It is critical to recognize that hepatitis C virus (HCV) infection is, in fact, a multifaceted systemic disease with both hepatic and extrahepatic complications. It is also important to recognize that the comprehensive burden of HCV should include not only its clinical burden but also its burden on the economic and patient-reported outcomes. It is only through this comprehensive approach to HCV infection that we can fully appreciate its true burden and understand the full benefit of curing HCV for the patient and the society.

Hepatitis C virus (HCV) infection is associated with a morbidity and mortality due to liver complications. HCV infection is also frequently associated with rheumatic disorders, such as arthralgia, myalgia, cryoglobulinemia vasculitis, and sicca syndrome, as well as the production of autoantibodies. The treatment of HCV infection with interferon alpha (IFN) has been contraindicated for a long time in many rheumatologic autoimmune/inflammatory disorders. New oral IFN-free combinations offer an opportunity for HCV-infected patients with extrahepatic manifestations, including rheumatologic autoimmune/inflammatory disorders, to be cured with a short treatment duration and a low risk of side effects.

Hepatitis C virus (HCV) infection is a prevalent condition associated with numerous extrahepatic manifestations. Epidemiologic studies have found that HCV is associated with increased cardiovascular morbidity and mortality, in particular with carotid atherosclerosis, cerebrovascular events, and coronary heart disease. The mechanisms involved encompass a chronic systemic inflammatory state, insulin resistance, and a potential, direct infection of the vascular endothelium. Sustained virologic response with interferon-based regimens is associated with reduced cardiovascular events, although this must be validated with newer direct-acting antivirals. This clear association between HCV and cardiovascular events may have significant economical and public health implications.
Metabolic Manifestations of Hepatitis C Virus: Diabetes Mellitus, Dyslipidemia 475
Lawrence Serfaty

Metabolic disorders are common in patients with chronic hepatitis C virus (HCV) infection. Epidemiologic and clinical data indicate an overprevalence of lipids abnormalities, steatosis, insuline resistance (IR) and diabetes mellitus in HCV patients, suggesting that HCV itself may interact with glucido-lipidic metabolism. HCV interacts with the host lipid metabolism by several mechanisms leading to hepatic steatosis and hypolipidemia which are reversible after viral eradication. Liver and peripheral IR are HCV genotype/viral load dependent and improved after viral eradication. This article examines the relationship between HCV, lipid abnormalities, steatosis, IR, and diabetes and the pathogenic mechanisms accounting for these events in HCV-infected patients.

Renal Manifestations of Hepatitis C Virus 487
Clodoveo Ferri, Dilia Giuggioli, and Michele Colaci

Hepatitis C virus (HCV) is a hepatotropic and lymphotropic virus responsible for hepatic and extrahepatic autoimmune and neoplastic disorders, including renal involvement, which is the consequence of immune-mediated organ damage due to glomerular deposition of immune-complex and/or anti-HCV IgG antibodies and complement. It can appear at any time during the natural history of HCV infection, more often as membranoproliferative glomerulonephritis, alone or in association with other HCV-related disorders. The presence of renal involvement should be investigated in HCV-infected individuals at the first referral and during clinical follow-up.

Hepatitis C Virus–Associated Non-Hodgkin Lymphomas: Biology, Epidemiology, and Treatment 499
Gabriele Pozzato, Cesare Mazzaro, and Valter Gattei

Eradication of hepatitis C virus (HCV) in indolent non-Hodgkin lymphomas (NHLs), especially in marginal zone lymphomas, determines the regression of the hematologic disorder in a significant fraction of cases. Because direct antiviral agents show an excellent profile in terms of efficacy, safety, and rapid onset of action, these drugs can be used in any clinical situation and in the presence of any comorbidities. To avoid the progression of the NHL, despite HCV eradication, antiviral therapy should be provided as soon as the viral infection is discovered; before that, the chronic antigenic stimulation determines the irreversible proliferation of neoplastic B cells.

Chronic Hepatitis C Virus Infection and Depression 517
Luigi Elio Adinolfi, Riccardo Nevola, Luca Rinaldi, Ciro Romano, and Mauro Giordano

Hepatitis C virus (HCV) infection is a systemic disease with hepatic and extrahepatic manifestations, including neuropsychiatric conditions. Depression is a frequent disorder, which has been reported in one-third of patients with HCV infection and has an estimated prevalence of 1.5 to
4.0 times higher than that observed in patients with chronic hepatitis B virus infection or the general population. HCV seems to play a direct and indirect role in the development of depression. Impaired quality of life and increasing health care costs have been reported for patients with HCV infection with depression. Treatment-induced HCV clearance has been associated with improvement of depression and quality of life.

**Neurologic Manifestations of Hepatitis C Virus Infection**  
Sentia Iriana, Michael P. Curry, and Nezam H. Afdhal

The extrahepatic manifestations of hepatitis C include effects on the central nervous system, which have been associated with the ability of hepatitis C virus (HCV) to replicate in microglial and endothelial cells and the chronic inflammation induced by HCV. HCV can induce impaired neurocognition, which is clinically manifested by impaired quality of life, fatigue, and brain fog. These cognitive defects can be present even in patients with mild histologic HCV and have been confirmed by neurocognitive testing and brain imaging by magnetic resonance spectroscopy. Neurocognitive defects include loss of functioning memory and subtle changes in attention and processing speed.

