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Extrahepatic Manifestations of Hepatitis C: Screening and Management

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In this Issue...

Extrahepatic manifestations (EHM) of hepatitis C have significant impacts on both morbidity and mortality over and above the contributions of liver disease. Fortunately, early recognition and treatment may reduce permanent disability and improve long-term prognosis. However, recognizing and treating EHM can be a challenge due to diverse presentations, multisystem involvement, and the historical lack of tolerable and effective treatments.

In this issue, Dr. Jordan J. Feld and Dr. Joel S. Emery from the University of Toronto review the recent literature describing:

- The direct impact of HCV-associated extrahepatic manifestations on patients
- The importance of antiviral treatment in patients with extrahepatic manifestations
- The efficacy and tolerability of direct acting antiviral treatment in the treatment of extra hepatic manifestations.

LEARNING OBJECTIVES

- Summarize important extrahepatic manifestations of hepatitis C virus infection and the strength of the associations.
- Describe the significant impact of extrahepatic manifestations on patient morbidity and mortality and the importance of regular screening for these complications.
- Identify management priorities in patients with extrahepatic manifestations and the impact of HCV eradication.

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Commentary & Reviews

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Guest Faculty Disclosure

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Dr. Emery has indicated that he has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

Unlabeled/Unapproved uses

Dr. Feld and Dr. Emery have indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

IN THIS ISSUE

COMMENTARY

Extrahepatic manifestations (EHM) of HCV describe diseases or conditions outside of the liver for which the prevalence is increased in the HCV population. Historically, the clinical significance of these conditions has been difficult to assess for a number of reasons. Practically, they are heterogeneous conditions, which may be common and subjective (fatigue), or they may be rare and poorly recognized (lichen planus). They also often cross multiple organ systems with which HCV providers may have limited management experience. Alternatively, they may represent common diseases where the impact of HCV is difficult to accurately assess (diabetes, coronary artery disease). Establishing a direct cause and effect relationship between HCV infection and EHM is often difficult. As a result, EHM may be overlooked in routine hepatitis C assessments with care focused on more objective hepatic markers. However, current literature suggests that the significance of EHM may be underappreciated and a potential missed opportunity for HCV care providers.

Over the last decade, HCV infection has been strongly linked to B-cell non-Hodgkin lymphoma (NHL) and mixed cryoglobulinemia (MC) by robust epidemiological and treatment response data, while associations with diabetes/insulin resistance, renal insufficiency, cardiovascular disorders, and depression have been more recently described but less convincingly demonstrated.[1] HCV itself is underdiagnosed in the general population, which may indicate that the true burden of EHM is much greater than appreciated.[2] The clearest example of this has been in the current understanding of MC, which was originally thought to be an idiopathic lymphoproliferative condition but is now thought to involve HCV infection in > 90% of cases.[3] As expected, newer reports continue to suggest that EHM are common, with most reviews suggesting rates of > 70%, depending on the classification used.[4]

Because EHM are so prevalent, it is perhaps surprising that systemic screening for EHM is not more commonly performed by HCV care providers.[5] Although practice likely varies, in our experience screening for diabetes, cardiovascular risk factors or symptoms of MC are seldom documented. Literature continues to build, however, that on a population level EHM cannot be ignored. As Younossi et al describe (reviewed in this issue), EHM have major impact on patient quality of life and health care costs — and may be the most pressing medical need for many noncirrhotic patients with HCV infection. The reviewed article by Lee et al also convincingly establishes that mortality from extrahepatic diseases is increased in people infected with HCV. Importantly, not only are HCV-related EHM associated with impaired health outcomes, but treatment of HCV, as confirmed by Hsu et al (also reviewed), results in improvements in all-cause mortality as well as in specific extrahepatic outcomes. However, little can be done to modify these outcomes if EHM are not recognized, suggesting screening must become a priority among HCV care providers.

