Liver Update

A publication of the Center for Liver Diseases and the Inova Transplant Center

The Hepatopulmonary Syndrome

James K. Stoller, MD, MS
Vice Chairman, Division of Medicine
Head, Section of Respiratory Therapy
Department of Pulmonary and Critical Care Medicine
Associate Chief of Staff
Cleveland Clinic Foundation

The hepatopulmonary syndrome (HPS) is defined as a triad consisting of liver disease, an increase in the alveolar to arterial oxygen gradient, and evidence of intrapulmonary vascular dilatations. Additional qualifiers are that the liver dysfunction need not be severe and that intrinsic cardiopulmonary disease must be excluded. However, coexisting pulmonary abnormalities such as pleural effusions or airflow obstruction have been noted to be frequent in patients with chronic liver disease and, therefore, should not exclude the diagnosis of HPS.

Estimates of the prevalence of the hepatopulmonary syndrome have varied, likely reflecting different diagnostic criteria and study populations. For example, hypoxemia occurs in about one third of patients with chronic liver disease and an elevated alveolar to arterial oxygen gradient has been found in 45 percent of patients with liver disease referred for transplant evaluation. Also, among patients with cirrhosis, the prevalence of hypoxemia with a room air arterial oxygen tension less than 70 mmHg is 28 percent. More severe hypoxemia ($PaO_2 < 60$ mmHg) is less common, occurring approximately in 8 percent of patients with cirrhosis.

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Depression and Hepatitis C

Catherine C. Crone, MD
Psychiatry
Inova Transplant Center
Inova Fairfax Hospital

Hepatitis C infects four million people in the United States and 100 million worldwide. Among them, over half will develop chronic hepatitis C, with a smaller proportion progressing to cirrhosis or hepatocellular carcinoma. Endstage disease will eventually lead many to liver transplantation.

Due to both the serious consequences and widespread nature of hepatitis C infection, attempts have been made to find therapies capable of halting the progression of this virus. Interferon-alpha remains the most successful treatment, especially when combined with ribavarin. This combination yields a 35 to 40 percent response rate, which can be raised to 55 to 60 percent when interferon-alpha is substituted by its pegylated

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Clinically, the signs and symptoms of underlying liver disease dominate the clinical presentation, though dyspnea is reported as the presenting symptom in approximately 18 percent of cases.

The pathophysiology of hypoxemia in the hepatopulmonary syndrome is multifactorial.

The pulmonary features include digital clubbing, cyanosis and the unusual symptoms of platypnea and orthodeoxia. Platypnea refers to experiencing breathlessness on assuming the upright posture and orthodeoxia refers to desaturation during the upright posture, i.e., variously defined as a 10 percent or 10 mmHg drop in the PaO2 on standing upright. Both signs reflect worsening of the shunt fraction by gravity-dependent shifting of blood to the dilated capillary beds of the lung bases and occur in approximately five percent of patients with cirrhosis and more commonly in patients with the hepatopulmonary syndrome. A hyperdynamic circulation with elevated cardiac output and systemic vasodilatation is another characteristic feature of the hepatopulmonary syndrome, mimicking the hemodynamics of sepsis.

The pathophysiology of hypoxemia in the hepatopulmonary syndrome is multifactorial. Dominant mechanisms include intrapulmonary shunting, ventilation-perfusion mismatching, diffusion impairment and a novel mechanism labeled diffusion-perfusion impairment or alveolar-capillary oxygen disequilibrium. The major cause of hypoxemia in the hepatopulmonary syndrome has generally been felt to be intrapulmonary vascular abnormalities, which are akin to the spider nevi found on the skin of patients with liver disease. Called intrapulmonary vascular dilatations, these abnormalities consist of precapillary dilatations ranging from 15 to 5000 microns in diameter and forming direct arteriovenous communications. Regarding the pathophysiology of the hepatopulmonary syndrome, potential mechanisms for intrapulmonary vascular dilatation have been long sought. Most hypotheses consider an imbalance between pulmonary vasodilators and vasoconstrictors. The imbalance could be a result of failure of clearance by the diseased liver of a vasodilator substance, production by the liver of a circulating vasodilator, or inhibition of a vasoconstrictor. Recent attention has focused on the role of nitric oxide (NO) as the vasoactive mediator of vascular dilatation and its associated hypoxemia, with several compelling lines of evidence supporting involvement of NO.

