals with mixed cryoglobulinemia have evidence of chronic HCV infection: studies have shown from 50 to 100% of persons with mixed cryoglobulinemia cases have HCV infection. Accordingly, all persons with a diagnosis of mixed cryoglobulinemia should undergo screening for HCV infection. Conversely, because individuals with HCV infection do not have mixed cryoglobulinemia routine screening of persons with chronic HCV for mixed cryoglobulinemia is not recommended. Treatment of HCV and achievement of sustained virologic response (SVR) reduces the risk of developing manifestations of mixed cryoglobulinemia.[24]

## Cryoglobulinemic Vasculitis

The term cryoglobulinemic vasculitis was previously termed essential cryoglobulinemic vasculitis because the cause of this disorder was unknown.[17] The following describes key features of cryoglobulinemic vasculitis.

### Pathophysiology of Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis is considered a systemic small-to-medium vessel vasculitis.[18] In this disorder, damage to the vessels is thought to result from the deposition of immune complexes on the vessel wall followed by subsequent activation of the complement cascade.[17] Only about 10 to 15% of persons with cryoglobulinemia develop cryoglobulinemic vasculitis.[17]

### Manifestations of Cryoglobulinemic Vasculitis

Individuals with chronic HCV infection who develop cryoglobulinemic vasculitis most often have cutaneous manifestations, though any organ may be affected. Palpable purpura is evident in more than 90% of persons with cryoglobulinemic vasculitis, and is usually the first sign of cryoglobulinemia.[17,18] The finding of palpable purpura in a person with chronic HCV should raise an immediate suspicion for cryoglobulinemic vasculitis.

### Diagnosis of Cryoglobulinemic Vasculitis

Specific criteria or classification for cryoglobulinemic vasculitis have not yet been defined.[16] The diagnosis is typically made from the combination of history, skin purpura, low complement levels, presence of cryoglobulins in serum, and histology that shows small vessel inflammation with immune deposits found in the vascular walls.[16]

## Treatment of HCV-related Cryoglobulinemic Vasculitis

The approach to treating HCV-related cryoglobulinemic vasculitis is complex and depends on the severity of the cryoglobulinemia and end-organ involvement. Due to complexity and potential severity of this disorder, treatment should be conducted by or performed in conjunction with a clinician who has expertise in this field. The three components of therapy that may be used in the treatment of HCV-related cryoglobulinemic vasculitis consist of: (1) antiviral therapy for chronic HCV infection, (2) conventional immunosuppressive agents, (3) biologic therapies that function as B-cell deleting monoclonal antibodies, and (4)

plasmapheresis.[16,17,25] In general, the approach to treatment depends on the severity of illness, which can range from mild-to-moderate (usually with only cutaneous involvement), to severe (with end organ involvement), to life-threatening (typically rapidly progressing).[16] The goals of treatment are to provide prompt relief of the active vasculitis and prevent further recurrences of cryoglobulinemic vasculitis. When immunosuppressing agents are being considered for treatment, it is important to screen for other possible viral infections, such as hepatitis B virus (HBV) and HIV, which may require prompt treatment before the initiation of immunosuppressive therapy.

## Treatment Modalities

The following lists treatment modalities often used in treating persons with cryoglobulinemic vasculitis.

