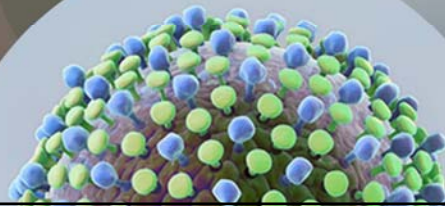




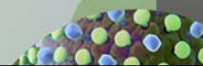
Focus on Extra-hepatic Manifestations

Presented by
Joseph Lim, MD
April 5th, 2017



AbbVie disclosures

- This is an AbbVie-sponsored educational webinar which is being presented by Joseph Lim, MD, on behalf of AbbVie
- The purpose of the medical educational webinar is to foster increased awareness of the latest science in the management of HCV



Speaker disclosures

- Consulting honoraria: AbbVie, Bristol-Myers Squibb, Gilead
- Research contracts (to Yale University): Bristol-Myers Squibb, Conatus, Genfit, Gilead, Hologic, Intercept

Objectives

- What EHMs are associated with HCV?
- What is the pathophysiology behind EHMs?
- What risks do HCV-infected patients have of developing specific EHMs?
- What is the cost associated with EHMs?

EHM, extra-hepatic manifestations; HCV, hepatitis C virus; SVR, sustained virologic response.

Introduction

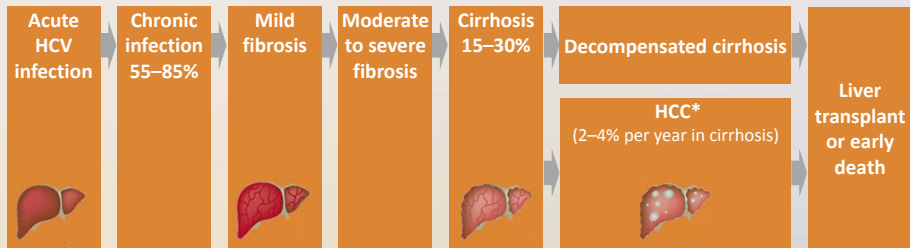
Approximately 2% of the world's population has chronic HCV infection¹⁻³



It is estimated that up to 50% of HCV-infected individuals in the USA are unaware of their infection status^{3,5}

1. WHO Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. April 2016. Available at: http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf Accessed February 2017;
2. Messina JP, et al. Hepatology. 2015;61:77-87;
3. El-Serag HB. Gastroenterology. 2012;142:1264-73.e1;
4. Chak E, et al. Liver Int. 2011;31:1090-1101.
5. Younossi ZM, et al. J Viral Hepat. 2013;20:550-5.

HCV can significantly impact the liver¹

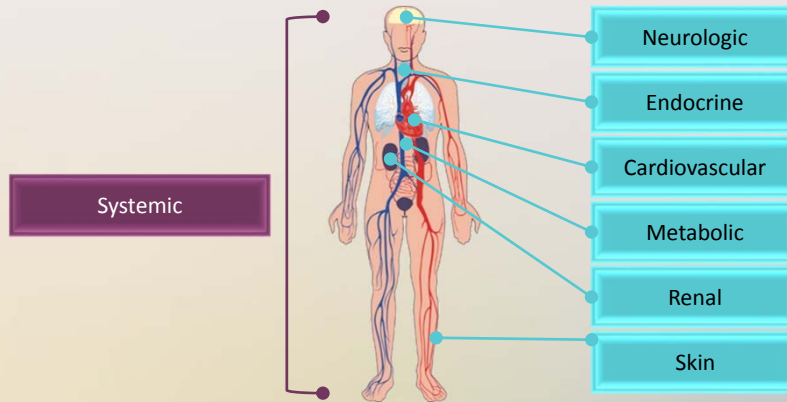


*HCC can occur in the absence of cirrhosis

1. WHO Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. April 2016. Available at: http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf Accessed February 2017.

HCV is associated with disease beyond the liver: EHMs¹⁻³

EHMs can be systemic or organ-specific



Up to 74% of patients experience at least one extra-hepatic manifestation⁴

1. Cacoub P, et al. Dig Liver Dis. 2014;46:S165-73; 2. Ferri C, et al. Autoimmun Rev. 2016;15:1145-60; 3. Younossi Z, et al. Gastroenterology. 2016;150:1599-608. 4. Cacoub P, et al. Arthritis Rheum. 1999;42:2204-12.

