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Hepatitis C Virus Infection Care Pathway—A Report From the American Gastroenterological Association Institute HCV Care Pathway Work Group

Fasiha Kanwal,[1] Bruce R. Bacon,[2] Lauren A. Beste,[3] Joel V. Brill,[4] Allen L. Gifford,[5] Stuart C. Gordon,[6] Michael A. Horberg,[7] Jacob G. Manthey,[8] Nancy Reau,[9] Vinod K. Rustgi,[10] and Zobair M. Younossi[11]

[1]Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; [2]Saint Louis University School of Medicine, St. Louis, Missouri; [3]VA Puget Sound Health Care System, Seattle, WA and University of Washington School of Medicine and [4]Predictive Health LLC, Paradise Valley, Arizona; [5]Boston University and VA Center for Healthcare Organization and Implementation Research, Boston, Massachusetts; [6]Henry Ford Health System, Detroit, Michigan; [7]Mid-Atlantic Permanente Research Institute, Kaiser Permanente Mid-Atlantic States, Rockville; [8]American Gastroenterological Association, Bethesda, Maryland; [9]Rush University Medical Center, Chicago, Illinois; [10]Robert Wood Johnson School of Medicine, New Brunswick, New Jersey; and [11]Virginia Commonwealth University and Inova Fairfax Hospital, Falls Church, Virginia

Chronic hepatitis C virus (HCV) infection is a common condition that affects more than 2.7 million individuals in the US.[1] New direct acting antiviral (DAA) treatments offer an unprecedented opportunity to cure HCV. In clinical trials as well as clinical practice, DAA treatments have resulted in sustained virological response (SVR–a surrogate for virological cure) in 90-100% of patients.[2–8] The population-level effectiveness of DAA remains limited by low rates of HCV case screening and identification[9]. However, recent updates in HCV screening guidelines recommend one-time testing for all persons born between 1945 and 1965,[10] which is expected to increase the number of individuals diagnosed with and subsequently treated for HCV.

The goal of the HCV Clinical Pathway is to provide guidance on the cascade of care and best practices for managing US-based patients with HCV in order to deliver value-based, efficient, safe, and effective care. The Pathway encompass the entire care spectrum of patients with HCV—from outreach and screening, to initial evaluation, antiviral treatment, and post treatment follow up care (Figure 1 outlines the scope of HCV Clinical Pathway). The target audience includes clinicians involved in managing patients with HCV (internists, infectious disease specialists, gastroenterologists and hepatologists, advanced practice providers, and others) as well as healthcare systems and plans in the US. Given the diversity in healthcare delivery systems across the world, this pathway may not be generalizable to patients and clinicians outside of the US.

Outreach and Screening

The first section of the HCV clinical pathway addresses active outreach and screening of individuals at risk for HCV. Approximately 50% of Americans with chronic HCV are unaware of their infection status, and far fewer have received curative antiviral therapy.[11] Therefore, needs exist both for increased screening to identify people with unrecognized infections, as well as for better processes to link diagnosed patients to antiviral treatment. Taskforce members recommend tailoring HCV outreach strategies to a variety of populations (Figure 2).

HCV screening is recommend for all persons born between 1945-1965, and for anyone with transmission risk factors (eg, history of injection drug use, transfusion or organ transplant before 1992, received clotting factors before 1987, history of long-term dialysis, HIV infection, persistently elevated liver enzymes, healthcare and public safety workers after needle sticks, sharps, or mucosal exposure to HCV-positive blood, and children born to HCV-positive women).[12–15] A large body of work supports the use of one-time HCV screening for at-risk patients, meriting its inclusion as a core measure in the Centers for Medicare and Medicaid Services quality reporting programs.[16] Additionally, HCV antibody testing is a covered service under the Affordable Care Act and is available without financial penalty to all insured patients in the 1945–1965 birth cohort.

Interventions to promote HCV awareness and appropriate viral testing have shown promise in both outpatient and inpatient settings.[17] Leveraging data resources, such as electronic health records, has been associated with increased testing rates.[18–21] HCV disproportionately affects persons who inject drugs, and homeless or incarcerated individuals. Emergency Department-based HCV screening, HCV testing in incarcerated populations, and outreach to people who inject drugs are potential means to reach underserved individuals.[22–24] HCV-related educational resources are readily available for both patients and clinicians on the AGA website (www.gastro.org).

Once HCV infection is recognized, linkage-to-care interventions are important to ensure that patients are