- **DAA Therapy for Chronic HCV Infection:** Available data suggest that persons with chronic HCV infection and cryoglobulinemic vasculitis have SVR rates greater than 90% when using with DAA therapy.[25,26,27] Unfortunately, successful treatment of HCV with DAA therapy often does not cause remission of cryoglobulinemic vasculitis, particularly in moderate-to-severe disease.[25,26,27] Thus, DAA therapy for HCV infection in persons with cryoglobulinemic vasculitis should be considered as a component of an overall treatment strategy to successfully manage this severe disorder.
- **Immunosuppressive Agents:** Commonly used immunosuppressive agents include high-dose corticosteroids, cytotoxic agents (e.g. cyclophosphamide), and mycophenolate mofetil.[16] Corticosteroids are used as component of treatment for most persons with moderate-to-severe cryoglobulinemia, with a dose range that correlates with the severity of the disease. The use of cytotoxic agents, such as cyclophosphamide, is generally reserved for life-threatening cases. Mycophenolate mofetil is an immunosuppressive drug that is more selective than cyclophosphamide in inhibiting lymphocyte proliferation and functions. Mycophenolate mofetil has been used as a less toxic alternative to cyclophosphamide, but there are limited data with this approach.[19]
- **B-Cell Depleting Monoclonal Antibody:** B-cell clonal expansion is a key aspect of mixed cryoglobulinemia. Rituximab, an anti-CD20 monoclonal antibody, modifies the dynamics of B cells by deleting expanded clones in persons with moderate-to-severe cryoglobulinemia. In addition, rituximab induced B-cell depletion reduces the number of B-cell clones that produce cryoglobulins.[16,17] This treatment may also provide protection against factors potentially involved in the pathogenesis of malignant B-cell transformation. Multiple studies have shown improved outcomes when rituximab has been used with or without treatment of HCV in persons with cryoglobulinemic vasculitis.[17,25,28] Treatment with rituximab should be administered by an expert (or in consultation with an expert) who has experience with use of rituximab.
- **Plasmapheresis:** Some experts have used plasmapheresis as an adjunct therapy in persons with rapidly progressing or life-threatening cryoglobulinemic vasculitis. The goal of plasmapheresis is to remove the circulating cryoglobulins to provide immediate benefit, but this approach does not alter the long-term progression of the disease.[19]

## Renal Disorders

### Renal Manifestations Associated with HCV Infection

A subset of renal glomerular diseases are strongly associated with HCV infection.[29,30] In addition, individuals with chronic HCV can develop albuminuria without overt renal disease, particularly persons 60 years of age or older.[31,32] The evidence for HCV infection causing renal disease is mainly supported by epidemiologic data.[6,33,34,35,36] When HCV-related glomerulonephritis develops, it typically occurs many years, often decades, after initial infection with HCV. In 2008, the Kidney Disease Improving Global Outcomes group (KDIGO) published clinical guidelines on Hepatitis C and Chronic Kidney Disease and recommended screening for kidney disease in all persons with chronic HCV infection, as well as testing for HCV for those individuals with chronic kidney disease.[37] The KDIGO and other guidelines are uniform in recommending HCV screening in all persons receiving long-term hemodialysis.[37,38,39,40]

### Mechanisms of HCV-Associated Renal Disease

Experts have postulated various potential mechanisms to explain how HCV potentially induces a wide range of renal diseases: (1) direct cytopathic effect of HCV RNA and proteins on renal cells, (2) systemic immune response to HCV mediated by cryoglobulins, HCV-antibody immune complexes, or amyloid deposition, (3) HCV-induced elevation in toll-like-receptor 3 messenger RNA expression and resultant proinflammatory cytokine production within glomeruli, and (4) insulin resistance and hyperinsulinemia have multiple pathways that may lead to a cascade of reactions that have deleterious effects on the kidney.[41]

### Clinical Syndromes of HCV-Related Renal Disease

The most common HCV-related renal disease is membranoproliferative glomerulonephritis associated with type II mixed cryoglobulinemia.[42] Most HCV-related membranoproliferative glomerulonephritis occurs as a result of mixed cryoglobulinemia (cryoglobulinemic membranoproliferative glomerulonephritis, or mononuclear cell-related membranoproliferative glomerulonephritis).[43] Conversely, renal disease occurs in only 30% of persons with cryoglobulinemia. Most individuals with HCV-related membranoproliferative glomerulonephritis develop hypertension, which is often severe and difficult to control. Approximately 5% of persons with HCV-related renal disease will develop glomerular renal disease that manifests as oliguric acute renal failure. Laboratory findings of cryoglobulinemia-associated renal disease include proteinuria, microscopic hematuria (with mild to moderate renal insufficiency), and low serum concentrations of complement components (C1q, C4, and C3). In addition to membranoproliferative glomerulonephritis, other types of HCV-related renal disease (mainly glomerular diseases) also exist, including IgA nephropathy, postinfectious glomerulonephritis, membranous nephropathy, thrombotic microangiopathies, focal and segmental glomerulosclerosis, fibrillary or immunotactoid glomerulopathy, and glomerulonephritis associated with polyarteritis nodosa. These disorders, however, are all less common among persons with chronic HCV than HCV-related membranoproliferative glomerulonephritis.

