2023 Year in Review

CLDF

Chronic Liver Disease Foundation

Unparalleled expertise, unprecedented access

Letter from the President

The Chronic Liver Disease Foundation (CLDF), a distinguished not-for-profit educational organization, proudly commemorates its 22nd anniversary. Guided by an all-volunteer board of trustees, the CLDF has consistently excelled in the field, offering outstanding educational programs covering comprehensive updates on liver disease.

A recent highlight in liver education is the evolution of the Liver Connect meeting. Following the success of the 3rd annual Liver Connect Conference, which educated over 550 live attendees and 999 virtual learners to date, we eagerly anticipate the 4th Annual CLDF Liver Connect Conference to be held in Scottsdale, Arizona, in April.

As the flagship educational CLDF conference, Liver Connect showcases worldwide experts, delivering cutting-edge educational presentations in an interactive format. Distinguished hepatologists spearhead educational content development, including emerging data from recent publications and congress abstracts, influencing current diagnostic and management approaches. Specialized sessions centered on NASH, cirrhosis, HBV-HDV, and women with liver disease deliver the most up-to-date and crucial information in these areas.

As an organization, the CLDF continues to provide state-of-the-art education to all stakeholders. Live events, broadcasts, and enduring webcasts grant healthcare providers nationwide the opportunity to learn from esteemed specialists. Practical clinical guidelines and algorithms offer valuable insights for managing patients. The collaboration of ambassadors and advisors in guiding educational initiatives has solidified the CLDF's position as an unparalleled organization for over two decades.

The dedication and expertise of our program staff, CME-accredited providers, and network of collaborators have propelled the organization through another thriving year of impactful initiatives in 2023. The CLDF remains committed to delivering exceptional education in 2024, thanks to the unwavering support and contributions of all involved.

Our heartfelt gratitude extends to everyone who has contributed to making the CLDF the outstanding entity it has become.

Sincerely,

Zobair M. Younossi, MD, MPH

President and Chairman, CLDF Board of Trustees

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2023 Programs

Cholestatic Liver Disease

Cirrhosis

Hepatorenal Syndrome

HCC

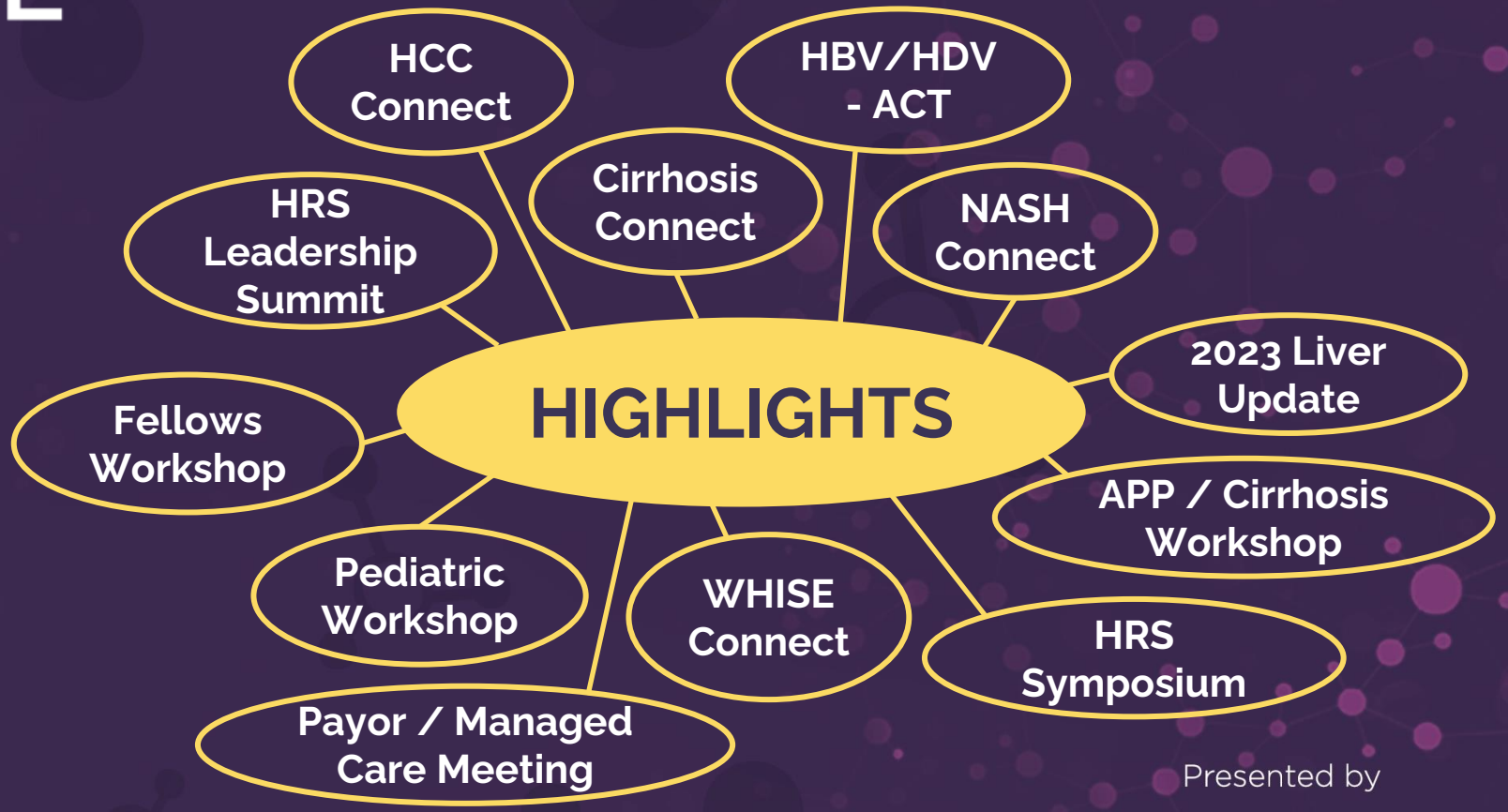
NAFLD/NASH

Pediatric Liver Disease

Viral Hepatitis

3RD ANNUAL LIVER CONNECT CONFERENCE

12 live activities
12.75 CME AMA PRA credits



Educated over **550** live attendees and **>1,000** virtual learners to date.

Accredited by

PURDUE UNIVERSITY

Presented by

CLDF
Chronic Liver Disease Foundation

HCV Webcast and Podcast

Sponsored by AbbVie.

NASH PATHway to Treatment

Friday, January 6, 2023

This activity is jointly provided by Medical Education Resources and the Chronic Liver Disease Foundation

Supported by an educational grant from Novo Nordisk, Inc.

Faculty

Michael Charlton, MBBS, FRCP
University of Chicago
Chicago, Illinois, USA

Rohit Loomba, MD, MHSc
University of California San Diego
San Diego, California, USA

Maru E. Rinella, MD
University of Chicago
Chicago, Illinois, USA

This symposium reviewed the pathophysiology, risk factors, clinical consequences, and guidelines for diagnosing and treating NAFLD/NASH.

Relevant advances and challenges in diagnosing and treating NASH and liver fibrosis, including the latest NASH screening guidelines.

Novel agents in development for the treatment of NASH were highlighted during this enlightening symposium.

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Introducing Recent HRS-AKI Advances into Clinical Care

Marcelo Kugelmas, MD

Nikolaos T. Pyrsopoulos, MD, PhD

https://chronicliverdisease.org/webcasts/special_event/HRS-AKI-Sympo23/

MEDICAL EDUCATION RESOURCES

This activity is jointly provided by Medical Education Resources and the Chronic Liver Disease Foundation.

Supported by an educational grant from Mallinckrodt Pharmaceuticals.

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2023 NEW ADVANCES IN HRS/AKI

CLINICAL UPDATE AND EXPERT RECOMMENDATIONS

This activity is jointly provided by Medical Education Resources and the Chronic Liver Disease Foundation.

MEDICAL EDUCATION RESOURCES

CLDF Chronic Liver Disease Foundation

Supported by an educational grant from Mallinckrodt Pharmaceuticals.