Immune-related EHMs

- Mixed cryoglobulinemia
- Cryoglobulinemic vasculitis
- B-cell NHL
- Sjögren's syndrome (Sicca)
- Autoantibodies
- Arthralgia/myalgia

Organ-related EHMs

- Fatigue
Depression
- Hypothyroidism
- Cardiovascular disorders
- Type 2 diabetes
Insulin resistance
- Glomerulonephritis
Renal insufficiency
- PCT
LP

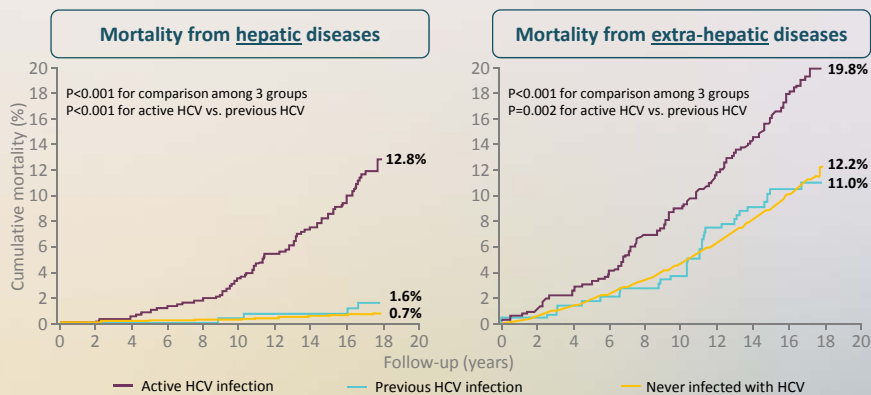
LP, lichen planus; NHL, non-Hodgkin lymphoma; PCT, porphyria cutanea tarda. Cacoub P, et al. Dig Liver Dis. 2014;46:S165-73; Ferri C, et al. Autoimmun Rev. 2016;15:1145-60; Younossi Z, et al. Gastroenterology. 2016;150:1599-608; Cacoub P, et al. Ther Adv Infect Dis. 2016;3:3-14.

Prevalence of EHMs

| | | Prevalence in HCV-infected patients | Prevalence in uninfected controls |
|-------------------------------|------------------------------|--|-----------------------------------|
| Mixed cryoglobulinemia | Asymptomatic and symptomatic | 30.1% | 1.9% |
| | Symptomatic only | 4.9% | 0 |
| Chronic renal disease | | 10.1% | 7.6% |
| Type 2 diabetes | | 15% | 10% |
| Cardiovascular disease | | 12.1% | 10.3 |
| Depression | | 24.5% | 17.2% |
| Malignancies | | 60% ↑ risk of lymphoma vs. uninfected controls | |

Younossi Z, et al. Gastroenterology. 2016;150:1599–608.

HCV increases the risk of mortality from both hepatic and extra-hepatic diseases



- Large prospective cohort study of 18,541 anti-HCV seronegative and 1095 anti-HCV seropositive adults followed for a mean of 16.2 years

Lee MH, et al. J Infect Dis. 2012;206:469–77.

Mixed Cryoglobulinemia

Mixed cryoglobulinemic syndrome has a significant prevalence in patients with HCV¹

Mixed cryoglobulinemia has a **significant association** to HCV, which is **directly involved** in disease pathogenesis^{1,2}

Cryoglobulinemia describes the presence of large amounts of proteins (antibody) in a patient's blood³

The proteins clump together to form complexes which are deposited in blood vessels³

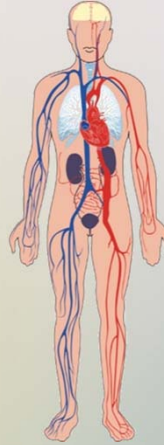
This causes vessels to become blocked and damaged = vasculitis³

- Serum cryoglobulins are detected in 50–70% of patients with HCV²
- 15–30% of patients may develop mixed cryoglobulinemia²
- HCV infection is the cause of cryoglobulinemia vasculitis in ~80% of cases¹

1. Cacoub P, et al. Dig Liver Dis. 2014;46:S165–73; 2. Ferri C, et al. Autoimmun Rev. 2016;15:1145–60; 3. Ragab G, et al. J Adv Res. 2017;8:99–111.

