**Curbside Consultation of the Liver: 49 Clinical Questions**  
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This is the first edition of *Curbside Consultation of the Liver* which is authored by Dr. Mitchell Shiffman and members of his academic practice. Dr. Shiffman has authored or co-authored well over 200 articles, editorials, reviews, and book chapters and is a leader in hepatology. This text was constructed as a guide with concise answers to many routine clinical questions in hepatology. Each question is answered efficiently with appropriate charts and figures. There are eight basic sections addressing 49 clinical questions regarding Hepatitis B and C, HIV co-infection, chronic liver disease, fatty liver disease, cholestatic liver diseases, cirrhosis, and liver transplantation.

Dr. Shiffman has co-authored the sections on Hepatitis B and C. These discussions include common questions with the most recent evidence from the medical literature. The authors distinguish between evidence, expert opinion, and the practical aspects of managing Hepatitis B and C. Examples of the latter include questions on measuring Hepatitis C RNA and the use of epoetin alfa during treatment. The bridge between medical literature and actual medical practice is a unique aspect to this text.

In Section III the text addresses liver disease in HIV patients and the impact of concurrent HIV on the treatment of Hepatitis B or C. Similarities and distinctive aspects of patients without HIV and those with co-infection are emphasized. Causes of jaundice “unique to HIV” are discussed and appear in a related chart. Screening and treatment of genetic disorders such as hemochromatosis, Wilson’s disease, and autoimmune hepatitis are addressed in Section IV.

Dr. Arun Sanyal is a co-author of Section V, which discusses the most critical questions regarding non-alcoholic fatty liver disease (NAFLD). These excellent discussions provide a balance between evidence, expert opinion and the pragmatism required in clinical practice. The decision algorithms regarding liver biopsy and the chart on the types of obesity surgery were informative. Section IV answers six common questions regarding cholestatic liver disease and other topics such as risk of primary sclerosing cholangitis in patients with ulcerative colitis with history of subtotal colectomy.

Section VII focuses on 13 questions pertaining to cirrhosis and is the most extensive part of this book. This section includes discussions of the major complications of cirrhosis including very practical treatment guidance. The final section on liver transplantation is limited in scope and content.

The authors have, for the most part, achieved the objectives set out by the editor. The authors do a great job of separating evidence-based guidelines from expert opinion or personal practice. A few errors were noted, but the overall quality of the text was excellent. *Curbside Consultation of the Liver* will be a welcome companion for hepatology textbooks and practice guidelines. Physicians, from the resident to the hepatologist, presented with these clinical questions will find this text to be a quick review and adjunct in clinical practice.

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**HCV and Hepatobiliary and Pancreatic Cancer**

A cohort study including 146,394 HCV-infected and 572,293 HCV-uninfected patients who received care at Veteran’s Affairs Healthcare facilities, was conducted. Patients with two visits between 1996 and 2004 with HCV infection were included as were up to four matched HCV-uninfected subjects for each HCV-infected subject. Risks of intrahepatic cholangiocarcinoma (ICC), extra-hepatic cholangiocarcinoma (ECC), pancreatic cancer and hepatocellular carcinoma (HCC) were assessed using proportional hazards regression. In the 1.37 million person-years of follow-up which began six months after the baseline visit, there were 75 cases of ECC, 37 cases of ICC, 617 cases of pancreatic cancer and 1,679 cases of HCC. As expected, the risk of HCC associated with HCV was very high (HR, 15.09). Risk for ICC was elevated with HCV 2.55, but risk for ECC was not significantly increased (1.5). Adjustments for cirrhosis, diabetes, IBD, hepatitis B, alcoholism and alcoholic liver disease did not reduce the risk for ICC below two-fold. The risk for pancreatic cancer was slightly elevated (1.23) but was attenuated after adjusting for alcohol use, pancreatitis and other variables.

It was concluded that the findings indicated that HCV infection concurred at more than two-fold elevated risk of ICC. A significant association with ECC and pancreatic cancer was not identified. (El-Serag H, Angles EA, Landgren O, et al. “Risk of Hepatobiliary and Pancreatic Cancers After Hepatitis C Virus Infection; A Population-Based Study of U.S. Veterans.” Hepatology, 2009; Vol. 49:116-123.