Contrast-enhanced echocardiography is considered the usual method of choice for diagnosing intrapulmonary vascular dilatations.

The diagnosis of the hepatopulmonary syndrome can be undertaken with several modalities, including contrast-enhanced echocardiography, technetium 99m pyrophosphate lung scanning with attention to scanning over other organs (e.g., brain or kidney), and pulmonary angiography. Contrast-enhanced echocardiography is considered the usual method of choice for diagnosing intrapulmonary vascular dilatations. Contrast can be provided by microbubbles generated by injecting indocyanine green dye, agitated saline, or modified fluid gelatin solutions. In the presence of a right-to-left shunt, the bubbles are not cleared by the pulmonary capillary bed and opacify the left heart chambers, with the timing of their appearance indicating the anatomic site of the right-to-left shunt. Specifically, visualization of the bubble contrast in the left heart within three heartbeats after their visualization in the right heart chambers indicates an intracardiac shunt. Alternatively, in intrapulmonary shunt, contrast transits through the pulmonary circulation, causing a delayed appearance in the left heart chambers, i.e., 4-5 beats after visualization in the right heart chambers.

Less sensitive than echocardiography, technetium 99m-labeled macroaggregated albumen scanning is a more specific and potentially quantitative method for characterizing anatomic shunt. Injected aggregates of albumen have a diameter of 20 to 50 microns and are normally trapped by the pulmonary capillary bed, which has a diameter of 8 to 15 microns. This usual situation permits the use of technetium macroaggregated albumen as the medium for lung scanning. In the case of intrapulmonary shunt, radionuclide uptake can be detected over the brain and kidneys, indicating transit through the lung. Quantitation of the magnitude of the shunt by calculating the ratio of systemic radionuclide to total body activity is possible.

Finally, pulmonary angiography has been used to demonstrate the hepatopulmonary syndrome and two distinct angiographic patterns have been described. The Type I pattern ranges from minimal changes with diffuse spider-like branches to more advanced changes with a "blotchy, spongy" appearance. Minimal changes are often associated with a normal response to 100 percent oxygen supplementation, whereas patients with the more advanced changes may be less responsive to supplemental oxygen. The Type II pattern is less common and is

characterized by discrete vascular dilatations, resembling arterial venous communications. This Type II pattern is said to be more amenable to embolization therapy.

Regarding therapy, many pharmacologic agents have been tried in treating the hepatopulmonary syndrome, most with disappointing results. Most recently, intriguing observations include treatment of the hepatopulmonary syndrome with garlic (allium sativum), which has been associated with improved oxygenation in 40% of patients with the hepatopulmonary syndrome. Although not studied in a randomized, controlled trial, garlic may represent an innocuous option for trial. Also, recent evidence suggests that nitric oxide inhibitors, such as methylene blue, can transiently improve oxygenation in the hepatopulmonary syndrome. In patients with a Type II angiographic pattern, embolization therapy can be considered.

Finally, liver transplantation is a treatment option in patients with hepatopulmonary syndrome. In recent years, recommendations have shifted radically away from a belief that the hepatopulmonary syndrome is a contraindication to liver transplantation and toward the view that HPS may be an indication for liver transplantation. Specifically, though certain predictors of response to liver transplantation remain elusive, available reports suggest that approximately 80 percent of patients undergoing successful liver transplantation can be expected to experience improvement or resolution of hypoxemia due to the hepatopulmonary syndrome following liver transplantation. ■

SELECTED REFERENCES

1. Krowka MJ, Cortese DA. Hepatopulmonary syndrome. *Chest* 1990;98:1053-1054.
2. Lange PA, Stoller JK. The hepatopulmonary syndrome. *Ann Intern Med* 1995;122:521-529.

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formulation. While advances in interferon therapy offer greater hope for patients with chronic hepatitis C, adverse effects hamper its tolerability. In particular, depression is a common occurrence that requires physician attention to allow patients to successfully navigate interferon treatment.

Interferon can produce a broad range of psychiatric side effects including depression, irritability, mania, personality changes, anxiety, impaired concentration, insomnia, delirium and psychosis. Irritability and depression are the most common psychiatric complications of interferon treatment. Rates of depression are reported to vary from three to 57 percent, with most reports ranging between 10 and 40 percent.