### Diagnosis of HCV-Related Renal Disease

The diagnosis of HCV-related renal disease is confirmed by renal biopsy. Renal biopsy characteristically shows a pattern of membranoproliferative glomerulonephritis, with immune complex deposition in glomeruli inflammatory cells—both mononuclear cells and polymorphonuclear leukocytes—that infiltrate the glomerular capillaries. Other findings may include mesangial matrix expansion, splitting of capillary basement membranes, and intracapillary globular accumulation of eosinophilic material (representing precipitated immune complexes or cryoglobulins).

### Clinical Outcomes of HCV-Related Renal Disease

A retrospective cohort study involving more than 470,000 adult veterans showed that persons with chronic

HCV infection were more likely to develop end-stage renal disease (4.3 per 1,000 person-years) than HCV-seronegative patients (3.1 per 1,000 person-years).[13] In a subsequent cross-sectional study showed that persons with HCV infection had a 40% higher likelihood for developing renal insufficiency—defined as serum creatinine levels greater than or equal to 1.5 mg/dL—compared with seronegative participants.[11]

## **Treatment of HCV-Related Renal Disease**

The treatment of HCV in persons with renal disease is addressed in detail in this curriculum in the topic review [Treatment of HCV in Persons with Renal Impairment](#). In general, modern DAA regimens are well tolerated, highly effective, and safe in persons with renal disease. The AASLD-IDSA HCV Guidance now recommends that no dose adjustment is required for HCV treatment in persons with renal impairment when the treatment regimen is a recommended DAA regimen; the one exception is that if ribavirin is added to a regimen, a dose adjustment of the ribavirin may be required.[44] The Treatment of HCV infection in persons undergoing renal replacement therapy or who have undergone renal transplantation is highly complicated and should be performed only by a medical provider who has expertise in this area.

## Dermatologic Manifestations

### Leukocytoclastic Vasculitis

Leukocytoclastic vasculitis is a pathological term that describes the microscopic findings of a neutrophilic small vessel vasculitis. Cutaneous leukocytoclastic vasculitis is a clinical term that describes leukocytoclastic vasculitis limited to the skin.

- **Clinical Manifestations:** The cutaneous manifestations of leukocytoclastic vasculitis include petechiae, palpable purpura, nodules, ulcers, and other findings. These cutaneous manifestations usually involve the lower extremities. Clinical features of leukocytoclastic vasculitis can resemble multiple other disorders and biopsy is necessary to confirm the diagnosis. In this setting, some individuals also develop peripheral neuropathy, and it may be asymmetric. Leukocytoclastic vasculitis may occur with cryoglobulinemia.
- **Diagnosis:** Histopathologic features of leukocytoclastic vasculitis include fibrinoid necrosis and a neutrophilic infiltrate invading or damaging the dermal blood vessel wall. Other tissues, such as lower extremity peripheral nerves, may show similar vasculitic changes involving the vasa nervorum.
- **Treatment:** Similar to the treatment of mixed cryoglobulinemia, the treatment of leukocytoclastic vasculitis may include HCV therapy.