Despite the growing evidence that EHM are clinically relevant, the clinician often has a number of considerations when screening for these diverse manifestations. First, the type of relationship each extrahepatic manifestation has to HCV clarifies the impact and urgency of treatment. Both MC and B-cell NHL have a strong evidence base confirming that antiviral therapy is efficacious, with SVR often leading to disease regression and prevention of relapse.[2] With a higher likelihood of cure in its milder stages, MC probably merits screening in all patients infected with HCV. Diabetes, renal (non-MC-related), and cardiovascular disease are important EHM, but associations with HCV are relatively weak, as these diseases are common even people not infected with HCV, and data on disease regression with HCV clearance are limited.[3,6] Nevertheless, antiviral therapy has been associated with improved renal and cardiovascular (CV) outcomes in diabetics, making early treatment a strong consideration.[7] Furthermore, screening for common but weakly associated EHM may have a different goal, whereby identification allows for traditional risk factor modification and

effective referrals even if HCV therapy is not deemed a priority. Other EHM, such as fatigue, arthritis, cognitive impairment, and depression do not reliably improve with treatment and should be screened for to ensure adequate symptom management and support is given, but may have less justification as an indication for therapy.

Another important theme from the reviewed articles is that using fibrosis staging alone to guide treatment coverage is shortsighted. In many jurisdictions EHM are not used as criteria for reimbursement, despite the significant impacts antiviral therapy has on nonhepatic disease morbidity and even mortality. With multiple studies documenting improved all-cause mortality from HCV clearance, the benefits of HCV treatment clearly extend beyond the liver.[4] Consequently, current cost effectiveness data likely underestimate the benefits of HCV treatment, an issue that may be compounded by the fact that the HCV-infected cohort is aging and the greatest risk of complications from many EHM occur at later decades.[2,8]

Expanding treatment criteria has become even more important as noninterferon-based therapies have become available. Historically, antiviral treatment was delayed in symptomatic MC patients. However, direct-acting antiviral agents (DAA) have been shown to be effective and well tolerated in symptomatic patients with MC (as described herein by Sissi et al). Early introduction of highly effective antiviral therapy may improve disease outcomes, as well as limit exposure to immunosuppressive therapy and its associated complications.

In summary, the extrahepatic manifestations of hepatitis C infection are common and may have important consequences to individual patients as well as to populations, affecting all-cause mortality and resource allocation. Viral eradication leads to major benefits beyond improving liver disease outcomes: from subtle improvements in quality of life to the potential for prevention and even reversal of life-threatening complications from EHM like NHL or MC. As data accumulate with the new therapies, screening for extrahepatic manifestations should become routine practice, with identified EHM used as expanded criteria for treatment.

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Impact of Extrahepatic Manifestations

Younossi Z, Park H, Henry L, Adeyemi A, Stepanova M. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. *Gastroenterology*. 2016 Feb 26.

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Extrahepatic manifestations (EHM) of hepatitis C virus (HCV) infection are well described in the literature[1] but are often underrecognized by clinicians. Understanding the types of EHM and the strengths of association to HCV is critical to recognition and clinical management.

This meta-analysis by Younossi and colleagues describes the epidemiological burden of EHM and the pooled risk or odds in HCV-infected patients. Based on 102 studies, the report reveals that EHM are generally common but the strength of association to HCV varies. Essential mixed cryoglobulinemia (MC), a B-cell disorder identified by immune complexes that cryoprecipitate and cause vasculitis with joint, skin, kidney, and neurological involvement, has one of the strongest associations with HCV infection (OR 11.50 [95% CI 4.56-29.00]). MC is also the most commonly observed EHM with a prevalence of 30.1% (21.4%-38.8%), yet clinically relevant (symptomatic MC) is much less frequently observed (prevalence: 4.9%, [3.4%-6.4%]). Non-Hodgkin lymphoma (NHL), particularly B cell lymphomas, is also strongly associated with HCV (adjusted RR 1.60; 95% CI 1.34 – 1.86); however, estimates of prevalence vary widely by study and geographic region, making it difficult to report an overall incidence of NHL in patients with HCV (rare according to most articles).[2] Similarly, porphyria cutanea tarda (PCT) has a strong association with HCV (OR = 8.53; 95% CI: 4.15-17.52) but is rare (prevalence: 0.5%; 0.1%-0.8%). In contrast, type 2 diabetes mellitus (DM) and chronic kidney disease (CKD) are both frequently identified in people infected with HCV (prevalence DM: 15%; CRD: 10.1%), but the strength of association of each condition to HCV is relatively weak (DM OR: 1.58 [1.3-1.86)]; CRD RR: 1.23 (1.12-1.34). Other dermatological (lichen planus) and rheumatological (sicca syndrome, inflammatory arthritis) diseases have been reported to be associated with HCV, but prevalence estimates vary widely. Associations between depression and cardiovascular disease (CVD) in patients with HCV are small, according to this meta-analysis.