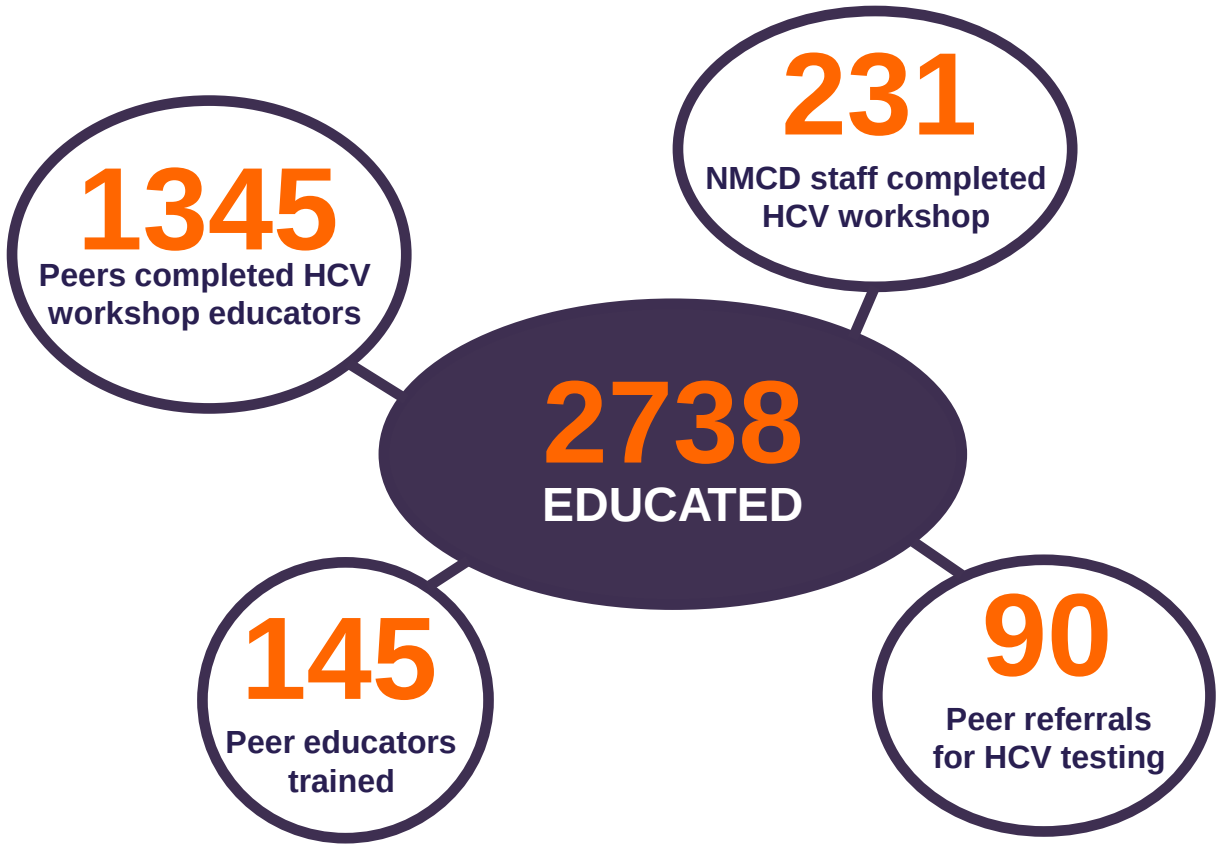
This ongoing series defines the prevalence, manifestations, and pathophysiology of Hepatorenal Syndrome (HRS) and reviews the diagnosis and management of Acute Kidney Injury in cirrhosis. The program discussions encompass updated HRS guidelines and recommendations, treatment goals in HRS, and the unmet treatment needs for HRS in the United States.

- 30 Meetings across the US
- 20 CLDF faculty participants
- 718 Attendees educated

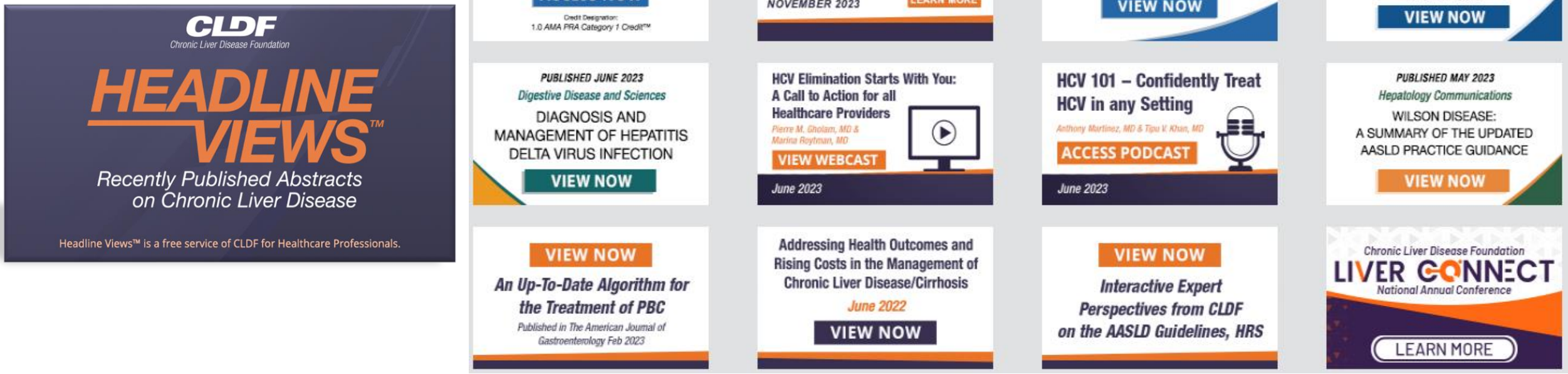
2023 Highlights CLDF & Project ECHO Collaboration Accomplishments:

The CLDF and The New Mexico Peer Education Project (NMPEP), continued collaborating with Project ECHO at the University of New Mexico Health Sciences Center and the New Mexico Corrections Department, leveraging the ECHO Model to make a powerful and lasting intervention in prison community health.

Supported by an educational grant from AbbVie.

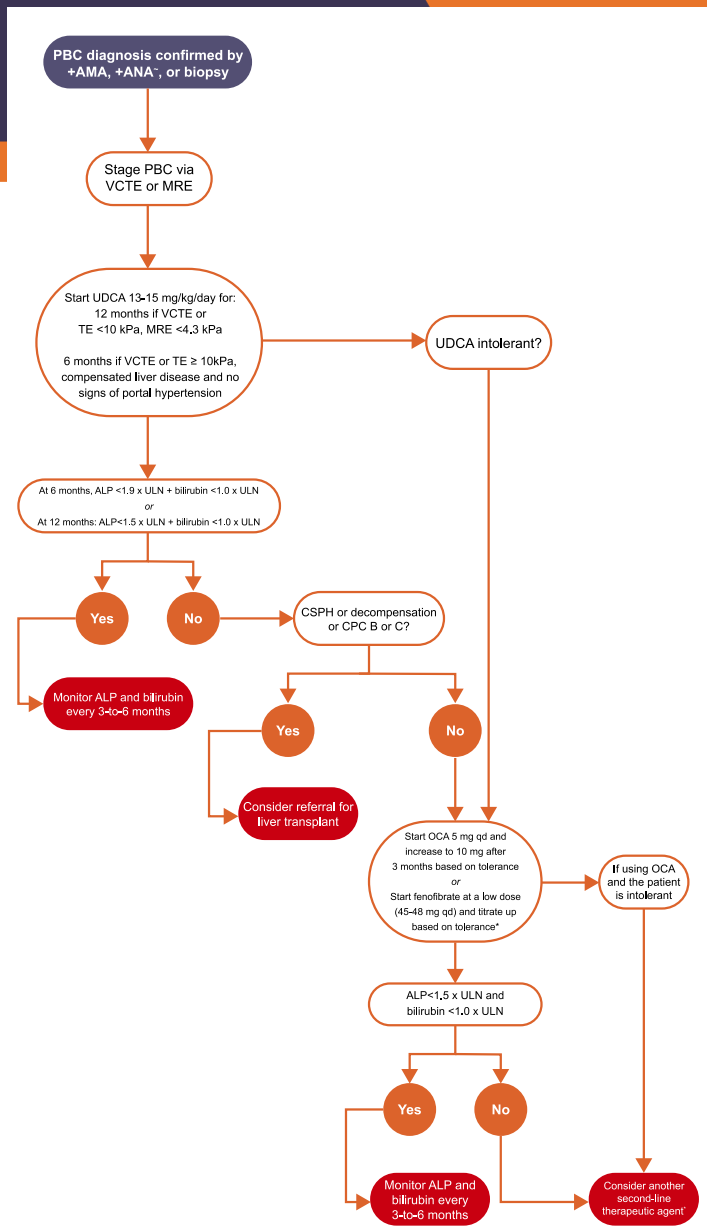


CLDF Education Portal
Online Tools – Featured Resources



An Up-To-Date Algorithm for the Treatment of PBC
Published in the American Journal of Hepatology Feb 2023

