



## Drug-Induced Hepatotoxicity Cases on the Rise

Expanding Pharmaceuticals and Alternative Medicines Contribute to Problem

By Maurizio Bonacini, M.D. and Laura Miyashita

### Contents

2

Drug Advancements  
Simplify Adult Hepatitis  
A and B Vaccination

2

Gastric Varices Treated  
with New Glue Injection  
Procedure

3

California Pacific  
Performs 1,000<sup>th</sup> Liver  
Transplant

4

Laparoscopic  
Fundoplication Offers  
Relief from Severe GERD  
Symptoms

Liver damage caused by medication ingestion—also known as drug-induced hepatotoxicity or DIH—has become an important public health problem, contributing to more than 50% of acute liver failure cases. Annually, California Pacific’s physicians see dozens of patients with drug-induced hepatotoxicity, a fraction of whom require immediate transplantation because of irreversible damage to their liver. Cases of severe drug-induced hepatotoxicity are defined as liver enzyme elevations five or more times the normal limit.

“Americans are consuming a growing number of medications, herbal remedies and complementary therapies which increase the possibility of liver toxicity,” says Maurizio Bonacini, M.D. a hepatologist with California Pacific’s Liver Disease Management & Transplant Program. “In fact, most drugs listed in the *Physician’s Desk Reference* and a number of over-the-counter preparations have been associated with different degrees of liver enzyme elevations. Resulting liver toxicity is the number one cause for FDA non-approval or withdrawal of medications from the market,” Bonacini explains.

Often, drug-induced hepatotoxicity is only detected after a drug enters the market because animal models cannot always predict human toxicity. For example, of 31 drugs that caused hepatotoxicity in humans, 13 showed no toxicity in animals. Conversely, of drugs associated with hepatotoxicity in animals, only one-third resulted in a rise in liver enzymes in humans.

#### Causes of Drug Reactions

Why do people react negatively to drugs? The main issue is an individual’s sensitivity (not necessarily allergic) to the drug or its metabolites. Reactions occur in .001 to 10 percent of exposed patients, depending on the medication. An individual’s metabolic pathways may by chance lead to toxic compounds and it is known that specific enzymes are genetically determined. Mechanisms of detoxification (neutralization of toxic compounds) may also be associated with genetic variations: an individual’s inefficient detoxification pathway may result in the occurrence of DIH.



Acetaminophen is one of the leading medications with the potential to cause severe liver injury, but is safe at or below 2 gm per day (4 extra strength tablets).

Patients with chronic viral illnesses are more prone to develop hepatotoxicity, possibly because of impaired defense mechanisms. Other categories of patients at higher risk for DIH include:

- Females
- Obese individuals
- Elderly patients

#### Diagnosing Hepatotoxicity

Patients with drug-induced hepatotoxicity may be asymptomatic, with liver injury diagnosed during routine blood testing, while others develop symptoms including nausea, fatigue, itching and jaundice. The latter symptom is significant, as patients with jaundice have a poorer outcome and don’t respond as well to treatment.

“The diagnosis of drug hepatotoxicity in any patient is complicated by several facts,” says Bonacini.

“First, there are no satisfactory criteria for the positive diagnosis of DIH and it is often a diagnosis of exclusion. Second, because patients often take several medications, teasing out the culprit can present challenges. Lastly, the histological expression of hepatotoxicity is extremely varied and therefore a liver biopsy is of limited use in making a positive diagnosis.”

# Drug Advancements Simplify Adult Hepatitis A and B Vaccination

## Hepatitis C Patients Urged to Get Twinrix® Vaccine

by Robert Gish, M.D. and Laura Miyashita

The development of a new combination vaccine for hepatitis A and B offers patients at risk for these diseases the ability to receive simultaneous immunization for both forms of hepatitis while reducing the total number of vaccinations from five to three. Approved by the U.S. Food and Drug Administration (FDA) last year, Twinrix [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] is the first on the market in a series of drugs being tested for combination vaccine delivery.

“It is now the standard of care to vaccinate people at high risk for hepatitis B and A, which includes any patient with hepatitis C (HCV),” says Robert Gish, M.D., medical director of California Pacific’s Liver Disease Management & Transplant Program. “This latest advancement greatly simplifies vaccination and represents a milestone in HBV drug development,” he adds.

