

## PORTAL VEIN THROMBOSIS AND LIVER TRANSPLANTATION

Our attention has been drawn to the June 1992 issue of HOSPITAL PHYSICIAN, particularly the section on Board Review in Internal Medicine.<sup>1</sup>

On the issue of portal vein thrombosis (PVT) in orthotopic liver transplantation (OLT), we wish to bring to your attention, the response to question 15: "Of the following, which represents the most important contraindication to liver transplantation?" The answer was Portal Vein Thrombosis (D); and the subsequent explanation, "Portal vein thrombosis technically precludes successful liver transplantation."

In 1992, PVT by itself, is not a contraindication to OLT. Rapid advances in liver transplantation over the years, particularly the last decade, have led to the identification and successful resolution of several problems that had previously contraindicated or made liver transplantation a hazardous enterprise.<sup>2</sup> Without question, the problem of PVT was a difficult one in OLT. However, by 1985, Shaw et al<sup>3</sup> had reported on the successful reconstruction of the portal vein in two patients with PVT undergoing OLT. Later in 1986, Lerut et al<sup>4</sup> published the University of Pittsburgh experience (from 1980 to 1984) at not only portal vein but also vena cava

reconstruction for various associated occlusive and hypoplastic abnormalities in patients undergoing OLT. Despite these successes, refinement in technique continues as demonstrated by Tzakis et al<sup>5</sup> using the venous jump grafts in PVT in 1989. Furthermore, just recently, Stieber et al<sup>6</sup> in 1991, expanded the work on the spectrum of PVT in liver transplantation replete with graphic details on the several techniques currently used to ensure successful revascularization in patients with PVT undergoing OLT.

As these developments unfolded, Maddrey and Van Thiel<sup>7</sup> as far back as 1988 indicated that several problems (PVT being one of them) that had originally been listed as contraindications to liver transplantation were no longer so.

Taken together, therefore, we are of the opinion that from our experience and from a review of the literature, PVT by itself no longer constitutes a contraindication to liver transplantation.

## REFERENCES

1. Babyatsky MW. Board review in internal medicine: liver diseases. *Hospital Physician*. 1992;28:63-88.
2. Starzl TE, Demetris AJ. Liver transplantation: a 31-year perspective. *Curr Probl Surg*. 1990;27:49-240.
3. Shaw BW, Jr, Iwatsuki S, Bron K, Starzl TE. Portal vein grafts in hepatic transplantation. *Surg Gynecol Obstet*.

1.5g or 3g q6h  
**Unasyn**<sup>TM</sup>  
 (ampicillin sodium/subactam sodium)

Reference: 1. Drug Topics  
 Red Book 1992. Montvale, NJ:  
 Medical Economics Data; 1992.

## BRIEF SUMMARY

### INDICATIONS AND USAGE

UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

**Skin and Skin Structure Infections** caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,<sup>\*</sup> *Klebsiella* spp.<sup>\*</sup> (including *K. pneumoniae*),<sup>\*</sup> *Proteus mirabilis*,<sup>\*</sup> *Bacteroides fragilis*,<sup>\*</sup> *Enterobacter* spp.,<sup>\*</sup> and *Acinetobacter calcoaceticus*.<sup>\*</sup>

**Intra-Abdominal Infections** caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae*),<sup>\*</sup> *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.<sup>\*</sup>

**Gynecological Infections** caused by beta-lactamase producing strains of *Escherichia coli*,<sup>\*</sup> and *Bacteroides* spp.<sup>\*</sup> (including *B. fragilis*).<sup>\*</sup>

\*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

### CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

### WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including UNASYN, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to mistigle and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

### PRECAUTIONS

**General:** A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

**Drug Interactions:** Probenecid decreases the renal tubular secretion of ampicillin and subactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and subactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rash in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rash is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

**Drug/Laboratory Test Interactions:** Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinistest<sup>TM</sup>, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix<sup>TM</sup> or Testape<sup>TM</sup>) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estradiol, estradiolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

### Pregnancy

**Pregnancy Category B:** Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See Drug/Laboratory Test Interactions.)

**Labor and Delivery:** Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or deliv-

ery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

**Nursing Mothers:** Low concentrations of ampicillin and subactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

**Pediatric Use:** The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

### ADVERSE REACTIONS

UNASYN is generally well tolerated. The following adverse reactions have been reported.

