CHIEF'S CORNER

Anil K. Rustgi, MD
T. Grier Miller Professor of Medicine & Genetics
Chief, Division of Gastroenterology

The gastroenterology team at the University of Pennsylvania School of Medicine and University of Pennsylvania Health System is nationally recognized for clinical research and state-of-the-art care for its patients. In this, as in past issues of the *Gastroenterology Newsletter,* I wish to highlight some of the recent achievements of our faculty and the honors they have been awarded.

I am pleased to announce that the following physicians have either been recognized as "Top Doctors" by *Philadelphia* magazine or were elected to the 2007-2008 "Best Doctors in America" registry by Best Doctors, Inc.:

Thomas W. Faust, MD
Gregory G. Ginsberg, MD
David L. Jaffe, MD
David A. Katzka, MD
Michael L. Kochman, MD
Gary R. Lichtenstein, MD
William B. Long, MD
David C. Metz, MD
K. Rajender Reddy, MD
Anil K. Rustgi, MD

Coming in 2008

In late 2008, Penn Gastroenterology Division outpatient clinics and outpatient endoscopy will move from the Hospital of the University of Pennsylvania to the Perelman Center for Advanced Medicine. Beginning in 2009, the Perelman Center will house all of Penn's gastroenterology team, including specialists in gastroenterology, gastrointestinal surgery, medical oncology, radiation oncology and pathology, along with nursing and nutritional staff.

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University of Pennsylvania Health System
Penn Digestive & Liver Center

GASTROENTEROLOGY NEWSLETTER

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Hospital of the University of Pennsylvania
3400 Spruce Street | 3 Dulles
Philadelphia, PA 19104
Phone: 215.349.8222

Penn Presbyterian Medical Center
38th and Market Streets
218 Wright-Saunders Building
Philadelphia, PA 19104
Phone: 215.662.8900

Penn Medicine at Radnor
250 King of Prussia Road | Module B
Radnor, PA 19087
Phone: 610.902.1500

MEDICAL INDICATIONS FOR LIVER TRANSPLANTATION

K. RAJENDER REDDY, MD* and THOMAS FAUST, MD§

*Medical Director of Liver Transplantation at the Hospital of the University of Pennsylvania.

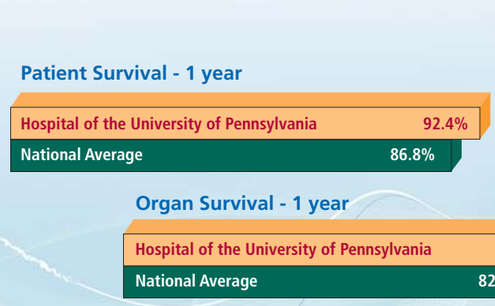
§Associate Professor of Clinical Medicine, Division of Gastroenterology, University of Pennsylvania School of Medicine.

Despite great strides in surgical technique and operative technologies, a variety of challenging medical issues continue to confront centers specializing in liver transplantation. Chief among these are the management of active HCV infection prior to surgery, and the prevention of recurrent liver disease and graft rejection in the months following surgery.

Avoiding these threats, according to Rajender Reddy, MD, and Thomas Faust, MD, of the Penn Transplant Institute—where combined liver transplant graft and patient survival rates at one year exceed national average rates by about 5 percent—involves a concentrated, multidisciplinary effort to optimize medical care for patients undergoing liver transplantation.

Authors of The Clinician's Guide to Liver Disease (Slack, 2006), Drs. Reddy and Faust have performed extensive research into chronic viral hepatitis and other leading indications for orthoptic liver transplantation (OLT). At the Penn Transplant Institute, the findings of these investigations have been applied to a framework for the perioperative medical management of transplant patients and to the management of potentially intractable complications in the postoperative period.

Penn has improved outcomes by tailoring interventions to reflect the heterogeneity of the transplant population. The majority of patients in the liver transplant program at Penn have chronic hepatitis C (HCV) or alcoholic liver disease; some have liver cancer, cholestatic hepatitis or other fatal conditions.