In addition to describing the strength of association, the meta-analysis also attempted to quantify the impact of EHM on patients and payers. Results from 23 studies using validated scales of quality of life (QoL) showed EHM to have negative impact on the lives of patients with HCV infection. Specifically, the domains of mental health, general health and wellbeing, and social functioning seemed to drive the reductions in QoL in patients with HCV infection. From a cost perspective, direct health care costs of EHM were found to be high (range: $2.73 – $443.39 million/year), with the majority of yearly costs driven by symptomatic MC, diabetes, depression, and cardiovascular disease, highlighting that common diseases with a weak association with HCV may have more overall impact than rare but strongly associated EHM.

The report has notable limitations. First, significant variability existed in the quality of the primary studies, with a high number of retrospective and small cohort studies. Significant heterogeneity was also apparent in definitions of individual EHM and the reporting of outcomes between studies. Publication bias toward positive studies is often observed in Forrest plots and may also be relevant in this meta-analysis, particularly for more controversial EHM like CVD and depression. Finally, quality of life measures did not adjust for cirrhosis and did not identify which EHM were driving overall effects, thus limiting their clinical utility.

Three main conclusions can be taken away from this study: 1) EHM are common; 2) EHM have significant impacts on patient-reported quality of life; 3) EHM have significant impacts on health care use. Specifically for clinicians, although EHM may have marked variability in strength of association to HCV, mixed cryoglobulinemia, lymphoma, and renal disease deserve specific attention because of the significant impact of antiviral treatment (as described below). Second, many extrahepatic diseases have effective medical therapy that may modify disease outcomes.[3] Because of these findings, clinicians should consider ongoing screening for EHM, especially in patients not eligible for antiviral therapy based on fibrosis staging. Perhaps most important, given the burden of disease from EHM and their lack of association with liver pathology, using fibrosis scores alone to guide treatment decision-making is likely to miss significant health and societal benefits from HCV eradication.

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HCV Infection Increases Extrahepatic Mortality

Lee MH, Yang HI, Lu SN, et al; R.E.V.E.A.L.- HCV Study Group. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis*. 2012 Aug 15;206(4):469-477.

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Because HCV is typically considered a primary infection of the liver, its eradication is thought to result in health benefits primarily from improved hepatic outcomes, with most literature supporting reductions in the development of cirrhosis and its complications.[1] The paradigm that HCV is a liver disease and mortality is driven by liver-related complications has guided clinical decision-making, and more recently, reimbursement criteria.[1,2] However, HCV is actually a multiorgan disease, with evidence of viral replication documented in various human tissues from the bone marrow to the brain, with a variety of direct and indirect extra - hepatic manifestations (EHM).[3] The clinical consequences and long-term health outcomes related to EHM may have important considerations.

By following a Taiwanese cohort of 1095 anti-HCV (positive) patients and comparing them to a similar cohort of 18,541 anti-HCV (negative) people, Lee and colleagues were able to report and compare mortality data during the period of 1991-2008. Using mortality rates per 100,000 person years, hazard ratios were reported and after multivariable adjustment confirmed that the main drivers of mortality in patients with HCV were hepatic disease (adjusted HR 12.48 [9.34-16.66]) and liver cancer (adjusted HR 21.63, [14.83-31.54]). However, extrahepatic mortality was also increased in this analysis with renal disease (adjusted HR 2.77 ([1.49-5.15)] and circulatory disease (adjusted HR 1.50 [1.10-2.03]), both contributing significantly to mortality. Extrahepatic cancer mortality was also increased, particularly esophageal, prostate, and thyroid cancer. The consequences of both liver and nonliver-related complications of HCV were most notable in those who were viremic, highlighting the importance of active infection on health outcomes rather than risk factors associated with disease acquisition. Cumulative mortality from all extrahepatic disease, as well as specifically from circulatory and renal disease, was significantly increased in patients who remained HCV RNA positive ($P < .01$).