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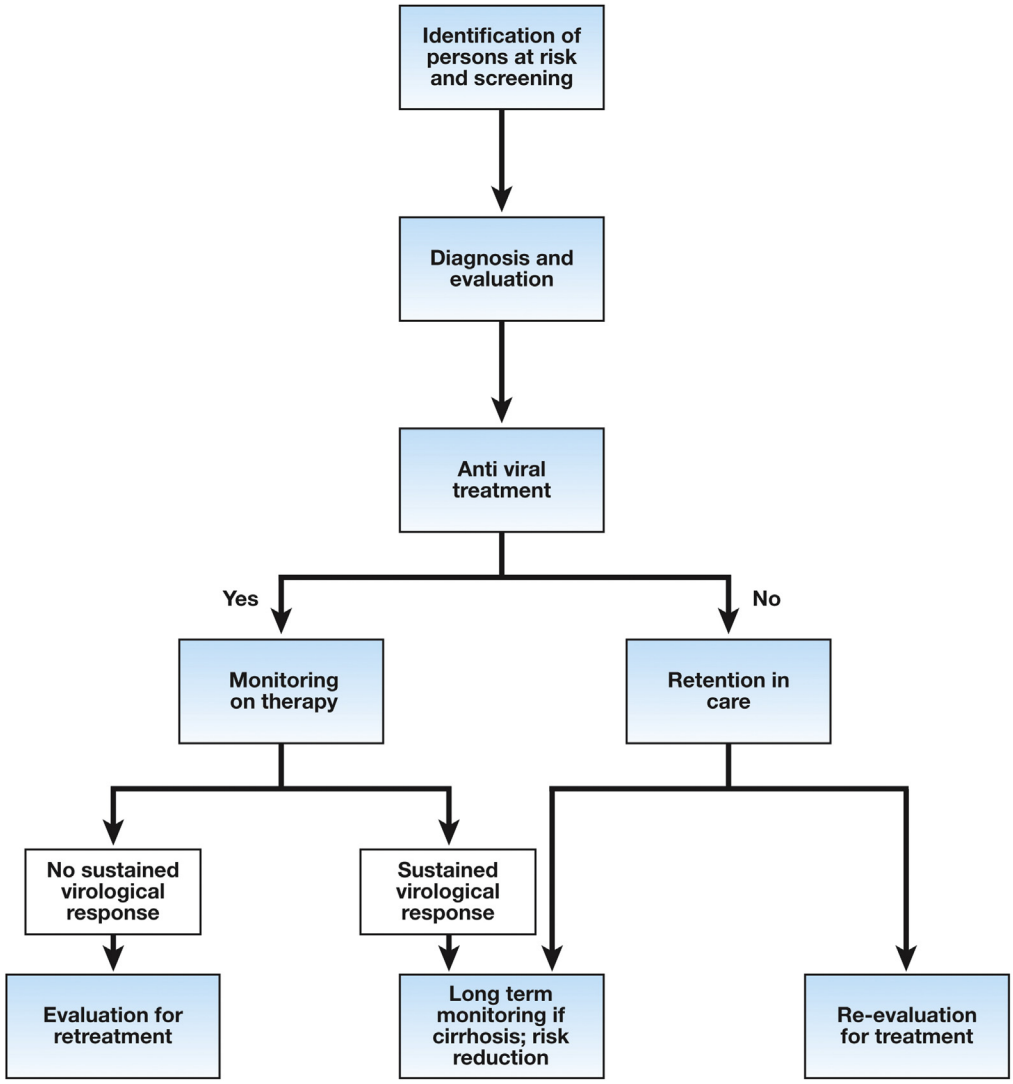

Figure 1. Overview of HCV care pathway.

afforded access to antiviral treatment.[25–27] Linkage to care may require the establishment or expansion of treatment referral networks and multidisciplinary teams. The use of support services, such as patient navigators, may reduce treatment barriers in selected circumstances.[17] Primary-care based HCV treatment, with appropriate specialty mentorship and support, may be a viable alternative for patients with limited specialty care access (see Organization of HCV Care Team section).[28]

Organization of HCV Care Team

Successful antiviral treatment requires coordination of clinical, behavioral, and administrative management activities. Significant public health impact requires outreach to engage populations that need treatment (as described in the previous section), followed by patient evaluation and prescribing, negotiation of prior authorizations, and treatment monitoring.

A multidisciplinary, patient-centered team approach is the optimal model for addressing these needs. Integrated multidisciplinary care has proven effective in improving HCV treatment initiation and SVR.[29] Examples of effective clinical team approaches are also found in HIV care, which similarly to HCV requires a high level of adherence and involves patients with complex behavioral and social problems.[30] Multidisciplinary teams for HCV care should encourage strong communication among team members, and place the patient at the center (Figure 3).

Practices will vary in their HCV caseloads, and thus the capacities of individual practices to dedicate staff to each role will likely vary. Some larger, more urban or safety-net practices may require larger teams, while smaller practices may access mental health or pharmacy clinical services through well-developed referral or "warm-handoff" arrangements. The size and configurations of patient-centered care teams depend on individual patient preferences and healthcare needs.[31] Connecting "spokes" of this team model may, in some circumstances, be created through use of remote telemedicine or related technologies (eg, Project Extension for Community Healthcare Outcomes

