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INSIDE

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Chronically Infected Patients with *Trypanosoma cruzi* Parasitemia: Further Support for Screening

ABSTRACT & COMMENTARY

By Brian Blackburn, MD

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Dr. Blackburn reports no financial relationships relevant to this field of study.

Synopsis: *A cohort of patients seropositive for Chagas disease were tested by PCR and hemoculture for patent* Trypanosoma cruzi *infection. Sixty-three percent had parasitemia, confirming the transmission potential in such persons.*

Source: Leiby DA, et al. *Trypanosoma cruzi* parasitemia in US blood donors with serologic evidence of infection. *J Infect Dis*. 2008;198:609-613.

CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS) IS CAUSED BY infection with the protozoan parasite *Trypanosoma cruzi*, and is spread primarily by triatomine insect vectors ("kissing bugs"). Although vector-borne transmission is primarily confined to rural Latin America, other routes of transmission (eg, blood transfusion) are also possible. Untreated infection seems to persist indefinitely, and the estimated lifetime risk of developing cardiac or other sequelae is about 20%-30%.[1] When combined with increasing migration from Latin America, this long-term infection persistence means there is an increasing risk of blood transfusion-associated T. cruzi transmission in non-endemic areas such as the United States; estimates of the number of infected US immigrants range from tens of thousands to over 100,000.2 Furthermore, some data indicate that the estimated T. cruzi-seropositivity rate among blood donors in Los Angeles rose between 1996 and 1998.[3]

In the United States, the largest contributor to the blood supply (the American Red Cross) began screening blood products for *T. cruzi* in 2007 with an ELISA-based test that had been FDA approved just months earlier.[4] Recent data suggest one in 4,655 donations to be positive by both ELISA and a confirmatory, second immunologic assay

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(data were derived from donors in California and Arizona) for *T. cruzi*.[4] Although hundreds of potentially infective blood products are transfused annually, only five US transfusion-associated cases have been documented to date.[5] This discordance raises the question of whether seropositive persons have patent infection and, thus, the potential to transmit *T. cruzi* to others through blood transfusion, or simply evidence of prior infection.

Leiby et al undertook a study that attempted to confirm that *T. cruzi*-seropositive donors do have persistent, patent infection by identifying 147 persons who had previously been identified as seropositive for *T. cruzi*. Fifty-two (35%) of these 147 persons consented to enrollment, and they were asked to provide both epidemiologic data and blood for analysis by *T. cruzi*-polymerase chain reaction (PCR) and hemoculture testing. Although three samples (drawn six months apart) were requested from all participants, only 17 (33%) of the 52 patients in the study submitted more than a single sample for analysis.

Overall, 33 (63%) of the 52 participants had *T. cruzi* detectable in their blood by PCR; three of the PCR-positive samples were also positive by hemoculture. Of the 11 PCR-positive persons who provided more than one blood sample for testing, eight (73%) were positive on multiple occasions, although most only intermittently (ie, not on every sample tested). Epidemiologic data indicated that 80% were from either Mexico or El Salvador, and the median time since immigration to the United States was 18 years. Eighty-six percent of the cohort reported living in substandard housing during their time in Latin America, and 64% reported seeing triatomine insects at some point in their lives.

■ COMMENTARY

This study supports the notion that untreated patients who are infected with *T. cruzi* probably remain so indefinitely (the patients in the study had immigrated to the United States approximately two decades, on average, before testing), and are at least intermittently parasitemic. Primarily through the use of PCR technology, Leiby et al confirmed that seropositive patients do likely pose some risk of *T. cruzi* transmission through blood transfusion. Almost two-thirds of the patients in the study were parasitemic, and it is also possible that the observed parasitemia prevalence was an underestimate, as suboptimal sensitivity could have occurred (depending on true vs false-negative PCR, and given the difficulties in properly performing hemoculture). Furthermore, most participants provided only one blood specimen (instead of the three requested). Given the intermittent parasitemia that was observed in the PCR-positive patients, the prevalence may have been higher if all patients had provided three samples; during the chronic phase of T. cruzi infection, fluctuating, low-level parasitemia is characteristic.