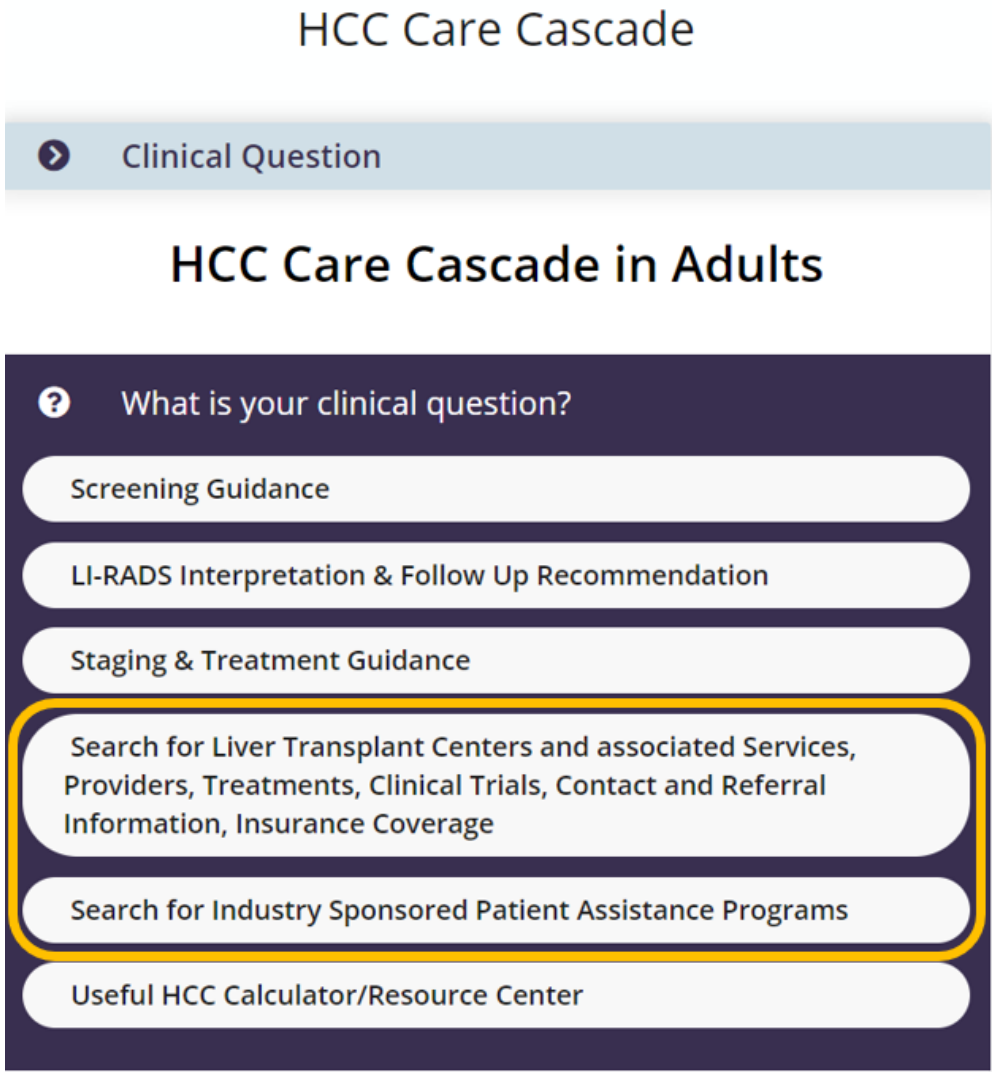
The key features of the algorithm include new guidance-informed suggestions for staging PBC using noninvasive testing (NIT), earlier assessment of lower thresholds to gauge ursodeoxycholic acid (UDCA) response after initiation of therapy, possible earlier initiation of second-line therapy with obeticholic acid (OCA) at lower levels of alkaline phosphatase (ALP) or bilirubin, avoidance of OCA in patients with cirrhosis complicated by portal hypertension or liver decompensation, and the safety and durability of response with long-term OCA therapy and off-label use of fibrates.



Unrestricted education grant supported by Intercept

HCC Care Cascade Decision-Support Tool

https://www.chronicliverdisease.org/disease_focus/hcc.cfm?dstate=hcc&sec=Algorithm



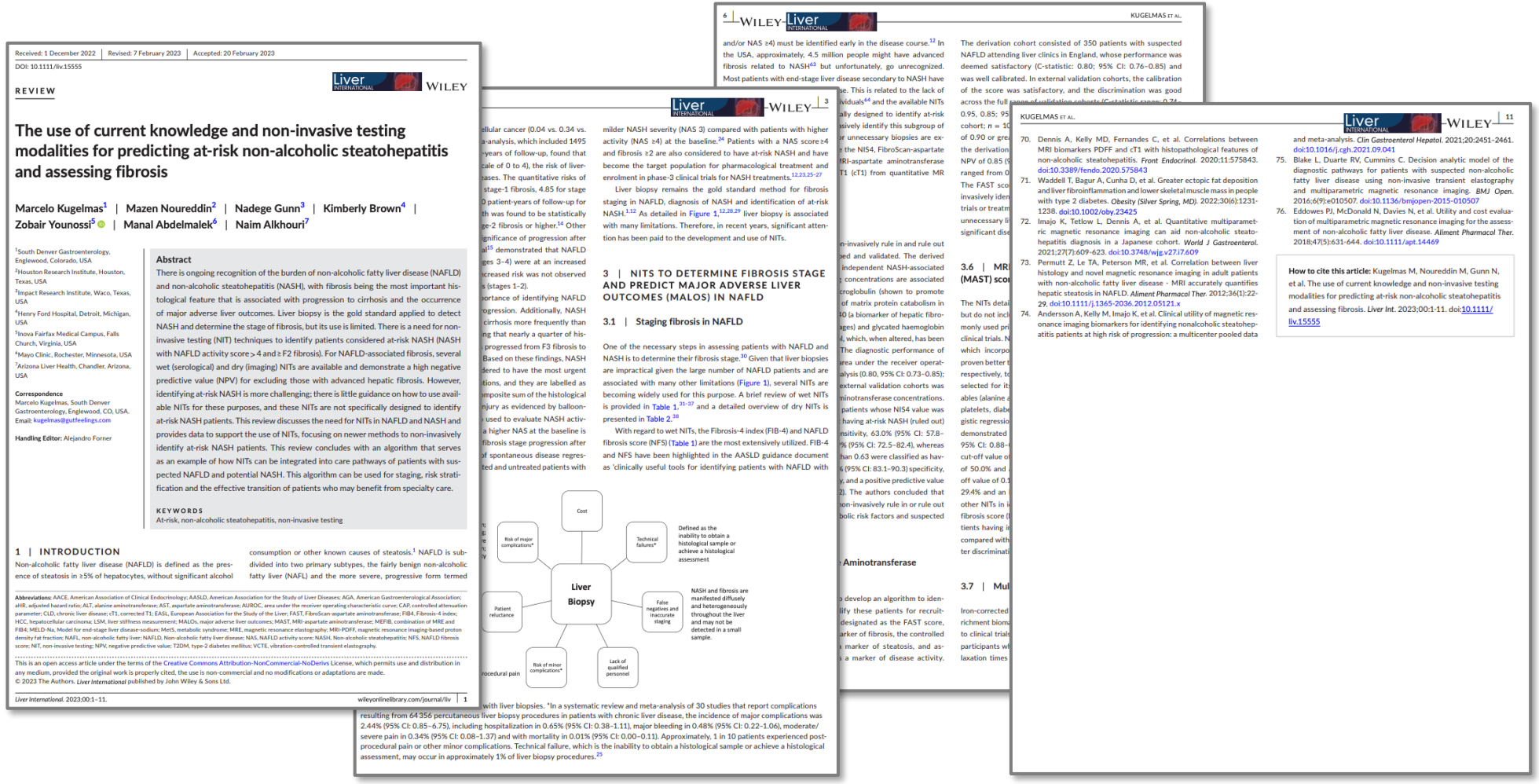
Supported by educational grants from AstraZeneca and Exelixis, Inc.

Publications

The use of current knowledge and non-invasive testing modalities for predicting at-risk non-alcoholic steatohepatitis and assessing fibrosis

Liver International

Feb. 2023



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DOI: 10.1111/liv.15555

REVIEW

Liver INTERNATIONAL WILEY

The use of current knowledge and non-invasive testing modalities for predicting at-risk non-alcoholic steatohepatitis and assessing fibrosis

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Abstract

There is ongoing recognition of the burden of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), with fibrosis being the most important histological feature that is associated with progression to cirrhosis and the occurrence of major adverse liver outcomes. Liver biopsy is the gold standard applied to detect NASH and determine the stage of fibrosis, but its use is limited. There is a need for non-invasive testing (NIT) techniques to identify patients considered at-risk NASH (NASH with NAFLD activity score > 4 and ≥ F2 fibrosis). For NAFLD-associated fibrosis, several wet (serological) and dry (imaging) NITs are available and demonstrate a high negative predictive value (NPV) for excluding those with advanced hepatic fibrosis. However, identifying at-risk NASH is more challenging; there is little guidance on how to use available NITs for these purposes, and these NITs are not specifically designed to identify at-risk NASH patients. This review discusses the need for NITs in NAFLD and NASH and provides data to support the use of NITs, focusing on newer methods to non-invasively identify at-risk NASH patients. This review concludes with an algorithm that serves as an example of how NITs can be integrated into care pathways of patients with suspected NAFLD and potential NASH. This algorithm can be used for staging, risk stratification and the effective transition of patients who may benefit from specialty care.

KEYWORDS
At-risk, non-alcoholic steatohepatitis, non-invasive testing

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of steatosis in ≥5% of hepatocytes, without significant alcohol consumption or other known causes of steatosis.[1] NAFLD is subdivided into two primary subtypes, the fairly benign non-alcoholic fatty liver (NAFL) and the more severe, progressive form termed

Abbreviations: AACE, American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; aHR, adjusted hazard ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; CLD, chronic liver disease; cT1, corrected T1; EASL, European Association for the Study of the Liver; FAST, FibroScan-aspartate aminotransferase; FIB4, Fibrosis-4 index; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; MALOs, major adverse liver outcomes; MAST, MRI-aspartate aminotransferase; MEFIB, combination of MRE and FIB4; MELD-Na, Model for end-stage liver disease-sodium; MetS, metabolic syndrome; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; NAFL, non-alcoholic fatty liver; NAFLD, Non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, Non-alcoholic steatohepatitis; NFS, NAFLD fibrosis score; NIT, non-invasive testing; NPV, negative predictive value; T2DM, type-2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

milder NASH severity (NAS 3) compared with patients with higher activity (NAS ≥4) at the baseline.[24] Patients with a NAS score ≥4 and fibrosis ≥2 are also considered to have at-risk NASH and have become the target population for pharmacological treatment and enrolment in phase-3 clinical trials for NASH treatments.[12,23,25–27]

Liver biopsy remains the gold standard method for fibrosis staging in NAFLD, diagnosis of NASH and identification of at-risk NASH.[1,12] As detailed in Figure 1,[12,28,29] liver biopsy is associated with many limitations. Therefore, in recent years, significant attention has been paid to the development and use of NITs.