Wide variability in these rates appears to be due to study design and differences in the definition of depression. Using validated scales for depression and prospective study design have yielded the higher-rates for interferon-induced mood disorder. Depression serious enough to require dosage reduction or withdrawal of interferon has been noted across many of the clinical trials for hepatitis C. Case reports strengthen these observations as severe depression with suicidal ideation, attempts or completed suicides have been reported in detail.

Given the potential risk of severe depression occurring in patients treated with interferon, investigators have tried to determine whether certain patients are at greater risk for interferon-induced mood disorder. Some have postulated that patients with histories of psychiatric illness would be more prone to problems while on interferon. While a few reports have suggested that higher ratings for depressive symptoms at the start of interferon therapy, presence of current psychiatric illness, or previous history of psychiatric disorder, correlate with a greater incidence of interferon-induced depression, other studies have failed to agree with these findings.

Furthermore, patients with serious psychiatric illness, including schizophrenia and schizoaffective disorder, have been reported to be successfully treated with interferon. Rather than focus on psychiatric history, some investigators have felt that it is more the dosage, duration and route of administration for interferon therapy that determines the risk for interferon-induced psychiatric disorders.

Patients experiencing greater emotional distress or difficulties coping with day-to-day life should be given serious consideration for antidepressant therapy.

Evaluating depression among those being treated with interferon requires familiarity with the diagnostic issues that arise in medical populations. Major depression mainly consists of a persistent depressed, sad or irritable mood, fatigue insomnia, anorexia, poor concentration, loss of pleasure/interest, and thoughts of guilt, worthlessness, hopelessness or death. Clearly a number of these symptoms overlap with those from interferon therapy, particularly fatigue, insomnia and impaired concentration.

The temptation is thus to discount these symptoms in patients on interferon, to not consider these related to underlying depression.

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Unfortunately, this exclusionary approach will likely lead to both under-diagnosis and under-treatment of interferon-induced mood disturbance. Instead, these symptoms should be included if trying to diagnose depression in those on interferon therapy.

Accurate diagnosis can also be facilitated by greater emphasis on assessing symptoms such as loss of pleasure or pessimistic outlook, which are not as typically caused by interferon. Additional input from family and significant others can be vital in providing a description of the patient's pre-interferon personality from which to compare from.

Treatment of interferon-induced depression depends on the severity of symptoms reported and the degree to which they impair a patient's daily functioning. Active input from patients and family members can be used to help in making these treatment decisions. For patients with milder depressive symptoms, help can come in the form of supportive therapy, lifestyle adjustments (e.g. reduced work hours, a regular exercise routine, relaxation techniques), and reassurance or education about the depression. Patients experiencing greater emotional distress or difficulties coping with day-to-day life should be given serious consideration for antidepressant therapy.

At present, there is minimal information about which antidepressant to select. A recent open clinical trial reported success with citalopram in those with both depression and hepatitis C, some of whom were also taking interferon. Case reports cite improvement with the use of other serotonin reuptake inhibitors such as sertraline, fluoxetine, and paroxetine.

The selection of these agents was likely due to their familiarity to medical providers, good tolerability and minimal drug-drug interactions. Their additional ability to raise serotonin levels may also help to correct changes in serotonin metabolism noted with interferon treatment. Other newer antidepressants may be equally effective to the SSRIs, but reports are lacking.

Bupropion, venlafaxine, and mirtazapine have been administered to medically ill populations and their particular characteristics can be used to a patient's advantage. For example, activating effects of bupropion can be beneficial to the depressed patient troubled by marked fatigue and apathy. Mirtazapine can be particularly helpful to those with significant insomnia, anorexia or weight loss. While nefazodone is also an effective antidepressant, reports of rare but serious liver impairment preclude its use in hepatitis C patients.

For patients with severe impairment from depression and/or suicidal ideation, discontinuation of interferon therapy is advisable.

Prophylactic therapy with antidepressants is another approach that has been reported as a means to reduce patient distress from interferon-induced depression and enable continuation of interferon treatment. In the clinical trial by Musselman, paroxetine was used in malignant melanoma patients being tried on high dose interferon. Compared to the half receiving placebo, those who took paroxetine had a significantly reduced rate of interferon-induced mood disturbance and a lower incidence of interferon discontinuation for severe depressive symptomatology. Beyond the use of antidepressants, decreasing the dose of interferon enables some patients to continue treatment with reduced mood impairment. For patients with severe impairment from depression and/or suicidal ideation, discontinuation of interferon therapy is advisable. Symptoms of mood disturbance normally abate after a few days, much sooner than the four to six weeks required to achieve an effect from most antidepressants.