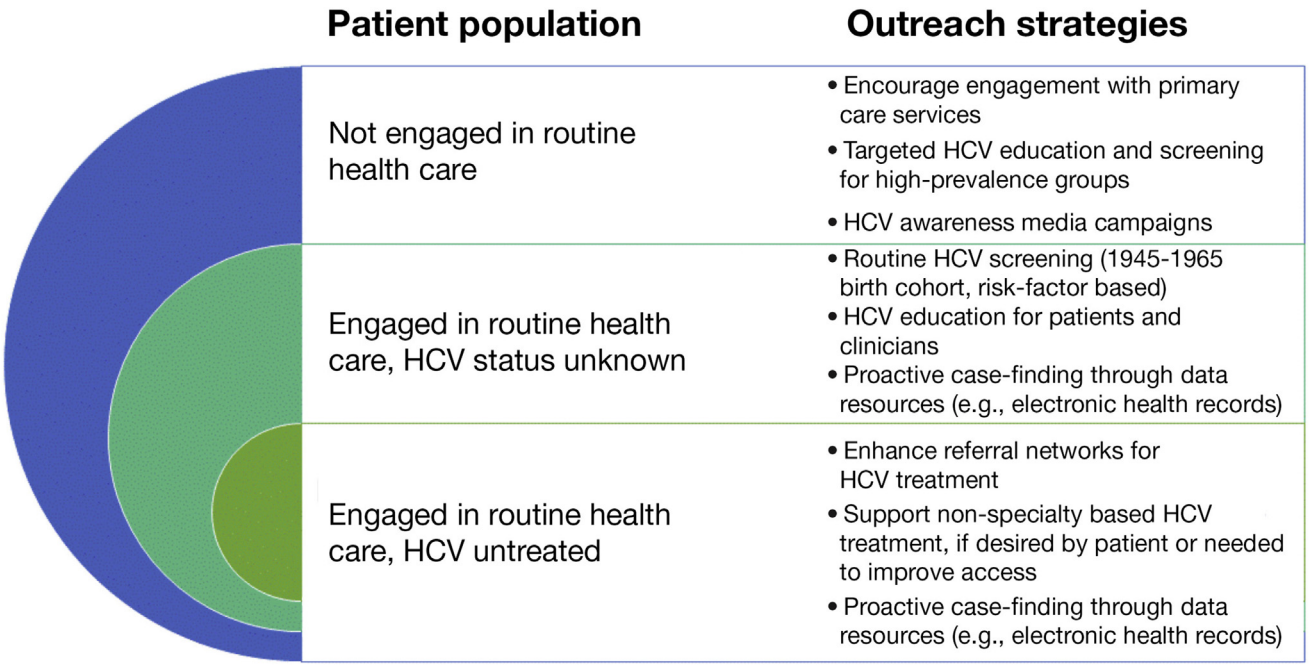

Figure 2. Outreach to patients not in treatment.

[ECHO]) to enable delivery of HCV care to remote settings.[28]

Within teams, pre-treatment evaluation and prescribing of HCV treatment is in the hands of an appropriate specialist, who may be trained in hepatology, gastroenterology, or infectious diseases, but in some cases with appropriate training and support, could be a general internist, or other primary care provider. The role of care coordinator is essential, generally serving as the principal point of contact for the patient, and assuring continuity of all aspects of treatment care. Care coordination may be done by a nurse, social worker, health technician, or another appropriate team member depending on the clinic configuration. Care coordination may involve case management, including prior authorization and benefits management. The clinical pharmacist can play an essential role in pre-treatment assessment for drug interactions, monitoring adherence, and preventing waste and diversion of expensive medications. Finally, access to mental health and substance abuse treatment is important, to help address the high prevalence of behavioral and mental health problems.

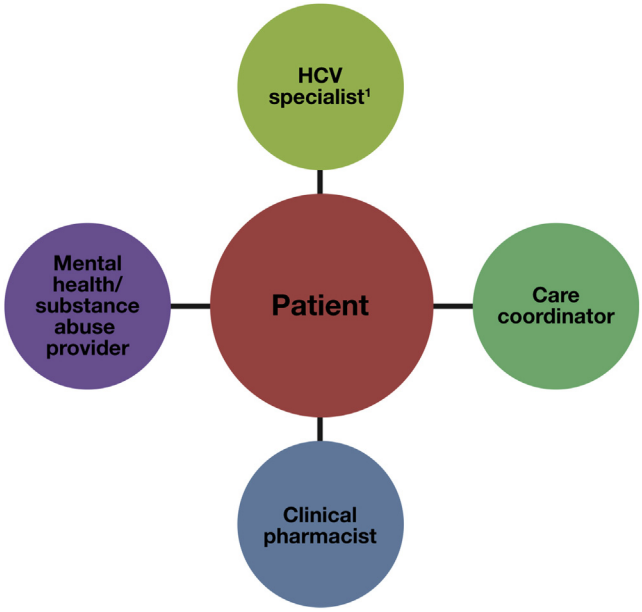

Figure 3. Composition of a clinical team.

Initial Evaluation of Patients With HCV

The initial assessment of an individual infected with HCV requires clinicians to efficiently gather data to weigh the risk of disease progression against the benefit of viral eradication. Although HCV eradication is considered beneficial in virtually all infected persons a patient must be physically and mentally ready for treatment. Conditions that could compromise treatment success must be carefully considered.

The first visit is an opportunity to assess medical conditions that may contribute to progression, risk of complications or impact the selection of treatment regimen (Figure 4). Physical examination and laboratory testing should be targeted to evaluate for conditions that impact treatment decisions, identify patients at risk for progression of liver fibrosis or advanced liver disease, and screen for HCV extra-hepatic manifestations. Some laboratory tests may be necessary to meet the requirements of the patient's health insurance provider.

Figure 5 displays the algorithm to evaluate patients for the degree of liver disease severity, including fibrosis and cirrhosis). The presence of stigmata of decompensated cirrhosis on physical examination (ascites, encephalopathy,