3 | NITS TO DETERMINE FIBROSIS STAGE AND PREDICT MAJOR ADVERSE LIVER OUTCOMES (MALOS) IN NAFLD

3.1 | Staging fibrosis in NAFLD

One of the necessary steps in assessing patients with NAFLD and NASH is to determine their fibrosis stage.[30] Given that liver biopsies are impractical given the large number of NAFLD patients and are associated with many other limitations (Figure 1), several NITs are becoming widely used for this purpose. A brief review of wet NITs is provided in Table 1,[31–37] and a detailed overview of dry NITs is presented in Table 2.[38]

With regard to wet NITs, the Fibrosis-4 index (FIB-4) and NAFLD fibrosis score (NFS) (Table 1) are the most extensively utilized. FIB-4 and NFS have been highlighted in the AASLD guidance document as 'clinically useful tools for identifying patients with NAFLD with

with liver biopsies. *In a systematic review and meta-analysis of 30 studies that report complications resulting from 64 356 percutaneous liver biopsy procedures in patients with chronic liver disease, the incidence of major complications was 2.44% (95% CI: 0.85–6.75), including hospitalization in 0.65% (95% CI: 0.38–1.11), major bleeding in 0.48% (95% CI: 0.22–1.06), moderate/severe pain in 0.34% (95% CI: 0.08–1.37) and with mortality in 0.01% (95% CI: 0.00–0.11). Approximately, 1 in 10 patients experienced post-procedural pain or other minor complications. Technical failure, which is the inability to obtain a histological sample or achieve a histological assessment, may occur in approximately 1% of liver biopsy procedures.[25]

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Wilson disease: A summary of the updated AASLD Practice Guidance

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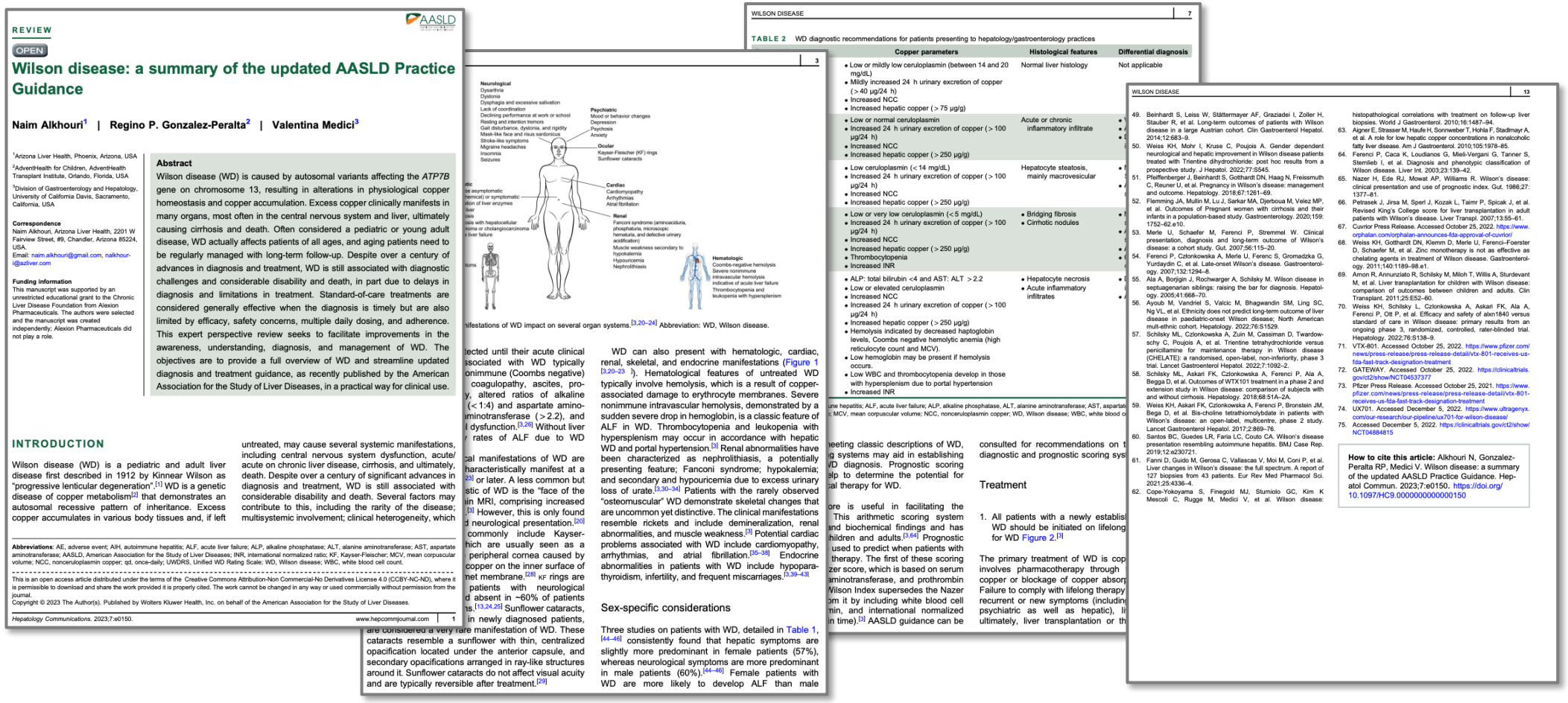

REVIEW

OPEN

Wilson disease: a summary of the updated AASLD Practice Guidance

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Abstract

Wilson disease (WD) is caused by autosomal variants affecting the *ATP7B* gene on chromosome 13, resulting in alterations in physiological copper homeostasis and copper accumulation. Excess copper clinically manifests in many organs, most often in the central nervous system and liver, ultimately causing cirrhosis and death. Often considered a pediatric or young adult disease, WD actually affects patients of all ages, and aging patients need to be regularly managed with long-term follow-up. Despite over a century of advances in diagnosis and treatment, WD is still associated with diagnostic challenges and considerable disability and death, in part due to delays in diagnosis and limitations in treatment. Standard-of-care treatments are considered generally effective when the diagnosis is timely but are also limited by efficacy, safety concerns, multiple daily dosing, and adherence. This expert perspective review seeks to facilitate improvements in the awareness, understanding, diagnosis, and management of WD. The objectives are to provide a full overview of WD and streamline updated diagnosis and treatment guidance, as recently published by the American Association for the Study of Liver Diseases, in a practical way for clinical use.

INTRODUCTION

Wilson disease (WD) is a pediatric and adult liver disease first described in 1912 by Kinnear Wilson as "progressive lenticular degeneration".[1] WD is a genetic disease of copper metabolism[2] that demonstrates an autosomal recessive pattern of inheritance. Excess copper accumulates in various body tissues and, if left untreated, may cause several systemic manifestations, including central nervous system dysfunction, acute/acute on chronic liver disease, cirrhosis, and ultimately, death. Despite over a century of significant advances in diagnosis and treatment, WD is still associated with considerable disability and death. Several factors may contribute to this, including the rarity of the disease; multisystemic involvement; clinical heterogeneity, which

Abbreviations: AE, adverse event; AIH, autoimmune hepatitis; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AASLD, American Association for the Study of Liver Diseases; INR, international normalized ratio; KF, Kayser-Fleischer; MCV, mean corpuscular volume; NCC, nonceruloplasmin copper; qd, once-daily; UWDRS, Unified WD Rating Scale; WD, Wilson disease; WBC, white blood cell count.

Neurological
Dysarthria
Dystonia
Dysphagia and excessive salivation
Lack of coordination
Declining performance at work or school
Resting and intention tremors
Gait disturbance, dystonia, and rigidity
Mask-like face and risus sardonicus
Stroke-like symptoms
Migraine headaches
Insomnia
Seizures

Psychiatric
Mood or behavior changes
Depression
Psychosis
Anxiety

Ocular
Kayser-Fleischer (KF) rings
Sunflower cataracts

Cardiac
Cardiomyopathy
Arrhythmias
Atrial fibrillation

Renal
Fanconi syndrome (aminoaciduria, phosphaturia, microscopic hematuria, and defective urinary acidification)
Muscle weakness secondary to hypokalemia
Hypouricemia
Nephrolithiasis

Hematologic
Coombs-negative hemolysis
Severe nonimmune intravascular hemolysis indicative of acute liver failure
Thrombocytopenia and leukopenia with hypersplenism

…nifestations of WD impact on several organ systems.[3,20–24] Abbreviation: WD, Wilson disease.