The data in this paper serve to strengthen the scientific basis for the development of screening programs to prevent transmission of Chagas disease in countries like the United States. With the FDA approval of the ELISA screening test in 2006, and subsequent initiation of the American Red Cross screening program in 2007, such programs are now beginning to appear. While the majority of the blood supply is now tested for *T. cruzi*, universal screening in the United States is not yet a reality. Donor testing also has the potential to lead to prevention of morbidity and mortality in persons who remain undiagnosed and untreated for *T. cruzi*. These findings are also applicable to the solid organ and bone marrow transplant communities, as transmission risk from *T. cruzi*-seropositive donors exist with these procedures as well. ■

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CMV Reactivation/Outcome in Critically Ill Patients

ABSTRACT & COMMENTARY

By Robert Muder, MD
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Dr. Muder does research for Aventis and Pharmacia.

Synopsis: *In a prospective study of immunocompetent patients admitted to critical care units, CMV viremia showed a significant association with prolonged ICU stay and death.*

Source: Limaye AP, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. *JAMA*.2008;300:413-422.

ALTHOUGH REACTIVATION OF CMV HAS SIGNIFICANT adverse consequences for immunocompromised patients, such as those receiving organ transplants, the effect of CMV reactivation in critically ill immunocompetent patients is unclear. Limaye et al prospectively studied immunocompetent adult patients admitted to six burn, trauma, cardiac, and medical intensive care units. Limaye et al collected blood from CMV seropositive patients three times weekly for quantitative CMV assay by PCR. They collected clinical patient data without knowledge of CMV assay results; CMV assays were performed after all clinical and outcome data had been collected. They used a composite endpoint of death or continued hospitalization in the ICU at day 30. In addition to peak level of CMV viremia, Limaye et al also calculated seven-day moving averages of CMV level and CMV area under the curve (analogous to the more familiar antibiotic serum level AUC). In order to account for different lengths of ICU stay as a potential confounding factor, they used a partial proportional odds model for the association of degree of CMV viremia and length of stay at 14-day intervals.

CMV viremia occurred in 33% of patients at a median of 12 days after admission. Twenty percent of patients had viremia level greater than 1000 copies/mL. By logistic regression, there was a significant association between CMV viremia at any level (OR 4.3; 95% CI 1.6-11.9) and > 1000 copies/mL OR13.9; 95% CI 3.2-60) and death or continued hospitalization at 30 days. There was also a significant association with CMV AUC (OR 3.2; 95% CI 2.1-1.3-3.2). In the partial proportional odds models, both CMV seven-day moving average and CMV AUC were independently associated with hospital length of stay.

■ COMMENTARY

CMV reactivation occurs in immunocompetent patients following trauma or severe illness; whether reactivation has adverse consequences, or is merely a marker for severity of illness is not clear. Limaye et al demonstrate a highly significant association between CMV reactivation and prolonged hospitalization and death in these patients. This study has a number of notable strengths which include a prospective design, inclusion of large number of patients with a variety of underlying illness, and blinding of the determination of clinical risk factors and outcome to the results of CMV assays. The association was significant when CMV viremia was measured in a variety of ways, and the results suggest a dose-response effect.

As Limaye et al point out, the association does not prove cause and effect; CMV viremia could be a marker for severity of illness that was not adequately captured by the clinical variables measured. However, an independent adverse effect of CMV reactivation is definitely plausible, and a clinical trial and anti-viral therapy directed against CMV reactivation in critically ill immunocompetent patients is clearly warranted. Initiating anti-viral treatment in immunocompetent patients with CMV reactivation who do not have good evidence of CMV disease is premature based on current evidence. ■

Pregnancy Counseling in HIV

ABSTRACT & COMMENTARY

By Carol A. Kemper, MD
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Dr. Kemper reports no financial relationships relevant to this field of study.

Source: Bridge DA, et al. Abstract, IAC, Mexico City, August 3-8, 2008.