Mixed cryoglobulinemia is associated with several EHM^s of HCV^{1,2}

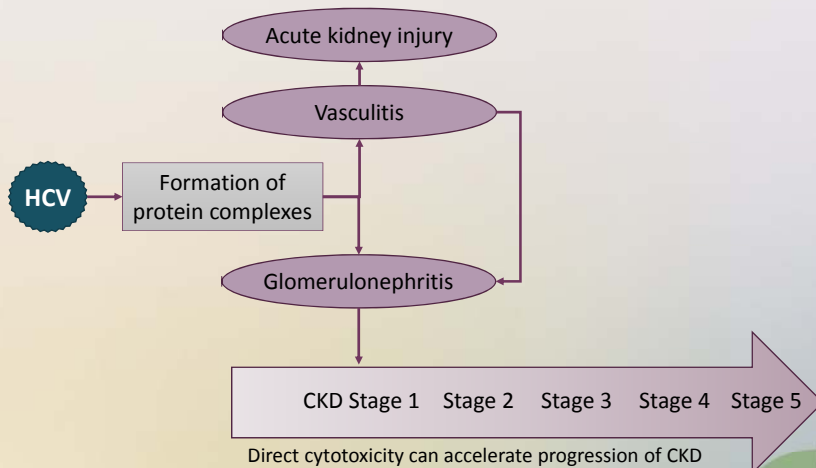
- **Mixed cryoglobulinemia contributes to the pathology of many EHM^s:**^{1,2}
 - **Skin** is the most frequently involved organ (eg, palpable purpura)
 - **Kidneys** (eg, glomerulonephritis)
 - **Nervous system** (eg, sensory axonopathy)
 - **Joints**
- Disease expression ranges from mild (arthralgia) to serious (widespread vasculitis)^{1,2}



1. Cacoub P, et al. Ther Adv Infect Dis. 2016;3:3–14; 2. Cacoub P, et al. Dig Liver Dis. 2014;46:S165–73.

Renal

HCV can induce acute and chronic renal disease

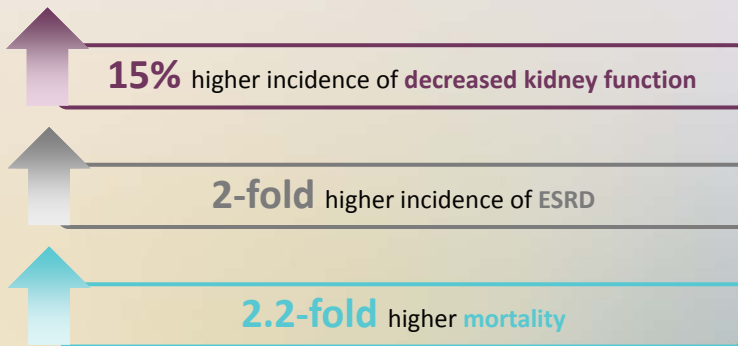


CKD, chronic kidney disease.
Barsoum RS, et al. J Adv Res. 2017;8:113–30.

HCV is associated with a higher incidence of CKD

HCV-infected patients have a **23% higher risk** of presenting with CKD vs. non-HCV-infected patients¹

Cohort study of US veterans data 2004–2006: n=100,518 HCV+ vs. n=920,531 HCV-²



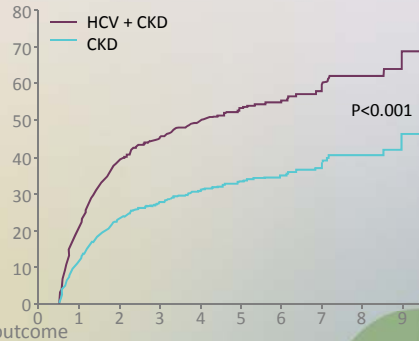
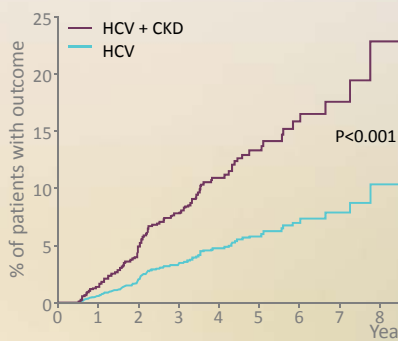
ESRD, end-stage renal disease.
1. Park H, et al. J Viral Hepat. 2015;22:897–905; 2. Molnar M, et Hepatology. 2015;61:1495–502.al.

Renal disease is associated with a faster progression of cirrhosis in patients with HCV

Database study evaluating the progression of liver disease and kidney disease in patients with HCV and CKD

Time to fibrosis stage progression:
784 patients with HCV and CKD vs.
1573 patients with HCV

Time to eGFR progression:
458 patients with HCV and CKD vs.
916 patients with CKD

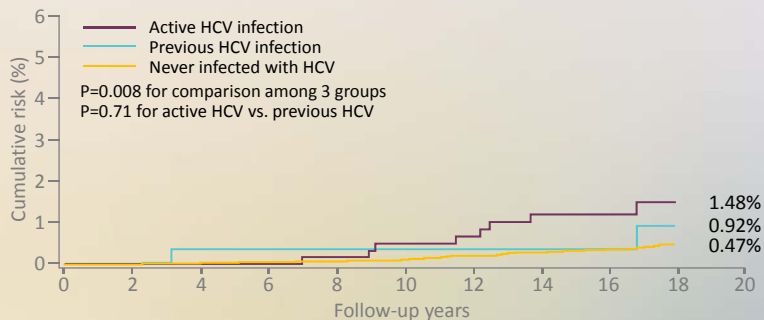


Liver disease progression is defined as an increase FIB4 stage: F0-F1 to F2 or F3-F4, and F2 to F3-F4.
Kidney disease progression is defined as a 4 mL/min/1.73 m² per year decline in eGFR.
eGFR, estimated glomerular filtration rate.
AbbVie Inc. Data on file H17.Dof.08

