



## SURGERY NEWS



DOUG BOYD/EAST CAROLINA UNIVERSITY

The perception of a high infection rate prompted the move toward eradication, said Dr. Walter E. Pofahl.

## MRSA Screening Used To Decrease SSIs

BY DAMIAN McNAMARA  
Elsevier Global Medical News

PALM BEACH, FLA. — Universal preoperative surveillance for methicillin-resistant *Staphylococcus aureus* infection coupled with eradication before all elective procedures was not significantly better than screening of high-risk patients and eradication for decreasing the rate of surgical site infections (SSIs) at a large, tertiary care hospital.

Clinicians at Pitt County Memorial Hospital in Greenville, N.C., began testing a nasal swab from all elective surgical patients in February 2007 in response to community concerns about the incidence of

methicillin-resistant *Staphylococcus aureus* (MRSA).

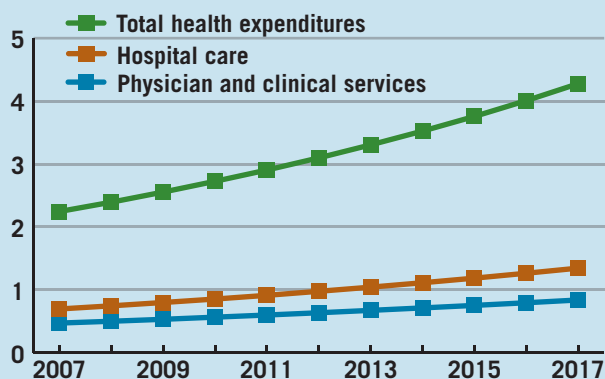
“There was a perception of a high infection rate at our tertiary care hospital, so our board thought it was important to eradicate and move toward zero infections,” said Dr. Walter E. Pofahl, an ACS Fellow who is chief of the division of advanced laparoscopic, gastrointestinal, and endocrine surgery, East Carolina University, also in Greenville.

“MRSA has garnered a tremendous amount of attention in the past few years,” said Dr. Michael F. Rotondo, an ACS Fellow who is chief of trauma

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## VITAL SIGNS

### Projected U.S. Health Expenditures (in trillions of dollars)



Note: Based on 2006 National Health Expenditures data.  
Source: Centers for Medicare and Medicaid Services

ELSEVIER GLOBAL MEDICAL NEWS

## Data Support Simultaneous Resection

*Colectomy, hepatectomy safely combined.*

BY DAMIAN McNAMARA  
Elsevier Global Medical News

PALM BEACH, FLA. — Simultaneous resection performed for primary adenocarcinoma of the large bowel and synchronous liver metastasis yielded complication and mortality rates similar to those seen after a staged approach, according to a review of more than 200 patients.

Total operative time, not surprisingly, was shorter with simultaneous resection, and overall hospital length of stay was significantly reduced.

Researchers identified 230 patients with colorectal cancer and synchronous liver metastases from 1,344 patients entered into a hepato-pancreatico-biliary database from July 1997 to June 2008. The mean age of the cohort was 61 years, and 130 were men.

A total of 70 participants (30%) underwent simultane-

ous resection, and the remainder had staged surgery. Patients who had simultaneous colectomy and hepatectomy tended to have liver metastases that were smaller (median 3.1 cm versus 4 cm) and fewer in number (median of two versus three) than those of patients undergoing staged procedures.

There was an equal distribution of patients by metastatic risk score (mean score of 3 in each group), but the staged group received more neoadjuvant or preoperative therapy—primarily 5-fluorouracil or irinotecan, Dr. Robert C.G. Martin II said at the annual meeting of the Southern Surgical Association.

A total of 39 patients in the simultaneous group (56%) experienced 63 complications, and 88 patients in the staged group (55%) had 162 compli-

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## UnitedHealth to Close Billing Database

BY MARY ELLEN SCHNEIDER

Elsevier Global Medical News

As part of an agreement with New York Attorney General Andrew Cuomo, UnitedHealth Group plans to shut down a national billing database used by health plans to determine reimbursements to members who use out-of-network physician services.

The billing database, which is operated by the UnitedHealth Group (UHG) subsidiary Ingenix Inc., will be replaced with an independent database run by a qualified nonprofit organization. Under the terms of the agreement, UHG will pay \$50 million to help establish the new database. In addition, the nonprofit organization will develop a

public Web site where consumers can research—before seeking services—how much they may be reimbursed for common out-of-network medical services in their area.

Aetna, the nation's third largest insurer, also has entered into an agreement with the New York attorney general to abandon its use of the Ingenix database in favor of the new one. Aetna also will contribute

\$20 million over 5 years for the creation of the new database.

The agreements follow an investigation by Mr. Cuomo's office into allegations that insurers were systematically underpaying consumers for their out-of-network medical expenses by saying that physician charges were higher than the “usual, customary, and reason-

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## Similar Survival

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cations. Blood transfusion predicted complications in both groups (odds ratio, 2.98). In addition, the extent of hepatic disease predicted complications in the simultaneous surgery group, said Dr. Martin, an ACS Fellow with the Louisville (Ky.) Oncology Center.

The investigators graded complications on a 5-point scale in which 1 equaled a minor complication and 5 equaled death. There was no significant difference between groups in the severity of complications. For example, grade 1 complications occurred in 17% of simultaneous patients and in 15% of staged patients. The other grades were as follows: grade 2, 36% simultaneous versus 53% staged; grade 3, 45% versus 30%; grade 4, 0% versus 2%; and grade 5, 2% versus 2%.

Mean operative time was 180 minutes in the simultaneous group, compared with 235 minutes in the staged surgery patients. Length of hospital stay was significantly shorter: a mean of 10 days for the simultaneous patients, compared with 18 days for the staged patients.

"Simultaneous resection is safe and acceptable for patients with synchronous, resectable liver metastases," Dr. Martin said. "Neither the location of the primary tumor nor of the liver disease poses a contraindication to simultaneous resection."

The particular hospital where surgery is performed might make a difference, however. "I feel strongly that patients with synchronous disease are a

different type of patient and should be referred to a tertiary center," Dr. Martin said. "It is not an individual surgeon issue, but it requires a team-coordinated approach. Why should we treat complex oncologic patients differently than we treat trauma patients who have better survival if treated at a level-1 or -2 tertiary center?"

"Is it true that hepatobiliary surgeons are really involved up front in the decision?" asked discussant Dr. Bryan M. Clary, an ACS Fellow who is professor of surgery at Duke University, Durham, N.C.

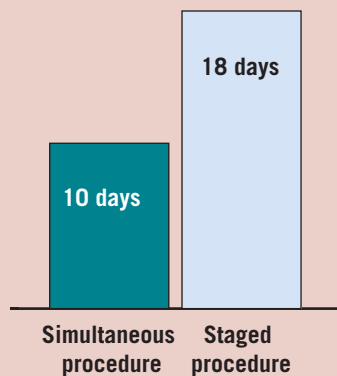
"When patients are diagnosed with synchronous lesions, we are consulted," Dr. Martin replied. "It allows general surgeons to do the colon and us to do the hepatic resection or ablation."

In response to a meeting attendee's question, Dr. Martin acknowledged surgeon bias in the study but said he considers that a strength because surgeon judgment is important in determining the extent of disease, comorbidities, the kind of medical oncology locally available to patients, and the distance they must travel to a tertiary center.

When Dr. Clary asked about patients who require major hepatectomy, Dr. Martin said that he would probably treat such patients using a staged approach. Other researchers found that simultaneous colorectal and minor hepatic resections were safe, but urged caution with major hepatic resections because of increased morbidity (Ann. Surg. Oncol. 2007;14:3481-91).

Dr. Martin said that median overall survival was 32 months for the simultaneous patients and 35 months in the staged group. ■

### Simultaneous Procedure Linked To Shorter Hospital Stays



Note: Based on a review of 230 patients who had synchronous colorectal-liver cancer.  
Source: Dr. Martin

ELSEVIER GLOBAL MEDICAL NEWS

## Eradication Effort Made

MRSA Screening from page 1

and surgical critical care at the hospital and professor and chairman of the department of surgery at East Carolina University.

"We felt pressure to do whatever we could to reduce surgical site infections in our community," he added.

In their study, which was presented at the annual meeting of the Southern Surgical Association, Dr. Rotondo, Dr. Pofahl, and their colleagues compared surgical site infection rates before and after adoption of the screening protocol, which involved use of the polymerase chain reaction (PCR) assay.

The researchers compared two groups of patients undergoing elective cardiac surgery, orthopedic procedures, and hysterectomies at the 761-bed hospital. For the 8,469 procedures performed in the 3 years prior to universal screening, patients who were at high risk for MRSA (for example, they had a history of infection or lived in a nursing home) were screened with a traditional culture and were isolated pending results.

For all 5,094 elective surgical procedures performed in the 20 months after universal screening, patients were submitted to PCR testing, which allows rapid identification of

MRSA carriers, Dr. Rotondo said.

All positive PCR tests were confirmed by traditional culture. Affected patients were treated with 2% mupirocin nasal ointment and chlorhexidine soap before hospital admission.

The universal screening and eradication protocol reduced the overall MRSA-associated surgical site infection rate from 0.23% to 0.09%. This was not a statistically significant difference, Dr. Rotondo said.

"It's significant if you are the one who gets infected," said study discussant Dr. Martin A. Croce, an ACS Fellow who is professor of general surgery and trauma at the University of Tennessee, Memphis.

Patients undergoing orthopedic surgery did experience a statistically significant decrease in MRSA surgical site infections, from 3% to 0%.

Screening must be done more than 10 days prior to elective surgery so there is sufficient time to treat carriers, Dr. Pofahl said. "Compliance has been the hardest part, because there are several other portals of entry into the system, such as through private physician groups. We have worked with them to make sure they are compliant." ■



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# Rectifying Consumer Payments

Database • from page 1

able” rates as calculated by the Ingenix database. As a result, insurers would only pay a percentage of the lower “usual, customary, and reasonable” rate, leaving consumers to pay their own portion plus the balance of the bill.

The investigation found that insurers were underpaying consumers for out-of-network expenses by 10%-28% for medical services across the state.

“For the past 10 years, American patients have suffered from unfair reimbursements for critical medical services due to a conflict-ridden system that has been owned, operated, and manipulated by the health insurance industry,” Mr. Cuomo said in a statement. “This agreement marks the end of that flawed system.”

According to UHG officials, the agreement with the New York attorney general will help increase the transparency of information related to physi-

cian fees for out-of-network services.

“We are committed to increasing the amount of useful information available in the health care marketplace so that people can make informed decisions, and this agreement is consistent with that approach and philosophy,” Thomas L. Strickland, executive vice president and chief legal officer for UnitedHealth Group, said in a statement. “We are pleased that an independent not-for-profit entity will play this important role for the marketplace.”

Just days after reaching an agreement with Mr. Cuomo’s office, UHG also settled a lawsuit with the American Medical Association and two state medical associations over the use of the Ingenix database. The \$350 million settlement is the largest monetary settlement of a class action lawsuit against a single health insurer in the United States, according to the AMA.

The suit, which has been pending since 2000, alleged that UHG had been understating the “usual, customary, and reasonable” charges in payments to physicians and in reimbursing patients for out-of-network expenses. Under the class action settlement, UHG subscribers who submitted a claim for out-of-network services and were not properly reimbursed are eligible to receive part of the settlement. Physicians also could be eligible to receive payment under the settlement if they were underpaid by UHG and did not receive the balance from the patient.

But the biggest gain for physicians under both the AMA settlement and the agreement with the New York attorney general won’t be money, but the rebuilding of the trust lost between patients and physicians, said Dr. Nancy H. Nielsen, AMA president.

When UHG and other insurers refused to pay the physician’s charge, they were telling patients that the charge was unreasonable, creating tension between the patient and physician, said Dr.

Michael H. Rosenberg, president of the Medical Society of the State of New York, which was part of the AMA’s class action lawsuit. “This was always a wedge between patients and physicians.”

But not everyone sees these agreements as a victory for physicians and patients. Robert Laszewski, president of Health Policy and Strategy Associates LLC, a Washington-based consulting firm, said he doesn’t expect to see significant changes in the “usual, customary, and reasonable” rates based on the creation of an independent database.

The fundamental problem for physicians is that, regardless of who calculates the usual rates, there is still a wide discrepancy between the in-network rates available to most patients and the out-of-network rates paid by some, said Mr. Laszewski. Increased transparency could end up benefiting the insurance industry if it shows physicians charging significantly more when patients are out-of-network.

“I think the insurance industry has won,” he said. ■

# Reimbursement for Vein Cases Will Vary Widely in 2009

BY PATRICE WENDLING

*Elsevier Global Medical News*

CHICAGO — The setting in which open and endovenous therapies are performed will greatly influence physician reimbursement in 2009.

Medicare reimbursement for most major inpatient vascular operations will increase by 3%-4%, whereas reimbursement for most office-based vein cases will decrease by about 10%, Dr. Robert Zwolak said at a symposium on vascular surgery sponsored by Northwestern University.

For example, Medicare reimbursement for open abdominal aortic aneurysm surgery (CPT code 35081) is up by 3.9% this year, to \$1,756, whereas reimbursement for carotid stenting (CPT 37215) is up by 3.6%, to \$1,101. On the flip side, reimbursement for endovenous vein ablation performed in the office (CPT 36475) is down by 10.6%, to \$1,699.

Several factors are at play, including the creation of new venous codes, the elimination of the Medicare budget neutrality work adjuster, and a 5.3% reduction in the Medicare conversion factor, said Dr. Zwolak, an ACS Fellow who is professor of surgery at Dartmouth Medical School and Dartmouth-Hitchcock Medical Center in Lebanon, N.H.

The three components of the Medicare reimbursement formula—work relative value units (RVUs), malpractice, and practice expenses—are multiplied by the conversion factor to derive a payment rate for each code. The conversion factor was \$38.09 per RVU in 2008, and is \$36.07 per RVU in 2009. The work adjuster was introduced in 2007 to bring overall Medicare expenditures down, and was applied to the physician work RVU portion of the formula.

It’s difficult initially to understand how inpatient procedure payments could increase when the conversion factor has been reduced, but it all has to do with the elimination of the work adjuster, Dr. Zwolak explained. For the past 2 years, Medicare discounted physician work by almost 12%. Therefore, in cases with large physician work components, such as aortic aneurysm repair, the positive effect of eliminating the physician work adjuster is greater in magnitude than is the negative effect of the 5.3% conversion factor reduction, and payments for these large cases actually go up by several percentage points.

In contrast, for cases with much more practice ex-

pense than physician work, such as endovenous vein ablation, the negative effect of the conversion factor reduction is much greater than the positive effect of work adjuster elimination, and these payments go down, he said.

RVUs are also assigned in part based on whether a procedure is performed in a “facility” (hospital), or a “non-facility” (meaning a physician’s office or similar location). Dr. Zwolak noted that when a procedure is performed in the hospital, Medicare and other payers must reimburse the hospital for a technical fee to cover the space, personnel, supplies, and equipment necessary to perform the procedure. In contrast, when a procedure is performed in the physician’s office, the technical fee—including the cost of all imaging—is rolled into the total payment to the physician.