…ected until their acute clinical …ssociated with WD typically …onimmune (Coombs negative) … coagulopathy, ascites, pro- …y, altered ratios of alkaline … (< 1:4) and aspartate amino- …minotransferase (> 2.2), and … dysfunction.[3,28] Without liver … rates of ALF due to WD …

…cal manifestations of WD are …haracteristically manifest at a …23] or later. A less common but …stic of WD is the "face of the …in MRI, comprising increased …[3] However, this is only found … neurological presentation.[20] … commonly include Kayser- …hich are usually seen as a … peripheral cornea caused by … copper on the inner surface of … net membrane.[28] KF rings are … patients with neurological … absent in ~60% of patients …[13,24,25] Sunflower cataracts, … in newly diagnosed patients, … are considered a very rare manifestation of WD. These cataracts resemble a sunflower with thin, centralized opacification located under the anterior capsule, and secondary opacifications arranged in ray-like structures around it. Sunflower cataracts do not affect visual acuity and are typically reversible after treatment.[29]

WD can also present with hematologic, cardiac, renal, skeletal, and endocrine manifestations (Figure 1 [3,20–23]). Hematological features of untreated WD typically involve hemolysis, which is a result of copper-associated damage to erythrocyte membranes. Severe nonimmune intravascular hemolysis, demonstrated by a sudden severe drop in hemoglobin, is a classic feature of ALF in WD. Thrombocytopenia and leukopenia with hypersplenism may occur in accordance with hepatic WD and portal hypertension.[3] Renal abnormalities have been characterized as nephrolithiasis, a potentially presenting feature; Fanconi syndrome; hypokalemia; and secondary and hypouricemia due to excess urinary loss of urate.[3,30–34] Patients with the rarely observed "osteomuscular" WD demonstrate skeletal changes that are uncommon yet distinctive. The clinical manifestations resemble rickets and include demineralization, renal abnormalities, and muscle weakness.[3] Potential cardiac problems associated with WD include cardiomyopathy, arrhythmias, and atrial fibrillation.[35–38] Endocrine abnormalities in patients with WD include hypoparathyroidism, infertility, and frequent miscarriages.[3,39–43]

Sex-specific considerations

Three studies on patients with WD, detailed in Table 1, [44–46] consistently found that hepatic symptoms are slightly more predominant in female patients (57%), whereas neurological symptoms are more predominant in male patients (60%).[44–46] Female patients with WD are more likely to develop ALF than male

TABLE 2 WD diagnostic recommendations for patients presenting to hepatology/gastroenterology practices

Copper parameters	Histological features	Differential diagnosis
• Low or mildly low ceruloplasmin (between 14 and 20 mg/dL) • Mildly increased 24 h urinary excretion of copper (> 40 μg/24 h) • Increased NCC • Increased hepatic copper (> 75 μg/g)	Normal liver histology	Not applicable
• Low or normal ceruloplasmin • Increased 24 h urinary excretion of copper (> 100 μg/24 h) • Increased NCC • Increased hepatic copper (> 250 μg/g)	Acute or chronic inflammatory infiltrate	•
• Low ceruloplasmin (< 14 mg/dL) • Increased 24 h urinary excretion of copper (> 100 μg/24 h) • Increased NCC • Increased hepatic copper (> 250 μg/g)	Hepatocyte steatosis, mainly macrovesicular	•
• Low or very low ceruloplasmin (< 5 mg/dL) • Increased 24 h urinary excretion of copper (> 100 μg/24 h) • Increased NCC • Increased hepatic copper (> 250 μg/g) • Thrombocytopenia • Increased INR	• Bridging fibrosis • Cirrhotic nodules	•
• ALP: total bilirubin <4 and AST: ALT > 2.2 • Low or elevated ceruloplasmin • Increased NCC • Increased 24 h urinary excretion of copper (> 100 μg/24 h) • Increased hepatic copper (> 250 μg/g) • Hemolysis indicated by decreased haptoglobin levels, Coombs negative hemolytic anemia (high reticulocyte count and MCV). • Low hemoglobin may be present if hemolysis occurs. • Low WBC and thrombocytopenia develop in those with hypersplenism due to portal hypertension • Increased INR	• Hepatocyte necrosis • Acute inflammatory infiltrates	•

…une hepatitis; ALF, acute liver failure; ALP, alkaline phosphatase, ALT, alanine aminotransferase; AST, aspartat… …: MCV, mean corpuscular volume; NCC, nonceruloplasmin copper; WD, Wilson disease; WBC, white blood c…

…eeting classic descriptions of WD, …g systems may aid in establishing …VD diagnosis. Prognostic scoring …elp to determine the potential for …al therapy for WD.

…ore is useful in facilitating the … This arithmetic scoring system …nd biochemical findings and has …hildren and adults.[3,64] Prognostic … used to predict when patients with … therapy. The first of these scoring …zer score, which is based on serum …aminotransferase, and prothrombin …Wilson Index supersedes the Nazer …om it by including white blood cell …min, and international normalized …in time).[3] AASLD guidance can be consulted for recommendations on t… diagnostic and prognostic scoring sys…

Treatment

1. All patients with a newly establis… WD should be initiated on lifelong… for WD Figure 2.[3]

The primary treatment of WD is cop… involves pharmacotherapy through … copper or blockage of copper absor… Failure to comply with lifelong therapy … recurrent or new symptoms (includin… psychiatric as well as hepatic), li… ultimately, liver transplantation or th…

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Diagnosis and Management of Hepatitis Delta Virus Infection

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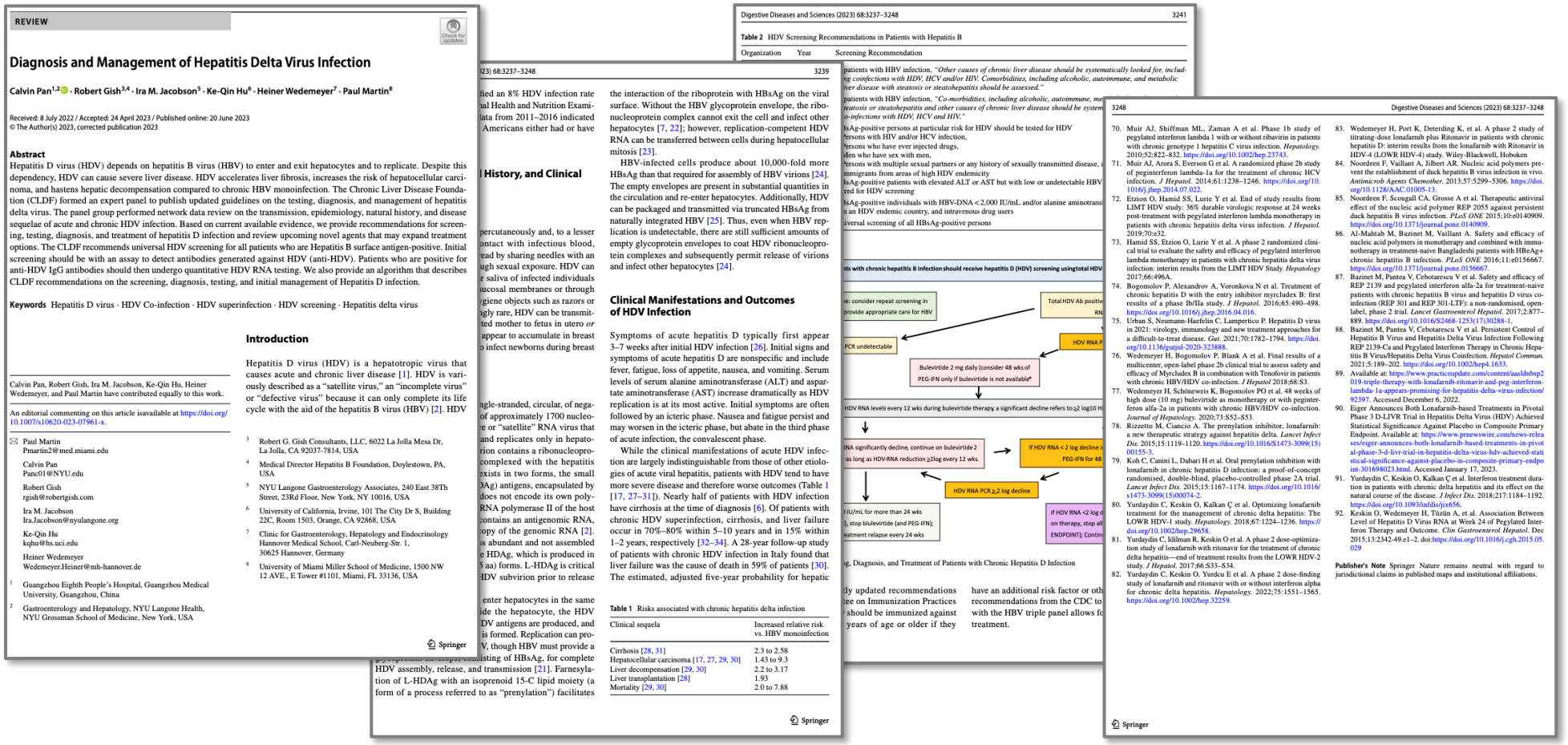

REVIEW

Diagnosis and Management of Hepatitis Delta Virus Infection

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Abstract
Hepatitis D virus (HDV) depends on hepatitis B virus (HBV) to enter and exit hepatocytes and to replicate. Despite this dependency, HDV can cause severe liver disease. HDV accelerates liver fibrosis, increases the risk of hepatocellular carcinoma, and hastens hepatic decompensation compared to chronic HBV monoinfection. The Chronic Liver Disease Foundation (CLDF) formed an expert panel to publish updated guidelines on the testing, diagnosis, and management of hepatitis delta virus. The panel group performed network data review on the transmission, epidemiology, natural history, and disease sequelae of acute and chronic HDV infection. Based on current available evidence, we provide recommendations for screening, testing, diagnosis, and treatment of hepatitis D infection and review upcoming novel agents that may expand treatment options. The CLDF recommends universal HDV screening for all patients who are Hepatitis B surface antigen-positive. Initial screening should be with an assay to detect antibodies generated against HDV (anti-HDV). Patients who are positive for anti-HDV IgG antibodies should then undergo quantitative HDV RNA testing. We also provide an algorithm that describes CLDF recommendations on the screening, diagnosis, testing, and initial management of Hepatitis D infection.