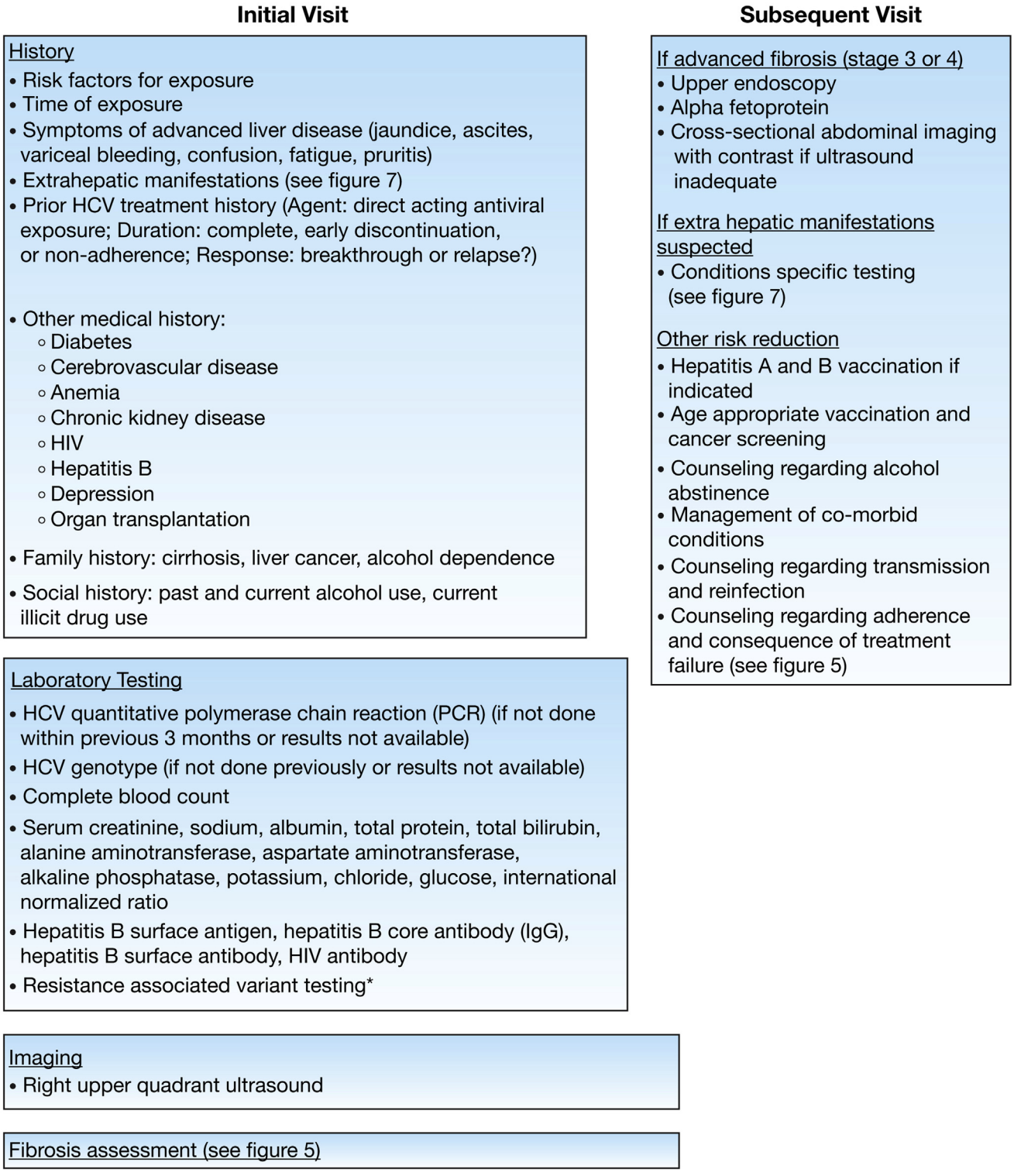

Figure 4. Diagnosis and evaluation.

etc.) indicate the need for abdominal imaging to both confirm the diagnosis of cirrhosis and rule out liver cancer. Such confirmation obviates the need for the various noninvasive measures of fibrosis, and biopsy would only be necessary if there was doubt as to etiology (ie, assess for concomitant non-alcoholic fatty liver disease). In the absence of clinically