HCV-infected patients have higher rates of mortality from renal diseases than uninfected patients

Community-based cohort study of 23,820 individuals aged 30–65 years enrolled from 1991 to 1992 and followed until December 2008

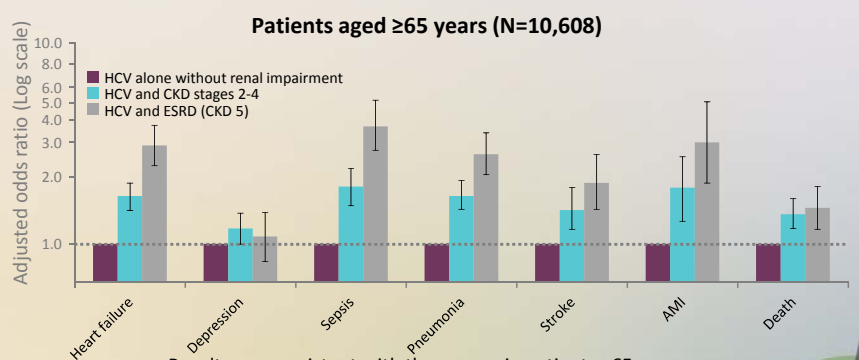
Cumulative mortality from nephritis, nephrotic syndrome, and nephrosis*



*Cumulative mortality by serostatus of antibodies against HCV (anti-HCV) and serum HCV RNA level at study entry.
RNA, ribonucleic acid.
Lee MH, et al. J Infect Dis. 2012;206:469–77.

Patients with HCV and CKD have a higher comorbidity burden and worse outcomes than those with HCV alone

US patients with HCV and renal impairment had a higher risk of clinical outcomes during 1-year follow-up than HCV patients without renal impairment



Results are consistent with those seen in patients <65 years

Diagnosis of HCV, CKD, and ESRD identified via ICD-9 and CPT code.
 CKD defined as GFR between 15-90 mL/min. ESRD is defined as GFR <15 mL/min.
 AMI, acute myocardial infarction; CPT, current procedural technology; ICD, International Classification of Diseases.
 Senaka P, et al. Hepatology. 2015;62(Suppl):1120A.

Metabolic

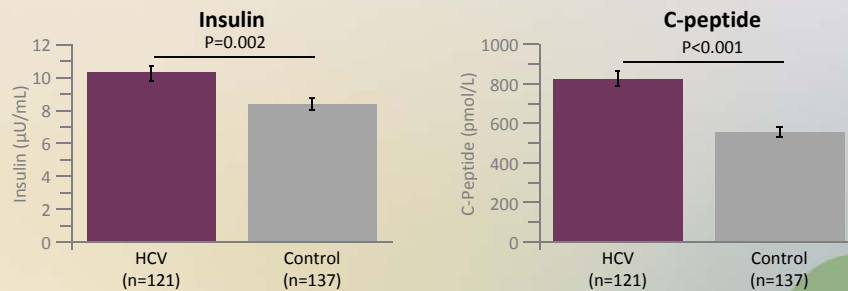
Type 2 diabetes and insulin resistance are more prevalent in HCV patients than in healthy individuals^{1,2}

HCV is associated with disturbances to the metabolic role of the liver, and possibly leading to insulin resistance and Type 2 diabetes mellitus³



Patients with HCV have a **2.3-fold increased risk of Type 2 diabetes**²

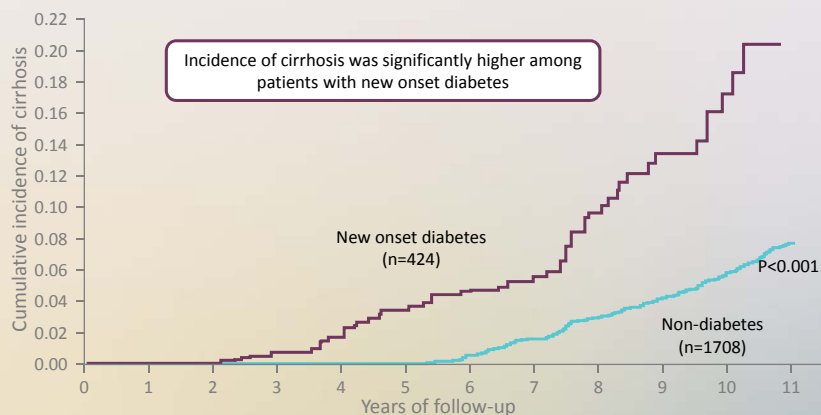
Insulin resistance parameters are higher in patients with HCV than healthy controls*¹



*Colored bars indicate the mean, error bars indicate standard deviation.