### Porphyria Cutanea Tarda

The dermatologic disorder porphyria cutanea tarda is the most common of the porphyrias, a group of disorders of heme synthesis. Both acquired factors and genetic factors typically play a role in the pathogenesis of porphyria cutanea tarda by reducing activity of the uroporphyrinogen decarboxylase enzyme.[\[45\]](#) Chronic HCV infection is one of the most commonly acquired factors associated with porphyria cutanea tarda—the reported prevalence of HCV infection in persons with porphyria cutanea tarda is approximately 50 to 60%.[\[46,47,48\]](#) The mechanism whereby chronic HCV infection increases the risk of porphyria cutanea tarda remains unknown.

- **Clinical Manifestations:** Porphyria cutanea tarda typically manifests as skin fragility, bruising, and blistering, which may become hemorrhagic in sun-exposed areas, particularly on the back of the hands.[\[45,47\]](#) Over time, hyperpigmentation, depigmentation, and a sclerodermoid appearance can develop, along with facial hirsutism.[\[49\]](#)
- **Diagnosis:** A preliminary diagnosis of porphyria cutanea tarda is usually made based on characteristic clinical manifestations in conjunction with an elevated plasma, serum, or urine porphyrin levels.[\[45\]](#) Persons with porphyria cutanea tarda should have studies performed that can detect the presence of iron overload, as well as testing for genetic mutations in the HFE (hemochromatosis) gene.
- **Treatment:** The mainstay of treatment consists of avoiding sunlight, avoiding alcohol, stopping any iron supplementation, stopping estrogen supplementation, and undergoing regular therapeutic phlebotomy (ranging from twice a week to every week), which reduces iron stores, improves heme synthesis, and effectively controls symptoms.[\[47\]](#) Individuals who cannot tolerate phlebotomy or who are anemic can take an oral iron chelator.[\[45\]](#) Low-dose oral chloroquine (125 mg twice weekly) or hydroxychloroquine (100 mg twice weekly) is an alternative to phlebotomy, but treatment with chloroquine or hydroxychloroquine requires monitoring for retinal damage, and it should be used with caution in persons with renal disease or cirrhosis.[\[50,51\]](#) There are case reports and small series describing improvement in porphyria cutanea tarda following successful treatment of HCV with DAA therapy.[\[52,53,54\]](#)

### Lichen Planus

The cutaneous disorder lichen planus results from an immunologically mediated reaction involving CD8-T-



lymphocytes to an unknown stimulus.[47,55] Several meta-analyses have shown that persons with lichen planus have about a 5 times higher risk of having chronic HCV infection compared with controls; other studies estimate that approximately 10 to 25% of persons with lichen planus have evidence of HCV infection.[14,15]

- **Clinical Manifestations:** Lichen planus lesions are flat-topped, polygonal, purple, pruritic papules, most often seen on the flexor surfaces of the extremities.[49] Lichen planus can also involve the face, oral cavity, gastrointestinal tract, scalp, or genital area hair, and nails.[2,56]
- **Diagnosis:** The biopsy findings typically show dense lymphocytic infiltration in the upper dermis, often referred to as an irregular sawtooth appearance that suggests epidermal hyperplasia.[47]
- **Treatment:** In most persons with lichen planus, the lesions spontaneously resolve within a year. Individuals with symptomatic lichen planus may require treatment; most often first-line therapy consists of a high-potency topical corticosteroid.[47,49,55] For persons with extensive or refractory disease, oral corticosteroids are often used.[55] Additional second- or third-line treatments include topical retinoids, systemic retinoids, and phototherapy.[55] In one report, four individuals from Japan with lichen planus had resolution of the skin lesions after successful treatment of HCV with DAA therapy, but more data are needed to fully understand the impact DAA treatment on lichen planus.[57]

# Insulin Resistance and Type 2 Diabetes

## Prevalence

Several longitudinal and cross-sectional studies have shown that persons with chronic HCV infection have an increased risk of developing type 2 diabetes.[[58,59,60](#)] One meta-analysis quantified this risk as a 1.7-fold increased risk of developing diabetes in persons with chronic HCV infection compared with those not infected with HCV.[[61](#)] Persons with chronic HCV also have an increased risk of developing insulin resistance without diabetes.[[62,63,64](#)]