INVESTIGATORS AT A NUMBER OF UNIVERSITY-AFFILIATED HIV clinics around the United States conducted the Living Positively Survey to explore the experiences and attitudes of HIV+ woman toward health care, treatment, pregnancy, and family issues. The telephone-based survey enrolled a total of 700 women, with a mean age of 42.5 years. The women had been HIV+ for a mean of 10.6

years, and had been receiving antiretroviral therapy for an average of 8.1 years, indicating this was a fairly HIV negative experienced and older population of women. Nearly three-fourths were ethnic minorities, including 43% African-Americans. The patients resided all over the United States.

In all, 39% of the woman had children. Since their HIV diagnosis, 22% reported they had been pregnant or were currently pregnant. Of these, 57% did not recall discussing pregnancy and HIV treatment options with their physician, and 41% did not recall discussing how pregnancy might change their HIV therapy. Twenty-nine percent had not discussed side effects or toxicities of medications during pregnancy. About 42% indicated they knew little or nothing about HIV treatment options when they became pregnant.

In addition, 31% of those interviewed indicated they were contemplating pregnancy in the future. Including women who were currently pregnant, or contemplating pregnancy in the future, nearly half did not recall their physician asking if they were interested in having a child now or in the future. Most indicated they would feel comfortable discussing these issues with their physician. The responses were similar across all races/ethnicities.

■ COMMENTARY

While I took issue with some of the rhetoric accompanying this report, it was not surprising that half of the woman interviewed in this telephone survey did not recall discussing pregnancy concerns with their physician. Aside from the fact that people do not always remember instructions or conversations with their physician, other published reports indicate that HIV health care providers discuss safer sex and prevention behaviors with about half of their patients. During 2000-2001, we participated in a CDC-sponsored program investigating safer sex counseling practices in a cross-sectional survey of 839 men and woman attending six California HIV clinics.1 Of these, men and women, 71% reported that a health care provider had at least once discussed safer sex with them within the previous three months (range across clinics varied from 52%-94%), and 50% recalled discussing HIV disclosure with a health care provider (range across clinics, 31%-78%). Physicians were more likely than other providers in the clinic to provide prevention messages to their patients. Clinics that employed a health educator or a risk counselor were more likely to provide safer sex messages than those without. Woman were significantly less likely to receive safer sex messages than men having sex with men (MSM).

Discussions of pregnancy should occur during initial conversations about HIV treatment options, especially in younger female patients of child-bearing age. The teratogenicity of efavirenz, otherwise a popular choice for newly diagnosed persons, is well recognized among HIV health care providers, and at least in our clinic is not administered to woman of child bearing age, especially not without some conversation about pregnancy risk. Pregnancy concerns would also seem to naturally flow from discussions regarding safer sex and prevention. Since about half of the women in this survey were over the age of 42 and 39% already had children, a physician might reasonably assume that pregnancy concerns were not paramount for many of these patients. Our HIV clinic employs a social worker, health educator, and a risk counselor, who make a point of discussing sexual behavior and safe sex at intake to the clinic, and at least annually. Evidence suggests that safe sex messages or interventions, even frequently repeated, do not significantly alter behavior (except perhaps in those who are frequently sexually active with multiple partners).[2]

In our experience, roughly half of the pregnant women in our clinic were found to be HIV+ during prenatal screening. The other half, who know they are HIV+ roughly split evenly into those who intentionally get pregnant and those whose pregnancies are unplanned. There are many reasons why an HIV+ woman may not receive pregnancy counseling before becoming pregnant, chief among them that many providers may not know what to say. While patients are living longer and the risk of HIV transmission during pregnancy is significantly improved with newer and better therapies, the risk of transmission is not negligible, especially in woman with varying compliance and underlying resistance. While I have been increasingly supportive of pregnancy plans in my female patients who have proven themselves compliant, are consistent with their visits, and have improved CD4 counts and undetectable viral loads, this is not always the case. One would imagine that a pregnant woman, in the interest of her child's health, would be more compelled to be adherent, but two recent patients of mine were not (one simply refused to take her medications). And what about those with more advanced disease, with CD4 counts less than 200 cells/mm^3; pregnancy simply seems like a bad idea, or at best should be deferred until the patient is in better health. And yet, I've had women ignore this advice and return pregnant.