For CPT 36475, the physician’s total RVU assignment was 9.30 if the endovenous vein ablation was performed in the hospital, or a reimbursement of about \$324 in 2008. If the same procedure was performed in the physician’s office, the total RVU was 50.69, with a corresponding reimbursement to the physician of about \$1,900, Dr. Zwolak said.

In 2009, total RVUs in the hospital setting are essentially unchanged, at 9.29, whereas total RVUs in the office setting will fall by about 7%, to 47.1, because of a reduction in practice expense. Thus, the reduction in total office-based RVUs, compounded by a 5% reduction in the conversion factor, results in a \$200 pay cut for this procedure when it’s done in the office, Dr. Zwolak explained.

“Medicare saves money when vein ablation is performed in your office, and with a \$200 office-based pay cut in 2009, [the agency will] save even more,” he said.

Introductory wording has been added to the 2009 CPT manual to remind physicians that all imaging is included in radiofrequency ablation and laser ablation CPT codes.

Physicians should also be aware that the “global period” for endovenous procedures such as 36475 and 36478 is “0-day,” meaning that all evaluation and management work on the day of the procedure is bundled into a single prospective payment. However, when the patient returns for reevaluation on subsequent days,

those office visits should be reported separately, Dr. Zwolak said.

He noted the following specific issues:

► **Procedures in search of a code.** There are vein procedures without specific category I codes, such as subcutaneous vein maceration and foam sclerotherapy. The default or “unlisted” vascular surgery code 37799 can be used for vein maceration, whereas codes 36470/36471 can be used when a sclerosing agent is injected. Ultrasound guidance for sclerotherapy should be coded as 76937, and this requires image documentation and an accompanying written report, Dr. Zwolak said.

Code 37799 is also appropriate for vena cava filter repositioning—another procedure without a specific code. Vena cava filter removal can be reported using CPT 37203 for removal of a foreign body.

CPT codes 37765 and 37766 were created for stab phlebectomy of varicose veins with 10-20 stab incisions and more than 20 incisions, respectively. Code 37799 should be used to report

stab phlebectomy with fewer than 10 stab incisions on an extremity, but many carriers will deny payment, he said.

► **Modifiers are a must.** Medicare will not pay for a diagnostic venogram during an intervention if a “recent” venogram has been performed. If you want to get paid for a diagnostic venogram performed at the same time as the therapeutic intervention, add a “-59 modifier” to the venogram, and be sure to dictate a full interpretation of the diagnostic portion of the study, Dr. Zwolak said. A “-26 modifier” should be used if you do not own the equipment or pay the staff.

► **Coding and reimbursement resources.** Key payment resources for physicians include the Medicare fee schedule, which can be downloaded from [www.cms.hhs.gov](http://www.cms.hhs.gov) as an easily searchable Microsoft Excel file, and the American Medical Association CPT manual and its “Code Manager” software. The Society for Vascular Surgery ([www.vascularweb.org](http://www.vascularweb.org)) and the Society of Interventional Radiology ([www.sirweb.org](http://www.sirweb.org)) also offer coding seminars and manuals. Among private products, Dr. Z’s (no relation to Zwolak) coding books are a more pricey option, but are extremely useful, said Dr. Zwolak, who reported no conflicts of interest. ■



DR. ZWOLAK

**Reimbursement for most inpatient procedures will rise by 3%-4%, but will drop by about 10% when done in an office.**

BY MARY ELLEN SCHNEIDER  
*Elsevier Global Medical News*

Physicians could face increased requirements when renewing their state medical licenses under a draft model policy currently being evaluated by the Federation of State Medical Boards.

Under the draft policy, relicensure would become more comprehensive and require physicians to demonstrate continuing skills and knowledge in their area of practice. As proposed, the maintenance of licensure process would closely mirror the American Board of Medical Specialties' requirements for maintenance of certification. The draft policy is a model that state medical boards could use, but actual implementation would be determined state by state.

Over the last 5 years, the Federation of

State Medical Boards (FSMB) has been considering how state medical boards could change these policies to ensure that licensees are competent. In 2008, the organization's House of Delegates approved guiding principles for developing maintenance of licensure and called for additional research on the impact that the new requirements would have on state medical boards and licensed physicians.

Once that research is complete, the draft policy would likely be considered by the FSMB House of Delegates at their meeting in May, said Carol Clothier, vice president of strategic planning and physician competency initiatives for the FSMB.

"Nobody wants to create more work for physicians," she said. The idea is to try to take advantage of what physicians already are doing to demonstrate competence and use those activities to satisfy state licensure requirements.

State medical boards are feeling pres-

sure from the public to ensure physician competency in light of rapidly changing science and technology. Current requirements generally include some continuing medical education, but don't meet the public's expectations of oversight of physicians, she said.

If the maintenance of licensure policy is accepted by the FSMB House of Delegates, it still would be a model policy only, Ms. Clothier said. Individual states and territories would decide whether to adopt, revise, or ignore the model policy on the basis of their politics, she said.

"I think it makes good sense," said Dr. Frank R. Lewis Jr., an ACS Fellow and executive director of the American Board of Surgery.

By allowing the elements of the maintenance of certification process to satisfy the relicensure requirements, it ensures that physicians don't have to fulfill requirements in two parallel processes, he said. And those already engaged in maintenance of certification can clear

any new licensing hurdles fairly easily.

Surgeons are just getting started with the maintenance of certification process, Dr. Lewis said. As time goes on, all surgeons will have to engage in maintenance of certification at the time of recertification. There are still a small number of general surgeons with lifetime certification through the board, he said, but they account for only about 3% of diplomates and all are nearing retirement age.

Defining a pathway for those surgeons who are licensed but not board certified (estimated to be from 10% to 15%) will be a more difficult task, Dr. Lewis said.

In addition to state medical boards, other entities also are looking to use maintenance of certification as a marker for physician competence, Dr. Lewis said. But he cautioned hospitals and payers to move slowly because inclusion of comprehensive outcomes data is still lacking in the maintenance of certification program. ■

## Hospitals Slowly Bestow EMR Aid to Physicians

BY MARY ELLEN SCHNEIDER  
*Elsevier Global Medical News*

Some hospitals are slowly offering subsidies on electronic medical record software to small groups of closely affiliated physicians, while others are offering only IT support services or extending their vendor discounts, according to an analysis of 24 hospitals by the Center for Studying Health System Change.

In 2006, the Health and Human Services Department announced that it had created two safe harbors that would allow hospitals to subsidize up to 85% of the cost of electronic medical record (EMR) software and IT support services for physicians. For their part, physicians would be responsible for the full cost of the required hardware. The regulations are scheduled to sunset at the end of 2013.

Funded by the Robert Wood Johnson Foundation, the analysis is based on in-depth interviews with hospital executives. According to the analysis, 11 of the 24 hospitals were considering offering some type of subsidy to physicians to help cover their EMR costs. The remaining 13 hospitals were not planning to provide direct subsidies to physicians, but some were considering extending their EMR vendor discounts or offering IT support services.

Some hospitals chose not to offer direct financial support to physicians because they opposed the idea of offering EMR subsidies to physicians. Others said that granting access to vendor discounts was a sufficient incentive for physicians preparing to adopt EMRs. And some hospitals were interested in providing the financial

subsidies directly to physicians but couldn't afford to do so.

For those hospital executives who were considering a direct subsidy to physicians, improving patient care and forging closer relationships with referring physicians were the top reasons to advance EMR assistance. "Hospital executives expected physicians would be more likely to maintain, and even expand, their relationship with the hospital because of the improved efficiency from interoperability with the hospital's IT systems," the researchers wrote.

One factor that appears not to be driving the trend toward hospital subsidies is interest on the part of physicians. The arrangement has some potential drawbacks for physicians, according to the analysis.

For example, under the safe harbors physicians are still responsible for 15% of the software costs and 100% of the hardware costs associated with setting up the EMR system. Physicians using the hospital-sponsored EMR may have difficulty storing records for patients treated at other hospitals where the physicians provide care for patients. Also, the hospital-sponsored EMR could serve as a barrier if physicians later wanted to switch their hospital affiliations, according to the analysis.

"While hospitals have strategic incentives to provide support, particularly to tie referring physicians to their institution, the effects of the regulatory changes on physician EMR adoption will ultimately depend both on hospitals' willingness to provide support and physicians' acceptance of hospital assistance," Joy M. Grossman, Ph.D., one of the study authors, said in a statement. ■

## COMMENTARY Value-Based Health Care

BY KAREN R. BORMAN, M.D., FACS

Imagine that you are a 66-year-old patient with intermittent claudication. You have Medicare Part A and Part B coverage, and a Medigap policy that covers your deductible and coinsurance. Which treatment would you choose?

A) Medical management (smoking cessation, exercise, and medications) and a less-than-5% risk of major amputation over 10 years.

B) A single major open revascularization procedure with a 95% chance of symptom resolution, a 5% chance of needing a second procedure within 10 years, and an all-cause periprocedural mortality risk of 5%.

C) An endovascular intervention with an 85% chance of symptom resolution, a 10% chance of needing a second procedure within 3 years, and an all-cause periprocedural mortality risk of 0.5%.

Imagine that the mean 10-year total cost of treatment (all interventions and their aftercare, including long-term surveillance) has been determined to be \$3,000 for Option A, \$15,000 for B, and \$20,000 for C. Which would you choose?

Imagine that your 10-year allowance to treat claudication from Medicare + Medigap combined is \$17,000. Which option would you choose?

*If you were the surgeon caring for this patient, which option would you recommend?*

Far-fetched? Not at all. Welcome to value-based health care delivery! Could this happen? Yes. Why? Read on.

Medicare is going bankrupt. In 2008, expenditures for the Hospital Insurance (HI) trust fund, which funds inpatient stays and other postacute care, exceeded

its annual income from Medicare payroll taxes. Beneficiary Part B premiums finance only 25% of Part B program spending. The rest comes from Treasury general revenues (personal and corporate taxes), which also fund 77% of Part D costs.

Medicare faces some tough choices if it is to remain sustainable for even the short-term future. What about increasing Part A income from payroll taxes? To finance Part A through 2080, the Medicare payroll tax have to increase from 2.9% to 6.44% of earned income. What about increasing personal and corporate income taxes? This solution will likely be necessary given our economic troubles, but fixing

Medicare would substantially drive up the increases needed. How about shifting more costs to beneficiaries? From 2004 to 2008, the Part A deductible was raised by 17%, and the Part B deductible by 35%. For 60% of the elderly, Social Security comprises 75% of their income, and more than 25% of their Social Security income is paid back into Part B plus Part D premiums.

Medicare must cut expenses, and since its administrative costs are among the lowest in the health care industry, savings must come from payments to facilities and providers. Value-based care is the leading viable alternative to wholesale Medicare payment cuts, and Congress has told Medicare to become a "value-based purchaser." Will you be ready? ■



DR. BORMAN

DR. BORMAN is professor of surgery at the University of Central Florida in Orlando and serves on the Medicare Payment Advisory Commission.

# ICD-10 Transition Set for 2013

BY MARY ELLEN SCHNEIDER  
*Elsevier Global Medical News*

In less than 5 years, physicians and other health care providers will be required to begin using a new system of code sets to report health care diagnoses and procedures.

Under a final rule published in the Federal Register in January, the Health and Human Services department is replacing the International Classification of Disease, 9th Edition, Clinical Modification (ICD-9-CM) code sets now used with significantly expanded ICD-10 code sets. Providers and health plans will have until Oct. 1, 2013, to implement the new code sets.

A final rule adopting new standards for electronic health care transactions requires health care providers to come into compliance with the updated X12 standard, Version 5010, which includes updated standards for claims, remittance advice, eligibility inquiries, referral authorization, and other administrative transactions. Use of the updated standard is necessary to use the ICD-10 code sets, according to HHS. Providers and health plans are required to be in compliance with the updated transaction standard by Jan. 1, 2012.

At press time, the Obama administration was in the process of reviewing and approving all new and pending regulations written under the previous administration, including the ICD-10 rules. A spokesman for the Centers for Medicare and Medicaid Services said that until the review is complete, it is not possible to determine which regulations are affected.

The ICD-9-CM contains about 17,000 codes, compared with 155,000 codes in the ICD-10 code sets.

"These regulations will move the nation toward a more efficient, quality-focused health care system by helping accelerate the widespread adoption of health information technology," Mike Leavitt, HHS Secretary, said in a statement. "The greatly expanded ICD-10 code sets will fully support quality reporting, pay-for-performance, biosurveillance, and other critical activities."

The final rule gives health care providers and plans almost 2 extra years to implement the Version 5010 transaction standard and a full 2 years to switch to ICD-10, compared with the timeline proposed in 2008.

Physician groups praised HHS for providing additional time for implementation.

In written comments on the proposed rule, the American College of Surgeons (ACS) asserted that HHS should allow at least 2 years for practices to convert to 5010, followed by at least 3 more years to adopt ICD-10. These suggestions correspond to recommendations by the National Committee on Vital and Health Statistics, a government advisory body. Like other physician groups, the ACS is concerned that because of administrative burdens, rapid movement to ICD-10 could slow adoption of health information technology and may make it more

difficult for physicians to engage in quality improvement efforts.

The ACS comments also stressed the importance of providing fully automated "crosswalks" that map ICD-9 to ICD-10, and vice versa, to allow payers, vendors, and other relevant parties to test their systems and minimize breaks in historical data. The final rule acknowledges the significance of the crosswalks and indicates that CMS intends to discuss their further development.

The Medical Group Management Association is calling on the federal government to develop some type of implementation assistance program to help physicians, especially those in small practices and rural communities, said Robert Tennant, senior policy adviser at MGMA.

HHS also should extend its outreach to the vendor community, Mr. Tennant said, since they will be the ones to provide updates to the practice manage-

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ment software. HHS also needs to work with private health plans to ensure there is no disruption in payments.

He advised physician practices to become familiar with the requirements and the compliance dates, find out when vendors plan to update the software and what it will cost, and then set a budget that includes training and testing. ■



## The power of negative thinking

*In treatment of gram-negative infections caused by susceptible gram-negative microorganisms*

**AZACTAM is indicated for**

- Complicated and uncomplicated urinary tract infections, lower respiratory tract infections, septicemia, skin and skin-structure infections, intra-abdominal infections, and gynecologic infections
- Adjunctive therapy to surgery in the management of infections caused by susceptible organisms. Effective against most commonly encountered gram-negative aerobic pathogens seen in general surgery

**Important Safety Information:** AZACTAM is contraindicated in patients with known hypersensitivity to aztreonam or any other component in the formulation.

While cross reactivity of aztreonam with other beta-lactam antibiotics is rare, this drug should be administered with caution to any patient with a history of hypersensitivity to beta-lactams.

*Clostridium difficile*-associated diarrhea (CDAD) occurs with use of nearly all antibacterial agents, including AZACTAM, and severity ranges from mild diarrhea to fatal colitis. Antibacterial agent use alters the normal flora of the colon leading to overgrowth of *C. difficile*. Consider CDAD in all patients presenting with diarrhea following antibiotic use. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.

In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy.

Please see brief summary of prescribing information on adjacent page.

*think negative.*

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# Triage May Rescue Delayed Trauma Transfers

BY DAMIAN McNAMARA  
Elsevier Global Medical News

PALM BEACH, FLA. — Effective triage of critically ill trauma patients might ameliorate the higher mortality associated with delayed emergency department transfers, a retrospective study indicates.