## Pathogenesis

Several potential mechanisms have been considered to explain the association between HCV and insulin resistance, including HCV induced fibrosis and cirrhosis, HCV direct viral effect on inflammatory cytokines, and the combined effects of obesity and HCV infection altering the insulin signaling cascade.[[65,66](#)]

## Clinical Consequences

The development of insulin resistance and type 2 diabetes has significant negative consequences for persons with chronic hepatitis C infection. Available data suggest that insulin resistance accelerates hepatic fibrogenesis and this effect may be more pronounced with HCV genotypes 1 and 4.[[60,63,67](#)] Diabetes mellitus is also a major risk factor for non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). For persons with HCV and co-existing NAFLD or NASH, it is thought that fibrosis progression is more rapid and more likely to become advanced. Therefore, the clinical consequence of DM in persons with HCV may include more advanced liver disease if the diabetes mellitus is not well controlled

## Management

The management of type 2 diabetes mellitus in persons with chronic HCV is multifactorial and includes treatment of HCV, weight loss (if needed), and pharmacologic therapy for diabetes.[[68,69](#)] One study with interferon-based therapy has shown a decrease in onset of type 2 diabetes mellitus in persons with chronic HCV following SVR, whereas others have not shown an impact of SVR on diabetes.[[70,71,72](#)] One study with DAA therapy showed no significant impact following SVR on hemoglobin A1c levels.[[71](#)] Most experts consider weight reduction and exercise as key elements in the management of persons with HCV and type 2 diabetes. In a study that examined a 3-month program of weight reduction and increased physical activity in 19 persons with chronic hepatitis C infection and steatosis, the authors reported progressive decreases in serum alanine aminotransferase and mean fasting insulin levels.[[73](#)] Chronic HCV infection is not considered a contraindication for the use of biguanides or thiazolidinediones for the treatment of type 2 diabetes.

## Lymphomas

### Relationship of HCV and Lymphomas

Chronic HCV infection has been associated with an increased risk of developing B-cell non-Hodgkin lymphoma (including diffuse large B-cell lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma, splenic lymphoma with villous lymphocytes, and extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue) as well as primary hepatic lymphoma.[74,75] There is a particularly strong association of HCV with B-cell non-Hodgkin lymphoma, with epidemiologic studies involving persons with chronic HCV showing a two-fold increased risk of developing non-Hodgkin lymphoma; this relative risk increases to approximately 35-fold in persons with symptomatic HCV-associated mixed cryoglobulinemia.[74,75,76,77] Roughly 5 to 10% of individuals with HCV-associated mixed cryoglobulinemia will develop non-Hodgkin lymphoma.[78] Among persons with B-cell non-Hodgkin lymphoma, the HCV prevalence is approximately 15%.[79] The increased risk of developing non-Hodgkin lymphoma is reduced, but not eliminated after eradication of HCV. One study examined 3,209 persons with HCV and the overall annual incidence of lymphoma was significantly lower in HCV-treated persons who achieved an SVR when compared with those who had persistent HCV infection (hazard ratio 0.13).[80]

### Pathogenesis

The exact mechanism that would explain the genesis of B-cell lymphomas in persons with chronic HCV infection remains unclear, but three major potential mechanisms have been proposed:[75,81]

- **Chronic Antigen Stimulation:** In this model, HCV antigens continuously stimulate external B-cell lymphocyte receptors (CD19, CD21, CD81) and this leads to upregulation of intracellular oncogenic signals and downregulation of tumor suppressive signals, with the end result being enhanced B-cell proliferation. Alternatively, the chronic HCV antigen production may upregulate expression of immunoglobulin variable genes.
- **Direct Transfer by Viral Proteins:** The replication of HCV within B-lymphocytes produces a number of HCV proteins that can lead to induction of oncogenic signals and thereby cause transforming oncogenic effects. The HCV core and NS3 proteins have the strongest association with this transformation process.
- **"Hit and Run" Theory:** In this model, HCV transiently infects B-lymphocytes and during this process the virus can cause double strand DNA breaks that induce cytidine deaminase and error-prone polymerases. These changes may involve mutations in tumor suppressor genes, including p53, BCL-6, and beta-catenin.