The power of this study is the very large cohort and relatively long follow-up period (mean 16.2 years). However, the average age of the cohort was relatively young (47.6 years), which may lead to underestimates of the consequences of some extrahepatic manifestations that may have larger impacts at later ages (eg, CVD). Considering this study only included a Taiwanese population, generalizability of the results from this study to other regions of the world may be limited.[4]

In summary, in this study, renal and cardiovascular disease showed the most significant effects on mortality. Renal mortality may be directly related to HCV as a consequence of symptomatic MC or independent renal disease (rare), or alternatively may be due to indirect effects of HCV such as diabetic renal disease. Similarly, cardiovascular disease may also be mediated by diabetes, or there may be a direct vascular effect related to the chronic inflammatory state.

Overall, these findings not only confirm the importance of HCV infection in increasing liver-related mortality but also provide evidence that extrahepatic manifestations can have significant impact on mortality in patients with HCV.

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Antiviral Treatment Improves Extrahepatic Disease Outcomes

Hsu YC, Ho HJ, Huang YT, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut*. 2015 Mar;64(3):495-503.

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The association between extrahepatic manifestations (EHM) and HCV has been well described. However, in many extra hepatic conditions such as cardiovascular disease and diabetes, a direct relationship with HCV is controversial.[1] One way to clarify the strength of association and support causality is by evaluating the effect of antiviral therapy. Furthermore, if viral clearance improves EHM disease outcomes, their presence becomes relevant when treatment is being considered.

To evaluate the effect of HCV treatment on extrahepatic disease outcomes, Hsu and colleagues evaluated a Taiwanese cohort of 12,384 HCV RNA-positive patients treated with peginterferon and ribavirin (PEG-RIBA) against a matched group of untreated HCV RNA-positive controls. Using extrahepatic disease outcomes of end-stage renal disease (ESRD), acute coronary syndrome (ACS), ischemic stroke, and catastrophic autoimmune disease (while controlling for demographics, comorbidities, medications, and hepatic dysfunction), the investigators showed significant reductions in EHM in the treated cohort ($P < .01$). Specifically, ESRD, ACS, and ischemic stroke were reduced by 85%, 23% and 38% (adjusted), respectively, in patients treated for at least 16 weeks.

One important consideration is the short duration of follow up in the cohort (mean 3.3 years [2.47]). Vascular, cardiac, and renal diseases are established over long time spans, and improved outcomes in typical risk factors often require long treatment periods. Thus, the significant reductions seen with antiviral treatment on extrahepatic outcomes are somewhat surprising; and although the findings could represent a strong effect of HCV on cardiovascular and renal outcomes, there may also be unmeasured confounders. Another important limitation of the study is that the effect of treatment, but not viral eradication, was considered. Although SVR rates with PEG-RIBA are high in Taiwan (> 70%), using virological outcomes rather than treatment alone would have been preferable. Importantly,

improved outcomes were only observed in patients who completed at least 16 weeks of therapy, supporting virological eradication as the underlying mechanism.

The results of the current study give some interesting perspective to both the pathogenesis of EHM and the effects of HCV treatment at a population level. First, the EHM of cardiovascular and renal disease are thought to be primarily driven by increased insulin resistance and diabetes seen in patients with HCV. Although Hsu's group has shown improved cardiovascular and renal outcomes in diabetic patients, the reduced cardiovascular events in this cohort were seen in primarily nondiabetic populations (86%).[2] Thus, although insulin resistance still may be the relevant factor, a more direct effect of HCV infection on the cardiovascular system may also be relevant. The second important consideration is the relevance of these data for the timing and allocation of antiviral treatment. The observation that treatment of an infectious and relatively organ-specific disease can modify the course of a seemingly unrelated chronic disease is potentially quite powerful. For many jurisdictions, antiviral treatment funding is based exclusively on the level of liver fibrosis, and this treatment restriction has become more common in recent years due to the high price of direct acting antiviral agents.[3] Therefore, if HCV is indeed driving cardiovascular disease outcomes, waiting to treat HCV may allow unmodifiable cardiovascular and renal disease progression and significantly limit the overall benefits of therapy.