1. Hui JM, et al. Gastroenterology. 2003;125:1695-704;
2. Tang L, et al. Infect Agents Cancer. 2016;11:29;
3. Antonelli A, et al. World J Diabetes. 2014;5:586-600.

Type 2 diabetes is an independent risk factor for cirrhosis in patients with chronic HCV



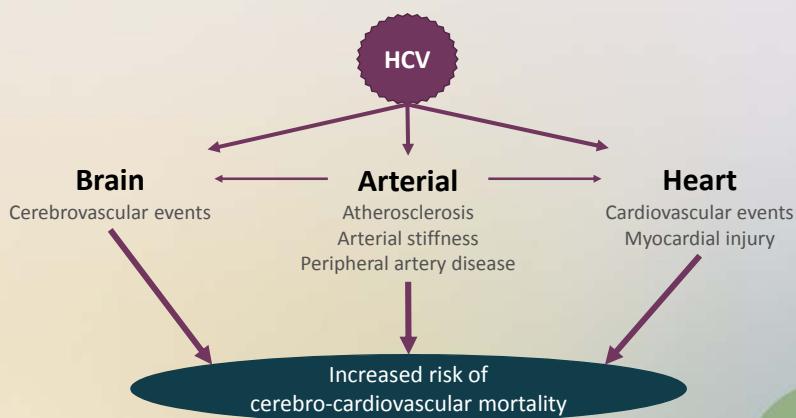
Large cohort study: 2132 patients with HCV (424 patients with new onset diabetes and 1708 patients without diabetes) were evaluated for development of cirrhosis or decompensation¹

1. Huang YW, et al. Hepatology. 2014;60:807-14.

Cardiovascular

HCV is a risk factor for the development of cardiovascular disease¹

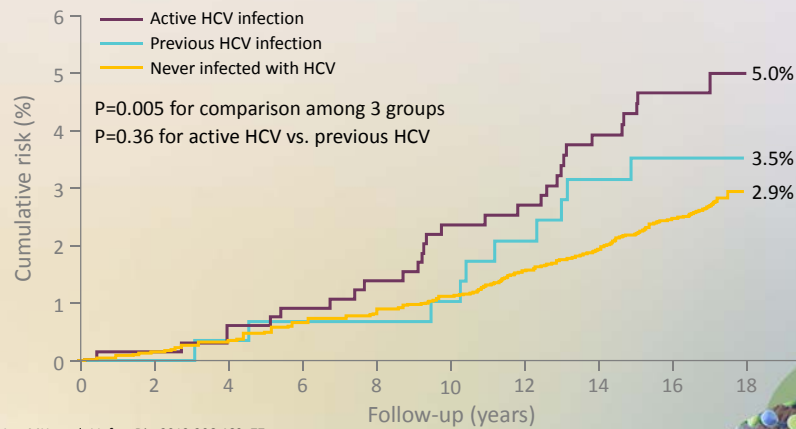
HCV infection is associated with multiple cardiovascular disorders²



1. Cacoub P, et al. Dig Liver Dis. 2014;46:S165-73; 2. Petta S. J Adv Res. 2017;8:161-8.

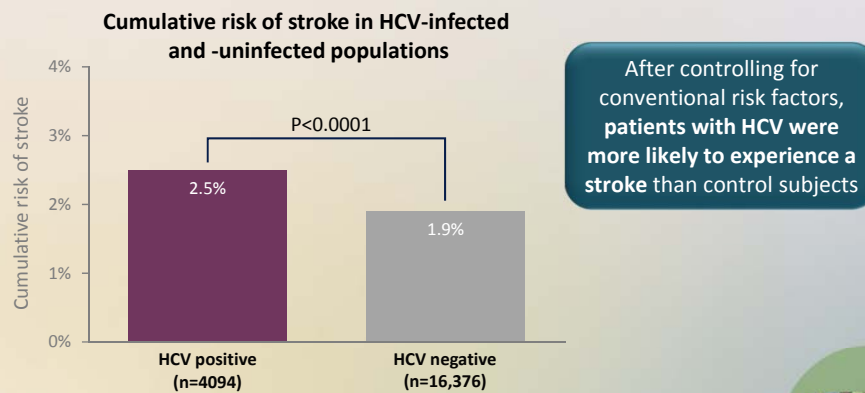
Chronic HCV infection is associated with an increased risk of cardiovascular mortality