ED crowding and delayed transfers are “a major problem” at some institutions nationwide, said Dr. J. David

Richardson, including the University of Louisville Hospital in Kentucky, where he is professor and vice chair of surgery.

He and his associates retrospectively assessed 3,918 emergency patients transferred from the trauma/acute care surgery service to critical care or a hospital bed. Their facility is a level 1 trauma center with 325 beds, including 24 ED beds and 55 ICU beds.

During the study period (January 2005 to April 2007), ED capacity exceeded 90%.

Despite the close cooperation between the ED and surgical teams in patient triage to ICU and floor beds, sometimes “there is poaching of general medicine beds or beds in the PACU [postanesthesia care unit]. We are not implying our situation is optimal care. We are planning greater capacity,” Dr. Richardson, an ACS Fellow, said at the annual meeting of the Southern Surgical Association.

The mean age of the trauma patients studied was 43 years; 74% were male,

and 75% were admitted to the ED following blunt trauma.

Dr. Richardson and his colleagues compared outcomes between the 29% of patients who remained 6 hours or less (mean stay of 3 hours) and the remainder, who stayed longer (mean stay of almost 15 hours). The overall mean ED length of stay was 11 hours.

There was 18% mortality in the early group compared with 2% in the delayed group. “Shorter ED length of stay patients had worse outcomes, which is certainly counterintuitive to previous reports that showed extended length of stay associated with worse outcomes,” he said. For example, researchers in New York City found that ED holds greater

## BRIEF SUMMARY

Please see package insert for full prescribing information.

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**INDICATIONS AND USAGE:** To reduce the development of drug-resistant bacteria and maintain the effectiveness of AZACTAM<sup>®</sup> (aztreonam for injection, USP) and other antibacterial drugs, AZACTAM should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of the susceptibility testing are available; subsequently, appropriate antibiotic therapy should be continued.

AZACTAM is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms:

**Urinary Tract Infections** (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Citrobacter* species\* and *Serratia marcescens*.\*

**Lower Respiratory Tract Infections**, including pneumonia and bronchitis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Proteus mirabilis*, *Enterobacter* species and *Serratia marcescens*.\*

**Septicemia** caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Serratia marcescens*\* and *Enterobacter* species.

**Skin and Skin-Structure Infections**, including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli*, *Proteus mirabilis*, *Serratia marcescens*, *Enterobacter* species, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Citrobacter* species.\*

**Intra-abdominal Infections**, including peritonitis caused by *Escherichia coli*, *Klebsiella* species including *K. pneumoniae*, *Enterobacter* species including *E. cloacae*,\* *Pseudomonas aeruginosa*, *Citrobacter* species\* including *C. freundii*\* and *Serratia* species\* including *S. marcescens*.\*

**Gynecologic Infections**, including endometritis and pelvic cellulitis caused by *Escherichia coli*, *Klebsiella pneumoniae*,\* *Enterobacter* species\* including *E. cloacae*\* and *Proteus mirabilis*.\*

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

**Concurrent Therapy:** Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected as etiologic agents, therapy should be initiated using an anti-anaerobic agent concurrently with AZACTAM (see **DOSE AND ADMINISTRATION**). Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing of the causative organism(s), appropriate antibiotic therapy should be continued.

**CONTRAINDICATIONS:** This preparation is contraindicated in patients with known hypersensitivity to aztreonam or any other component in the formulation.

**WARNINGS:** Both animal and human data suggest that AZACTAM is rarely cross-reactive with other beta-lactam antibiotics and weakly immunogenic. Treatment with aztreonam can result in hypersensitivity reactions in patients with or without prior exposure. (See **CONTRAINDICATIONS**.)

Careful inquiry should be made to determine whether the patient has any history of hypersensitivity reactions to any allergens.

While cross-reactivity of aztreonam with other beta-lactam antibiotics is rare, this drug should be administered with caution to any patient with a history of hypersensitivity to beta-lactams (e.g., penicillins, cephalosporins, and/or carbapenems). Treatment with aztreonam can result in hypersensitivity reactions in patients with or without prior exposure to aztreonam. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures. (See **ADVERSE REACTIONS**.)

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AZACTAM and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Rare cases of toxic epidermal necrolysis have been reported in association with aztreonam in patients undergoing bone marrow transplant with multiple risk factors including sepsis, radiation therapy and other concomitantly administered drugs associated with toxic epidermal necrolysis.

**PRECAUTIONS: General:** In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy.

If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms (*Staphylococcus aureus* and *Streptococcus faecalis*) and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies in animals have not been performed.

Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level.

Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

**Pregnancy: Pregnancy Category B:** Aztreonam crosses the placenta and enters the fetal circulation.

Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal, or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Aztreonam is excreted in human milk in concentrations that are less than 1 percent of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

**Pediatric Use:** The safety and effectiveness of intravenous AZACTAM (aztreonam for injection, USP) have been established in the age groups 9 months to 16 years. Use of AZACTAM in these age groups is supported by evidence from adequate and well-controlled studies of AZACTAM in adults with additional efficacy, safety, and pharmacokinetic data from non-comparative clinical studies in pediatric patients. Sufficient data are not available for pediatric patients under 9 months of age or for the following treatment indications/pathogens: septicemia and skin and skin-structure infections (where the skin infection is believed or known to be due to *H. influenzae* type b). In pediatric patients with cystic fibrosis, higher doses of AZACTAM may be warranted. (See **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**, and **CLINICAL STUDIES**.)

**Geriatric Use:** Clinical studies of AZACTAM did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.<sup>1,2</sup> In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Because elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments made accordingly (see **DOSE AND ADMINISTRATION: Renal Impairment in Adult Patients and Dosage in the Elderly**).

**ADVERSE REACTIONS:** Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9 percent and 2.4 percent, respectively.

Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3 percent include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1 percent are listed within each body system in order of decreasing severity:

**Hypersensitivity**—anaphylaxis, angioedema, bronchospasm  
**Hematologic**—pancytopenia, neutropenia, thrombocytopenia, anemia, eosinophilia, leukocytosis, thrombocytosis

**Gastrointestinal**—abdominal cramps; rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See **WARNINGS**.)

**Dermatologic**—toxic epidermal necrolysis (see **WARNINGS**), purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis

**Cardiovascular**—hypotension, transient ECG changes (ventricular bigeminy and PVC), flushing  
**Respiratory**—wheezing, dyspnea, confusion, vertigo, paresthesia, insomnia, dizziness

**Hepatobiliary**—hepatitis, jaundice  
**Nervous System**—seizure, confusion, vertigo, paresthesia, insomnia, dizziness

**Musculoskeletal**—muscular aches  
**Special Senses**—tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing, nasal congestion, halitosis

**Other**—vaginal candidiasis, vaginitis, breast tenderness  
**Body as a Whole**—weakness, headache, fever, malaise

**Pediatric Adverse Reactions:** Of the 612 pediatric patients who were treated with AZACTAM in clinical trials, less than 1% required discontinuation of therapy due to adverse events. The following systemic adverse events, regardless of drug relationship, occurred in at least 1% of treated patients in domestic clinical trials: rash (4.3%), diarrhea (1.4%), and fever (1.0%). These adverse events were comparable to those observed in adult clinical trials.

In 343 pediatric patients receiving intravenous therapy, the following local reactions were noted: pain (12%), erythema (2.9%), induration (0.9%), and phlebitis (2.1%). In the US patient population, pain occurred in 1.5% of patients, while each of the remaining three local reactions had an incidence of 0.5%.

The following laboratory adverse events, regardless of drug relationship, occurred in at least 1% of treated patients: increased eosinophils (6.3%), increased platelets (3.6%), neutropenia (3.2%), increased AST (3.8%), increased ALT (6.5%), and increased serum creatinine (5.8%).

In US pediatric clinical trials, neutropenia (absolute neutrophil count less than 1000/mm<sup>3</sup>) occurred in 11.3% of patients (8/71) younger than 2 years receiving 30 mg/kg q6h. AST and ALT elevations to greater than 3 times the upper limit of normal were noted in 15–20% of patients aged 2 years or above receiving 50 mg/kg q6h. The increased frequency of these reported laboratory adverse events may be due to either increased severity of illness treated or higher doses of AZACTAM administered.

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

**Hepatic**—elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1 percent of recipients (see above).

**Hematologic**—increases in prothrombin and partial thromboplastin times, positive Coombs' test.  
**Renal**—increases in serum creatinine.

**OVERDOSAGE:** If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

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

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There is 'very little science' to address ED boarding, and this is a well designed, well written study.

DR. MEREDITH

than 6 hours were predictive of increased morbidity and mortality (Crit. Care Med. 2007;35:1477-83).

In the current study, 1,643 trauma patients (42%) were transferred to the ICU. The mean length of stay in critical care was 10 hours for the nondelayed group versus 7 hours for the delayed group. Among the ICU-only patients, there was 17% mortality in the nondelayed group versus 5% in the delayed group.

When asked whether head injury patients accounted for some of the early deaths, Dr. Richardson replied that priority is given to salvageable brain injury patients. The investigators found 47% of the nondelayed group and 23% of the delayed group had positive head CT findings. However, the mean Glasgow Coma Score in nondelayed patients was 12 compared with 14 in the delayed group.

Although there is no formal transfer protocol at his hospital, priority is also given to hypotensive patients not requiring operating room admission and to those who need a ventilator or invasive monitoring, Dr. Richardson said.

The leading causes of death included severe head injury, advanced age, use of anticoagulant/antiplatelet therapy, multiorgan failure, and respiratory failure. Of the 266 patients who died in the hospital, there were two “deaths of concern” where delay may have contributed to mortality, Dr. Richardson said.

“There is very little science about how to address ED boarding,” discussed J. Wayne Meredith said at the meeting. He called it a well designed, well written study, but said “it’s open to question if [the acute trauma] patients would have done better if they had been moved later than 6 hours. This study was retrospective, so it could not address that,” noted Dr. Meredith, an ACS Fellow who is professor and chairman of surgery, Wake Forest University Baptist Medical Center, Winston-Salem, N.C. ■

# Surgeons Help Craft Mass Casualty Triage Model

BY CHRISTINE KILGORE  
Elsevier Global Medical News

Surgeons have played an integral role in developing a proposed national guideline on mass casualty triage designed to improve the consistency of disaster triage practices.

The guideline, titled SALT (Sort, Assess, Life-Saving Interventions, Treatment and/or Transport), establishes a standardized set of priority categories and color designations for primary field triage and formalizes processes for sorting patients and applying lifesaving interventions (Disaster Med. Public Health Prep. 2008;2 [suppl.1]:S25-34).

Surgery's participation reflects a growing recognition that disaster preparedness—including field triage—is not just an emergency medicine issue, said the two surgeons who helped write the guideline.

"Our argument has always been that we have something to contribute to the science and the thought process, and that we need to be involved because we're going to be the recipients [of the victims]," said Dr. Jeffrey Hammond, an ACS Fellow who is a trauma and critical care surgeon at the Robert Wood Johnson Medical School, New Brunswick, N.J.

Dr. Jeffrey Salomone, an ACS Fellow who is associate professor of surgery at Emory University, Atlanta, and deputy chief of surgery at Grady Memorial Hospital in that city, concurred: "Trauma surgeons need to be involved in trauma care, from the prehospital phase to the hospital phase to rehab."

Dr. Hammond, Dr. Salomone, Dr. Eileen Bulger, also an ACS Fellow, Dr. Sharon Henry, and Dr. Howard Taekman participated in the multidisciplinary guideline development work group, which was established and supported by the Department of Health and Human Services; the Centers for Disease Control and Prevention; and the Terrorism Injuries Information, Dissemination, and Exchange (TIDE) Project, a cooperative partnership led by the American College of Emergency Physicians.

The 20-plus members of the work group used bits of published evidence supporting various components of nine main mass triage systems—along with consensus opinion—to formulate a guideline that they emphasize is a "beginning rather than a final product."

"The guideline picks the best [aspects] of all the systems and pulls them together," said Dr. Salomone.

SALT's first step calls for a global sorting process in which patients are prioritized for individual assessment through simple voice commands. Since patients who can walk may have injuries that need immediate or delayed treatment, they should be individually assessed before being designated as "minimally injured."

The wave command is recommended for further distinguishing patients who cannot follow a command, and thus need assessment first, from those who cannot walk but can still follow a command and make purposeful movements.

(This latter group should be assessed first.)

The first priority in individual assessment, the document says, is to provide rapid lifesaving interventions that likely will have a profound impact on survival: controlling major hemorrhage, opening the airway (and two rescue breaths for children), decompressing the chest of patients with tension pneumothorax, and providing anecdotes for chemical exposures.

Next, patients should be prioritized for treatment based on assignment to one of five color-coded categories: red, for patients in need of immediate care; yellow, for patients who need care but not immediately; green, for patients who can tolerate a delay in care without an increased risk for mortality; black, for patients who are dead; and gray, for patients who are likely to die given the available resources. The gray category is intended to be flexible and dynamic,

with patients reevaluated frequently—and their triage category changed as appropriate.

The American Medical Association is integrating the proposed triage methodology into its disaster medicine courses. Other organizations, including the ACS, are calling for substantive field trials.

"SALT is a good approach, but before [the ACS] jumps fully behind it, they want to have some evidence," said Dr. Salomone. ■

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## ACS Urges MedPAC to Modify Payment Plan

The ACS and 67 other physician organizations joined together in sending a letter to the Medicare Payment Advisory Commission (MedPAC) supporting a 2.4% increase in Medicare payments and opposing MedPAC's recommendation to adjust pay on the basis of productivity.

Under the proposal discussed at MedPAC's December meeting, physicians would receive only a 1.1% payment increase, because estimated growth in productivity (1.3%) would be subtracted from expected growth in price outputs (2.4%).

The January 5 letter noted that current payment rates are only slightly higher than in 2001, yet the Medicare Economic Index, which estimates rising practice costs, has grown by more than 22% since then. The letter also noted that MedPAC supports full inflationary updates with no productivity adjustment for hospitals.

During MedPAC's January 8 meeting, several commissioners—including Karen Borman, M.D., FACS—voiced concern about the inclusion of

the productivity adjustment when other providers such as hospitals are not subject to such an adjustment. Unfortunately, this discussion did not result in a higher recommended increase in Medicare payments. Instead, MedPAC removed any mention of price inputs or productivity and unanimously approved a 1.1% increase in Medicare payments in 2010.

MedPAC also approved a recommendation to finance increased payments to primary care physicians through cuts in payments for other services, including major surgical procedures. Dr. Borman was one of two commissioners to oppose this.

The College will continue to strongly oppose MedPAC's recommendation to cut surgical payments to finance increased payments for other services, and will advocate for increased Medicare reimbursement rates that recognize the rising costs facing surgical practices. For more information about MedPAC's discussions of these and other policy issues, go to [www.medpac.gov/](http://www.medpac.gov/). ■

## Register Now for Leadership And Advocacy Conferences

The College's 2009 Leadership Conference for Young Surgeons and Chapter Leaders will take place March 22, followed by the Second Annual Joint Surgical Advocacy Conference (JSAC), March 22-24. College members may register by contacting the Grand Hyatt Washington at 800-233-1235. (Mention the "Joint Surgical Advocacy Conference" to receive the discounted group rate.)