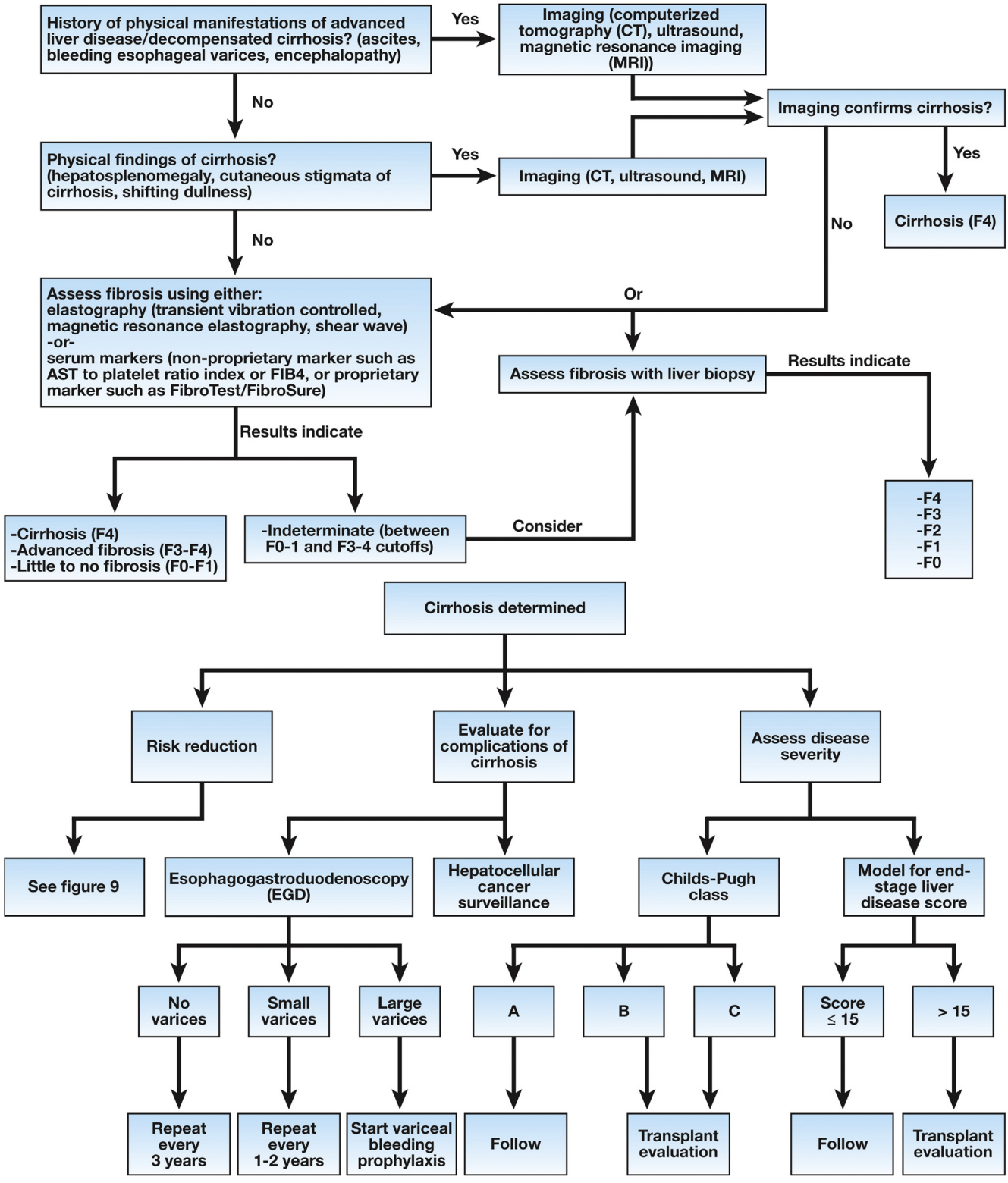

Figure 5. HCV fibrosis assessment algorithm.

apparent cirrhosis, there is the need to assess degree of liver fibrosis. Such assessment can be done noninvasively via elastography (usually "vibration-controlled" or Fibroscan®), serum biomarkers (FIB4 or aspartate aminotransferase to platelet ratio index), or various proprietary markers.[32] The routine use of the invasive gold standard liver biopsy has become less popular, recognizing that even liver biopsy may miss the presence of cirrhosis. The results of non-invasive

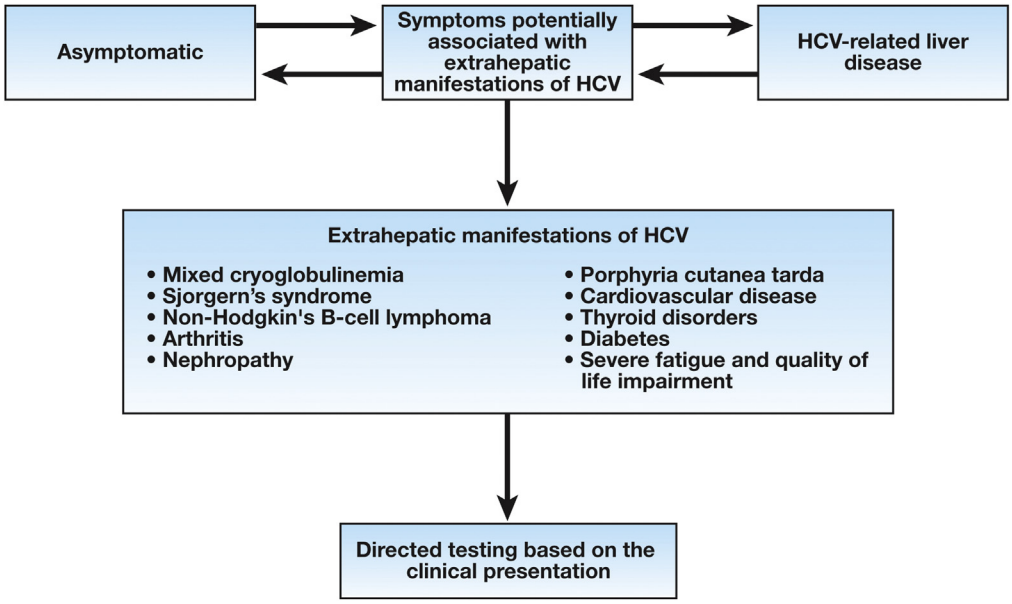

Figure 6. Assess disease severity.

Table 1. Clinical Assessment and Diagnosis of Extrahepatic Manifestation of HCV

Clinical presentation	Diagnostic investigation	Diagnosis
Orthostatic purpura, skin ulcers, ischemic digits, arthralgia, peripheral neuropathy	• Serum cryoblobulins, low C4, RF+ • Skin biopsy showing leukocytoclastic vasculitis	Mixed Cryoglobulinemia
Mono/oligo-arthritis	• Non-erosive synovitis (x-ray) • RF+, anti-CCP-,	Arthritis
Xerostomia Xeroftalmia	• Schirmer's test+, mild salivary gland involvement • Absent or low titer autoAntibody (ANA/ENA)	Sicca Syndrome
Skin hyperpigmentation, erosions at sun-exposed areas and bullae	• Elevated serum & urinary porphyrins, URO-D deficiency	Porphyria Cutanea Tarda
Hypothyroidism	• Increased TSH, anti-Tg/TPO Ab • Ultrasonographic alterations, FNA	Thyroiditis
Peripheral sensory/moto neuropathy fatigue, depression, cognitive disorder, stroke	• EMG alterations • Doppler-US of cranial vessels • Brain MRI/PET, CT • Neuropsychiatric evaluation	Neuropathy and central nervous system involvement
Edema and/or hypertension	• Proteinuria, increased serum creatinine • Glomerulonephritis at renal biopsy	Glomerulonephritis
Arterial ischemic disease or heart failure	• Arterial and cardiac Doppler- US studies • EKG • Cardiac stress test • ?angiogram	Cardiovascular disease
Adenopathy, splenomegaly, cytopenias, lymphocytosis, monoclonal components, systemic symptoms	• Nodal or extranodal biopsy, bone marrow biopsy, CT/PET scan	Non-Hodgkin's B-cell Lymphoma
Chronic fatigue and impaired quality of life	• Rule out other chronic diseases (hypothyroidism, fatty liver, rheumatologic disorders)- medical evaluation • Rule out psychiatric disorders (depression), psychological evaluation	HCV –related chronic fatigue