### Treatment and Prognosis

Treatment of any patient with an HCV-related lymphoma should involve a hematologist-oncologist who has significant experience in managing lymphomas and a medical provider who has expertise in managing and treating HCV infection. The approach to treatment of HCV-associated B-cell lymphomas highly depends on whether the tumor is an indolent (low-grade) or more aggressive tumor, as well as the B-cell tumor subtype.[75,82,83]

#### Indolent B-Cell Lymphoma

Multiple reports and studies in persons with HCV-associated B-cell non-Hodgkin lymphoma have shown that successful HCV treatment can cause regression of low-grade lymphomas.[84,85,86,87,88,89] In these individuals, some experts now recommend initiating HCV treatment with direct-acting antiviral therapy if there is no immediate need for chemotherapy, with very close follow-up.[83,90]

#### Aggressive B-Cell Lymphomas

Treatment of aggressive B-cell lymphoma with chemotherapy in persons with chronic HCV infection (with ongoing viremia) is associated with increased rates of hepatotoxicity when compared with persons who do not have active HCV infection; results are mixed on whether HCV impacts the prognosis and survival of persons who undergo chemotherapy for B-cell lymphomas.[[91,92,93](#)] In persons with newly detected active HCV at the time of diagnosis of the B-cell lymphoma, available data suggest that simultaneous treatment of HCV during chemotherapy improves rates of lymphoma response.[[84,94,95,96](#)] These studies have mainly involved interferon-based HCV treatment, but it is reasonable to expect the same benefit, with less toxicity, using interferon-free direct-acting antiviral therapy.[[94](#)] Most chemotherapy regimens used to treat HCV-associated B-cell lymphomas include rituximab in the overall multi-drug chemotherapy regimen.[[84,90,92](#)]

## Autoimmune Disorders

### Asymptomatic Autoantibodies

Chronic HCV has been associated with a number of autoantibodies, the most common of which include antinuclear antibodies, rheumatoid factor, anticardiolipin antibodies, smooth muscle antibodies, and antithyroid antibodies.[[97,98,99,100](#)] In two studies, the prevalence of antinuclear antibodies and rheumatoid factor has ranged from 14 to 41% and 38 to 76%, respectively.[[98,99](#)] Many of these antibodies are not associated with extrahepatic disease, but their presence may lead to diagnostic dilemmas.

### Autoimmune Hepatitis

In contrast to the multitude of largely asymptomatic autoantibodies found in persons with chronic HCV, anti-LKM-1 antibodies may be associated with autoimmune hepatitis in persons with chronic HCV.[[101,102](#)] If a person with chronic HCV has positive anti-LKM-1 antibodies, it can be challenging to determine the primary cause of liver injury, but DAA treatment for HCV is recommended regardless. It is not routinely recommended that clinicians screen for antibodies associated with autoimmune hepatitis, unless there is a specific reason to do so, such as persistently elevated aminotransferase levels of unclear etiology following successful HCV treatment.

### Thyroid Disease

Thyroid disease occurs in an estimated 2 to 13% of persons with chronic HCV.[[103,104](#)] In a study of 630 participants with chronic HCV and no cirrhosis, investigators found that 17% had anti-thyroglobulin antibodies, and 21% had anti-thyroid peroxidase antibodies.[[103](#)] The proportion of HCV-positive patients with hypothyroidism in this study was 13%, and serum thyroid stimulating hormone (TSH) levels were significantly higher in those with chronic HCV when compared to control arms from both iodine deficient and sufficient areas.[[103](#)]