The following national specialty societies are sponsoring this year's JSAC: American Academy of Facial Plastic and Reconstructive Surgery, American Academy of Ophthalmology, American Academy of Otolaryngology—Head and Neck Surgery,

American Association of Neurological Surgeons/Congress of Neurological Surgeons, American Association of Orthopaedic Surgeons, American College of Obstetricians and Gynecologists, American College of Osteopathic Surgeons, American College of Surgeons, American Osteopathic Academy of Orthopedics, American Society of Cataract and Refractive Surgery, American Society of Plastic Surgeons, American Urological Association, Society of American Gastrointestinal and Endoscopic Surgeons, and Society for Vascular Surgery.

For more information or assistance, call 888-857-7545. ■

## Practice Management Tools Include Calendar of Events, Web Casts

The ACS and Economedix have released a 2009 calendar of events with tips for ensuring a successful practice in 2009 and details on a practice management Web cast series.

Each Web cast will be conducted by Tom Loughrey, M.B.A., CCS-P, and presented on a Wednesday, beginning at 1 p.m. eastern, noon central, 11 a.m. mountain, and 10 a.m. Pacific times. The 90-minute sessions will include a question-and-answer period. Each Web cast will be recorded for registrants who want to listen to the course a second time or who

miss all or part of the program.

To download the calendar, go to [www.YourMedPractice.com/WorkPlan-2009.pdf](http://www.YourMedPractice.com/WorkPlan-2009.pdf). To register for the Web casts, go to [www.YourMedPractice.com/ACS](http://www.YourMedPractice.com/ACS). For additional information, contact Economedix by e-mail at [rley@economedix.com](mailto:rley@economedix.com) or by phone at 877-401-9655.

ACS members can get free answers to their questions by going to [www.yourmedpractice.com/Ex/12/PMQs-ACS.htm](http://www.yourmedpractice.com/Ex/12/PMQs-ACS.htm). Responses to queries will be e-mailed from a practice management adviser at Economedix. ■

## One-Year Surgical Ethics Fellowship Available

The MacLean Center for Clinical Medical Ethics at the University of Chicago is accepting applications for an ACS-endorsed surgical ethics fellowship. This program will provide training in medical ethics and is intended to prepare surgeons for academic work related to medical ethics.

The program will begin with a 6-week, full-time intensive introduction in July and August 2010. From September to June, fellows will meet 1 day a week for a structured ethics curriculum including "Topics in Clinical Ethics," "Conceptual Foundations of Health Law," "Analytic Philosophy," and research-in-progress seminars. Fellows will also receive training in ethics consultation, and will be expected to take 2 to 3 months of consult service, plus design and carry out research projects with the aid of faculty mentors. Additional activities for each surgical ethics fellow will be individualized.

Funding of up to \$50,000 for participation in the year-long fellowship training program is available to a limited number of applicants. An additional option of a part-time surgical ethics fellowship is also available.

Applicants should prepare a personal statement plan that explains how the surgical ethics fellowship will be useful in their career; how much projected time the applicant will have to pursue his or her goals during the fellowship year; and how and whether the funding will ensure the necessary projected time to achieve these goals.

Applications, which are due by March 15, are available at <http://medicine.uchicago.edu/centers/ccme/SurgicalSite/Fellowships.html>.

For further information, contact Peter Angelos, M.D., FACS, at [pangelos@surgery.bsd.uchicago.edu](mailto:pangelos@surgery.bsd.uchicago.edu) or Mark Siegler, M.D., at [msiegler@medicine.bsd.uchicago.edu](mailto:msiegler@medicine.bsd.uchicago.edu). ■

## Director Named for Division of Advocacy and Health Policy

Christian Shalgian, a longtime College employee based in the Washington, D.C., office, has been named Director of the Division of Advocacy and Health Policy. He has been Acting Director since April 2007.

Mr. Shalgian joined the College in 1998 as a Government Affairs Associate. In 2000, he was promoted to Senior Government Affairs Associate, and in 2004 he became Manager of Legislative Affairs. He served as Assistant Director of Legislative Affairs before being named Acting Director.

From 2002 to 2007, Mr. Shalgian was also Chairman of the Board of Directors of the Health Coalition on Liabili-



MR. SHALGIAN

ty and Access, a Washington, D.C.-based partnership of associations organized to support medical liability reform. During his tenure, the membership expanded from 25 to 60 members.

Previously, Mr. Shalgian was the associate director of government relations (1997-1998) at the Ameri-

can Osteopathic Association (AOA) in Washington, D.C. Prior to holding that position, he was a legislative assistant for AOA from 1996 to 1997.

A graduate of Saint Anselm College in Manchester, N.H., Mr. Shalgian holds a bachelor's degree in political science. He lives in Germantown, Md., with his family. ■

## CMS Announces Sites for Bundled Payment Demonstration Project

Early in January, the Centers for Medicare & Medicaid Services (CMS) announced site selections for the agency's acute care episode (ACE) demonstration project. ACE, a new hospital-based pilot program, will evaluate the use of a bundled payment for hospital and physician services. CMS's goal is to determine whether bundled payments will serve as an incentive for health care professionals and hospitals to deliver coordinated, high-quality, efficient care. The demonstration also will test the effect of transparent price and quality information on beneficiary choice for selected inpatient care.

Participating institutions are Baptist Health System, San Antonio, Tex.; Oklahoma Heart Hospital LLC, Oklahoma City; Exempla Saint Joseph Hospital, Denver, Colo.; Hillcrest Medical Center, Tulsa, Okla.; and Lovelace Health System, Albuquerque, N.M.

For this demonstration, a bundled payment is a single payment for both Part A and Part B Medicare inpatient services. Included are 28 cardiac and 9 orthopedic inpatient surgical services. Visit at [www.cms.hhs.gov/DemoProjectsEvalRpts/MD/list.asp](http://www.cms.hhs.gov/DemoProjectsEvalRpts/MD/list.asp), and click on Medicare Acute Episode (ACE) Demonstration. ■

## College Issues Statement On CME Support

The following statement was developed by the Committee on Ethics and approved by the ACS Board of Regents in June 2008.

Collaboration between surgical organizations and the medical industry has benefited patient care in North America for many years. The primary objective of professional interactions between surgical organizations and industry should be the improvement of patient care, and such interactions should not be driven by financial or proprietary interests. Likewise, industry continues to be one source of support for continuing medical education (CME) for surgeons; however, surgical organizations must ensure that education is not influenced by collaboration with industry. These guidelines seek to provide a framework to permit corporate support of CME programs while maintaining the autonomy and impartiality of individual surgeons and surgical organizations.

The guidelines are consistent with the Updated Standards for Commercial Support.\*

### I. Independence in planning and implementation of educational programs

**A.** Surgical organizations have the ultimate responsibility for the planning and development of CME programs. They must ensure that all decisions are made without any influence by commercial interests. Industry supporters of CME programs must not influence the planning, content, or implementation of an organization's CME program.

**B.** The organization must ensure that everyone who is in a position to influence the content of an education activity has disclosed all relevant financial relationships with any commercial interests within the last 12 months. Potential conflicts of interest must be managed through appropriate mechanisms established by the organization and disclosed in writing to the learners prior to the start of the activity.

**C.** All individuals who have any role that has influence over or responsibility for the development, management, presentation, or evaluation of the CME activity must disclose relevant financial relationships. Refusal to do so will preclude their participation in that role.

### II. Commercial support for educational programs

**A.** The terms, conditions, and purposes of the commercial support must be documented in a written agreement between the commercial supporter and surgical organization.

**B.** A commercial entity must not directly pay a speaker or an individual involved with the development or implementation of the program. All commercial support must be provided to the surgical organization. Expenses for travel, accommodations, or honoraria for speakers are to be paid by the organization in compliance with its written policies and procedures. The surgical organization is responsible for all decisions regarding the disposition and disbursement of the funding. Accurate documentation detailing the receipt and ex-

penditure of the commercial support should be maintained.

**C.** Industry support through educational grants should be acknowledged in a printed announcement at the meeting, but reference must not be made to any specific product. When commercial support is provided in kind, the nature of the support must also be disclosed to the learners.

**D.** Financial support of CME activities may also be provided through advertising and exhibit opportunities. Advertisements must not be placed in proximity to educational content and must be limited to non-scientific publications such as schedules and content descriptions. Advertisement and exhibit fees must not be combined with an educational grant.

**E.** No industry promotional materials are to be displayed or distributed in the same room as scientific presentations at single session meetings. In larger meetings with multiple simultaneous sessions, the access to promotional materials must be controlled by the surgical organization in order to avoid the appearance of any connection between the distribution of promotional materials and scientific presentations.

**F.** Industry supporters are prohibited from use of the surgical organization's name, logo, or seal in conjunction with advertising or promotion without written permission of the organization.

**G.** Industry supporters must not organize any functions involving attendees that conflict with sessions of the meeting program. All industry-sponsored functions must be approved by the surgical organization prior to implementation. Industry exhibits should enhance the scientific activities of the CME program and not interfere with the scientific program.

**H.** For industry-sponsored symposia, a disclaimer is to appear on all printed materials, stating that the activity has no connection with the official organization's program. All proposals and printed materials developed in connection with sponsored symposia must be submitted to the organization for approval prior to publication. Such symposia must not interfere with the scientific program of the organization.

**I.** Representatives of industry sponsors must not engage in sales or promotional activities during sessions of the meeting program. Sales and promotional activities must be limited strictly to the exhibit floor or industry events approved by the surgical organization and will not be conducted in conjunction with CME activities.

**J.** If work that is supported by industry is presented, the poster, presentation, or manuscript must include an acknowledgment of the funding source.

**K.** Written or recorded details of the scientific program must not be reproduced without the written consent of the surgical organization. ■

\*Accreditation Council for Continuing Medical Education. *ACCME Standards for Commercial Support: Standards to Ensure the Independence of CME Activities*. Revised 2007. Available at [www.accme.org](http://www.accme.org). Accessed December 30, 2008.

## CoC Urges Participation In Paper Competition

The Commission on Cancer (CoC) is encouraging members of the College to share the CoC Paper Competition information with surgical residents and oncology fellows. The competition offers these young surgeons an excellent opportunity to gain presentation skills, visibility, and networking opportunities.

The competition is open to general surgery residents, surgical specialty residents, subspecialty residents, and oncology fellows in the United States. Abstracts should describe original research in cancer care, including basic laboratory research, clinical investigation, and quality of care/health services research.

Abstracts must be submitted to the CoC Office by March 31. Five finalists will be chosen and asked

to submit their full paper to the CoC office by July 1. The final three winners will be announced in August.

First-place winning residents and/or fellows will receive a \$1,000 award and will present at the CoC Annual Meeting on Sunday, Oct. 11, 2009, in Chicago. Second- and third-place winners will be granted a \$500 award and will present a poster at the CoC Annual Meeting.

This competition has been funded by the CoC along with a memorial gift from Mrs. A. Lee Campione in honor of her late husband, Matthew P. Campione, M.D., FACS.

For more information, visit [www.facs.org/cancer/cannews.html](http://www.facs.org/cancer/cannews.html), call 312-202-5183, or e-mail [cjones@facs.org](mailto:cjones@facs.org). ■

## Japan Traveling Fellow Selected for 2009

Lorenzo Ferri, M.D., FACS, FRCSC, assistant professor of surgery, McGill University, Montreal, has been selected as the 2009 ACS Traveling Fellow to Japan. Dr. Ferri will participate in the annual meeting of the Japan Surgical Society in Fukuoka,



DR. FERRI

Japan, April 2-4. He will also attend and participate in the ACS Japan Chapter meeting during that event, and will travel to several surgical centers in Japan, with assistance from mentors provided by the Japan Surgical

Society and the Japan Chapter. Dr. Ferri performs and researches surgical oncology and cardiothoracic surgery, with a particular interest in esophageal and lung carcinoma.

The deadline for receipt of all application materials for the

2010 Traveling Fellowship to Japan is June 1, 2009. The requirements are posted on the College's Scholarship Web page at [www.facs.org/memberservices/acsjapan.html](http://www.facs.org/memberservices/acsjapan.html) and will be published in the Bulletin. ■

## Traveling Fellow Will Head to Germany in April 2009

Richard A. Santucci, M.D., FACS, professor of urology in the College of Osteopathic Medicine at Michigan State University, East Lansing, has been selected as the 2009 ACS Traveling Fellow to Ger-



DR. SANTUCCI

He will participate in the annual meeting of the German Surgical Society in Munich, April 28-May 1, 2009. He will attend and participate in ACS's Germany Chapter meeting during that event. Dr. Santucci will also travel to several surgical centers

in Germany, with assistance from mentors provided by the German Surgical Society and the Germany Chapter.

Dr. Santucci has researched and written on genitourinary trauma and reconstruction, and on customary urological topics.

The application deadline for the 2010 Traveling Fellowship to Germany is April 1, 2009. The requirements have been posted on the College's Web site at [www.facs.org/memberservices/acsgermany.html](http://www.facs.org/memberservices/acsgermany.html). ■

## EDITORIAL

# MedSun: A Ray of Hope for the FDA



BY LAZAR J. GREENFIELD, M.D., FACS

In a previous editorial, I was critical of the Food and Drug Administration ("Truth Decay at the FDA," November 2005, p. 6). Since then, leadership changes and restructuring have occurred in response to critical reviews from the Institute of Medicine and the FDA's own science board. But we still have a combination of starvation funding and mounting public health responsibilities. The result is a persistently lumbering, bureaucratic, disaster-in-waiting. Little wonder that lead paint on imported toys, heparin contaminated by crude but cheap production abroad, and *Escherichia coli* food contamination not only escaped detection but were handled abysmally.

Why can't the FDA get its act together? FDA inspectors' reports are handwritten and slowed by layers of administration, reports of product dangers are not rapidly compared and analyzed, and old computers can't distinguish between shipments of road salt and table salt. (For details, visit [www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b\\_02\\_00\\_index.html](http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_00_index.html).) But instead of fixing the problems, FDA officials spent \$300,000 on a public relations firm. Instead of directly hiring the one they wanted, they used a minority firm to circumvent the bidding regulations. That Native Alaskan group was supposed to

subcontract the deal to the Washington firm the FDA wanted, but after the Washington Post discovered the ruse, the FDA suspended the contract, and ordered an investigation (New York Times, Oct. 5, 2008).

Public outrage over such events is having an effect. Last year, the Bush administration added \$275 million in FDA funding to the agency's budget request

for FY 2009, and passage of the FDA Amendments Act of 2007 (FDAAA) increased user fees paid by industry for timely reviews while expanding the FDA's authority to review drugs and medical devices. The cozy relationship between industry and the FDA remains problematic, however, as dependence grows on industry's contributions.

One bright spot is the FDA's MedSun

program, which was started in 2002 by the agency's Center for Devices and Radiological Health. This program trains risk managers to report online problems that cause serious injury, illness, or death, as well as near misses. It was legislated because health care facilities have traditionally ignored their legal requirement to report medical device problems. MedSun includes 350 sites with separate sub-

## How can you accelerate upper and lower GI recovery?



### Find Out More on CDRH/FDA Sites

► **Device Listing and Establishment Registration.** Users can

search for information on medical devices in commercial distribution, and establishments engaged in device manufacture or preparation ([www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm)).