Community-based cohort study of 23,820 individuals aged 30–65 years enrolled from 1991 to 1992 and followed until December 2008



HCV is associated with an increased the risk of stroke

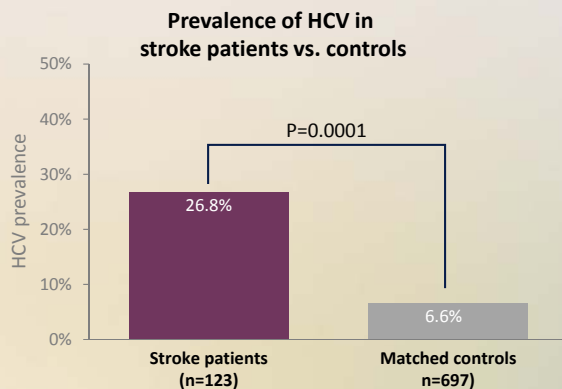
A population-based cohort study of 4094 patients with newly diagnosed HCV and 16,376 age- and gender-matched controls monitored for incidence of stroke between 2002–2008



Liao CC, et al. PLoS ONE. 2012;7:e31527.

HCV is more prevalent in stroke patients

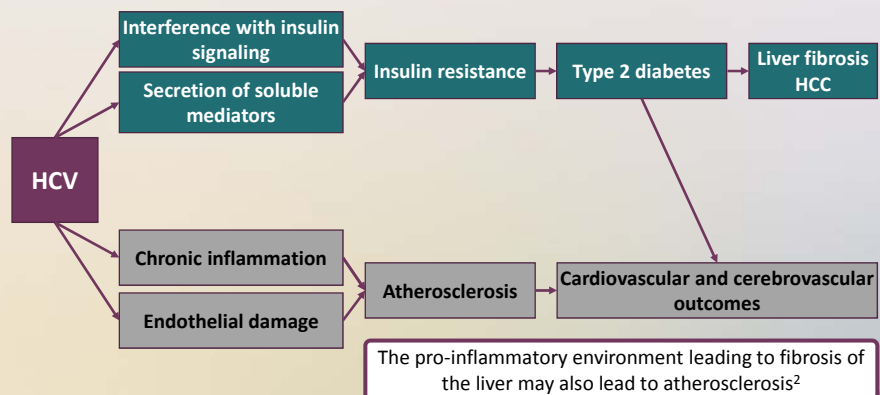
Case-controlled study of 820 patients admitted in 2010–2012 (123 patients with ischemic stroke vs. 697 matched controls) were evaluated for HCV infection



HCV was more prevalent in stroke patients than in control patients

Adinolfi LE, et al. *Atherosclerosis*. 2013;231:22–6.

Presumed mechanism of Type 2 diabetes and CV disease development in HCV-infected patients¹



CV, cardiovascular.

1. Negro F. *J Hepatol*. 2014;61:S69–S78; 2. Negro F, et al. *Gastroenterology*. 2015;149:1345–60.

Malignancies

HCV is associated with higher incidence of extra-hepatic malignancies

In the United States (2006–2010), incidence and age-adjusted mortality of several extra-hepatic malignancies were higher in patients with chronic HCV infection than in general population¹

| Malignancy | Incidence, SSR (95% CI) | Age-adjusted mortality, RR (95% CI) |
|------------|-------------------------|-------------------------------------|
| Pancreas | 2.5 (1.7–3.2)* | 1.6 (1.6–1.7)* |
| Oral | 2.5 (0.9–4.1) | 5.2 (5.1–5.4)* |
| Rectum | 2.1 (1.3–2.8)* | 2.6 (2.5–2.7)* |
| Kidney | 1.7 (1.1–2.2)* | 0.5 (0.4–0.5) |
| NHL | 1.6 (1.2–2.1)* | 2.3 (2.2–2.3) |
| Lung | 1.6 (1.3–1.9)* | 1.0 (1.0–1.0) |

In addition, chronic HCV infection has been associated with B-cell NHL, intrahepatic cholangiocarcinoma, and pancreatic cancer²

CI, confidence interval; RR, relative risk; SSR, standardized rate ratio.
*Significantly greater in patients with chronic HCV infection vs. the general US population.
1. Allison RD, et al. J Hepatol. 2015;63:822–8; 2. Fiorino S, et al. World J Gastroenterol. 2015;21:12896–953.

HCV infection is strongly associated with hematologic malignancies, including B-cell NHL¹

Mixed cryoglobulinemia may be a precursor to B-cell NHL²



Patients with cryoglobulinemia have a

35x

greater risk of developing B-cell NHL²

Most patients with HCV-associated B-cell NHL have mild liver disease at diagnosis³



In a single center study of 89 patients with HCV-associated B-cell NHL,

82%

of patients had mild -to-moderate fibrosis at time of diagnosis³

NHL, non-Hodgkin lymphoma.