Secondly, there remain valid concerns about the effects of pregnancy on the health of the HIV+ mother, as well as the long-term risk of HIV medications on the child, which have not been well characterized, and longer term data is simply not available. HIV+ mothers are at increased risk for complications during pregnancy, as well as premature delivery, especially those who receive protease inhibitors.[3] Insulin resistance, lactic acidosis, and mitochondrial toxicity occur with increased frequency in HIV+ pregnant women, and concerns have been raised about the effects

of antiretrovirals on neonatal bone density. Data on the safety and long-term effects of antiretroviral therapy in pregnant women and their infants is needed but only sporadically captured. Physicians can participate in the HIV Pregnancy Registry, a non-governmental, pharmaceutically-sponsored national database.[4]

Thirdly, many female HIV+ patients have HIV negative partners, making pregnancy essentially an unsafe sex activity. Only recently have some centers been providing artificial insemination for these woman. (Although I recently had a young woman who figured it out herself, using a 3 cc syringe.)

Finally, and at the risk of sounding like an old curmudgeon — social concerns must factor into conversations about pregnancy in these woman, some of whom are undocmented, unmarried, with limited resources, and with little family support, and all of whom are already grappling with their own diagnosis and health, and sometimes the health of their partner or another child with HIV. Some may also have serious alcohol and drug problems, or psychiatric issues that do not preclude them from getting pregnant, but may preclude them from being a good pregnant patient or a capable parent.

Finally, not all women chose pregnancy for "good" reasons; one newly diagnosed unmarried and undocumented 20-year-old woman recently told me she had to get pregnant because her parents (in Mexico) were becoming suspicious there was something wrong with her; others have admitted they wanted their children to be US citizens.

Case in point: a 40-year-old HIV+ patient of mine, whom I have cared for about 10 years. She is undocumented, from Mexico, has an errant partner who provides no support (we've never met him, he's never been HIV tested, and it is not even clear that he knows about her status), and she is completely dependent on her sister. She was first diagnosed with HIV during prenatal screening and, despite reservations, opted for a therapeutic abortion at the time. She has repeatedly refused HIV therapy, and her CD4 count gradually drifted down into the 100s. Just over three years ago, she indicated her desire for a child. Those wishes were supported with the proviso that she takes antiretrovirals during her pregnancy. Her use of medications during pregnancy was sporadic, with frequent elevations in HIV viral load, and she developed resistance to lopinavir. Fortunately, she delivered a beautiful HIV negative boy, who is now 3-years-old (and the joy of his mother). Following delivery, she vanished for about a year and stopped her HIV medications. Like many HIV+ mothers who neglect their own care, she was good about bringing her child for his appointments.

A year ago, I began receiving a series of pregnancy test results for this patient from urgent care and other affiliated clinics. Shortly thereafter, she appeared in the clinic three months pregnant and on no HIV meds. Suspecting I would not be supportive, she actually requested another provider in the clinic. She was reluctant to take medications, and failed to fill her prescriptions for many weeks. Prenatal studies suggested she may be carrying a Downs Syndrome child. Unable to have an amniocentesis, and many tears later, she elected to proceed with the pregnancy (I have to add, against the strong opposition of her sister and my own advice). Her use of medications was again sporadic; by all estimates she took about half of her HIV medications, despite repeated interventions by the HIV pharmacy specialist, pill boxes, and visits by a health educator. Her HIV viral load was repeatedly detectable, at least up until one month before her delivery, when under duress her compliance improved. She delivered another healthy HIV negative baby boy. Three months later, she is exhausted, her sister is ready to kick her out, her CD4 is only 240, and she has once again stopped her medications. She was so overwhelmed at her last visit, she asked if I wanted to take one of the children.