This article supports the association between HCV infection and cardiovascular and renal disease outcomes, possibly explaining the benefits of SVR on not only liver-related mortality but also on all-cause mortality. Beyond the clinical message to screen for these EHM, this study has important implications for payers, as early treatment of HCV may have benefits beyond the liver. EHM should be taken into account when considering the cost-effectiveness of antiviral therapy. While prospective data further documenting the benefits of antiviral therapy on cardiovascular and renal outcomes are still needed, this study goes a long way in highlighting the significance of HCV outside the liver.

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Treatment of EHM with Antiviral Therapy May Be Curative

Peveling-Oberhag J, Arcaini L, Bankov K, Zeuzem S, Herrmann E. The anti-lymphoma activity of antiviral therapy in HCV-associated B-cell non-Hodgkin lymphomas: a meta-analysis. *J Viral Hepat*. 2016 Jul;23(7):536-544.

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Mixed cryoglobulinemia (MC) and non-Hodgkin lymphoma (NHL) have the strongest association of all EHM to HCV infection.[1] For patients with mixed cryoglobulinemia, over 90% will have evidence of HCV infection.[2] Similarly, in patients with specific types of NHL, particularly less common forms such as marginal zone and splenic lymphoma, the association with HCV is very strong.[3] For these two EHM, the strong epidemiological associations and increasingly robust pathogenetic data support a causal relationship.[1] However, perhaps the most compelling data inferring causation is the direct response to antiviral therapy (AVT).

In their 2015 report, Gragnani et al present data on the long-term effects of AVT in patients with mixed cryoglobulinemia. Prospectively, 121 patients with symptomatic MC and 132 patients with asymptomatic MC were treated with a combination of peginterferon and ribavirin (PEG-RIBA) and followed for a mean duration of 92.5 months. Virological, immunological, and clinical responses were evaluated. SVR was achieved in 55% of asymptomatic and 56.8% of symptomatic patients. Immunological and clinical response (loss of cryoglobulins) was directly related to SVR, with virological nonresponders having no significant clinical or immunological response. Specifically, 57% of patients that achieved SVR also had a complete loss of cryoglobulins and resolution of symptoms, with an additional 40% of patients showing stabilization with milder, isolated symptoms after successful treatment. The study confirms the importance of successful viral eradication in ensuring a durable cure of MC.

As MC is a disorder of B-cell proliferation and dysregulation, it should perhaps not be surprising that the prognosis of certain B-cell NHL may also be affected by HCV treatment. The 2016 meta-analysis by Peveling-Oberhag et al included 20 studies evaluating the response of HCV-associated NHL to antiviral therapy (N = 254). Importantly, studies using combination chemotherapy and AVT were excluded. Overall, 73% of treated patients had regression of lymphoma, with SVR significantly associated with lymphoma response (P = .0002). Patients with marginal zone lymphoma (MZL) were highly represented in the sample (N = 157), but benefit of AVT was also seen in other subtypes. Importantly, most of these studies involved the use of suboptimal antiviral treatment (monotherapy with interferon), which likely underestimates the benefit of AVT. Focusing on patients who achieved SVR, oncologic cure was seen in up to 87% of patients, comparable to results with traditional chemotherapy. Notably, many of these studies also demonstrated reduced relapse of NHL after viral clearance.[4,]

The curative potential of antiviral therapy on MC and B-cell lymphoma supports a direct, causative relationship with HCV and presents itself as a key opportunity for care providers.[1] Symptomatic MC can lead to devastating renal and neurological damage, with significant morbidity and even mortality.[2] Similarly, HCV-associated lymphoma can progress to aggressive subtypes with a poor prognosis. As a result, these two extrahepatic manifestations should be routinely considered when the clinical status of HCV-infected patients changes, and their presence should justify antiviral therapy even in the absence of liver damage. For those with aggressive forms of NHL, antiviral therapy should be instituted after chemotherapy to prevent disease recurrence. Although the benefits of antiviral therapy

with noninterferon-based treatments must to be documented, it is likely that viral eradication will still provide important clinical benefit to these patients. The remarkable improvements in treatment success and tolerability of antiviral therapy will make treatment of patients with MC and NHL more feasible.

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Efficacy and Safety of DAA when Treating Symptomatic Mixed Cryoglobulinemia

Sise ME, Bloom AK, Wisocky J, et al. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents. *Hepatology*. 2016 Feb;63(2):408-417.