ANA, anti-nuclear antibody; anti-CCP, cyclic citrullinated peptide antibodies; anti-Tg/TPO, anti-thyroid antibodies; C4, complement 4; CT, computerized tomography; RF, rheumatoid factor; EKG, electrocardiogram; EMG, electromyogram; ENA, extractable nuclear antigen; FNA, fine needle aspiration; MRI, magnetic resonance imaging; PET, Positron emission tomography; TSH, thyroid stimulating hormone; URO-D, uroporphyrinogen decarboxylase (URO-D); US, ultrasound.

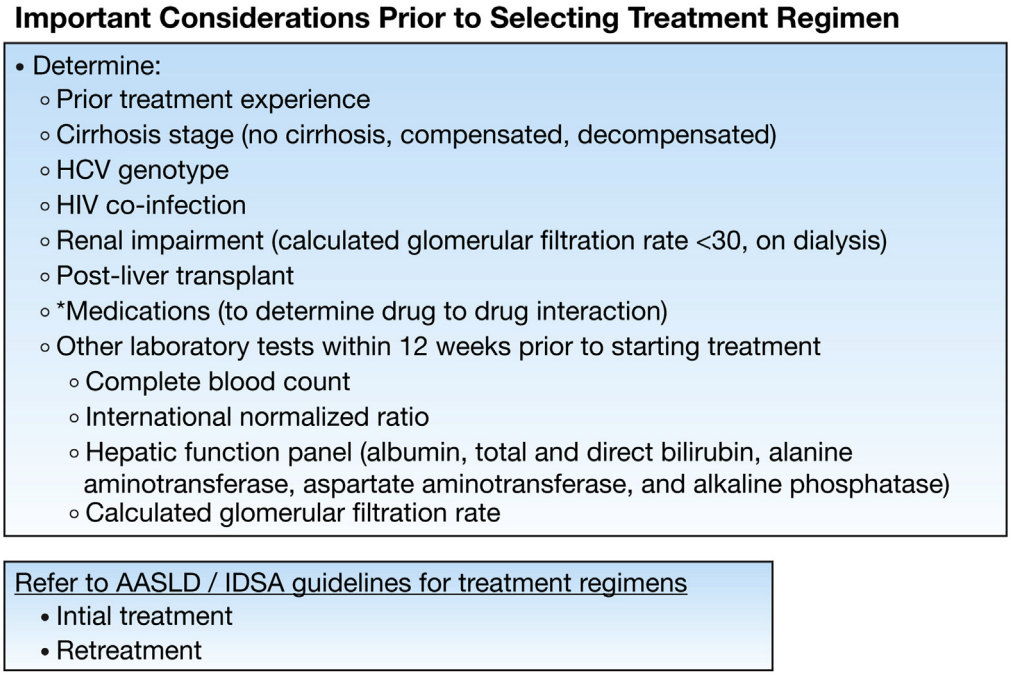

Figure 7. Algorithm assessing extrahepatic manifestation of HCV.

studies provide helpful information to patient and clinician regarding fibrosis stage, though all may suffer from occasional false readings and must be tempered by clinical judgment. Concordant results on two non-invasive studies (such a FIB-4 and Fibroscan) may preclude the need for invasive or expensive testing to assess liver fibrosis.

Patients should be assessed for signs and symptoms of extrahepatic manifestations, which may indicate a compelling need for treatment. Some EHMs have mild or moderate clinical presentations (sicca syndrome, arthralgia, peripheral neuropathy) while others present with life-threatening complications such as intestinal vasculitis and malignant