In short, I am not sure how to counsel some of these women about pregnancy, although the issue is addressed with all of my female patients. And, I am empathetic, perhaps too empathetic; I don't know how some of these women make it through the week. And I realize my counsel and concerns for their health (or the health and welfare of their unborn child) may run up against strong personal desires, family expectations, and cultural norms different from my own experience. But I do believe that, while pregnancy is the exclusive privilege of the female sex, it is not a requisite. ■

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Prevention of Influenza: 2008-2009

SPECIAL FEATURE

Synopsis: *The Advisory Committee on Immunization Practices has provided updated recommendations for the influenza season.*

Source: CDC. Prevention and control of influenz: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR*. 2008;579:1-60. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5707a1.htm

THE YEARLY UPDATE OF RECOMMENDATIONS FOR PREvention and control of influenza is available. There have been only few changes from last year. The following focuses on areas of particular interest, including those which seem to generate the most questions. Changes for this year are indicated by their italicization.

Who should be vaccinated?

• All children 6 months to 18 years of age. The inclusion of children age 5 to 18 years is a new recommendaton as is the statement that vaccination of all children 6 months through 4 years of age continue to be a primary focus of vaccination efforts.

• All adults who wish to reduce the risk of becoming ill with influenza and/or wish to avoid transmitting influenza to others.

• In both children and adults, those at high risk of influenza complications or of transmission to vulnerable individuals should be a focus of vaccination programs. This includes those with relevant comorbidities, impending pregnancy during the influenza season, residence in chronic care facilities, health care personnel (CP), household contacts and caregivers of children aged < 5 years (and especially children < 6 months) and adults > 50 years of age.

Which vaccine should be used?

• The 2008--09 trivalent vaccine virus strains are A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens.

• Either trivalent inactivated vaccine (TIV) or live attenuated influenza vaccine (LAIV) can be used when vaccinating healthy persons aged 2--49 years.

• LAIV is licensed for use among nonpregnant persons aged 2--49 years; safety has not been established in persons with underlying medical conditions that confer a higher risk of influenza complications. TIV is licensed for use among persons aged > 6 months, including those who are healthy and those with chronic medical conditions.

• LAIV should not be administered to children aged <5 years with possible reactive airways disease, such as those who have had recurrent wheezing or a recent wheezing episode. Children with possible reactive airways disease, persons at higher risk for influenza complications because of underlying medical conditions, children aged 6--23 months, and persons aged >49 years should receive TIV.

• Healthy HCP and persons aged 2--49 years who are contacts of persons in these groups and who are not contacts of severely immunosuppressed persons should receive either LAIV or TIV when indicated or requested. All other persons, including pregnant women, should receive TIV.

• TIV is preferred for vaccinating household members, HCP, and others who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) during those periods in which the immunosuppressed person requires care in a protective environment (typically defined as a specialized patient-care area with a positive airflow relative to the corridor, high-efficiency particulate air filtration, and frequent air changes).

Is there a danger of viral shedding from LAIV recipients?

• Available data indicate that both children and adults vaccinated with LAIV can shed vaccine viruses after vaccination, although in lower amounts than occur typically with shedding of wild-type influenza viruses. In rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons. However, serious illnesses have not been reported among unvaccinated persons who have been infected inadvertently with vaccine viruses.

Table 2

Influenza Vaccination Recommendations 2008: Adults

Annual recommendations for adults have not changed. Annual vaccination against influenza is recommended for any adult who wants to reduce the risk for becoming ill with influenza or of transmitting it to others. Vaccination also is recommended for all adults in the following groups because these persons are either at high risk for influenza complications or are close contacts of persons at higher risk:

• persons aged ≥ 50 years;

• women who will be pregnant during the influenza season;

• persons who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes mellitus);

• persons who have immunosuppression (including immunosuppression caused by medications or by human immunodefiiciency virus);

• persons who have any condition (eg, cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration;