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It is easy to declare the importance of screening and early initiation of antiviral therapy (AVT) for nonliver-related complications of HCV, yet the use of conventional AVT had major limitations. Peginterferon and ribavirin (PEG-RIBA) required 24-48 weeks of therapy and were associated with significant side effects, making treatment particularly challenging in an already symptomatic group. Many reports documented marked delays in clinical benefit, even in those patients who responded to treatment.[1,2] Thus, despite clear evidence of benefit, many position papers advocated for use of antiviral therapy only in mild cases of mixed cryoglobulinemia or lymphoma, or after severe manifestations had been controlled with rituximab or other chemotherapy.[3-5] Development of extremely well-tolerated, highly efficacious, direct-acting antiviral treatments will likely have significant impacts on which patients with EHM are treated, and when.

In this 2016 paper, Sise and colleagues describe a case series of 12 patients with symptomatic mixed cryoglobulinemic vasculitis treated with interferon-free, direct-acting antivirals (DAA). Outcomes were compared to a historical cohort of symptomatic MC patients treated with PEG-RIBA. Overall, SVR12 was achieved in 83% (N = 10/12). Loss of cryoglobulins (full immunological response) occurred in 44% of cases (4/9 who had cryocrit levels rechecked). In terms of clinical response, 33% (N = 4/12) of patients had a complete resolution of symptoms — specifically, resolution of renal symptoms occurred in 33% (N = 3/9). Significant improvements in symptoms were confined to those who achieved SVR. Overall treatment was well tolerated in the DAA group, with only two patients reporting significant side effects, and both of them achieved SVR12.

In contrast, the historical cohort only had one patient with a full virological (SVR12), immunological, and clinical response (N = 1/10). This historical cohort had a 50% rate of treatment discontinuation, and all patients reported side effects. In this study, lower clinical response may be related to established end-organ damage, as many patients had a long duration of disease before treatment initiation. Specifically in the case of renal disease, the mean duration of disease before treatment was 6.2 years.

An abstract presented at the International Liver Congress 2016 also retrospectively recorded the response of symptomatic MC to DAA therapy[6]. Observed virological response rates (SVR12) were 89% (N = 16/18), with complete loss of measurable cryoglobulins and resolution of symptoms in 27.7% (N = 5/18) and 33.3 % (N = 6/18) of patients, respectively. Importantly, interferon-free DAA regimens in the cohort had very low rates of adverse events or hospitalization (16%, N = 3/18), with no patients discontinuing therapy.
While additional studies specifically evaluating the efficacy of DAAs on EHM of HCV are needed, the long-term studies with PEG-RIBA have clearly shown that eradication of HCV results in clinical improvement in the majority of patients with MC. Given the excellent tolerability and high rates of virological response with the new DAA-based regimens, antiviral therapy can likely be introduced immediately in most symptomatic patients with EHM, potentially avoiding or at least reducing the need for immunosuppressive therapy and the potential for end-organ damage.

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KEY TAKEAWAYS

- EHM of HCV are diverse systemic conditions with significant variability in clinical presentation, organ involvement, and severity.
- HCV has the strongest associations with mixed cryoglobulinemia and B-cell NHL.
- HCV related EHM have dramatic impacts on morbidity and mortality that is independent from liver disease.
- Routine screening for mixed cryoglobulinemia and B-cell NHL is justified, as early recognition and treatment have the potential to significantly improve patient QOL and health costs.
- Antiviral treatment has been shown to reduce all-cause mortality and improve extra hepatic disease outcomes and can be considered as a first line therapy in most

patients with EHM.

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IMPORTANT CME/CE INFORMATION

ACCREDITATION STATEMENTS

Physicians

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CREDIT DESIGNATION STATEMENT

Physicians

*e*Newsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses

*e*Newsletter: This 1 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 1 contact hour, or a total of 8 contact hours for the 8 newsletters in this program.

INTERNET CME/CE POLICY

DISCLAIMER STATEMENT

STATEMENT OF RESPONSIBILITY

STATEMENT OF NEED

CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS

INTENDED AUDIENCE

HARDWARE & SOFTWARE REQUIREMENTS

COMPLETE THE POST-TEST

Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST

This activity was developed in collaboration with DKBmed.