► **MAUDE (Manufacturer and User Facility Device Experience).** Users can search for reports of adverse events involving medical devices ([www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM)).

► **Medical Device Safety Web Site.** This site includes published safety tips, alerts, and recalls ([www.fda.gov/cdrh/medicaldevicesafety/](http://www.fda.gov/cdrh/medicaldevicesafety/)).

► **Product Classification.** Users can find the classification of a device and the regulations it is subject to ([www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm)).

► **Warning Letters.** This database contains all Warning Letters issued since 2003 and some issued before ([www.fda.gov/foi/warning.htm](http://www.fda.gov/foi/warning.htm)).

### Important Safety Information

**WARNING: FOR SHORT-TERM HOSPITAL USE ONLY**

ENTEREG is available only for short-term (15 doses) use in hospitalized patients. Only hospitals that have registered in and met all of the requirements for the ENTEREG Access Support & Education (E.A.S.E.™) Program may use ENTEREG.

- ENTEREG is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking ENTEREG
- There were more reports of myocardial infarctions in patients treated with alvimopan 0.5 mg twice daily compared with placebo-treated patients in a 12-month study of patients treated with opioids for chronic pain. In this study, the majority of myocardial infarctions occurred between 1 and 4 months after initiation of treatment. This imbalance has not been observed in other studies of alvimopan, including studies of patients undergoing bowel resection surgery who received alvimopan 12 mg twice daily for up to 7 days. A causal relationship with alvimopan has not been established

Reference: 1. ENTEREG Prescribing Information. Exton, PA: Adolor Corporation; 2008.

networks to track device problems in homes, cardiac cases, ophthalmology, pediatric units, and laboratories (see [www.fda.gov/cdrh/medsun](http://www.fda.gov/cdrh/medsun)).

The FDA also has announced plans for a “Sentinel Initiative” to monitor the safety of medical products using a new system that taps into large databases to detect early signs of emerging problems. By partnering with the Centers for Medicare and Medicaid Services, the Department of Veterans Affairs, the Department of Defense, and selected private health care organizations, it should be possible to monitor a product’s per-

formance in millions of patients in real time. Privacy concerns are resolved under Medicare guidelines for handling patient care information.

But most of these sources are claims data, which register only when a physician or hospital is seeking payment; are not risk adjusted; and are far less accurate than an actual health record. As an example, a hospital bill for a heart attack doesn’t mean the patient actually had one. And Medicare patients use an average of 28 prescriptions annually compared with an average of 13 among all Americans. Figuring out which medica-

tion caused the problem or whether it resulted from the underlying disease will not be easy. So far, MedSun is not a part of the initiative.

The FDAAA has been called the law inspired by 27,000 lawsuits since that was Merck’s experience after Vioxx was withdrawn. But as irritating as these suits can be, they are the only way to force the disclosure of clinical experience manufacturers would prefer to hide. A recent Supreme Court decision favoring industry (*Riegel v. Medtronic*, U.S. Court of Appeals for the 2nd Circuit, No. 06-179, Feb. 20, 2008) preempted a product liability

claim in state court based on the federal supremacy clause in the Constitution. As a result, device manufacturers who gain FDA approval are now immunized against any subsequent liability suit.

You certainly wouldn’t want to see a manufacturer forced to change or withdraw a product that injured or killed someone. A similar drug case (*Wyeth v. Levine*) is on the agenda of the Supreme Court (N. Engl. J. Med. 2008;358:1883-5). Patient safety is not. ■

DR. GREENFIELD is editor in chief of SURGERY NEWS.

## ENTEREG accelerates GI recovery<sup>1</sup>

**The first and only FDA-approved agent indicated to accelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis**

- Reduced time to recovery by up to 1 day
- Reduced time to discharge order written (DOW)—by approximately 13 to 21 hours



**ENTEREG**<sup>®</sup>  
(alvimopan)

### Important Safety Information

- ENTEREG should be administered with caution to patients receiving more than 3 doses of an opioid within the week prior to surgery. These patients may be more sensitive to ENTEREG and may experience GI side effects (eg, abdominal pain, nausea and vomiting, diarrhea)
- ENTEREG is not recommended for use in patients with severe hepatic impairment, end-stage renal disease, or in patients undergoing surgery for correction of complete bowel obstruction
- ENTEREG is available only to hospitals that enroll in the E.A.S.E. Program. To enroll in the E.A.S.E. Program, the hospital must acknowledge that:
  - Hospital staff who prescribe, dispense, or administer ENTEREG have been provided the educational materials on the need to limit use of ENTEREG to short-term, inpatient use
  - Patients will not receive more than 15 doses of ENTEREG
  - ENTEREG will not be dispensed to patients after they have been discharged from the hospital

For more information on the E.A.S.E. Program, contact Adolor Corporation at 1-866-4ADOLOR (1-866-423-6567) or visit [www.entereg.com](http://www.entereg.com).

Please see Brief Summary of Prescribing Information on next page.

 Adolor

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November 2008

# Preop MRI in Breast Cancer Patients Not Beneficial

BY BRUCE JANCIN  
Elsevier Global Medical News

SAN ANTONIO — Preoperative evaluation by breast MRI did not reduce reoperation or mastectomy rates following planned wide local excision for breast cancer in the randomized U.K. COMICE trial.

COMICE (the Comparative Effectiveness of Magnetic Resonance Imaging in Breast Cancer) was a large multicenter

technology assessment study undertaken at the request of the U.K. National Health Service, which sought to determine whether preoperative MRI in patients diagnosed with breast cancer is cost effective.

“This was a simple study that asked a very simple question, and here is the answer: There was no reduction in reoperation rates. End of story,” Dr. Phil Drew declared at the San Antonio Breast Cancer Symposium.

COMICE involved 1,623 breast cancer patients who were scheduled at 45 medical centers for wide local excision based upon standard triple assessment by physical exam, mammography, and ultrasound. On a randomized basis, half of them underwent preoperative contrast-enhanced MRI. Unlike prior retrospective studies of the utility of breast MRI for preoperative cancer staging, COMICE was an inclusive study not limited to specialized centers.

The reoperation rate within 6 months was 18.75% in the MRI group and closely similar at 19.33% in controls.

Preoperative MRI led to a change in management from the planned wide local excision to more extensive surgery in 6.1% of patients; however, 28% of these revised operations were found after the fact based upon pathology not to have been necessary, said Dr. Drew of at the University of Hull (England).

Disease-free survival at a median 3.1 years of follow-up was 93.9% in the MRI group and statistically similar at 96.5% in women who did not undergo MRI.

MRI had no net effect upon quality of life as reflected in formal assessment of patient distress. Thirty-four percent of

## ENTEREG® (alvimopan) Capsules

The following is a brief summary only; see full prescribing information for complete product information.

### WARNING: FOR SHORT-TERM HOSPITAL USE ONLY

ENTEREG is available only for short-term (15 doses) use in hospitalized patients. Only hospitals that have registered in and met all of the requirements for the ENTEREG Access Support and Education (E.A.S.E.) program may use ENTEREG. [See Warnings and Precautions (5.1 and 5.2)]

### 4 CONTRAINDICATIONS

ENTEREG is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking ENTEREG.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Myocardial Infarction in a 12-Month Study in Patients treated with Opioids for Chronic Pain

There were more reports of myocardial infarctions in patients treated with alvimopan 0.5 mg twice daily compared with placebo-treated patients in a 12-month study of patients treated with opioids for chronic pain. In this study, the majority of myocardial infarctions occurred between 1 and 4 months after initiation of treatment. This imbalance has not been observed in other studies of alvimopan, including studies in patients undergoing bowel resection surgery who received alvimopan 12 mg twice daily for up to 7 days. A causal relationship with alvimopan has not been established.

#### 5.2 Distribution Program for ENTEREG

ENTEREG is available only to hospitals that enroll in the E.A.S.E. program. To enroll in the E.A.S.E. program, the hospital must acknowledge that hospital staff who prescribe, dispense, or administer ENTEREG have been provided the educational materials on the need to limit use of ENTEREG to short-term, inpatient use; patients will not receive more than 15 doses of alvimopan; and ENTEREG will not be dispensed to patients after they have been discharged from the hospital. Contact the E.A.S.E. program at 1-866-4ADOLOR (1-866-423-6567).

#### 5.3 Opioid Tolerance and Gastrointestinal-Related Adverse Effects

Patients recently exposed to opioids are expected to be more sensitive to the effects of  $\mu$ -opioid receptor antagonists. Since ENTEREG acts peripherally, clinical signs and symptoms of increased sensitivity would likely be limited to the gastrointestinal tract (e.g., abdominal pain, nausea and vomiting, diarrhea). Patients receiving more than 3 doses of an opioid within the week prior to surgery were not studied in the postoperative ileus clinical trials; therefore, ENTEREG 12 mg capsules should be administered with caution to these patients.

#### 5.4 Severe Hepatic Impairment

In patients with severe hepatic impairment, there is a potential for 10-fold higher plasma levels of drug [see Clinical Pharmacology (12.3) of full prescribing information]. There are no studies of ENTEREG in patients with severe hepatic impairment undergoing bowel resection. Because of the limited data available, ENTEREG is not recommended for use in patients with severe hepatic impairment.

#### 5.5 End-Stage Renal Disease

No studies have been conducted with end-stage renal disease. ENTEREG is not recommended for use in these patients.

#### 5.6 Bowel Obstruction

Use of ENTEREG in patients undergoing surgery for correction of complete bowel obstruction is not recommended.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The adverse event information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to ENTEREG in 1,650 patients in 9 placebo-controlled studies worldwide. The population was 19 to 97 years old, 68% were female, and 83% were Caucasian; 61% were undergoing bowel resection surgery. The first dose of ENTEREG was administered 30 minutes to 5 hours before the scheduled start of surgery and then twice daily until hospital discharge (or for a maximum of 7 days of postoperative treatment).

Table 1 presents treatment-emergent adverse reactions reported in  $\geq 3\%$  patients treated with ENTEREG and for which the rate for ENTEREG was  $\geq 1\%$  than placebo. Treatment-emergent adverse reactions are those events occurring after the first dose of study medication treatment and within 7 days of the last dose of study medication or those events present at baseline that increased in severity after the start of study medication treatment.

**Table 1. Treatment-Emergent Adverse Reactions That Were Reported in  $\geq 3\%$  of Either Bowel Resection Patients Treated With ENTEREG or All Surgical Patients Treated With ENTEREG and for Which the Rate for ENTEREG Was  $\geq 1\%$  Than Placebo**

System Organ Class	Bowel Resection Patients		All Surgical Patients	
	Placebo (n = 986) %	ENTEREG (n = 999) %	Placebo (n = 1,365) %	ENTEREG (n = 1,650) %
Blood and lymphatic system disorders				
Anemia	4.2	5.2	5.4	5.4
Gastrointestinal disorders				
Constipation	3.9	4.0	7.6	9.7
Dyspepsia	4.6	7.0	4.8	5.9
Flatulence	4.5	3.1	7.7	8.7
Metabolism and nutrition disorders				
Hypokalemia	8.5	9.5	7.5	6.9
Musculoskeletal and connective tissue disorders				
Back pain	1.7	3.3	2.6	3.4
Renal and urinary disorders				
Urinary retention	2.1	3.2	2.3	3.5

### 7 DRUG INTERACTIONS

#### 7.1 Potential for Drugs to Affect Alvimopan Pharmacokinetics

Based on *in vitro* data, alvimopan is not a substrate of CYP enzymes. Therefore, concomitant administration of ENTEREG with inducers or inhibitors of CYP enzymes is unlikely to alter the metabolism of alvimopan. No clinical studies have been performed to assess the effect of concomitant administration of inducers or inhibitors of cytochrome P450 enzymes on alvimopan pharmacokinetics.

*In vitro* studies suggest that alvimopan and its 'metabolite' are substrates for p-glycoprotein. A population PK analysis did not reveal any evidence that alvimopan or 'metabolite' pharmacokinetics were influenced by concomitant medications that are mild-to-moderate p-glycoprotein inhibitors. No clinical studies of concomitant administration of alvimopan and strong inhibitors of p-glycoprotein (e.g., verapamil, cyclosporine, amiodarone, itraconazole, quinidine, spirinolactone, quinidine, diltiazem, bepridil) have been conducted.

A population PK analysis suggests that the pharmacokinetics of alvimopan were not affected by concomitant administration of acid blockers or antibiotics. However, plasma concentrations of the 'metabolite' were lower in patients receiving acid blockers or preoperative oral antibiotics (49% and 81%, respectively). Because the 'metabolite' is not required for efficacy, no dosage adjustments are necessary in these patients.

#### 7.2 Potential for Alvimopan to Affect the Pharmacokinetics of Other Drugs

Alvimopan and its 'metabolite' are not inhibitors of CYP 1A2, 2C9, 2C19, 3A4, 2D6, and 2E1 *in vitro* at concentrations far in excess of those observed clinically. Alvimopan and its 'metabolite' are not inducers of CYP 1A2, 2B6, 2C9, 2C19 and 3A4. *In vitro* studies also suggest that alvimopan and its 'metabolite' are not inhibitors of p-glycoprotein. These *in vitro* findings suggest that ENTEREG is unlikely to alter the pharmacokinetics of coadministered drugs through inhibition or induction of CYP enzymes or inhibition of p-glycoprotein.

### BRIEF SUMMARY

Coadministration of alvimopan does not appear to alter the pharmacokinetics of morphine and its metabolite, morphine-6-glucuronide, to a clinically significant degree when morphine is administered intravenously. Dosage adjustment for intravenously administered morphine is not necessary when it is coadministered with alvimopan.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Teratogenic Effects: Pregnancy Category B:** Reproduction studies have been performed in pregnant rats at about 68 to 136 times the recommended human oral dose based on the body surface area and intravenous doses of about 3.4 to 6.8 times the recommended human oral dose based on the body surface area and in pregnant rabbits at intravenous doses at about 5 to 10 times the recommended human oral dose based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to alvimopan. 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.

#### 8.2 Nursing Mothers

Alvimopan and its 'metabolite' are detected in the milk of lactating rats. It is not known whether alvimopan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ENTEREG is administered to a nursing woman.

#### 8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### 8.4 Geriatric Use

Of the total number of patients in 5 clinical efficacy studies treated with ENTEREG or placebo, 45% were 65 years of age and over, while 18% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment based on increased age is required [see Clinical Pharmacology (12.3) of full prescribing information].

#### 8.5 Hepatic Impairment

Although there is a potential for higher plasma levels of drug in patients with mild-to-moderate hepatic impairment [see Clinical Pharmacology (12.3)], dosage adjustment in these patients is not required. Patients with mild-to-moderate hepatic impairment should be closely monitored for possible adverse effects (e.g., diarrhea, gastrointestinal pain, cramping) that could indicate high drug or 'metabolite' levels, and ENTEREG should be discontinued if adverse events occur. ENTEREG is not recommended for use in patients with severe hepatic impairment. [See Warnings and Precautions (5.4) and Dosage and Administration (2.2) and Clinical Pharmacology (12.3) of full prescribing information].