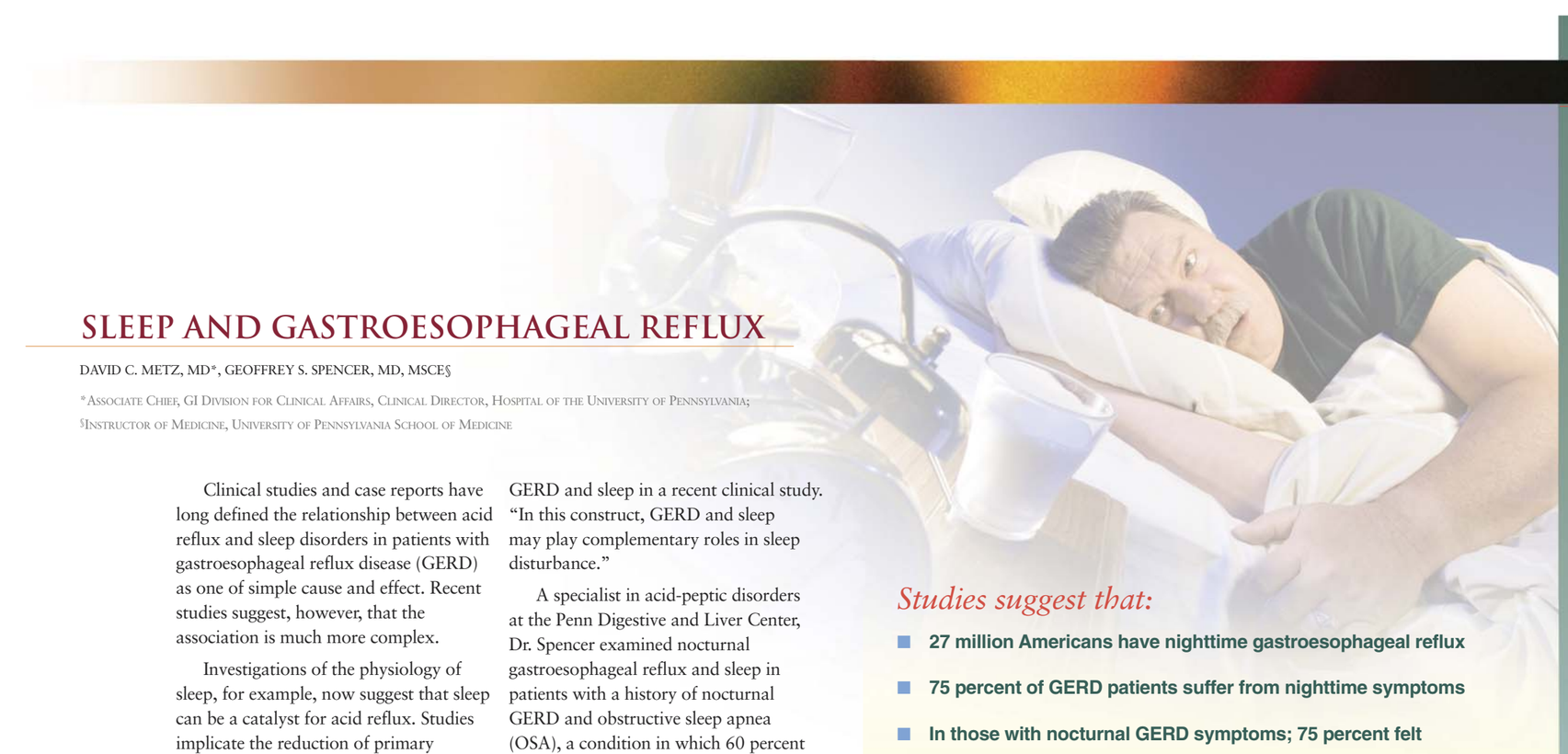
Patient and graft survival at one year among liver transplant patients at the Penn Transplant Institute compared to national averages.

CONTINUED ON PAGE 3

SLEEP AND GASTROESOPHAGEAL REFLUX

DAVID C. METZ, MD*, GEOFFREY S. SPENCER, MD, MSCE§

*Associate Chief, GI Division for Clinical Affairs, Clinical Director, Hospital of the University of Pennsylvania;
§Instructor of Medicine, University of Pennsylvania School of Medicine



Clinical studies and case reports have long defined the relationship between acid reflux and sleep disorders in patients with gastroesophageal reflux disease (GERD) as one of simple cause and effect. Recent studies suggest, however, that the association is much more complex.

Investigations of the physiology of sleep, for example, now suggest that sleep can be a catalyst for acid reflux. Studies implicate the reduction of primary peristalsis and saliva production during sleep and sleep-induced relaxation of the lower esophageal sphincter (LES) in precipitating nocturnal GERD injury due to prolonged esophageal contact time in the supine position. On the other hand, postprandial refluxate lingering in the esophagus may provoke reflexes in the airways while reclining, interrupting breathing, disrupting sleep—and shifting the onus of causality back to acid.

"It's likely that what we're seeing are reciprocal, corresponding effects," says Geoffrey S. Spencer, MD, who investigated the relationship between GERD and sleep in a recent clinical study. "In this construct, GERD and sleep may play complementary roles in sleep disturbance."

A specialist in acid-peptic disorders at the Penn Digestive and Liver Center, Dr. Spencer examined nocturnal gastroesophageal reflux and sleep in patients with a history of nocturnal GERD and obstructive sleep apnea (OSA), a condition in which 60 percent of patients report abnormal reflux. All patients used continuous positive airway pressure (CPAP), a therapy commonly used to treat OSA. In addition to assessing the efficacy of CPAP in OSA, the study was designed to determine whether sleep disturbances prompt reflux events or vice versa.