Keywords Hepatitis D virus · HDV Co-infection · HDV superinfection · HDV screening · Hepatitis delta virus

Introduction

Hepatitis D virus (HDV) is a hepatotropic virus that causes acute and chronic liver disease [1]. HDV is variously described as a "satellite virus," an "incomplete virus" or "defective virus" because it can only complete its life cycle with the aid of the hepatitis B virus (HBV) [2]. HDV

Calvin Pan, Robert Gish, Ira M. Jacobson, Ke-Qin Hu, Heiner Wedemeyer, and Paul Martin have contributed equally to this work.

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fied an 8% HDV infection rate
al Health and Nutrition Exami-
lata from 2011–2016 indicated
Americans either had or have

History, and Clinical

percutaneously and, to a lesser
ontact with infectious blood,
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ugh sexual exposure. HDV can
r saliva of infected individuals
ucosal membranes or through
giene objects such as razors or
gly rare, HDV can be transmit-
ted mother to fetus in utero *or*
appear to accumulate in breast
infect newborns during breast

ngle-stranded, circular, of nega-
of approximately 1700 nucleo-
e or "satellite" RNA virus that
and replicates only in hepato-
rion contains a ribonucleopro-
complexed with the hepatitis
exists in two forms, the small
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does not encode its own poly-
RNA polymerase II of the host
contains an antigenomic RNA,
opy of the genomic RNA [2].
s abundant and not assembled
e HDAg, which is produced in
5 aa) forms. L-HDAg is critical
HDV subvirion prior to release

enter hepatocytes in the same
ide the hepatocyte, the HDV
DV antigens are produced, and
is formed. Replication can pro-
V, though HBV must provide a
sisting of HBsAg, for complete
HDV assembly, release, and transmission [21]. Farnesylation of L-HDAg with an isoprenoid 15-C lipid moiety (a form of a process referred to as "prenylation") facilitates the interaction of the riboprotein with HBsAg on the viral surface. Without the HBV glycoprotein envelope, the ribonucleoprotein complex cannot exit the cell and infect other hepatocytes [7, 22]; however, replication-competent HDV RNA can be transferred between cells during hepatocellular mitosis [23].

HBV-infected cells produce about 10,000-fold more HBsAg than that required for assembly of HBV virions [24]. The empty envelopes are present in substantial quantities in the circulation and re-enter hepatocytes. Additionally, HDV can be packaged and transmitted via truncated HBsAg from naturally integrated HBV [25]. Thus, even when HBV replication is undetectable, there are still sufficient amounts of empty glycoprotein envelopes to coat HDV ribonucleoprotein complexes and subsequently permit release of virions and infect other hepatocytes [24].

Clinical Manifestations and Outcomes of HDV Infection

Symptoms of acute hepatitis D typically first appear 3–7 weeks after initial HDV infection [26]. Initial signs and symptoms of acute hepatitis D are nonspecific and include fever, fatigue, loss of appetite, nausea, and vomiting. Serum levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase dramatically as HDV replication is at its most active. Initial symptoms are often followed by an icteric phase. Nausea and fatigue persist and may worsen in the icteric phase, but abate in the third phase of acute infection, the convalescent phase.

While the clinical manifestations of acute HDV infection are largely indistinguishable from those of other etiologies of acute viral hepatitis, patients with HDV tend to have more severe disease and therefore worse outcomes (Table 1 [17, 27–31]). Nearly half of patients with HDV infection have cirrhosis at the time of diagnosis [6]. Of patients with chronic HDV superinfection, cirrhosis, and liver failure occur in 70%–80% within 5–10 years and in 15% within 1–2 years, respectively [32–34]. A 28-year follow-up study of patients with chronic HDV infection in Italy found that liver failure was the cause of death in 59% of patients [30]. The estimated, adjusted five-year probability for hepatic

Table 1 Risks associated with chronic hepatitis delta infection

Clinical sequela	Increased relative risk vs. HBV monoinfection
Cirrhosis [28, 31]	2.3 to 2.58
Hepatocellular carcinoma [17, 27, 29, 30]	1.43 to 9.3
Liver decompensation [29, 30]	2.2 to 3.17
Liver transplantation [28]	1.93
Mortality [29, 30]	2.0 to 7.88

Table 2 HDV Screening Recommendations in Patients with Hepatitis B

Organization	Year	Screening Recommendation

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Expert perspectives for the pharmacist on facilitating and improving the use of albumin in cirrhosis

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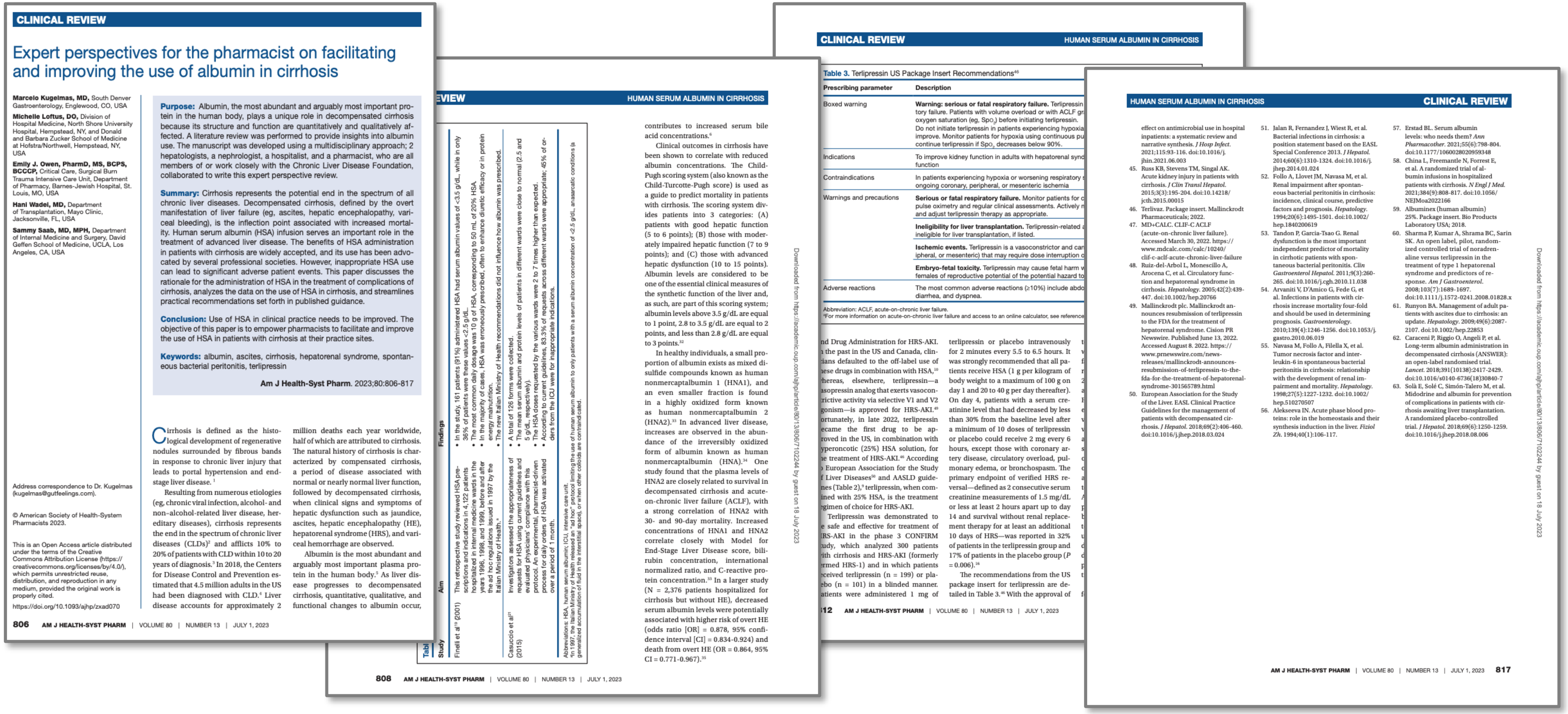

CLINICAL REVIEW

Expert perspectives for the pharmacist on facilitating and improving the use of albumin in cirrhosis

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Purpose: Albumin, the most abundant and arguably most important protein in the human body, plays a unique role in decompensated cirrhosis because its structure and function are quantitatively and qualitatively affected. A literature review was performed to provide insights into albumin use. The manuscript was developed using a multidisciplinary approach; 2 hepatologists, a nephrologist, a hospitalist, and a pharmacist, who are all members of or work closely with the Chronic Liver Disease Foundation, collaborated to write this expert perspective review.