1. Cacoub P, et al. Dig Liver Dis. 2014;46:S165-73; 2. Tang L, et al. Infect Agents Cancer. 2016;11:29

3. Torres HA, et al. Liver Int. 2015;35:1661-1664.

Other Extra-Hepatic Manifestations

Neurocognitive morbidity is associated with HCV infection¹

~50% of patients with HCV report neuropsychiatric symptoms²

HCV Brain Syndrome³

Depression is commonly reported in patients with HCV^{3,4}

Fatigue has been reported in 20–80% of patients with HCV^{3,5}

Cognitive impairment has been reported in patients with HCV^{3,5}

Quality of life is impaired, even in the absence of significant liver disease³

1. Cacoub P, et al. Dig Liver Dis. 2014;46:S165–73; 2. Mathew S, et al. World J Hepatol. 2016;8:545–56; 3. Yarlott L, et al. J Adv Res. 2017;8:139–48; 4. Younossi Z, et al. Gastroenterology. 2016;150:1599–608; 5. Monaco S, et al. World J Gastroenterol. 2015;21:11974–83.

Additional EHM's associated with HCV

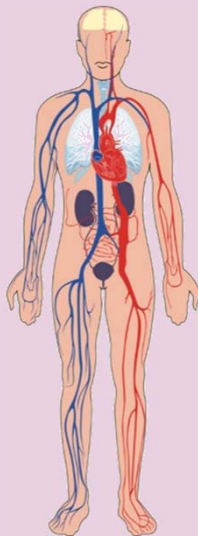
Thrombocytopenia^{1,2}
most frequent cytopenia associated with HCV: 10x higher in HCV+ vs. HCV–

Monoclonal gammopathies^{1,3}
are strongly associated with HCV and can progress to B-cell NHL

Sjögren's (Sicca) syndrome¹
eye or mouth symptoms reported in 20–30% of patients with HCV

Autoantibody¹
prevalence is high in patients with chronic HCV

Arthralgia/myalgia¹
reported in 40–80% of patients with mixed cryoglobulinemia



Hypothyroidism^{1,4}
prevalence is 3 times higher in patients with chronic HCV

Polyarthritis/fibromyalgia^{1,5}
widespread pain is reported by 2–57% of patients with chronic HCV

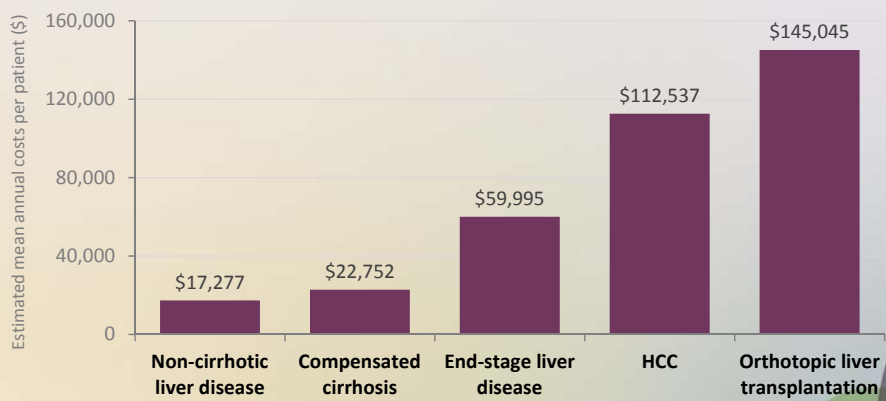
PCT^{1,6}
reported in <5% of patients with HCV; 66% of patients with PCT have HCV

LP^{1,6}
reported in 2% of patients with HCV; 4–24% of patients with LP have HCV

1. Cacoub P, et al. Dig Liver Dis. 2014;46:S165–73; 2. Ferri C, et al. Autoimmun Rev. 2016;15:1145–60; 3. Mihăilă RG. World J Gastroenterol 2016;22:6214–23; 4. Shen Y, et al. J Gastrointestin Liver Dis. 2016 Jun;25(2):227–234. 5. Palazzi C, et al. World J Gastroenterol 2016;22:1405–10; 6. Dedania J Clin Trans Hepatol 2015;3:127–133.

Economic Burden

Chronic HCV has a substantial economic burden that increases with severity of disease



Gordon SC, et al. Hepatology. 2012;56:1651-60.