Sleep data and pH were recorded on a single instrument using a calibrated transnasal pH catheter and polysomnographic monitor. The primary endpoints included percentage of time at pH <4 in the distal esophagus and occurrences per hour of pH <4 for more than 4 seconds. Independent of the CPAP findings, the study linked sleep disturbances (awakenings and arousals) to exacerbations of GERD, but found no association between reflux and standard sleep events. CPAP reduced nocturnal acid exposure to normal or near normal levels in 73 percent of those with abnormal reflux.

Studies suggest that:

- **27 million Americans have nighttime gastroesophageal reflux**
- **75 percent of GERD patients suffer from nighttime symptoms**
- **In those with nocturnal GERD symptoms; 75 percent felt symptoms impaired sleep; 40 percent felt impaired ability to function the next day**

David C. Metz, MD, Director of the Acid-Peptic Program at Penn, provides further insight into the role of sleep in GERD-associated nocturnal events. A longtime investigator of GERD, Dr. Metz observes that some aberrations of sleep—snoring or apnea, for example—may induce a negative intrathoracic pressure sufficient to draw refluxate into the esophagus.

"Studies suggest that sleep impairs esophageal clearance," says Dr. Metz. "Thus, acid introduced into the esophagus during sleep remains in contact with the mucosa for an extended period, worsening the injury and in the process increasing both the likelihood of injury to the esophageal mucosa and of sleep disruption."

The search for a protagonist in sleep-associated injuries attributable to gastric acid seems far from over. A recent study proposes that the volume of nocturnal reflux, independent of acidity, is responsible for obstructing the esophagus during sleep disturbances. Earlier findings, however, indicate that distal gastric acid exposure during sleep enhances proximal migration of gastric contents. Other studies diagram a complex series of actions and reactions over time involving both the gastrointestinal and respiratory systems.

"It's clear that the relationship between gastroesophageal reflux and sleep needs further investigation," says Dr. Spencer, "but the information we've gathered so far and the methodologies we've developed for further study suggest that we're well on the way to that resolution."

RESOURCES

For Penn's GI division academic website:
http://www.med.upenn.edu/gastro/
For the Penn Abramson Cancer Center website:
www.penncancer.org
For Penn's cancer information:
www.oncolink.org
For the NCI program project on esophageal cancer at Penn:
www.uphs.upenn.edu/gastro/nci

MEDICAL INDICATIONS FOR LIVER TRANSPLANTATION

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Given the continuing organ shortage, the program strives to achieve an equitable balance between these etiologies in the transplant population.

The challenges inherent in optimizing medical treatment in OLT are illustrated by the treatment regimen for patients with histological evidence of HCV infection before and after surgery. Active HCV infection is associated with post-transplantation re-infection and graft failure, and its presence mandates the use of interferon-based therapies. Tolerance for these drugs is typically low in patients with HCV infection after transplantation as a consequence of renal insufficiency and other comorbidities that might be present.

"The ideal candidate for therapy," Dr. Reddy says, "is someone who has a positive HCV-RNA and abnormal ALT, with histologic evidence of chronic hepatitis and absence of decompensated liver disease."

Patients with this profile typically respond well to interferon and ribavirin, the combination of drugs used to suppress viral activity. The drugs are toxic, and rigorous monitoring is necessary to minimize complications, which may include anemia, leucopenia and other side effects, as well as drug interactions. Optimal dosing can be maintained via patient education to promote compliance and the addition of granulocyte colony-stimulating factor or erythropoietin when necessary.

"The ideal candidate for therapy," Dr. Reddy says, "is someone who has a positive HCV-RNA and abnormal ALT, with histologic evidence of chronic hepatitis and absence of decompensated liver disease."

Treatment of recurrent HCV infection in the post-operative period is a paramount concern, as well, says Dr. Faust, noting that 50 percent of liver recipients demonstrate histological evidence of HCV-RNA within the first year of surgery.

"Interferon and ribavirin can suppress viral load in the majority of post-transplant patients," said Dr. Faust, "but sustained virologic clearance is uncommon."

To this end, current research at Penn (see below) is focusing on the use of nucleoside analogues and other agents designed to inhibit replication of the hepatitis C virus.

"With effective inhibition of HCV replication," said Dr. Reddy, "the primary indication for liver transplantation and the prevailing threat to allograft failure would be greatly diminished."

Moreover, Dr. Reddy observes, the paradigm for liver transplantation would be altered to permit greater access to organs for patients with cancer, cholestatic hepatitis and other compelling immediate needs.

Penn Clinical Trials

CURRENTLY RECRUITING PARTICIPANTS

Adaptive phase I HCV study with nucleoside analogue, in combination with interferon and ribavirin

Study to evaluate the safety, tolerability, and pharmacokinetics of orally administered silymarin (Legalon) in non-cirrhotic subjects with chronic hepatitis C or non-alcoholic fatty liver disease