Summary: Cirrhosis represents the potential end in the spectrum of all chronic liver diseases. Decompensated cirrhosis, defined by the overt manifestation of liver failure (eg, ascites, hepatic encephalopathy, variceal bleeding), is the inflection point associated with increased mortality. Human serum albumin (HSA) infusion serves an important role in the treatment of advanced liver disease. The benefits of HSA administration in patients with cirrhosis are widely accepted, and its use has been advocated by several professional societies. However, inappropriate HSA use can lead to significant adverse patient events. This paper discusses the rationale for the administration of HSA in the treatment of complications of cirrhosis, analyzes the data on the use of HSA in cirrhosis, and streamlines practical recommendations set forth in published guidance.

Conclusion: Use of HSA in clinical practice needs to be improved. The objective of this paper is to empower pharmacists to facilitate and improve the use of HSA in patients with cirrhosis at their practice sites.

Keywords: albumin, ascites, cirrhosis, hepatorenal syndrome, spontaneous bacterial peritonitis, terlipressin

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Improving the Management of Hepatorenal Syndrome–Acute Kidney Injury Using an Updated Guidance and a New Treatment Paradigm

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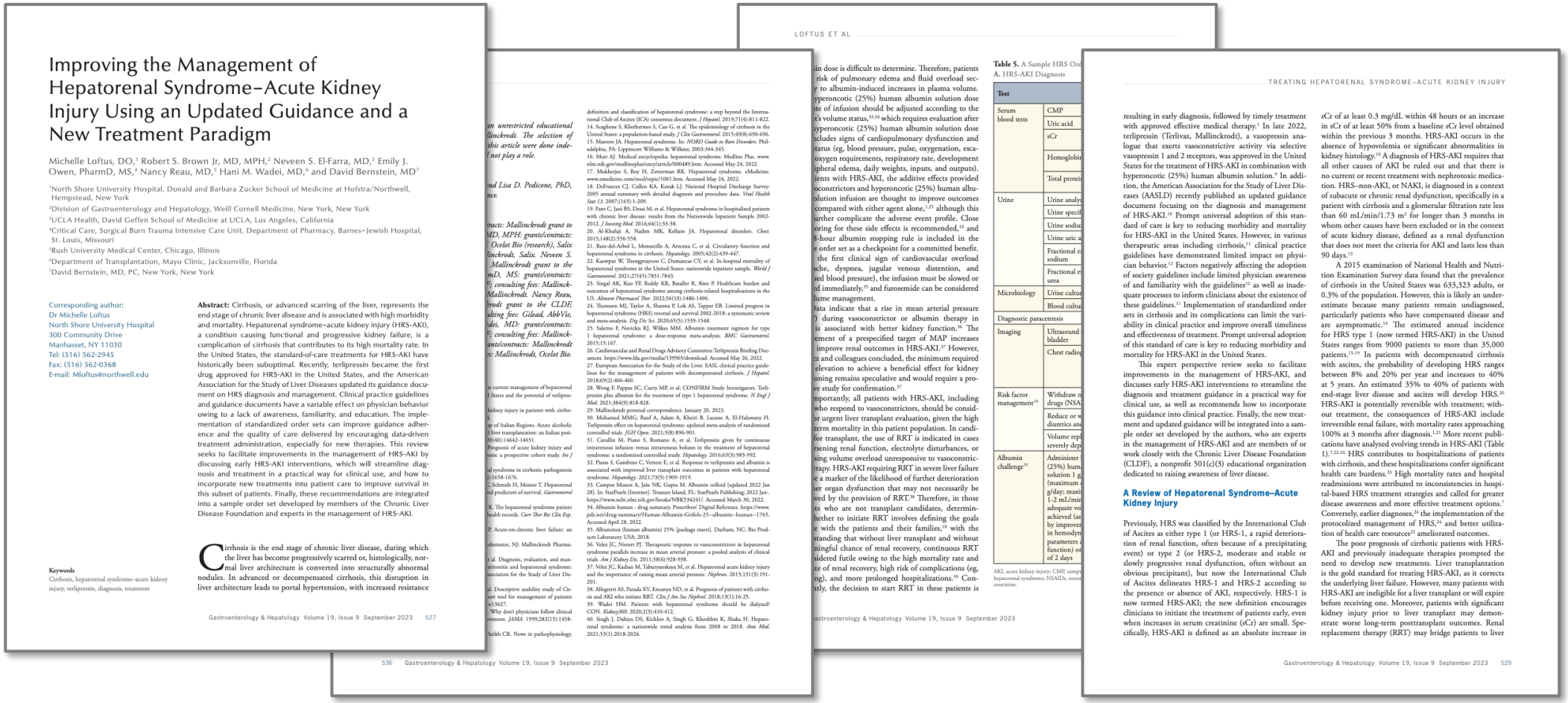

Improving the Management of Hepatorenal Syndrome–Acute Kidney Injury Using an Updated Guidance and a New Treatment Paradigm

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Abstract: Cirrhosis, or advanced scarring of the liver, represents the end stage of chronic liver disease and is associated with high morbidity and mortality. Hepatorenal syndrome–acute kidney injury (HRS-AKI), a condition causing functional and progressive kidney failure, is a complication of cirrhosis that contributes to its high mortality rate. In the United States, the standard-of-care treatments for HRS-AKI have historically been suboptimal. Recently, terlipressin became the first drug approved for HRS-AKI in the United States, and the American Association for the Study of Liver Diseases updated its guidance document on HRS diagnosis and management. Clinical practice guidelines and guidance documents have a variable effect on physician behavior owing to a lack of awareness, familiarity, and education. The implementation of standardized order sets can improve guidance adherence and the quality of care delivered by encouraging data-driven treatment administration, especially for new therapies. This review seeks to facilitate improvements in the management of HRS-AKI by discussing early HRS-AKI interventions, which will streamline diagnosis and treatment in a practical way for clinical use, and how to incorporate new treatments into patient care to improve survival in this subset of patients. Finally, these recommendations are integrated into a sample order set developed by members of the Chronic Liver Disease Foundation and experts in the management of HRS-AKI.

Keywords
Cirrhosis, hepatorenal syndrome–acute kidney injury, terlipressin, diagnosis, treatment

Cirrhosis is the end stage of chronic liver disease, during which the liver has become progressively scarred or, histologically, normal liver architecture is converted into structurally abnormal nodules. In advanced or decompensated cirrhosis, this disruption in liver architecture leads to portal hypertension, with increased resistance

Table 5. A Sample HRS Ord
A. HRS-AKI Diagnosis

Test	
Serum blood tests	CMP
	Uric acid
	sCr
	Hemoglobin
	Total protein
Urine	Urine analysis
	Urine specific
	Urine sodium
	Urine uric a
	Fractional ex sodium
	Fractional ex urea
Microbiology	Urine culture
	Blood culture
Diagnostic paracentesis	
Imaging	Ultrasound bladder
	Chest radiog
Risk factor management[10]	Withdraw n drugs (NSA
	Reduce or w diuretics an
	Volume repl severely dep
Albumin challenge[10]	Administer (25%) humi solution 1 g (maximum g/day; maxi
	1-2 mL/min
	adequate vo achieved (as by improver in hemodyn parameters function) or of 2 days

AKI, acute kidney injury; CMP, compr hepatorenal syndrome; NSAIDs, nonst creatinine.

resulting in early diagnosis, followed by timely treatment with approved effective medical therapy.[1] In late 2022, terlipressin (Terlivaz, Mallinckrodt), a vasopressin analogue that exerts vasoconstrictive activity via selective vasopressin 1 and 2 receptors, was approved in the United States for the treatment of HRS-AKI in combination with hyperoncotic (25%) human albumin solution.[9] In addition, the American Association for the Study of Liver Diseases (AASLD) recently published an updated guidance document focusing on the diagnosis and management of HRS-AKI.[10] Prompt universal adoption of this standard of care is key to reducing morbidity and mortality for HRS-AKI in the United States. However, in various therapeutic areas including cirrhosis,[11] clinical practice guidelines have demonstrated limited impact on physician behavior.[12] Factors negatively affecting the adoption of society guidelines include limited physician awareness of and familiarity with the guidelines[12] as well as inadequate processes to inform clinicians about the existence of these guidelines.[11] Implementation of standardized order sets in cirrhosis and its complications can limit the variability in clinical practice and improve overall timeliness and effectiveness of treatment. Prompt universal adoption of this standard of care is key to reducing morbidity and mortality for HRS-AKI in the United States.

This expert perspective review seeks to facilitate improvements in the management of HRS-AKI, and discusses early HRS-AKI interventions to streamline the diagnosis and treatment guidance in a practical way for clinical use, as well as recommends how to incorporate this guidance into clinical practice. Finally, the new treatment and updated guidance will be integrated into a sample order set developed by the authors, who are experts in the management of HRS-AKI and are members of or work closely with the Chronic Liver Disease Foundation (CLDF), a nonprofit 501(c)(3) educational organization dedicated to raising awareness of liver disease.