Vaccinations for hepatitis B have been available for nearly two decades and in the U.S., patients at risk for HBV infection have been given injections with

either Energix-B or Recombivax HB to prevent transmission of the virus. Because of the high mortality rate for acute hepatitis A virus infections in chronic HBV carriers, combination vaccination for HAV and HBV is emerging as the standard of care in many countries. With the combined vaccine, primary immunization consists of three doses, given on a 0-, 1- and 6-month schedule. (see table)

**New Delivery System Explored**  
To ease delivery of hepatitis B vaccination, additional research is underway to explore an oral vaccination delivery system that would eliminate the need for injection immunizations. A patented liposomal delivery system is currently undergoing research in animals and may be in human trials in the next one to two years. If vaccines could be delivered orally, it would revolutionize medical delivery of preventive treatments for hepatitis and other diseases. ∞

### Comparison of Twinrix with Adult Formulations of Energix\* B and HAVRIX\*\*

Vaccine	Dosage		Schedule
	Hepatitis A	Hepatitis B	
Twinrix	720 EL.U.†	20 mcg.	0, 1, 6 months
Energix B		20 mcg.	0, 1, 6 months
HAVRIX	1440 EL.U.		0, 6 months

From Centers for Disease Control

\*Recombinant hepatitis B vaccine, manufactured by GlaxoSmithKline

\*\* Inactivated hepatitis A vaccine, manufactured by GlaxoSmithKline

†ELISA Units

Populations to screen for HBV and to subsequently vaccinate if not infected include:

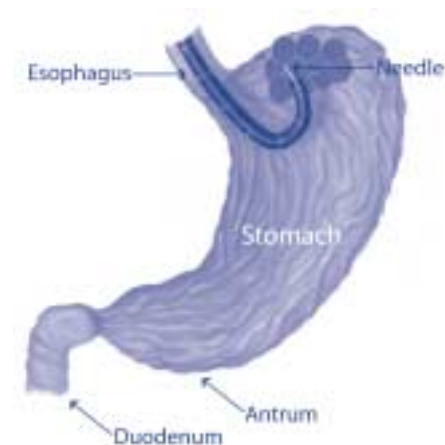
- Patients who are born in endemic regions of the world
- Patients with a history of high-risk sexual activity or more than 50 lifetime sexual partners
- Household contacts of HBV carriers
- Sexual contacts of HBV carriers
- Users of illicit injection drugs
- Persons who have had medical care or injections in a developing country
- Any person with acutely or chronically elevated liver enzymes
- Carriers of HIV or HCV infection

If patients fall into these categories, their primary care physician should offer immunization.

## Gastric Varices Treated with New Glue Injection Procedure

California Pacific and Mayo Clinic Only U.S. Centers Offering Cyanoacrylate Treatment for Gastric Varices

by Laura Miyashita



Cyanoacrylate is delivered endoscopically via an injection needle to treat gastric varices.

Adapted from “Therapeutic Endoscopy” ©1998 Georg Thieme Verlag

Cyanoacrylate glue injection—a treatment used for years in neurological and ophthalmology procedures and in treatment of cerebral aneurysms—is now offering promise for patients with gastric varices. Pioneered by Kenneth Binmoeller, M.D., director of California Pacific’s Interventional Endoscopy Service, and Nib Soehendra, M.D. in Hamburg, Germany, this ‘super glue’ substance, which is similar in consistency to water, rapidly transforms into a hard, solid substance when added to a physiological medium such as blood.

Gastric varices develop in roughly 25% of patients with portal hypertension and represent about 10% of

bleeding sites in variceal hemorrhage. “With this new procedure, the cyanoacrylate glue is injected into the gastric varix, then disperses within the tissue, ultimately plugging the varix lumen,” explains Binmoeller. He adds, “This enables not only rapid termination of active bleeding, but also prevents rebleeding from the treated varix.” The elimination of varices is usually achieved with a single treatment. Over time, the cyanoacrylate is expelled from the varix lumen, leaving scarred mucosa behind.

The use of cyanoacrylate glue for gastric varices is expected to overcome the shortfalls of transjugular intrahepatic portal shunt (TIPS) treatment. While

# California Pacific Performs Its 1,000<sup>th</sup> Liver Transplant

Success Rates Continue to Rank Among Top Nationwide

In June, California Pacific's Liver Team performed its 1,000<sup>th</sup> liver transplant, a milestone for the program that began in 1988. "While the number of organs available limits our ability to transplant more patients, we continue to be pleased with our success rates and the decision of families and individuals who pursue organ donation and offer others a new chance at life," says Robert Osorio, M.D., surgical director of California Pacific's Liver Disease Management & Transplant Program.