**Hepatitis C and Risk of Nonhepatic Malignancies**  
Maya Balakrishnan, Matthew T. Glover, and Fasiha Kanwal

Epidemiologic studies show an increased risk of mortality among hepatitis C virus (HCV)-infected individuals compared with uninfected individuals from hepatic and nonhepatic causes. This article reviews the biologic plausibility of and epidemiologic evidence for the association between HCV and five extrahepatic malignancies: cholangiocarcinoma (CCA), pancreatic adenocarcinoma, papillary thyroid cancer, oral squamous cell cancer, and renal/kidney cancer. There is sufficient evidence to suggest that HCV is associated with intrahepatic CCA. The evidence for the link between HCV and pancreatic adenocarcinoma, oral squamous cell cancer, and renal/kidney cancer is compelling but requires further study. Based on available studies, there is no significant association between HCV, extrahepatic CCA, and papillary thyroid cancer.

**Dermatologic Manifestations of Chronic Hepatitis C Infection**  
Mehmet Sayiner, Pegah Golabi, Freba Farhat, and Zobair M. Younossi

Chronic hepatitis C virus (HCV) infection is associated with various extrahepatic manifestations, including dermatologic involvement mostly caused by immune complexes. Mixed cryoglobulinemia has a strong relationship with HCV with 95% of these patients being infected with HCV. Lichen planus is a disease of the squamous epithelium and may affect any part of the skin, with 4% to 24% of patients with lichen planus reported to have chronic HCV infection. Porphyria cutanea tarda is the most common form of porphyria, and it is thought that HCV interferes with iron stores, which can promote porphyria cutanea tarda. Finally, necrolytic acral erythema is a rare, psoriasis-like disease closely associated with HCV.
Fatigue is a common symptom. Diagnosis is difficult. Fatigue is often a complex symptom. In the recent years, fatigue has gained considerable amount of attention. It has 2 major types, central and peripheral, which may occur together or alone. Although fatigue has many strong relations with depression and sleep disorders, it is a separate entity. For the diagnosis of fatigue, self-reports and patient-reported outcomes are highly valuable tools because these methods can reflect patients’ perceptions. Treating the underlying disease with newly developed direct-acting antivirals often improves the perceived fatigue. Healthy lifestyle changes are the cornerstone of the treatment.

The economic burden of chronic hepatitis C might exceed $10 billion annually in the United States alone. This disease has a worldwide prevalence of up to 3%, making the global burden of the disease comparably tremendous. The cost of the disease includes direct medical expenses for its hepatic and extrahepatic manifestations, and also indirect costs incurred from impaired quality of life and the loss of work productivity. Recent emergence of treatment options that are not only highly effective and safe but also costly has emphasized the need to study the disease from the economic point of view.

Chronic hepatitis C virus (HCV) infection remains a leading cause of chronic liver disease in the United States. Although the hepatic impact of chronic HCV leading to cirrhosis and the need for liver transplantation is paramount, the extrahepatic manifestations of chronic HCV infection are equally important. In particular, a better understanding of the prevalence and impact of extrahepatic manifestations of chronic HCV infection in the post-liver transplant setting relies on understanding the interplay between the effects of chronic HCV infection in a posttransplant environment characterized by strong immunosuppression and the associated risks of this milieu.

Extrahepatic manifestations of hepatitis C virus (HCV) infection are a rare but serious condition. This article summarizes the current literature on the association between HCV and endocrine and pulmonary manifestations, as well as idiopathic thrombocytopenic purpura (ITP). HCV may directly infect extrahepatic tissues and interact with the immune system predisposing for obstructive and interstitial lung disease, ITP, autoimmune thyroiditis, infertility, growth hormone and adrenal deficiencies, osteoporosis, and
potentially lung and thyroid cancers. However, in many cases, the current evidence is divergent and cannot sufficiently confirm a true association, which emphasizes the need for future targeted projects in this field.

Treatment of Extrahepatic Manifestations of Hepatitis C Virus

Elisabetta Degasperi, Alessio Aghemo, and Massimo Colombo

Chronic infection with hepatitis C virus (HCV) is a multifaceted disease characterized by many extrahepatic manifestations (EHMs) that affect outcome and quality of life. HCV eradication by antiviral treatment has been proved beneficial in preventing the development of EHMs and is also able to improve many HCV-related severe disorders and neurocognitive outcomes and quality of life. Until recently, antiviral therapy of EHMs was limited to the presence of interferon-based treatment, and was contraindicated in many patients because of hematologic toxicity or risk of exacerbating immune-mediated disorders. The availability of interferon-free regimens solves this issue allowing for enhanced safety and efficacy to provide universal treatment of HCV-related EHMs.