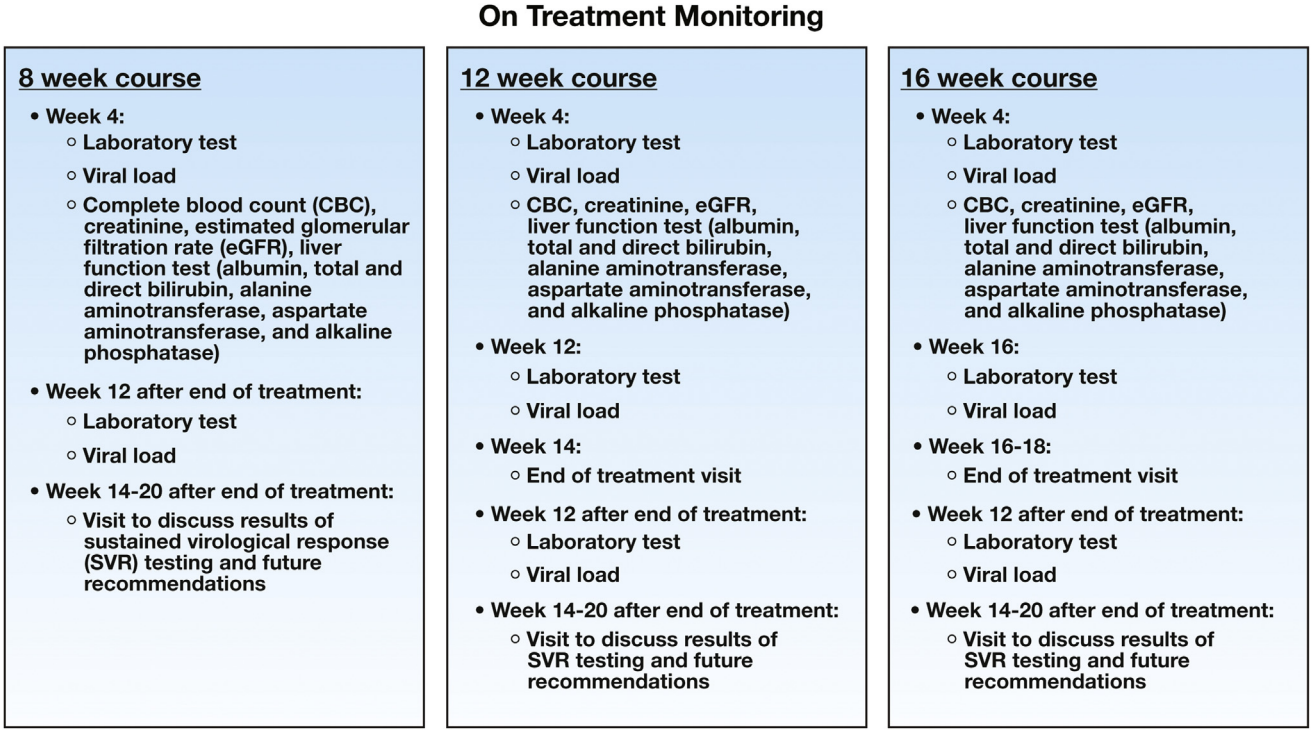

Figure 8. Monitoring while on antiviral treatment.

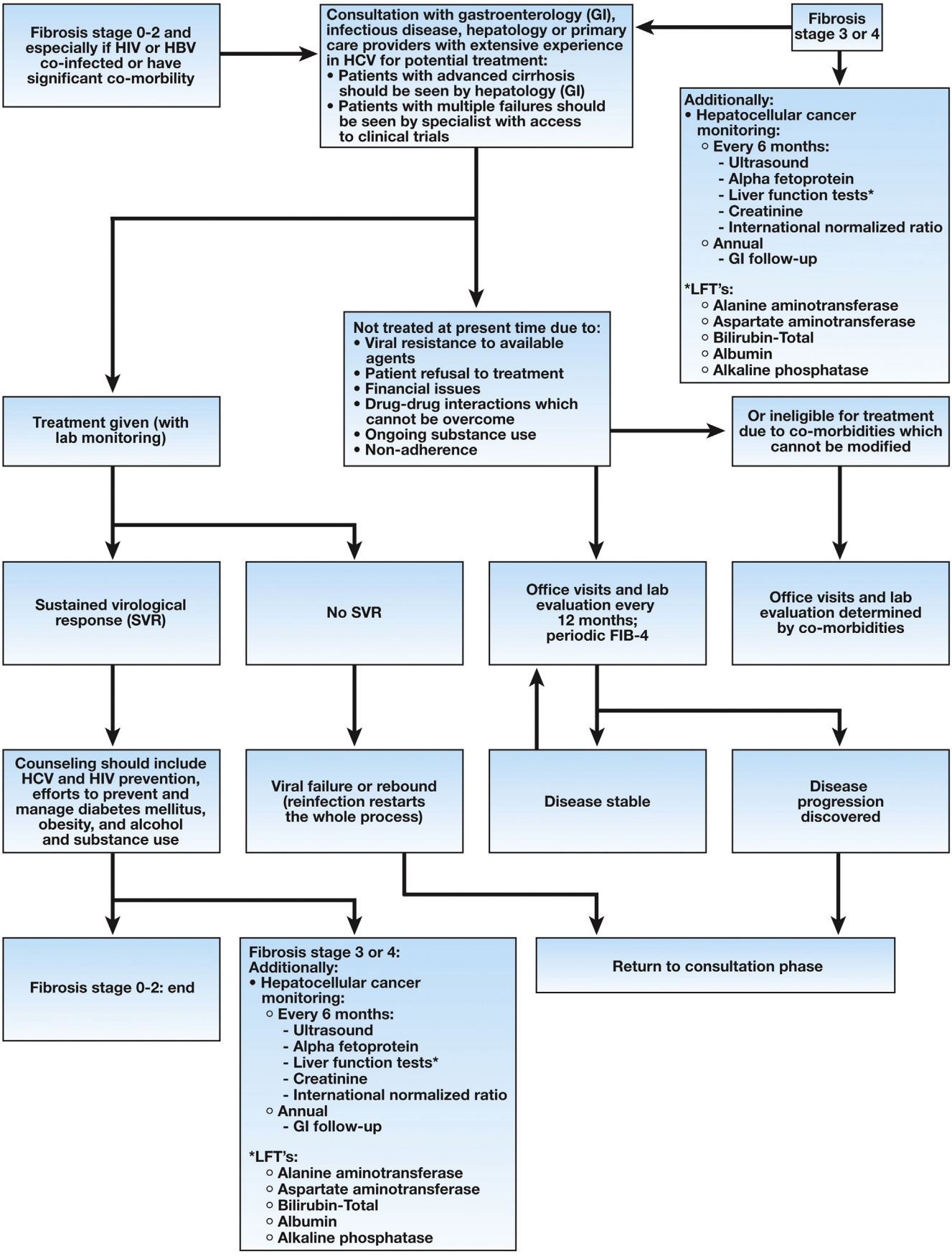

Figure 9. Long-term follow-up.

complications. Occasionally, extrahepatic manifestations have no or minimal clinical manifestation and are discovered during routine laboratory testing of HCV infected patients. In this context, it is important to note that testing and management should be focused on the symptomatic patients with extrahepatic manifestations (Figure 6).