#### 8.6 Renal Impairment

Alvimopan has not been studied in patients with end-stage renal disease and ENTEREG is not recommended for use in these patients. Patients with mild-to-severe renal impairment do not require dosage adjustment, but they should be monitored for adverse effects. [See Dosage and Administration (2.2) and Clinical Pharmacology (12.3) of full prescribing information]. Patients with severe impairment should be closely monitored for possible adverse effects (e.g., diarrhea, gastrointestinal pain, cramping) that could indicate high drug or 'metabolite' levels, and ENTEREG should be discontinued if adverse events occur.

### 9 DRUG ABUSE AND DEPENDENCE

ENTEREG has no known potential for abuse or dependence.

### 10 OVERDOSAGE

There is no specific antidote for overdosage with ENTEREG. Patients should be managed with appropriate supportive therapy. Single doses up to 120 mg and multiple doses up to 48 mg for 7 days have been administered to normal, healthy subjects in clinical studies and were well tolerated.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two year carcinogenicity studies have been conducted with alvimopan in CD-1 mice at oral doses up to 4000 mg/kg/day and in Sprague Dawley rats at oral doses up to 500 mg/kg/day. Oral administration of alvimopan for 104 weeks produced significant increases in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis, and osteoma/osteosarcoma in bones of female mice at 4000 mg/kg/day (about 674 times the recommended human dose based on body surface area). In rats, oral administration of alvimopan for 104 weeks did not produce any tumor up to 500 mg/kg/day (about 166 times the recommended human dose based on body surface area).

Alvimopan was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK<sup>+</sup>) forward mutation test, the Chinese Hamster Ovary (CHO) cell chromosome aberration test or the mouse micronucleus test. The pharmacologically active 'metabolite' ADL 08-0011 was negative in the Ames test, chromosome aberration test in CHO cells and mouse micronucleus test.

Alvimopan at intravenous doses up to 10 mg/kg/day (about 3.4 to 6.8 times the recommended human oral dose based on the body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

#### 13.2 Animal Toxicology and/or Pharmacology

A single oral dose of 500 mg/kg of alvimopan was not lethal to mice and rats.

Reproduction studies have been performed in pregnant rats at oral doses up to 200 mg/kg/day (about 68 to 136 times the recommended human oral dose based on the body surface area) and intravenous doses up to 10 mg/kg/day (about 3.4 to 6.8 times the recommended human oral dose based on the body surface area) and in pregnant rabbits at intravenous doses up to 15 mg/kg/day (about 5 to 10 times the recommended human oral dose based on the body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to alvimopan.

### 17 PATIENT COUNSELING INFORMATION

#### 17.1 Recent Use of Opioids

Patients should be informed that they must disclose long-term or intermittent opioid pain therapy, including any use of opioids in the week prior to receiving ENTEREG. They should understand that recent use of opioids may make them more susceptible to adverse reactions to ENTEREG, primarily those limited to the gastrointestinal tract (e.g., abdominal pain, nausea and vomiting, diarrhea).

#### 17.2 Hospital Use Only

Patients should be informed that ENTEREG is for hospital use only for no more than 7 days after their bowel resection surgery.

#### 17.3 Most Common Side Effects

Patients should be informed that the most common side effects with ENTEREG in patients undergoing bowel resection are constipation, dyspepsia, and flatulence.

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Surgeons are unable to translate the imaging information into the operating environment.

DR. DREW

patients found the experience of undergoing MRI to be anxiety provoking, but paradoxically an identical percentage of patients in the control group were anxious that they had not had an MRI.

Dr. Drew opined that the problem with MRI is not the technology itself, but rather the inability of surgeons to effectively translate the imaging information into the operating environment, where the goal is to take out just enough but not too much breast tissue the first time around rather than in two operations.

“We don’t really want to look at how we find the tumor; we want to look at how we remove it. We haven’t changed how we take tumors out in 50 years,” Dr. Drew said.

In her plenary lecture, Dr. Monica Morrow cited the COMICE findings in a multipronged argument that preoperative MRI is vastly overutilized in breast cancer patients (see story on p. 13).

“The routine use of MRI in cancer patients requires some evidence of clinical benefit. To date, this does not exist,” said Dr. Morrow, chief of the breast service in the department of surgery at Memorial Sloan-Kettering Cancer Center, New York.

COMICE was funded by the U.K. National Institute of Health Research. Dr. Drew reported having no financial conflicts of interest.

## TALK BACK

What has been your experience with preoperative MRI use in breast cancer patients?

Share your thoughts!

Send e-mail to  
[surgerynews@facs.org](mailto:surgerynews@facs.org)

or write to Surgery News,  
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# Expert Argues Against Routine MRI for Breast Cancer

BY BRUCE JANCIN  
Elsevier Global Medical News

SAN ANTONIO — Magnetic resonance imaging should not be part of the routine presurgical evaluation of breast cancer patients, because evidence of its clinical benefit does not exist, a leading surgeon said in a plenary lecture at the San Antonio Breast Cancer Symposium.

"MRI finds two to three times more disease than observed rates of local recurrence in patients selected [for breast-conserving surgery] without MRI. This results in an increased mastectomy rate for questionable patient benefit. To date, neither short-term surgical outcomes nor long-term local control or contralateral breast cancer rates are improved with MRI," said Dr. Monica Morrow, an ACS Fellow and chief of the breast service in the department of surgery at Memorial Sloan-Kettering Cancer Center, New York.

And yet, MRI is routinely used presurgically in breast cancer patients because

superior to conventional adjuvant therapy. Endocrine therapy will not result in a survival advantage; chemotherapy is better. Treatment of breast cancer with less than mastectomy is dangerous. Local therapy does not influence survival. And to that list I would add, MRI finds cancer not found by other modalities and therefore must be helpful."

She argued that MRI benefits breast cancer patients only in relatively uncommon circumstances, such as when

looking for an occult primary tumor in women with axillary adenopathy in whom standard imaging and clinical examination are uninformative; assessing response to neoadjuvant therapy in patients who desire breast-conserving therapy; and resolving discrepancies between conventional imaging and clinical examination findings.

"To me, this was the most important talk of the day in terms of changing clinical practice. This information needs to

get out to the community," said Dr. Richard L. Crownover, a radiation oncologist at the University of Texas, San Antonio, who commented on the lecture.

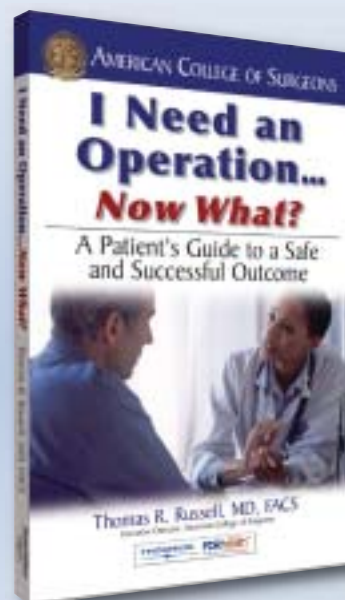
"We've really adopted MRI fanatically. It costs about \$1,600 per study out of somebody's pocket. There is this consistent finding of an increased mastectomy rate—almost twofold for the patients who've taken the path through MRI," he said. ■

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**MRI improves neither short-term surgical outcomes nor long-term local control or breast cancer rates.**

DR. MORROW

it is thought to reduce the number of excisions needed to obtain negative margins or prevent mastectomy. Dr. Morrow cited a recent survey of active members of the Society of Breast Imaging that showed 94% considered preoperative determination of the extent of cancer to be a leading indication for the imaging procedure (AJR Am. J. Roentgenol. 2008;191:332-9).

A recent retrospective study of 756 women who underwent breast-conserving therapy at the Hospital of the University of Pennsylvania, Philadelphia, found that the 8-year local failure rate was 3% in women who underwent preop MRI and 4% in those who did not. Contralateral breast cancer rates were 6% in each group. The overall survival rate was 86% with MRI and 87% without (J. Clin. Oncol. 2008;26:386-91).

Similarly, in a retrospective study of the effect of MRI on short-term outcomes in 577 breast cancer patients, Dr. Morrow and her coworkers found a 21.6% positive-margin rate at initial lumpectomy in 130 women with a preoperative MRI versus 14% in those with no MRI. The conversion rate from breast-conserving therapy to mastectomy was 9.8% in the MRI group versus 5.9% with no MRI. After the researchers controlled for tumor stage, MRI was associated with a 1.8-fold increased likelihood of mastectomy.

"The history of breast cancer is littered with intuitively obvious concepts that were wrong," Dr. Morrow said. "Some of my favorites: High-dose chemotherapy and bone marrow transplantation is

# Thromboses After Liver Transplant Cut Patient Survival

BY DAMIAN McNAMARA  
Elsevier Global Medical News

PALM BEACH, FLA. — Although thrombosis of the hepatic artery and portal vein each reduce graft survival after orthotopic liver transplantation, portal vein thrombosis also significantly reduces patient survival, according to a single-center study of more than 4,000 consecutive transplants over 24 years.

The long-term outcomes in patients

who experience these vascular complications remain undefined. For that reason, Dr. John P. Duffy and his associates reviewed portal vein thrombosis (PVT) and hepatic artery thrombosis (HAT) experience for 4,234 orthotopic liver transplants in 3,558 patients at the University of California, Los Angeles. The median follow-up was 6 years, and 80% were adults.

PVT, which occurred in 84 patients (2%), significantly decreased patient survival after orthotopic liver transplanta-

tion. At 1 year, for example, 73% of those with PVT survived, compared with 83% of the no-PVT group; at 5 years, survival rates were 58% and 74%, respectively; and at 10 years, 58% and 71%, said Dr. Duffy at the annual meeting of the Southern Surgical Association.

PVT also significantly reduced graft survival. At 1 year, graft survival was 37%, versus 85% in the no-PVT group; at 5 years, it was 27% versus 81%; and at 10 years, it was 24% versus 79%. These

differences were significant.

PVT is not readily treatable with retransplantation, and thromboendovenectomy is the treatment of choice, said Dr. Duffy, a surgeon in the division of liver, pancreas, and intestinal transplantation at the university. A total of 80% of PVT patients had thromboendovenectomy, and the remaining 20% had venous grafting.

HAT occurred in 203 cases (5%), including 69 pediatric transplants. The mean age of patients experiencing this complication was 31 years.

Overall survival of patients with HAT did not significantly differ, compared with the 95% of patients who did not ex-

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'We need improved protocols for early recognition of the prethrombotic state.'

DR. DUFFY

perience HAT. For example, at 1 year post transplant, 87% of the HAT group survived, as did 84% of the no-HAT group. Five-year survival rates were 76% and 75%, respectively, and 10-year survival rates were 73% and 71%.

HAT significantly reduced graft survival, however. At 1 year, 32% of grafts survived in the HAT group, versus 86% in the no-HAT patients; at 5 years, survival was 25% versus 82%; and at 10 years, graft survival fell to 23% and 80%. Retransplantation was required in most cases, with 58 patients (29%) requiring urgent retransplantation.

Among the HAT interventions were thrombectomy or revision, performed in 90 patients; primary retransplantation in 59 patients; and catheter-based thrombolytic therapy in 4 patients. Retransplantation was "clinically superior" to revision or thrombolysis, Dr. Duffy said. Retransplantation improved patient survival in the first year but not significantly thereafter. Thrombectomy, revision, and catheter-directed thrombolysis had limited success, he said.

"It is critical to lower the number of retransplantations [in patients with HAT], with the number of patients awaiting livers and dying on waiting lists," said Dr. Devin Eckhoff, an ACS Fellow and director of the division of transplantation surgery, University of Alabama at Birmingham, a study discussant.

"We might be able to salvage more of these patients using thrombectomy, revision, or catheter-based therapy if we could identify those in a pre-embolic state," said study coauthor Dr. Ronald W. Busuttill, an ACS Fellow and chair of the surgery department at the University of California, Los Angeles. Dr. Duffy agreed, stating "we need improved protocols for early recognition of the prethrombotic state."

In 2002, the university began to use early common hepatic artery inflow occlusion in transplant patients. This procedure lowered the incidence of HAT from 3.7% to 1.1% in adult patients. ■

# Dashboard Drives Down VAP in Surgical ICU

BY JANE SALODOF MACNEIL  
Elsevier Global Medical News

SANTA FE, N.M. — Putting a screen saver “dashboard” with red alerts on computers in a surgical intensive care unit helped staff to increase compliance with measures to prevent ventilator-associated pneumonia and to reduce the incidence of these potentially deadly infections.

The rate of ventilator-associated pneumonia (VAP) fell from 15.2 cases per 1,000 ventilator days during the 18 months before the dashboard was introduced in July 2007 to 9.3 per 1,000 ventilator days during the following 12 months, Dr. Victor Zaydfudim reported at the annual meeting of the Western

Surgical Association.

Complete compliance with a bundle of six measures designed to prevent VAP rose from barely over 30% to around 90% during the same time frames, said Dr. Zaydfudim of the department of general surgery at Vanderbilt University, Nashville, Tenn. The bundle had been implemented in 2002, he noted, but compliance was low and VAP rates had not gone down prior to dashboard use.

The bundle requires spontaneous breathing trials by respiratory therapists; administration of the Richmond Agitation Sedation Scale by physicians and registered nurses; and head of bed elevation, oral care, dental hygiene, and hypopharyngeal suction by registered nurses. “All critically ill patients received stress ulcer

prophylaxis and deep venous thrombosis prophylaxis,” he added.

As described by Dr. Zaydfudim, the dashboard tracks compliance in real time for every patient in the ICU. Each measure in the bundle corresponds on the dashboard to a colored box in a row assigned to each patient. Green means that the patient’s care is up to date with that item, yellow shows that compliance for that item is about to expire, and red means the patient’s care no longer meets the standard set forth in the bundle.

All computers in the ICU are equipped with the screen saver, which appears for everyone to see whenever a computer is not being used.

The closed, intensivist-run, 21-bed surgical ICU where the dashboard was tested is in a tertiary referral center that admits about 1,300 patients per year. Except for the average APACHE II score, which increased from 17.8 to 22, and a small rise in body mass index, Dr. Zaydfudim said patient case mix did not change significantly during the study. The rate of bloodstream infection was 4.5 per 1,000 catheter days before and 5 per 1,000 catheter days after the dashboard.

VAP accounts for 60% of hospital-acquired pneumonia deaths, prolongs hospital stays by 4 days, and increases direct hospital costs by about \$40,000 per patient, he said. The study defined VAP by the following criteria: mechanical ventilation lasting more than 48 hours; fever higher than 38.5 °C and/or leukocytosis greater than 12,000 cells per microliter, and/or infiltrate on chest radiograph; and positive bronchoalveolar lavage culture with greater than 10<sup>4</sup> cfu/mL.

Despite the reduction in VAP, further efforts are needed to meet the goal of 4.1 cases or less per 1,000 ventilator days, based on data published by the Centers for Disease Control and Prevention (Am.

J. Infect. Control 2007;35:290-301), he said.

“I am not sure we are ready to accept those benchmarks as stated,” said Dr. Charles Wright Pinson, an ACS Fellow who is the H. William Scott Professor of Surgery at Vanderbilt and senior author of the study.