In most studies, discontinuation of interferon leads to prompt resolution of psychiatric symptoms.

Length of antidepressant therapy partly depends upon the length of interferon therapy selected. In most studies, discontinuation of interferon leads to prompt resolution of psychiatric symptoms. These findings suggest that antidepressants can be tapered off soon after interferon treatment is completed.

While most patients will likely tolerate this approach, Hosada reported cases where psychiatric treatment was needed more than 24 weeks after discontinuing interferon. While this represents only a limited group of patients, antidepressant treatment may need to be extended for those who have experienced marked depression on interferon. Gradual tapering of antidepressants over several months can also be used, along with active monitoring for resurgence in depressive symptoms. Those who experience a return of depression can be quickly returned to effective antidepressant dosages. ■

RESEARCH PROTOCOLS

The following is a list of the research protocols at the Center for Liver Diseases at Inova Fairfax Hospital:

- Pegylated Interferon Alfa 2b and Ribavirin for chronic hepatitis C.
- Triple regimen of Pegylated Interferon Alfa 2b, Ribavirin and Amantadine for treatment of chronic hepatitis C.
- Pegylated Interferon Alfa 2a in combination with Ribavirin for chronic hepatitis C.
- Growth Factors for treatment of cytopenia in patients with hepatitis C on Ribavirin/PEG-IFN.
- The use of Interferon Gamma-1b as an anti-fibrotic agent in hepatitis C.
- Pegylated interferon Alpha 2a with or without Thymosin Alpha 1 for chronic hepatitis C.
- Pegylated Interferon Alpha 2A Maintenance Protocol for Prevention of Complication of HCV-Related Cirrhosis.
- Lamivudine with or with out monoclonal HBV antibody for chronic hepatitis B.
- Adefovir Dipivoxil for the treatment of hepatitis B.
- Epidemiology for hepatitis B in the United States.
- Epidemiology of Hepatocellular carcinoma in the United States.
- Epidemiology of Non-Alcoholic Fatty Liver Disease.
- Efficacy trials in Non-Alcoholic Fatty Liver Disease.

For patient screening or additional information, please call the Center for Liver Diseases at **703-698-3182**, or fax **703-698-3481**.

Publications and Presentations

PUBLICATIONS

- J Ong and Z Younossi. "Is Hepatocellular Carcinoma Part of the Natural History of Nonalcoholic Steatohepatitis?" Gastroenterology. July 2002.

PRESENTATIONS

- Current Treatment and Research Protocols in the Treatment of Hepatitis C, UNOS Region 2 Clinical Forum, Bethesda, MD.
- Natural History of NASH; Clinical Symposium, Digestive Disease Week, San Francisco, CA
- Impact of Ascites on Health-Related Quality of Life; EASL Conference, London UK.

Medical Grand Rounds —

Sponsored by the Center for Liver Diseases

August 27

James Stoller, MD

Dept. of Pulmonary and Critical Care Medicine

The Cleveland Clinic Foundation

October 17

Jeff Ponsky, MD

Division of Surgery

The Cleveland Clinic Foundation

October 22

Adrian DiBisceglie, MD

Dept. of Gastroenterology

St. Louis University Hospital

October 29

Joel Richter, MD,

Dept. of Gastroenterology

The Cleveland Clinic Foundation

American Liver Foundation Corner

Hepatitis C Support Groups

Inova Fairfax Hospital and the ALF sponsor Hepatitis C Support Groups in the Washington, DC area. The group will meet at the hospital in Conference Rooms D, E and F on the following dates:

Aug. 20:

Cathy Crone, MD

Psychiatry

Inova Transplant Center

Depression/Side Effects of Interferon

Inova Health System is a not-for-profit health care system in Northern Virginia that consists of hospitals and other health services including home care, nursing homes, mental health services, wellness classes, and emergency and urgent care centers. Governed by a voluntary board of community members, Inova's mission is to provide quality care and to improve the health of the diverse communities we serve.

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3300 Gallows Road,
Falls Church, VA 22042-3300

Medical Editor
Zobair M. Younossi, MD, MPH

Managing Editor
Denise Tatu
703-321-2912

Inova Transplant Center
Inova Fairfax Hospital
3300 Gallows Road
Falls Church, VA 22042-3300

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