**Transaminase Elevations in HIV Disease and Treatment**

Liver damage associated with chronic unexplained high serum transaminases in HIV-infected patients under combined antiretroviral therapy has not been well characterized. Liver histology was prospectively investigated in patients presenting serum transaminase elevations for more than six months after exclusion of alcohol abuse, HCV or HBV infection, autoimmune and genetic liver diseases. In a subgroup of patients, liver mitochondrial activities were measured by spectrophotometry and mitochondrial DNA by real-time polymerase chain reaction (PCR). Thirty patients with median values of ALT levels, 80 u/L, age 46 years, body mass index 23, HIV RNA 200 copies/ml, CD4 count 365, duration of HIV infection 13 years, duration of treatment exposure 118, 41 and 53 months for nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors and protease inhibitors, respectively.

Histological anomalies were found in 22 of 30 patients. Steatosis was present in 18 patients, severe in nine patients and associated with inflammation in 16 patients with a diagnosis of NASH. Fibrosis was found in 18 patients, severe in six patients and associated with steatosis in 13 patients.

Significant liver, respiratory complex I defect contrasting with high complex IV activity and normal mitochondrial DNA content was observed in a group of patients compared with controls.

The presence of NASH was correlated with high fasting glycemia and insulin levels, not with liver mitochondrial function or mitochondrial DNA content.

It was concluded that HIV-infected patients on combined antiretroviral therapy with chronic transaminase elevation of unknown origin have a high rate of liver lesions, most consistent with NASH related to insulin resistance. (Ingiliz T, Velantin M, Uvidier C, et al. “Liver Damage Underlying Unexplained Transaminase Elevations in Immunodeficiency Virus-1 Mono-Infected Patients on Antiretroviral Therapy.” Hepatology, 2009; Vol. 49, 436-442.)
PEGASYS® Proven Effective as Hepatitis C Treatment for Latino Patients, According to Article in The New England Journal of Medicine

Largest Prospective Study Demonstrates Treatment Success, and Highlights Potential Factors that Affect Health Outcomes, in Latino Population Suffering from Chronic Hepatitis C

Results from the LATINO study, the largest study conducted to-date in Latino patients with the hepatitis C virus (HCV), were published in The New England Journal of Medicine. This Roche study demonstrated that HCV can be successfully treated among Latino patients, a patient population that is historically difficult to treat. The study, “Peginterferon Alfa-2a and Ribavirin in Latino and Non-Latino Whites with Hepatitis C,” was conducted to better understand how previously untreated Latino patients with HCV genotype 1, the most difficult-to-treat genotype, responded to treatment with PEGASYS® (peginterferon alfa-2a) plus COPEGUS® (ribavirin) as compared to non-Latino whites.

“We know that the hepatitis C virus affects Latino patients differently than non-Latino patients, but there was little data available to support what we have seen clinically. The LATINO data are important because, for the first time, a large-scale study was conducted that focused on Latino patients, providing insight into this growing population,” said Maribel Rodriguez-Torres, M.D., of the Fundación de Investigación de Diego in Puerto Rico. “We hope that this landmark LATINO study will be the beginning of more clinical trials with greater numbers of Latino patients, which will help address the unmet medical need of this population.”

The data showed that Latino patients achieved sustained virological response (SVR) at a lower rate than non-Latino whites, and demonstrated that there were differences in predictors of SVR between the two patient populations. The results of this study add to a growing body of evidence of differences in treatment responses among ethnic groups and underscore the need to optimize treatment strategies in order to improve the rate of SVR among Latino patients infected with HCV genotype 1.

“As leaders in hepatology, we are proud to have conducted the largest prospective study of the Latino population with hepatitis C,” said Dr. Lars Birgerson, Head of Global Medical Affairs, Roche. “We look forward to further investigating unmet medical needs and providing future treatment options, for Latinos and other hard-to-treat populations, through our clinical research program.”

Restech Dx–pH Measurement System Accurately Measures Laryngopharyngeal Reflux in Children

Innovative pharyngeal pH probe helps differentiate baseline pH and potential etiology for various upper airway symptoms believed to be caused by acid reflux

Respiratory Technology Corporation (dba Restech) has announced that the Restech Dx–pH Measurement System played a key role in a study by Dr. David J. Malis, MD, FACS, FAAP, of Melbourne, Florida, to accurately measure reflux in children. The study, entitled “A New pH Probe for the Detection of Laryngopharyngeal Reflux (LPR) in Children©,” was presented at the 2008 Annual Meeting of the American Society of Pediatric Otolaryngology (ASPO) as a podium presentation. The study of 100 pediatric patients helped differentiate baseline pH and potential etiology for various upper airway symptoms believed to be caused by acid reflux.

An alarming increase in the incidence of gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux disease (LPRD) in Americans has led to the need for accurate diagnosis of extraesophageal acid reflux as provided by the Restech Dx–pH Measurement System.