Last year, 54 patients received liver transplants at California Pacific. The primary indication for liver transplantation at the Medical Center is hepatitis C (HCV), followed by alcoholic cirrhosis and hepatitis B (HBV) (see Figure 1). The majority of patients undergoing transplantation range in age from 40 to 60 years, and more males (58.3%) than females (41.7%) necessitate liver transplantation.

In the past 10 years, the waiting time for transplantation in California and throughout the nation has significantly increased, from an average of 79 days in 1991 at California Pacific to 510 days in 2001. In the same period, the average length of stay during a liver transplant has decreased from 22 days a decade ago to 10 days in 2001.

## Graft Survival at California Pacific Outperforms National Average

At one- and three-years following liver transplantation, the graft survival for liver transplants at California Pacific Medical Center significantly exceeds the national average. For instance, California Pacific's one-year graft survival is 87% versus 80% nationally for patients transplanted between July 1998 to July 2000. Similarly, the three-year graft survival at California Pacific is 82% compared to the nationwide average of 72% (see table).

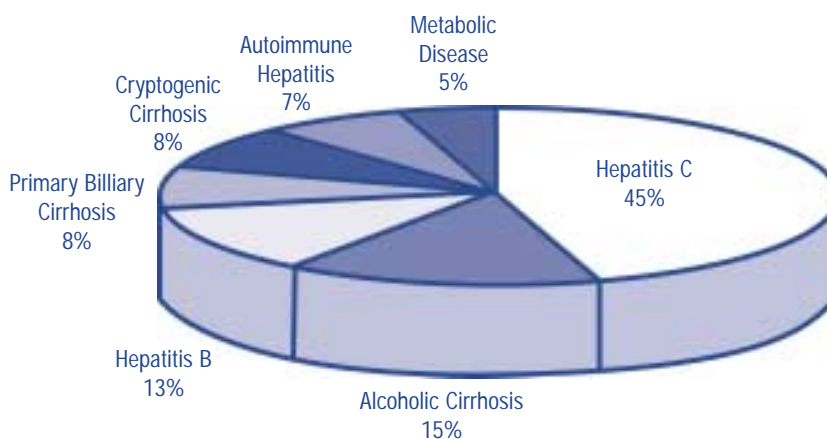


Figure 1. Diagnostic indications for liver transplant.

"Our outcomes highlight California Pacific's success and expertise in treating patients with end-stage liver disease," says Robert Gish, M.D., medical director of California Pacific's Liver Program. "With the impact of hepatitis C expected to continue growing, we anticipate a similar if not greater volume of transplants in the years to come and hope to continue maintaining our excellent results."

The Liver Team visits more than 20 outreach sites in Northern California and Nevada to evaluate and monitor patients with end-stage liver disease. For a list of outreach sites, visit [www.cpmc.org/liver](http://www.cpmc.org/liver) or call Dawn Griffin at (415) 600-1003 or Kymberly Robinson at (415) 600-1004. ∞

## Graft Survival by Time Since Transplant

Adult (age 18+)	California Pacific		United States	
	1 Year	3 Year	1 Year	3 Year
Transplants	102	75	8,121	7,057
Graft Survival (%)	87.04	82.20	80.21	72.34
Expected Graft Survival (%)	78.68	69.59	NA	NA

From Scientific Registry of Transplant Recipients ([www.ustransplant.org](http://www.ustransplant.org)) for transplants from 7/1/98-6/3/00 (1-year data) and 7/1/96-6/30/98 (3-year data)

TIPS is the standard treatment for gastric varices in the U.S., recurrent bleeding is high, ranging from 29% to 53%. In comparison, rebleeding rates following cyanoacrylate glue injection range between 5% to 25%. TIPS also requires an open and adequately sized portal vein. Other procedures used successfully for esophageal varices, such as band ligation and sclerotherapy, are not effective for gastric varices and may result in severe complications.

Numerous studies have validated the safety and efficacy of cyanoacrylate for the treatment of gastric varices and the procedure has been in clinical use in Europe, Asia and the Middle East for over a decade.