EHMs increase the economic burden of HCV^{1,2}

Chronic HCV has a substantial economic burden that increases with severity of disease and complications of EHMs¹⁻³

Based on a 2014 estimate of 2.68 million people infected with HCV in the United States, direct medical costs of associated EHMs per patient per year ranged from:

\$127 (lichen planus) to **\$71,000** (ESRD)²

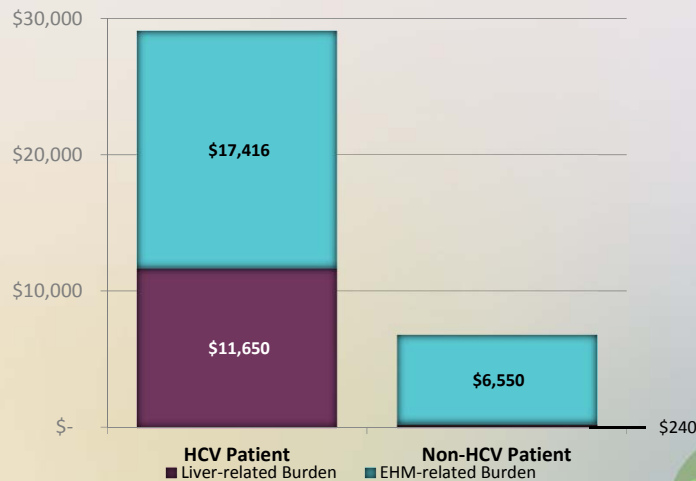
The total annual direct cost associated with HCV-associated EHMs in the United States was estimated to be \$1.5 billion in 2014²

ESRD, end stage renal disease.

1. Gordon SC, et al. Hepatology. 2012;56:1651-60; 2. Younossi Z, et al. Gastroenterology. 2016;150:1599-608; 3. Cacoub P, et al. Dig Liver Dis. 2014;46:S165-73.

Economic burden of EHM and liver-related medical costs in HCV and non-HCV patients

Annual weighted mean medical costs per patient (2016 USD)



HCV cohort (n=17,054), Non-HCV cohort (n=85,270)
AbbVie Data on File H17.DOF.06

Summary

In addition to hepatic complications, HCV is associated with many EHM^s ^{1,2}

Patients with chronic HCV are at an increased risks of complications from EHM^s ^{1,2}

| | |
|------------------|--|
| Renal | <ul style="list-style-type: none">• Increased risk of ESRD³ |
| Metabolic | <ul style="list-style-type: none">• Increased risk of insulin resistance and Type 2 diabetes^{4,5}• Increased risk of renal and cardiovascular comorbidities in diabetics⁶ |
| Cardiovascular | <ul style="list-style-type: none">• Increased incidence of acute coronary syndrome and stroke³• Increased risk of cardiovascular mortality⁷ |
| Cryoglobulinemia | <ul style="list-style-type: none">• Increased risk of mixed cryoglobulinemia and downstream associated EHM^s^{4,8} |
| Malignancies | <ul style="list-style-type: none">• Increased incidence of lymphoma^{4,9} |
| Neurologic | <ul style="list-style-type: none">• Decreased cognitive performance⁴• Increase in fatigue⁴ |

1. Cacoub P, et al. Arthritis Rheum. 1999;42:2204–12. 2. Cacoub P, et al. Dig Liver Dis. 2014;46:S165–73. 3. Hsu YC, et al. Gut. 2015;64:495–503; 4. Negro F, et al. Gastroenterology. 2015;149:1345–60; 5. Arase Y, et al. Hepatology. 2009;49:739–44; 6. Hsu, YC, et al. Hepatology. 2014;59:1293–302; 7. Lee MH, et al. J Infect Dis. 2012;206:469–77. 8. Gagnani L, et al. Hepatology. 2015;61:1145–53; 9. Kawamura Y, et al. Am J Med. 2007;120:1034–41.

Summary: The importance of EHMs in HCV

Up to 74% of individuals with chronic HCV also suffer from EHMs of HCV¹

EHMs strongly associated with HCV infection include mixed cryoglobulinemia, CKD, Type 2 diabetes, and cardiovascular disease⁷

Renal disease is associated with a faster progression of cirrhosis in patients with HCV²

Chronic HCV increases risk of insulin resistance, stroke, and cardiovascular mortality³⁻⁶

EHMs of HCV have been associated with increased mortality, reduced quality of life, and increased health care spending^{6,8}

1. Cacoub P, et al. Arthritis Rheum 1999;42:2204-12; 2. AbbVie Inc. Data on File H17.DoF.08 3. Antonelli A, et al. World J Diabetes. 2014;5:586-600. 4. Petta S. J Adv Res. 2017;8:161-8. 5. Liao CC, et al. PLoS ONE. 2012;7:e31527 6. Cacoub P, et al. Dig Liver Dis. 2014;46:S165-73; 7. Ferri C, et al. Autoimmun Rev. 2016;15:1145-60; 8. Nuño Solinis R, et al. Infect Dis Ther. 2016;5:491-508;

abbvie