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 is 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—the Medical Director of Liver Transplantation at the Hospital of the University of Pennsylvania and the Associate Professor of Clinical Medicine, Division of Gastroenterology, University of Pennsylvania School of Medicine—requires a concentrated, multidisciplinary effort to optimize medical care for patients undergoing liver transplantation.

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.
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.

David C. Metz, MD, Director of the Acid-Pepitic 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 alterations 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.”

For 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 air passing through the esophagus and the airways during sleep is matched to the amount of acid reflux. To this end, current research at Penn (see below) is focusing on the use of nucliose analogues and other agents designed to inhibit replication of the hepatitis C virus.

“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 dose–response monitoring is necessary to minimize complications, which may include anemia, leukopenia and other side effects, as well as drug interactions. Optimally dosing can be maintained with patient education to promote compliance and the addition of granulocyte colony-stimulating factor or erythropoietin when necessary.

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.”

Treatment of recurrent HCV infection in the post-operative period is a paramount concern, as well, says Dr. Faust, noting that 30 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.

“Ineffective 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, cholestatis hepatitis and other compelling immediate needs.