In determining the etiology of conditions such as chronic cough, recurrent laryngitis, sinusitis and asthma, it is important for physicians to be able to rule reflux in or out as a possible contributing factor. Instead of treating “in the blind” with a medication based on symptoms alone, physicians will be able to prescribe treatment based on definitive quantification of acidic reflux in the upper airway.

Current diagnostic techniques available to pediatric otolaryngologists include panendoscopy with biopsy, lipid-laden macrophages score and histology, the Bravo™ capsule, an esophagram/Barium swallow, or an empiric therapeutic trial with H2 Blockers or PPIs.
Schering-Plough Completes Enrollment of Boceprevir Registration Studies in Treatment-Naive and Treatment-Experienced HCV Patients

Schering-Plough Corporation reports that it has completed patient enrollment in the boceprevir HCV SPRINT-2 study, a pivotal Phase III study in treatment-naive patients. Together with the HCV RESPOND-2 study, a pivotal Phase III study in patients who failed prior treatment that completed enrollment in November 2008, the company has fully enrolled its registration studies for boceprevir, its lead investigational oral hepatitis C protease inhibitor. A total of more than 1,500 patients were enrolled in these studies at U.S. and international sites.

“We believe boceprevir has the potential to be a first-in-class and best-in-class protease inhibitor for treating chronic hepatitis C,” said Thomas P. Koestler, Ph.D., executive vice president and president, Schering-Plough Research Institute. “We are very encouraged by the boceprevir study results reported to date and look forward to the completion of these registration studies.” The Company expects to complete the studies in mid-2010.

Schering-Plough previously reported Phase II study results from Part I of the HCV SPRINT-1 study in 595 treatment-naïve patients with chronic hepatitis C virus (HCV) genotype 1. In that study, a 48-week boceprevir regimen achieved a 75% SVR rate in patients who received 4 weeks of PEGINTRON® (peginterferon alfa-2b) and REBETOL® (ribavirin, USP) prior to the addition of boceprevir (P/R lead-in, n = 103). This represents a near doubling of the 38% SVR rate for patients in the control group receiving 48-weeks of PEGINTRON and REBETOL alone (n = 104) (ITT). 1,2 In a 28-week boceprevir P/R lead-in regimen, the SVR rate was 56% (n = 103). Importantly, for patients who received the boceprevir P/R lead-in regimen and had rapid virologic response (RVR), defined as undetectable virus (HCV-RNA) in plasma after 4 weeks of boceprevir treatment, SVR was 94% in the 48 week regimen (n = 66) and 82% in the 28-week regimen (n = 66). RVR has been shown to be a reliable predictor for achieving SVR.

Treatment discontinuations for boceprevir patients due to viral breakthrough were fewer in the 28- and 48-week lead-in arms (4% and 5%, respectively) compared to the no lead-in arms (7% and 12%, respectively). Treatment discontinuations due to adverse events were between 9% and 19% for patients in the boceprevir arms, compared to 8% for the control arm.

Safety data from the HCV SPRINT-1 study showed that the most common adverse events reported in the boceprevir arms were fatigue, anemia, nausea and headache. The incidence of skin adverse events (rash or pruritus) observed in the boceprevir arms was comparable to that seen in the PEGINTRON and REBETOL control arm.

About the Boceprevir Phase III Registration Studies

The two randomized, double-blind, placebo-controlled registration studies evaluate boceprevir in combination with PEGINTRON and REBETOL compared to standard of care with PEGINTRON and REBETOL alone. The HCV SPRINT-2 study evaluates the efficacy of 28- and 48-week regimens of boceprevir (800 mg TID) in combination with PEGINTRON (1.5 mcg/kg/week) and REBETOL (600–1400 mg/day) compared to a control of PEGINTRON and REBETOL alone for 48 weeks in treatment-naïve adult patients with chronic HCV genotype 1. The study enrolled a total of 1,099 patients, including 158 African-American/Black patients. The HCV RESPOND-2 study evaluates 36- and 48-week regimens of boceprevir in combination with PEGINTRON and REBETOL at the same doses as described above compared to a control of PEGINTRON and REBETOL alone for 48 weeks in adult patients with chronic HCV genotype 1 who failed prior treatment (relapsers and nonresponders) with peginterferon and ribavirin combination therapy. The study enrolled a total of 404 patients. In both studies, RVR criteria at 4 weeks of boceprevir treatment (treatment week 8) is used to determine which boceprevir patients can stop all treatment at 28 weeks (HCV SPRINT-2) or 36 weeks (HCV RESPOND-2).

For more information about these ongoing registration studies, please visit www.clinicaltrials.gov, search term boceprevir.