“The presence of a complication is directly proportional to how hard you look



**VAP rates fell from 15.2 to 9.3 cases per 1,000 ventilator days after the dashboard was implemented.**

DR. ZAYDFUDIM

Bed	Pt. name	Age	LOS	Orders				SBT			RASS			Hb	WBC	Lact	Cult	Hx	
								Ver	Sten	Trial	INT	STP	QAL						FL
3001B	C, MF	51y	19 d		flowsheet	MAR	labs						0	30					
3002A	S, E K	76y	2 d		flowsheet	MAR	labs	+	+										
3002B	C, N	64y	3 d	STAT	flowsheet	MAR	labs	+											
3003X	M, R	83y	14 d		flowsheet	MAR	labs						0	30					
3004B	S, J A	51y	29 d		flowsheet	MAR	labs						0	30					
3005B	H, J W	58y	2 d		flowsheet	MAR	labs						0	30					
3006X	W, B J	78y	6 d		flowsheet	MAR	labs	+	+										
3007X	H, J	68y	21 d	STAT	flowsheet	MAR	labs	+					0	40					
3008X	H, G R	71y	32 d		flowsheet	MAR	labs	+	+										
3009X	B, T L	67y	38 d	STAT	flowsheet	MAR	labs	+											
3011A	C, J V	62y	3 d	STAT	flowsheet	MAR	labs						0	48					
3011B	D, R	82y	21 d		flowsheet	MAR	labs						1	48					
3011D	D, C T	55y	2 d		flowsheet	MAR	labs	+	+										
3011E	D, I M	81y	6 d	STAT	flowsheet	MAR	labs	+											
3011F	L, E	75y	2 d		flowsheet	MAR	labs						-1						
3012A	B, E	66y	8 d		flowsheet	MAR	labs						0	48					
3012B	W, K	86y	3 d		flowsheet	MAR	labs						-1	30					
3013A	T, C N	65y	3 d		flowsheet	MAR	labs						0	48					
3013B	R, J A	82y	2 d		flowsheet	MAR	labs						0	30					

A sample screenshot of the dashboard shows the green, yellow, and red boxes that alert staff to each patient’s level of compliance with the VAP bundle.

COURTESY DR. VICTOR ZAYDFUDIM

for it. And so I would submit that people who report very low VAP rates, like zero VAP rates, are not looking for it very hard,” Dr. Pinson said, questioning whether generalized targets are realistic for specific subgroups of surgical ICU patients. The Vanderbilt surgical ICU was limited to general surgery, vascular surgery, and patients from surgical specialties such as thoracic, plastic, orthopedics, and otolaryngology, as well as transplant patients, he noted; it did not include cardiac and trauma patients.

Asked how Vanderbilt kept staff motivated once the dashboard was no longer a novelty, he said, “We set this up as a management goal, so all personnel in this unit were responsible for the outcome.”

He did not have cost data, but said that putting the dashboard on a screen saver, where it serves as a constant reminder, was helpful.

Neither Dr. Zaydfudim nor Dr. Pinson disclosed any conflicts of interest. ■

## HHS Sets Goals to Reduce Health Care–Associated Infections

BY MARY ELLEN SCHNEIDER  
Elsevier Global Medical News

Federal officials are seeking significant reductions in some of the most common health care–associated infections over the next 5 years.

In a new “action plan” issued in January, officials at the Department of Health and Human Services outlined goals related to six categories of health care–associated infections: central line–associated bloodstream infections, *Clostridium difficile* infections, catheter-associated urinary tract infections, methicillin-resistant *Staphylococcus aureus* (MRSA) infections, surgical-site infections, and ventilator-associated pneumonia.

The seven national prevention targets identified in the HHS action plan call for the following:

- ▶ Reducing the number of central line–associated bloodstream infections per 1,000 device days to below the current 25th percentile set by the National Healthcare Safety Network by location type.
- ▶ Achieving full compliance with the central line bundle in nonemergent insertions.
- ▶ Reducing by 30% the case rate per patient days and administrative/discharge data for ICD-9-CM–coded *C. difficile* infections.
- ▶ Reducing by 25% the number of symptomatic urinary

tract infections per 1,000 urinary catheter days.

- ▶ Reducing by half the incidence rate of all health care–associated invasive MRSA infections.

- ▶ Reducing the median deep-incision and organ-space infection rate for each procedure/risk group to at or below the current National Healthcare Safety Network 25th percentile.

- ▶ Achieving 95% adherence rates for each Surgical Care Improvement Project/National Quality Forum infection process measure for surgical-site infections.

“This plan will serve as our road map on how the department addresses this important public health and patient safety issue,” said Mike Leavitt, former HHS secretary.

The goals outlined by HHS are “reasonable,” said Kathy Warye, CEO of the Association for Professionals in Infection Control and Epidemiology. The action plan targets the most costly infections, both in terms of dollars and harm to patients, she said. The 5-year timeline also gives hospitals time to achieve reductions. At first, many hospitals may see increases in these infections, because the more you look, the more you find, she said.

The action plan may also play an important role by giving infection-control specialists more clout when they lobby their hospital administrators for resources for infection prevention, she said. “When the federal

government gets into the act, it raises the stakes,” Ms. Warye added.

The plan also addresses concerns that there has been a lack of coordination among the various federal agencies and departments that have some responsibility for health care–associated infections, said Dr. Patrick J. Brennan, chairman of the Healthcare Infection Control Practices Advisory Committee. Dr. Brennan, who served on the steering committee that prepared the report, said that improved coordination is especially important at a time when federal budget dollars are tight.

For example, the HHS plan addresses the role of information technology as a way to improve coordination of federal departments with databases of infection information. The action plan also outlines a research agenda related to the prevention of health care–associated infections, notably research on the barriers to adherence of recommended infection-control practices, and strategies to overcome those barriers. HHS also calls for more basic, epidemiologic, and translational research into how health care–associated pathogens are acquired. Many current infection-control practices are based on empirical observation, according to HHS. ■

The plan is available at the HHS Web site [www.hhs.gov/oph/initiatives/ha](http://www.hhs.gov/oph/initiatives/ha).

# New Data Show Poor Results After TAAA Repair

BY NANCY WALSH  
Elsevier Global Medical News

NEW YORK — The morbidity and mortality associated with hybrid repair of thoracoabdominal aneurysms in high-risk patients remain substantial, according to data from four vascular centers.

The hybrid procedure, which involves combined visceral/renal debranching and endovascular exclusion, is intended to be a less invasive approach for patients

who are considered high risk for open surgery, the clinical standard. However, even though aortic cross-clamping, extracorporeal perfusion, thoracotomy, and single-lung ventilation are avoided, “hybrid procedures may not be so benign, even in centers of excellence,” said Dr. Dittmar Bockler at the Veith symposium on vascular medicine sponsored by the Cleveland Clinic.

In the initial report of 29 patients who underwent the hybrid procedure, there

were three deaths and no cases of paraplegia (a devastating complication seen with the open surgery). The authors described their results as “encouraging” (*J. Vasc. Surg.* 2006;43:1081-9).

Subsequent experience has been less promising. “Because the numbers in published series are small, we pooled data from three centers, in Heidelberg, Munich, and London,” said Dr. Bockler of the University of Heidelberg (Germany).

Among the 87 patients included in the

analysis, most were male, 24 had chronic expanding dissections, 3 had mycotic aneurysms, and 8 had Marfan syndrome or a connective tissue disease. Mean aneurysm diameter was 74 mm.

Previous aortic procedures were common among the patients, all of whom were considered high risk, he noted. Analysis revealed that, at 30 days, mortality was 13%, paraplegia was 8%, dialysis and renal insufficiency was 3%, graft occlusion resulting in gut resection was 2%, and overall graft occlusion was 6%.

At 1 year, the overall mortality was 25%, and rates of paraplegia, dialysis, and graft occlusion remained the same as at 30 days. The endoleakage rate was 11%. The eight type I endoleaks were treated with proximal extension in six patients; two patients had spontaneous sealing of the endoleaks. Five type III endoleaks that were treated endovascularly.

Many questions about the hybrid procedure remain to be answered, Dr. Bockler said. “Should it be simultaneous or staged? What about cerebrospinal fluid drainage? We don’t know about long-term results, and we don’t know if it’s a good option for patients with [Marfan syndrome] and chronic dissection.

Hybrid procedures are an alternative for repair of types I-III degenerative thoracoabdominal aortic aneurysms in very select high-risk patients who are not considered fit for open surgery, Dr. Bockler said. He added that mortality and paraplegia rates are still too high.

Similar experience was reported at the symposium by Dr. Richard P. Cambria, an ACS Fellow with the division of vascular and endovascular surgery, Massachusetts General Hospital and Harvard Medical School, Boston.

Between June 2005 and December 2007, 23 high-risk patients with thoracoabdominal aneurysms underwent mesenteric and renal debranching and subsequent placement of a thoracic stent graft, whereas 77 underwent open repair.

The hybrid and open groups had similar mean ages (77 and 73 years, respectively) and mean aneurysm size (6.5 cm in both groups). The mean Society for Vascular Surgery (SVS) risk score was 9 in the hybrid group and 6 in the open group, and more patients in the hybrid group than in the open group had oxygen-dependent chronic obstructive pulmonary disease and prior thoracic or thoracoabdominal repairs.

“Composite mortality and/or paraplegia was doubled in the hybrid group, at 22%, compared with 12% in the open group,” Dr. Cambria said. Similarly, the rate of any type of reoperation was 39% in the hybrid group, compared with 21% in the open group. Actuarial survival rates at 1 year were 74% and 72% in the hybrid and open groups, respectively.

“While touted as an operation of limited extent, the hybrid repair in high-risk patients has substantial morbidity, and to really clarify its role, a prospective study in equivalent risk patients would be needed,” Dr. Cambria concluded.

Dr. Bockler and Dr. Cambria declared no conflicts of interest. ■

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# Presurgical Bisoprolol Triggers No Excess Strokes

BY MITCHEL L. ZOLER  
Elsevier Global Medical News

MUNICH — Patients undergoing non-cardiac surgery benefited from pre- and postoperative treatment with the  $\beta$ -blocker bisoprolol and had no excess risk for stroke, based on an analysis of about 2,000 patients who had been enrolled in three separate studies.

This finding contrasts with results from a major trial first reported in November 2007 and published last May. Results from the Perioperative Ischemic Evaluation (POISE) trial found that starting the  $\beta$ -blocker metoprolol, the extended-release formulation, just hours before non-cardiac surgery and continued for a month was linked with about a twofold increase in strokes (Lancet 2008;371:1839-47).

The reason for this difference in stroke rates is unknown, but one speculative explanation is that the studies

**A PREVIOUS STUDY RAISED DOUBTS, BUT THE NEW RESULTS FROM THE BISOPROLOL ANALYSIS PROVIDE REASSURANCE THAT THIS PRESURGICAL REGIMEN IS SAFE.**

using bisoprolol started patients on a low-dose regimen weeks before their surgery and the dosage never rose much higher for all patients. In the metoprolol study, patients were started on the maximum recommended therapeutic dose and underwent surgery just hours after treatment began, Dr. Olaf Schouten said at the annual congress of the European Society of Cardiology.

The results from the metoprolol study raised doubts about the safety of starting patients on a  $\beta$ -blocker before surgery, but the new results from the bisoprolol analysis provide reassurance that this presurgical regimen is safe, said Dr. Schouten, a vascular surgeon at Erasmus Medical Center in Rotterdam, the Netherlands.

"We continue to use bisoprolol starting about 30 days before surgery. We have not changed our  $\beta$ -blocker guidelines," he said. Their protocol involves starting patients on a 2.5-mg/day dosage of bisoprolol, which is about 10%-15% of the maximum recommended dose. One day prior to surgery, the dosage is adjusted to achieve a target heart rate of 60-65 beats per minute. In most patients the 2.5-mg/day dosage is already maintaining this heart rate; in a minority, the dosage is raised to 3.75 mg or 5 mg/day, still substantially below the maximum dose, Dr. Schouten said.

The data reviewed by Dr. Schouten were collected in three studies from the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) series run at Erasmus. The DECREASE-I study included 59 patients treated with bisoprolol and 53 who did not receive a  $\beta$ -blocker (N. Engl. J. Med. 1999;341:1789-94). DECREASE-II included 1,476 patients who were all treat-

ed with bisoprolol (J. Am. Coll. Card. 2006;48:964-9). DECREASE-IV included about 530 patients treated with bisoprolol and a similar number treated with placebo. Dr. Schouten presented the findings in a poster at the meeting.

Dr. Schouten's analysis showed that, among patients not on a  $\beta$ -blocker, the incidence of stroke was 0.4% in the DECREASE studies and 0.5% in the POISE study. Among patients on a  $\beta$ -blocker, the stroke rate was 0.5% in the DECREASE

studies and 1.0% in POISE, a statistically significant difference. In a multivariate analysis of the DECREASE results that controlled for baseline differences among patients, those who were treated with bisoprolol had no significant increase in strokes, compared with patients not treated with bisoprolol, Dr. Schouten said.

The DECREASE-IV results presented at the meeting also highlighted the benefit from bisoprolol treatment in cutting the rate of death and nonfatal myocar-

dial infarction in patients undergoing noncardiac vascular surgery. The combined rate of death and MI during the first 30 days following surgery was about 2% in patients treated with bisoprolol and about 6% in those on placebo, reported Dr. Martin Dunkelgrun and his associates from Erasmus.

The DECREASE studies did not receive any commercial funding. Dr. Schouten and associates at Erasmus had no disclosures relevant to these studies. ■

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# Weigh Diabetes-Related Risks of Bariatric Surgery

BY JEFF EVANS

Elsevier Global Medical News

**B**ariatric surgery procedures in patients with type 2 diabetes affect the hormones that control insulin secretion and sensitivity, and these effects must be taken into consideration to maintain postoperative glycemic control, according to a review of bariatric surgery studies that reported diabetes-related outcomes.

"Caloric intake is minimal after any bariatric procedure, and patients are at high risk for hypoglycemia if their preoperative regimens are not appropriately adjusted," wrote Dr. Marion L. Vetter and her associates at the University of Pennsylvania, Philadelphia (Ann. Intern. Med. 2009;150:94-103).

Bariatric procedures that have been broadly classified as malabsorptive, such as biliopancreatic diversion (BPD) with duodenal switch, have reportedly had a greater effect on the gastrointestinal hormones known as incretins (which stimulate insulin release after enteral nutrition) than do so-called restrictive procedures, such as laparoscopic adjustable gastric banding (LAGB) and vertical banded gastroplasty (VBG).

Roux-en-Y gastric bypass (RYGB), which Dr. Vetter and her colleagues called the "current gold standard treat-

ment for severe obesity," incorporates both malabsorptive and restrictive properties. In one large meta-analysis of bariatric studies, type 2 diabetes resolved in 84% of patients after RYGB, in 98% of patients after BPD, and in 48%-72% of patients after LAGB or VBG. Diabetes resolution seemed to be predicted across techniques according to body-mass index, sex, preoperative hemoglobin A<sub>1c</sub>,

## MALABSORPTIVE PROCEDURES REPORTEDLY HAVE HAD A GREATER EFFECT ON GASTROINTESTINAL HORMONES THAN HAVE 'RESTRICTIVE' PROCEDURES.

and duration of diabetes.