### Sjogren's Syndrome

Several studies suggest an association between HCV infection and Sjogren's syndrome.[[105,106](#)] In a meta-analysis evaluating the frequency of extrahepatic manifestations of HCV, authors found that the pooled prevalence of Sjogren's syndrome, across 11 studies, was 11.9% among HCV-positive individuals, in comparison to 0.7% among HCV-negative controls.[[6](#)] Similarly, in a multicenter registry of patients with chronic HCV and systemic autoimmune diseases, Sjogren's syndrome was the most frequently reported (47.5%) systemic autoimmune disease (47.5%).[[100](#)]

## Cardiovascular Events

### Association Between HCV and Cardiovascular Events

Multiple retrospective and observational studies have shown an association between HCV infection and cardiovascular disease (and cerebrovascular events), with the highest risk occurring among those who are HCV RNA positive.[[5](#),[107](#),[108](#),[109](#)] The following summarizes three key studies that support an association of HCV and increased cardiovascular disease risk.

- In a retrospective cohort study, investigators compared cardiovascular events in 8,251 HCV antibody-positive, 1,434 HCV RNA-positive, and 14,799 HCV-negative persons.[[109](#)] Individuals who were HCV seropositive had a higher incidence of cardiovascular events, including coronary artery disease, chronic stable angina, unstable angina, or acute myocardial infarction, when compared to HCV-negative persons (4.9% vs. 3.2%, P

## Summary Points

- Chronic HCV infection is associated with a broad range of clinical conditions other than liver disease. The quality of the evidence for these extrahepatic associations is variable.
- Manifestations of HCV are thought to include (but are not limited to) cryoglobulinemic vasculitis, renal disease with or without cryoglobulinemia, skin disorders including cutaneous leukocytoclastic vasculitis and porphyria cutanea tarda, diabetes mellitus and metabolic syndrome, lymphomas, and autoimmune conditions.
- Successful treatment of HCV appears to: (1) have benefit on some extrahepatic conditions, such as cryoglobulinemic vasculitis and renal disease, and (2) reduce the risk of some extrahepatic manifestations, such as lymphoma and diabetes.
- Clinicians should have an awareness of the potential for these conditions among persons with HCV infection, and clinicians should consider HCV as a potential etiology of these conditions in persons with unknown HCV infection status.
- For persons with chronic HCV infection, the development of an extrahepatic HCV-related manifestation is typically considered as an urgent indication for HCV treatment.
- Payers (public and commercial) usually consider extrahepatic manifestations of HCV as reason to authorize coverage of DAAs.