A Review of Hepatorenal Syndrome–Acute Kidney Injury

Previously, HRS was classified by the International Club of Ascites as either type 1 (or HRS-1, a rapid deterioration of renal function, often because of a precipitating event) or type 2 (or HRS-2, moderate and stable or slowly progressive renal dysfunction, often without an obvious precipitant), but now the International Club of Ascites delineates HRS-1 and HRS-2 according to the presence or absence of AKI, respectively. HRS-1 is now termed HRS-AKI; the new definition encourages clinicians to initiate the treatment of patients early, even when increases in serum creatinine (sCr) are small. Specifically, HRS-AKI is defined as an absolute increase in sCr of at least 0.3 mg/dL within 48 hours or an increase in sCr of at least 50% from a baseline sCr level obtained within the previous 3 months. HRS-AKI occurs in the absence of hypovolemia or significant abnormalities in kidney histology.[16] A diagnosis of HRS-AKI requires that all other causes of AKI be ruled out and that there is no current or recent treatment with nephrotoxic medication. HRS–non-AKI, or NAKI, is diagnosed in a context of subacute or chronic renal dysfunction, specifically in a patient with cirrhosis and a glomerular filtration rate less than 60 mL/min/1.73 m² for longer than 3 months in whom other causes have been excluded or in the context of acute kidney disease, defined as a renal dysfunction that does not meet the criteria for AKI and lasts less than 90 days.[13]

A 2015 examination of National Health and Nutrition Examination Survey data found that the prevalence of cirrhosis in the United States was 633,323 adults, or 0.3% of the population. However, this is likely an underestimate because many patients remain undiagnosed, particularly patients who have compensated disease and are asymptomatic.[14] The estimated annual incidence for HRS type 1 (now termed HRS-AKI) in the United States ranges from 9000 patients to more than 35,000 patients.[15–19] In patients with decompensated cirrhosis with ascites, the probability of developing HRS ranges between 8% and 20% per year and increases to 40% at 5 years. An estimated 35% to 40% of patients with end-stage liver disease and ascites will develop HRS.[20] HRS-AKI is potentially reversible with treatment; without treatment, the consequences of HRS-AKI include irreversible renal failure, with mortality rates approaching 100% at 3 months after diagnosis.[1,21] More recent publications have analyzed evolving trends in HRS-AKI (Table 1).[7,22-24] HRS contributes to hospitalizations of patients with cirrhosis, and these hospitalizations confer significant health care burdens.[23] High mortality rates and hospital readmissions were attributed to inconsistencies in hospital-based HRS treatment strategies and called for greater disease awareness and more effective treatment options.[7] Conversely, earlier diagnoses,[24] the implementation of the protocolized management of HRS,[24] and better utilization of health care resources[22] ameliorated outcomes.

The poor prognosis of cirrhotic patients with HRS-AKI and previously inadequate therapies prompted the need to develop new treatments. Liver transplantation is the gold standard for treating HRS-AKI, as it corrects the underlying liver failure. However, many patients with HRS-AKI are ineligible for a liver transplant or will expire before receiving one. Moreover, patients with significant kidney injury prior to liver transplant may demonstrate worse long-term posttransplant outcomes. Renal replacement therapy (RRT) may bridge patients to liver

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Improving Outcomes in Hepatorenal Syndrome–Acute Kidney Injury With Early Diagnoses and Implementation of Approved Treatment Regimens

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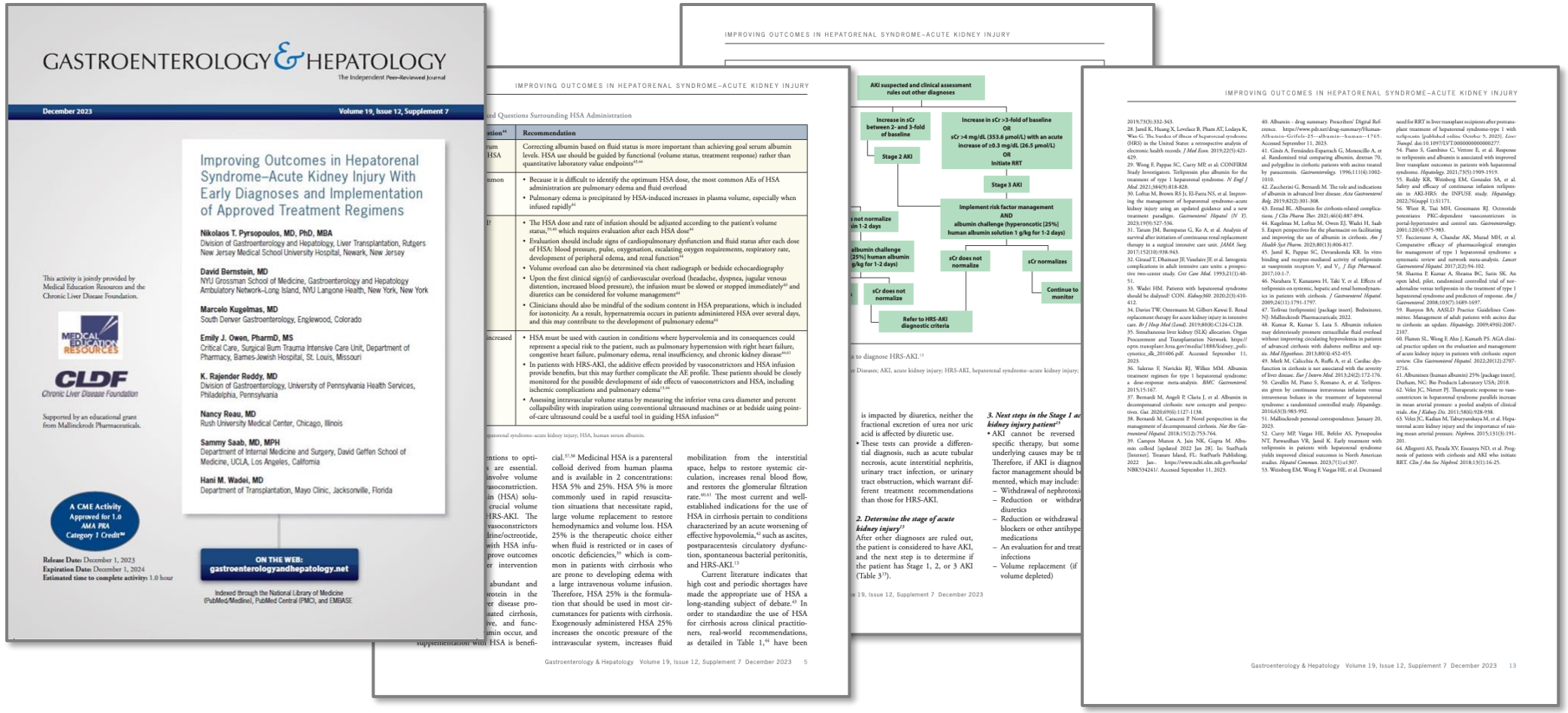

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Alcohol Liver Disease

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Complications of Cirrhosis

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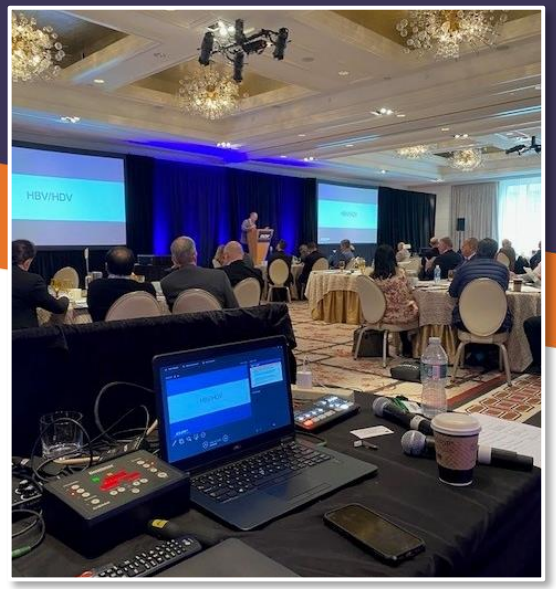

Complications of Cirrhosis

Abstract No.	Title	Grade
210 (Oral)	HIGH DOSES OF ALBUMIN INCREASES MORTALITY AND COMPLICATIONS IN TERLIPRESSIN TREATED PATIENTS WITH CIRRHOSIS: INSIGHTS FROM THE ATTIRE TRIAL	A

Abstract No.	Title	Grade
211 (Oral)	ALBUMIN DOSING WITH TERLIPRESSIN FOR THE TREATMENT OF HRS-AKI: A DOUBLE-EDGED SWORD	A
223 (Oral)	MEAN ARTERIAL PRESSURE: A TARGET FOR ACUTE KIDNEY INJURY RESPONSE REGARDLESS OF ACUTE KIDNEY INJURY TYPE	A
224 (Oral)	IMPROVED MEAN ARTERIAL PRESSURE FROM BASELINE TO THE END OF TREATMENT WITH TERLIPRESSIN IS ASSOCIATED WITH HEPATORENAL SYNDROME REVERSAL: A POOLED ANALYSIS OF 3 PHASE III STUDIES	A

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