Dr. Vetter and her colleagues found that decreased caloric intake has an immediate impact on insulin sensitivity but does not alone account for lower blood glucose levels. Studies have shown that complete diabetes resolution occurs within days of intestinal bypass procedures but takes months to occur after LAGB. Even with the same postoperative caloric intake, blood glucose levels have been shown to drop further and faster after RYGB than after VBG.

Changes in the levels of the incretins called glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), as well as the levels of non-incretin gut peptides known as peptide YY (PYY) and ghrelin, appear to occur rapidly after gastric bypass. GLP-1, which is released by special cells of the distal ileum, is known to slow gastric emptying. It acts on pancreatic  $\beta$  islet cells to augment glucose-dependent insulin secretion and on the central nervous system to induce satiety and decrease food intake. GLP-1 remains elevated for 1 year after gastric bypass, but restrictive procedures do not change GLP-1 levels, in part because they do not alter gastric emptying.

GIP is secreted by cells in the proximal gut and also acts on  $\beta$  islet cells to increase insulin secretion, but it is less potent than GLP-1 and does not affect gastric emptying or satiety. Lower levels of GIP have been reported several months after RYGB, but this has not been a consistent result.

Specialized cells in the distal ileum produce PYY, which increases satiety and delays gastric emptying, increases as early as 2 days after RYGB, and remains elevated for at least 6 weeks, which "may account for the immediate decrease in appetite after surgery," the researchers wrote.

The response of PYY is blunted after meals in gastric banding patients, but no other studies have been published about its level in the weeks after banding or other restrictive procedures.

Ghrelin is released from the gastric fundus and proximal small intestine to increase appetite by acting on the hypothalamus. Reports of the effect of gastric bypass on ghrelin levels have been inconsistent. Such studies may have included subtle variations in surgical technique that may have affected ghrelin levels.

Because insulin requirements often rapidly decline after bariatric surgery, Dr. Vetter and her coauthors suggested that "patients may require only long-acting basal insulin in the immediate postoperative period, with rapid-acting insulin for correction of hyperglycemia as necessary."

Rapid-acting insulin can be used for prandial coverage when patients resume eating, but they recommended avoiding sulfonylureas and meglitinides until patients begin eating regularly. Barring any contraindications, the researchers said that thiazolidinediones are safe once regular eating is occurring.

Dr. Nayyar Iqbal, the senior author, is employed by Bristol-Myers Squibb. No other authors reported potential financial conflicts of interest. ■

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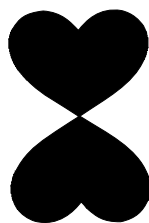
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# Large Scanners Lacking for Obese Patients

BY MICHELE G. SULLIVAN  
Elsevier Global Medical News

**M**orbidly obese patients who need emergency imaging are probably out of luck in much of the United States, because most hospitals don't have the necessary equipment, and zoos and veterinary hospitals with large-capacity scanners won't accept human patients.

Only 10% of 396 hospitals surveyed were able to image patients weighing 450 pounds or more, and 90% of the hospitals designated as bariatric surgery centers of excellence lacked the super-sized scanners, according to Dr. Adit A. Ginde and colleagues.

The lack of large-sized scanners in bariatric surgery centers is "of particular concern, given that the number of gastric bypass surgeries performed in the United States has increased from 67,000 in 2002 to 140,000 in 2005, and that up to one-third of patients undergoing gastric bypass surgery will require an emergency department visit in the postoperative period," wrote the investigators (*Obesity* 2008;16:2549-51).

Indeed, they suggested that some surgeons might not even consider bariatric surgery for patients who exceed the weight capacity on available imaging equipment.

Dr. Ginde, an emergency physician at the University of Colorado Denver School of Medicine, Aurora, and his coauthors surveyed 5% of U.S. hospitals with emergency departments, all primary affiliate hospitals of U.S. academic emergency departments, and all the country's zoos and veterinary schools. Respondents at the hospitals included radiology technicians, department supervisors, and physicians. They were asked about the weight limits on their computed tomography and magnetic resonance imaging equipment.

At animal facilities, veterinary personnel were asked the same question, as well as whether they had ever imaged human patients, had considered doing so, or had policies about it.

Dr. Ginde and his team collected responses from 396 hospitals, 136 zoos, and 28 veterinary schools. Only 10% of the hospitals designated as bariatric surgery centers of excellence had high-weight CT scanners. Similarly, high-capacity scanners were available in just 3% of critical-access hospitals, 5% of rural hospitals, 26% of stroke centers, and 34% of trauma centers.

Academic centers were more likely than were nonacademic centers to have the large scanners (28% vs 10%), whereas 8% of both academic and nonacademic centers had large MRI scanners, the researchers found.

Only two zoos had large animal CT scanners, and neither would accept human patients. Veterinary schools appeared to be somewhat more accommodating of human patients. More than half of the schools (57%) had big scan-

ners, but only four institutions said they would consider imaging a human. The majority (82%) had formal policies against it.

The inability to image obese patients is a serious problem, the authors said. "CT or MRI imaging was required for 11% of all emergency department visits in 2005 and is the standard of care of ED evaluation for many acute medical conditions. Almost all emergency departments—at least 90%—would not be able

to obtain CT or MRI imaging studies for patients weighing more than 450 pounds."

Personal communications with some respondents at animal facilities confirmed the need for large scanners for humans: "Informally, many animal facilities reported that they receive regular phone calls regarding their capacity and willingness to image human patients, despite efforts to correct the misconception that this practice is usually permitted." ■

## TYGACIL® (tigecycline) Brief Summary

See package insert for full Prescribing Information. For further product information and current package insert, please visit [www.wyeth.com](http://www.wyeth.com) or call our medical communications department toll-free at 1-800-934-5556.

### CONTRAINDICATIONS

TYGACIL is contraindicated for use in patients who have known hypersensitivity to tigecycline.

### WARNINGS

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects. TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics.

**TYGACIL may cause fetal harm when administered to a pregnant woman.** If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline. (See **PRECAUTIONS, Pregnancy**.)

**The use of TYGACIL during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown).** Results of studies in rats with TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxic producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

### PRECAUTIONS

#### General

Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIA) secondary to clinically apparent intestinal perforation. (See **ADVERSE REACTIONS**.) In Phase 3 cIA studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL had higher APACHE II scores (median = 13) vs the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL.

The safety and efficacy of TYGACIL in patients with hospital acquired pneumonia have not been established. In a study of patients with hospital acquired pneumonia, patients were randomized to receive TYGACIL (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received TYGACIL had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 15/122 [12.3%]) than the comparator.

As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

Prescribing TYGACIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

#### Information for Patients

Patients should be counseled that antibacterial drugs including TYGACIL should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When TYGACIL is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by TYGACIL or other antibacterial drugs in the future. Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

#### Drug Interactions

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin. (See **CLINICAL PHARMACOLOGY, Drug-Drug Interactions** in full prescribing information.)

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

#### Drug/Laboratory Test Interactions

There are no reported drug-laboratory test interactions.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline. No mutagenic or clastogenic potential was found in a battery of tests, including in vitro chromosome aberration assay in Chinese hamster ovary (CHO) cells, in vitro forward mutation assay in CHO cells (HGPRT locus), in vitro forward mutation assays in mouse lymphoma cells, and in vivo mouse micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 5 times the human daily dose based on AUC. In female rats, there were no compound-related effects on ovaries or estrous cycles at exposures up to 5 times the human daily dose based on AUC.

#### Pregnancy

##### Teratogenic Effects—Pregnancy Category D

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, <sup>14</sup>C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively. An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

#### Labor and Delivery

TYGACIL has not been studied for use during labor and delivery.

#### Nursing Mothers

Results from animal studies using <sup>14</sup>C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman. (See **WARNINGS**.)

#### Use in Patients with Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response. (See **CLINICAL PHARMACOLOGY, Special Populations, Use in Patients with Hepatic Impairment and DOSAGE AND ADMINISTRATION** in full prescribing information.)

#### Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established. (See **WARNINGS**.) Therefore, use in patients under 18 years of age is not recommended.

#### Geriatric Use

Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=1415), 278 were 65 and over, while 110 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

#### ADVERSE REACTIONS

Because clinical studies are conducted under varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Phase 3 clinical studies enrolled 1415 patients treated with TYGACIL. TYGACIL was discontinued due to treatment-emergent adverse events in 5.0% of patients compared to 4.7% for all comparators (5.3% for vancomycin/aztreonam and 4.4% for imipenem/cilastatin). Table 4 shows the incidence of treatment-emergent adverse events through test of cure reported in ≥2% of patients in these studies regardless of causality.

Table 4. Incidence (%) of Treatment-Emergent Adverse Events Through Test of Cure Reported in ≥2% of Patients Treated in Phase 3 Clinical Studies

Body System Adverse Events	TYGACIL <sup>a</sup> (N=1415)	Comparators <sup>b</sup> (N=1382)
<b>Body as a Whole</b>		
Abdominal pain	6.8	5.7
Abscess	3.2	2.6
Asthenia	2.5	1.7
Back Pain	1.2	2.3
Fever	7.1	9.8
Headache	5.9	6.5
Infection	8.3	5.4
Pain	3.7	2.9
<b>Cardiovascular System</b>		
Hypertension	4.9	5.6
Hypotension	2.3	1.7
Pleuritis	1.8	3.8
<b>Digestive System</b>		
Constipation	2.8	4.1
Diarrhea	12.7	10.8
Dyspepsia	2.9	1.6
Nausea	29.5	15.8
Vomiting	19.7	10.8
<b>Hemic and Lymphatic System</b>		
Anemia	4.2	4.8
Leukocytosis	3.7	2.5
Thrombocytopenia	6.1	6.2
<b>Metabolic and Nutritional</b>		
Alkaline Phosphatase Increased	3.5	2.6
Amylase Increased	3.1	1.4
Bilirubinemia	2.3	0.9
BUN Increased	2.1	0.2
Healing Abnormal	3.5	2.6
Hyperglycemia	1.8	2.9
Hypokalemia	2.1	2.9
Hypoproteinemia	4.5	3.0
Lactic Dehydrogenase Increased	4.0	3.5
Peripheral Edema	3.3	3.3
SGOT Increased <sup>c</sup>	4.3	4.4
SGPT Increased <sup>c</sup>	5.6	4.7
<b>Nervous System</b>		
Dizziness	3.5	2.7
Insomnia	2.3	3.3
<b>Respiratory System</b>		
Cough Increased	3.7	3.8
Dyspnea	2.9	2.7
Pulmonary Physical Finding	1.9	2.2
<b>Skin and Appendages</b>		
Pruritus	2.6	4.1
Rash	2.4	4.1
Sweating	2.3	1.6
<b>Other</b>		
Local Reaction to Procedure	9.0	9.1

<sup>a</sup> 100 mg initially, followed by 50 mg every 12 hours

<sup>b</sup> Vancomycin/Aztreonam, Imipenem/Cilastatin, Linezolid

<sup>c</sup> LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

In Phase 3 cSSSI and cIAI studies, death occurred in 2.3% (32/1383) of patients receiving TYGACIL and 1.6% (22/1375) of patients receiving comparator drugs; this difference is not statistically significant and relationship to treatment cannot be established. In all treatment groups, mortality was associated with higher baseline comorbidity and/or greater severity of baseline infections.

In Phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (6.7%) vs comparators (4.6%). Significant differences in sepsis/septic shock with TYGACIL (1.5%) vs comparators (0.5%) were observed. Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established. (See **PRECAUTIONS**.) Other events included nonsignificant differences in abscess (1.8% vs 1.6%) and infections, including wound infections (1.7% vs 1.1%) for TYGACIL vs comparators, respectively.

The most common treatment-emergent adverse events were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 29.5% (19.6% mild, 8.5% moderate, 1.4% severe) and vomiting incidence was 19.7% (12.3% mild, 6.3% moderate, 1.1% severe). In patients treated for cSSSI, nausea incidence was 35.0% for TYGACIL and 8.9% for vancomycin/aztreonam; vomiting incidence was 20.0% for TYGACIL and 4.2% for vancomycin/aztreonam. In patients treated for cIAI, nausea incidence was 25.3% for TYGACIL and 20.5% for imipenem/cilastatin; vomiting incidence was 19.5% for TYGACIL and 15.3% for imipenem/cilastatin.

Discontinuation from tigecycline was most frequently associated with nausea (1.3%) and vomiting (1.0%). For comparators, discontinuations were most frequently associated with rash (1.1%), vancomycin/aztreonam and nausea (1.0%), imipenem/cilastatin.

The following drug-related adverse events were reported infrequently (≥0.2% and <2%) in patients receiving TYGACIL in Phase 3 clinical studies:

**Body as a Whole:** injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis

**Cardiovascular System:** thrombophlebitis, bradycardia, tachycardia, vasodilatation

**Digestive System:** anorexia, dry mouth, jaundice, abnormal stools

**Metabolic/Nutritional System:** increased creatinine, hypocalcemia, hypoglycemia, hyponatremia

**Nervous System:** somnolence

**Special Senses:** taste perversion

**Hemic and Lymphatic System:** prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia

**Urogenital System:** vaginal moniliasis, vaginitis, leukorrhea

**Post-Marketing Experience**

Worldwide post-marketing adverse events not previously listed in the product label include: anaphylaxis/anaphylactoid reactions, acute pancreatitis.

#### OVERDOSAGE

No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose IV toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD<sub>50</sub>) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD<sub>50</sub> was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

This Brief Summary is based on TYGACIL direction circular W10521C002 ET01, revised 06/07.

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Expanded broad-spectrum  
coverage is on your side<sup>1\*†</sup>

Gram positives  
Gram negatives  
Anaerobes  
Resistant gram positives  
Resistant gram negatives



\* The clinical significance of in vitro activity is unknown.

† TYGACIL does not cover *Pseudomonas aeruginosa*.

## TYGACIL is indicated for

- The treatment of adults with complicated skin and skin structure infections caused by *E. coli*, *E. faecalis* (vancomycin-susceptible isolates only), *S. aureus* (methicillin-susceptible and -resistant isolates), *S. agalactiae*, *S. anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *S. pyogenes*, and *B. fragilis*
- The treatment of adults with complicated intra-abdominal infections caused by *C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *E. faecalis* (vancomycin-susceptible isolates only), *S. aureus* (methicillin-susceptible isolates only), *S. anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *C. perfringens*, and *P. micros*

## Important Safety Information

- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat infections proven or strongly suspected to be caused by susceptible bacteria
- Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening
- TYGACIL is contraindicated in patients with known hypersensitivity to tigecycline
- TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics
- Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL
- The safety and efficacy of TYGACIL in patients with hospital-acquired pneumonia have not been established
- In clinical trials, the most common treatment-emergent adverse events in patients treated with TYGACIL were nausea (29.5%) and vomiting (19.7%)
- **TYGACIL may cause fetal harm when administered to a pregnant woman**
- The safety and effectiveness of TYGACIL in patients below age 18 and lactating women have not been established
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis
- **The use of TYGACIL during tooth development may cause permanent discoloration of the teeth.** TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated

Please see brief summary of Prescribing Information on adjacent page.

Reference: 1. TYGACIL® (tigecycline) Prescribing Information, Wyeth Pharmaceuticals Inc.

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**Tygacil**<sup>®</sup>  
tigecycline IV

Expanded coverage for resistant pathogens