For more information on cyanoacrylate treatment for gastric varices or our Interventional Endoscopy Service, call our Specialty Referral Program at 1 (888) 637-2762. ∞

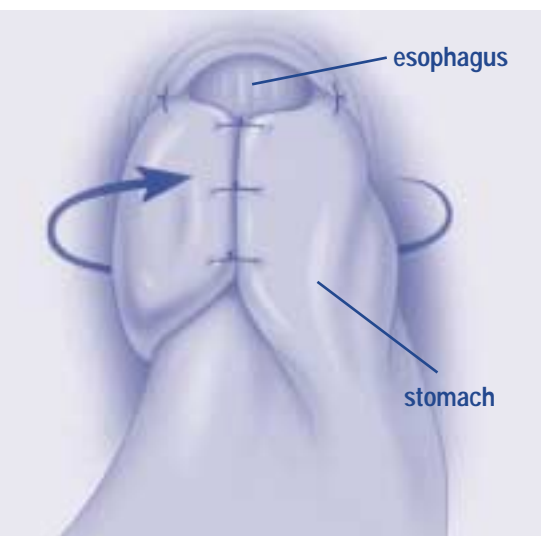
## HEPATOTOXICITY, continued from page 1

The management of drug-induced hepatotoxicity is immediate discontinuation of the offending medication. Because drugs taken together may cause toxicity, it is often useful to discontinue several medications as their combination may be the culprit. Acetaminophen toxicity is treated with N-acetylcysteine and this compound is being studied as a therapy for other drug injuries as well. Other compounds used as therapy for DIH include vitamin B1 and B6, carnitine, coenzyme Q and ursodeoxycholic acid, but none of these have undergone rigorous clinical trials. In cases of liver failure, liver transplantation may be indicated. ∞

# Laparoscopic Fundoplication Offers Relief from Severe Acid Reflux

Treatment Involves Constructing Esophageal Valve to Stop Movement of Stomach Acid

by Gregg Jossart, M.D., director, Minimally Invasive Surgery and Laura Miyashita



In laparoscopic fundoplication, a new valve is constructed by wrapping the upper portion of the stomach around the lower end of the esophagus, as shown in the above image.



Paraesophageal hernias, which can be treated with laparoscopic fundoplication, occur when half of the stomach is herniated into the chest, often causing obstruction.

Most Americans have more than one episode of acid reflux each week and over 20 million Americans take powerful prescription antacids. For patients with heartburn that is either not well controlled with these antacids or who cannot tolerate their side effects, other treatments are available.

“The use of medications to suppress stomach acid treats only the *symptom* of acid reflux and not the *cause*,” explains Gregg Jossart, M.D., director of minimally invasive surgery at California Pacific Medical Center. “For cases in which the esophagus is repetitively exposed to harsh stomach acids and inflammation causing ulcers, strictures and dysphagia, surgical intervention is often necessary,” he adds.

Among the surgical interventions for acid reflux, laparoscopic fundoplication has emerged as the standard of care for patients with severe acid reflux and hiatal hernias larger than 2 cm. Patients who have failed therapy with H<sub>2</sub> blockers and proton pump inhibitors are also candidates for this procedure.

During laparoscopic fundoplication, a new esophageal valve is constructed by wrapping the upper portion of the stomach (fundus) around the lower end of the esophagus. The wrap is sutured into place and supports the sphincter muscle controlling the esophageal valve so stomach acid cannot push its way into the esophagus. The hiatal opening where the stomach herniates above the diaphragm muscle is also closed around the esophagus to prevent the stomach from herniating again. The procedure lasts between 90 minutes to two hours, followed by a one to two day hospital stay.

In addition to treating patients with chronic acid reflux, laparoscopic fundoplication is appropriate for patients with acid reflux accompanied by paraesophageal hernias. These hernias, caused by a large opening in the diaphragm that allows half the stomach to bulge into the chest cavity, can cause severe pain and difficulty swallowing.

For more information on laparoscopic fundoplication or other surgical interventions for GERD, call our Specialty Referral Program at 1 (888) 637-2762. ∞



Liver Disease Management and Transplant Program

Center for Complex Digestive Disease

California Pacific Medical Center  
2340 Clay Street, 4th Floor  
San Francisco, California 94115  
(415) 600-1000

[www.cpmc.org/liver](http://www.cpmc.org/liver)

**Liver & GI Review** is a quarterly publication of California Pacific Medical Center. If you wish to be removed from the Liver & GI Review mailing list or have received duplicate copies of this publication, please call (415) 600-3596 or email [miyashl@sutterhealth.org](mailto:miyashl@sutterhealth.org).

Copyright © 2002 California Pacific Medical Center. All rights reserved.

Laura Miyashita *Managing Editor*

Robert Gish, M.D.  
Robert Osorio, M.D.  
Maurizio Bonacini, M.D.  
Natalie Bzowej, M.D., PhD  
Adil “Ed” Wakil, M.D. *Editorial Advisors*

Cindy Dove *Graphic Design*

Non-Profit  
Organization  
U.S. Postage  
PAID  
Permit No. 10108  
San Francisco, CA