#### Local Adverse Reactions

Pain at IM injection site — 16%

Pain at IV injection site — 3%

Thrombophlebitis — 3%

#### Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, subcutaneous pain, epistaxis and mucosal bleeding.

#### Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

**Hepatic:** Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.

**Hematologic:** Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.

**Blood Chemistry:** Decreased serum albumin and total protein.

**Urea:** Increased BUN and creatinine.

**Urinology:** Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

**Gastrointestinal:** Gastritis, stomatitis, black "hairy" tongue, and enterocolitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

**Hypersensitivity Reactions:** Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

**Hematology:** In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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4. Lerut J, Tzakis AG, Bronk, et al. Complications of venous reconstruction in human orthotopic liver transplantation. *Ann Surg.* 1986;205:404-414.

5. Tzakis A, Todo S, Stieber AC, Starzl TE. Venous jump grafts for liver transplantation in patients with portal vein thrombosis. *Transplantation.* 1989;48:530-531.

6. Stieber AC, Zetti G, Todo S, Tzakis AG, et al. The spectrum of portal vein thrombosis in liver transplantation. *Ann Surg.* 1991;213:199-206.

7. Maddrey WC, Van Thiel DH. Liver transplantation: an overview. *Hepatology.* 1988;8:948-959.

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**EDITOR'S NOTE:**

*The author of the original article concurs with the conclusions of Odocha et al.*

**ICE WATER: NOT THE ANSWER TO HEAT STROKE**

I was intrigued to read the article in the September 1992 issue on heatstroke (Ukiwe J. Heat stroke. *Hospital Physician.* 1992;28:46-49.). The author recommended using icepacks rubbed on the body to get the temperature below 101°F. He is aware that ice water and similarly cold substances will induce vasoconstriction, thereby making the job of heat dissipation harder.

Saudi Arabia, the site of the Annual HAJJ, is frequently faced with the problem of older and otherwise unacclimatized individuals descending en masse for weeks at a time. They have tried a variety of treatments for this condition and found that the most effective was placing the patient in a temperate room and exposing them to a strong ventilating system. I cannot cite you the appropriate references, but this was a topic discussed in our tropical medicine journal club about two years ago.

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**TORADOL INFORMATION CLARIFIED**

In your September 1992 issue [Rx Update. *Hospital Physician*, 1992;28(9):52], information about Toradol

(ketorolac tromethamine), the nonsteroidal anti-inflammatory drug (NSAID) marketed by Syntex Laboratories and Roche Laboratories, was discussed. We would like to clarify the information presented regarding the safety of using ketorolac for periods beyond 5 days. Although both intramuscular (IM) and oral ketorolac are indicated in the management of pain, the recommended duration of use is different for the two forms of ketorolac. Toradol<sup>IM</sup> is indicated for the short-term management of pain for up to 5 days. Safety studies of IM ketorolac have not been conducted beyond 5 days. The use of Toradol<sup>ORAL</sup> is, however, not restricted to 5 days. Oral ketorolac is indicated for limited duration use, as needed in the management of pain.

Ketorolac shares the risks associated with other NSAIDs when taken chronically, including the potential to cause gastrointestinal (GI) bleeding, ulceration, and perforation. As with other NSAIDs, ketorolac should be used with caution in patients with a prior history of serious GI events, and patients with other risk factors known to be associated with peptic ulcer disease (particularly elderly patients); patients with impaired renal or hepatic function, or a history of kidney or liver disease; patients with coagulation disorders, and patients receiving drug therapy that interferes with hemostasis. It should also be noted that ketorolac is contraindicated in patients with previously demonstrated hypersensitivity to ketorolac, or in those with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity (eg, asthma) or other allergic manifestations to aspirin or other NSAIDs. The Toradol package insert should be consulted for full prescribing information.

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***Hospital Physician welcomes your comments on these and other important medical issues.***

***Please send your comments to:***

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