Diagnostic testing for various extrahepatic manifestations will depend on the clinical presentation and will be based on the established diagnostic modalities of the specific condition (Table 1). Once diagnosed, both extrahepatic manifestation-specific and HCV-specific treatment must be considered.

The second visit is an ideal time for continued patient education and obtaining follow-up data for conditions identified at the first assessment. This visit offers an opportunity to initiate treatment or treatment planning. This visit is particularly important for individuals with cirrhosis who require ongoing management and surveillance for cirrhosis complications (see Section on follow-up care) and those with extrahepatic manifestations who require treatment of both HCV and specific extrahepatic manifestations.

Figure 7 displays the characteristics that guide selection of appropriate type and duration of DAA regimen. These factors are determined from patient history and laboratory assessment discussed in the previous section. Figure 7 also shows the laboratory tests that should be performed prior to the initiation of DAA treatment. HCV treatment recommendations are changing at a fast pace. Given the scope of the HCV Pathway, the Taskforce recommended referring to the American Association for the Study of Liver Disease and Infectious Diseases Society of America guidance on antiviral treatment. Figure 8 presents the frequency of laboratory monitoring as well as clinic visits for patients who are on treatment.

Post Treatment Monitoring and Follow-up Care

Appropriate follow up recommendations and ongoing linkage to liver-related care is important for excellent HCV care (Figure 9). Patients who do not achieve SVR after antiviral treatment should continue to receive ongoing monitoring for progressive liver fibrosis. Alternative antiviral treatments should be considered. At this point, patients may be referred to an experienced HCV provider, preferably one with access to clinical trials for patients who did not respond to the current DAAs.

Follow up recommendations for patients who achieve SVR vary based on the stage of liver fibrosis. In patients with fibrosis stage of $\leq$2, the care course can be considered complete. However, prior to discharge from liver care, patients with ongoing high-risk behaviors (eg, street drug use or high risk sexual exposure) should be educated about the risk of re-infection. Patients should be educated about risk of progressive disease in the presence of other potential causes of liver disease, such as excessive alcohol use and nonalcoholic fatty liver disease. Liver-related care should continue for patients with advanced fibrosis (fibrosis stage 3 or 4) at the time of SVR and should include liver cancer screening and monitoring of liver function every 6 months. Annual follow-up with liver/GI specialty care is recommended. Patients with established cirrhosis should be periodically screened for gastroesophageal varices in accordance with AGA guidelines.

Antiviral treatment can be deferred for many reasons, including: viral resistance to available agents, patient refusal, drug-drug interactions which cannot be overcome, or other biopsychosocial issues. Regular monitoring to assess liver function is necessary. Also, periodic physical examination and consultation with the experienced HCV specialist is recommended. Treatment should be considered as soon as the underlying reason for deferring treatment is resolved.

Summary

The HCV Clinical Pathway provides guidance regarding the best practices for managing patients with HCV. By implementing HCV Care Pathway in practice settings, clinicians and healthcare systems will be able to provide care that is consistent with evidence based guidelines and available performance measures in the 2016 CMS PQRS HCV Measures Group.[33] The HCV Care Pathway will promote reduce variation in clinical practice and improve patient outcomes.

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Reprint requests
Address requests for reprints to: Jacob Manthey, Practice and Quality Manager, AGA National Office, 4930 Del Ray Avenue, Bethesda, Maryland, 20814. e-mail: jmanthey@gastro.org.

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This care pathway framework is not intended to impose requirements on practices or to establish a local, regional, or national legal standard of care. There are various appropriate treatment modalities for each patient, and the physician must use his or her judgement in selecting from among feasible treatment options. The ultimate judgement regarding appropriateness of any specific procedure or course of action must be made by the physician along with the patient, in light of all the circumstances presented. All that should be expected is that the physician will follow a reasonable course of action

based on current knowledge, available resources, and the needs of the patient, in order to deliver effective and safe medical care.

Conflicts of interest

The authors disclose the following: Bruce R. Bacon has completed promotional lectures for AbbVie, BMS, Gilead, Merck, and Salix; paid on a per lecture basis. Joel V. Brill personally owns shares in Endochoice and is a consultant for GeneNews. Stuart C. Gordon sits on the advisory board for Gilead, Merck, AbbVie, Intercept, and BMS; provides grant and research support for Gilead, Merck, AbbVie, Intercept, CymaBay, Exalenz, Conatus, and BMS; is a member of the speaker's bureau for Gilead; and is a scientific advisor for CVS-Caremark. Nancy Reau is a member of the US National Advisory Boards for Abbvie, Gilead, Merck, and BMS. Vinod K. Rustgi sits on the advisory boards of Gilead, Merck, and AbbVie and the speaker's bureau for Gilead, AbbVie, BMS, and Salix. Zobair M. Younossi provides consulting services or has received research funds from Intercept, Gilead, BMS, GSK, and Tobira. The remaining authors disclose no conflicts.