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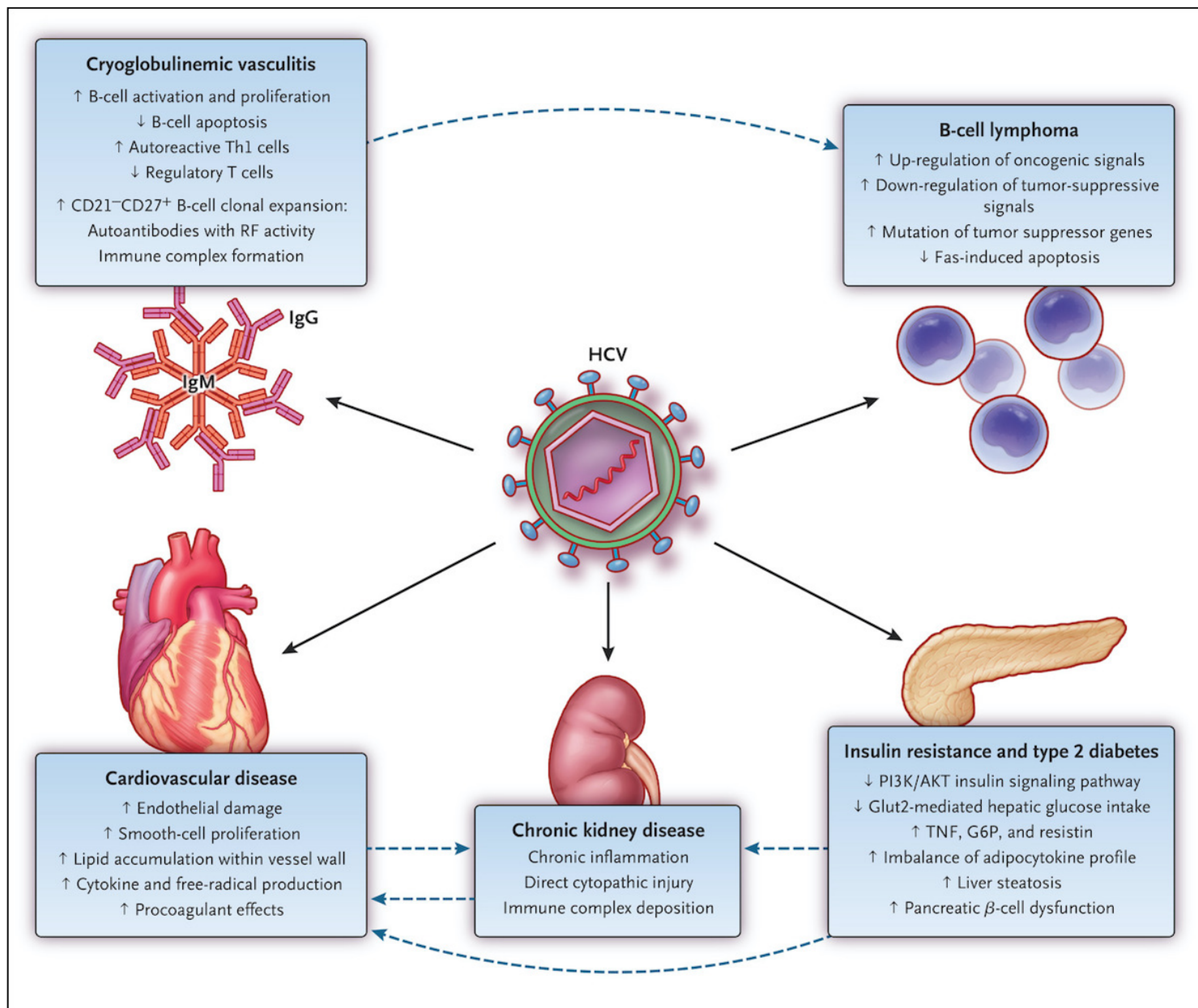
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## Figures

**Figure 1 Major Pathophysiological Mechanisms Implicated in Extrahepatic Manifestations of HCV Infection.**

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**Figure 2 Hepatitis C-Related Extrahepatic Manifestations**

Patients with hepatitis C-related extrahepatic manifestations can develop an array of symptoms and clinical manifestations.

<b>Hepatitis C-Related Extrahepatic Manifestations</b>	
<b>Symptom/Manifestation</b>	<b>Potential HCV-Related Syndrome</b>
Hypertension	Membranoproliferative glomerulonephritis Nephropathy Cryoglobulinemia
Skin disease	Lichen planus Porphyria cutanea tarda Leukocytoclastic vasculitis Cryoglobulinemia vasculitis
Purpura	Cryoglobulinemic vasculitis Leukocytoclastic vasculitis
Distal neuropathic pain	Membranoproliferative glomerulonephritis without cryoglobulin Cryoglobulinemia-Membranoproliferative glomerulonephritis
Renal insufficiency Hematuria	Membranoproliferative glomerulonephritis without cryoglobulin Cryoglobulinemia-Membranoproliferative glomerulonephritis
Lymphadenopathy	Lymphoproliferative disorder
Fever	Cryoglobulinemia Cryoglobulinemic vasculitis Lymphoproliferative disorder
Arthralgia, weakness	Cryoglobulinemia Lymphoma Cryoglobulinemic vasculitis