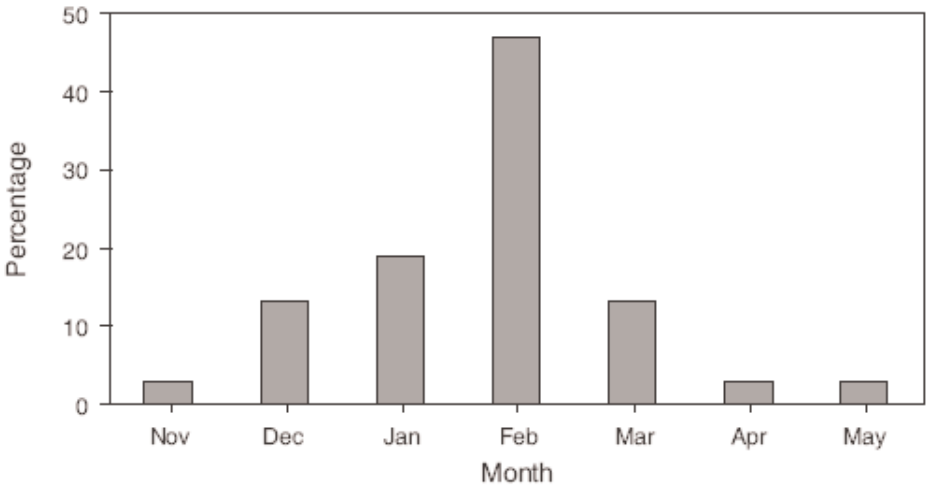
• residents of nursing homes and other chronic-care facilities;

• health care personnel;

• household contacts and caregivers of children aged < 5 and adults aged ≥ 50 years, with particular emphasis on vaccinating contacts of children aged > 6 months; and

• household contacts and caregivers of persons with medical conditions that put them at high risk for severe complications from influenza.

FIGURE 1. Peak influenza activity, by month — United States, 1976–77 through 2007–08 influenza seasons



What should be done if a health care worker has received LAIV?

• As a precautionary measure, HCP who receive LAIV should avoid providing care for severely immunosuppressed patients for 7 days after vaccination.

What about hospital visitors who have received LAIV?

• Hospital visitors who have received LAIV should avoid contact with severely immunosuppressed persons in protected environments for 7 days after vaccination but should not be restricted from visiting less severely immunosuppressed patients.

What is recommended regarding vaccination and health care personnel?

• All HCP, as well as those in training for health-care professions, should be vaccinated annually against influenza (TIV is preferred). Persons working in health-care settings who should be vaccinated include physicians, nurses, and other workers in both hospital and outpatient-care settings, medical emergency-response workers (e.g., paramedics and emergency medical technicians), employees of nursing home and chronic-care facilities who have contact with patients or residents, and students in these professions who will have contact with patients.

• Health-care administrators should consider the level of vaccination coverage among HCP to be one measure of a patient safety quality program and consider obtaining signed declinations from personnel who decline influenza vaccination for reasons other than medical contraindications. Influenza vaccination rates among HCP within facilities should be regularly measured and reported, and ward-, unit-, and specialty-specific coverage rates should be provided to staff and administration.

• The Infectious Diseases Society of America has recommended mandatory vaccination for HCP, with a provision for declination of vaccination for religious or medical reasons. ■

Pharmacokinetics of Antimicrobials in Patients with Burn Wounds

ABSTRACT & COMMENTARY

By Catherine J. Hill, PharmD, Jessica C. Song, MA, PharmD

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Catherine Hill and Jessica Song report no financial relationships relevant to this field of study.

PATIENTS WITH BURN INJURIES ARE AT HIGH RISK FOR major infections, given their impaired humoral and cellular immunity. Moreover, this patient population displays numerous physiologic alterations affecting organ function and drug metabolism. Pathological changes that occur after burn injury can be divided into two phases; the acute phase and the hypermetabolic phase.[1-4] The acute phase occurs within the first 48 hours after thermal injury. During this phase, loss of protein rich fluid occurs as a result of increased capillary permeability.[1,2] A decrease in cardiac output occurs as a result of hypovolemia, and this causes a

decrease in oxygen delivery as well as a decrease in glomerular filtration rate (GFR).[1,3,4] The hypermetabolic phase occurs more than 48 hours after thermal injury, assuming that adequate fluid replacement occurs. A doubling of the metabolic rate occurs gradually over several days and results in an increase in oxygen consumption, heat production, protein catabolism, and blood flow.[2] Increasing blood flow culminates in an increase in GFR and liver blood flow, which affect clearance of numerous medications.[1,3,4]

The purpose of this review is to discuss the pharmacokinetic alterations of various antimicrobials likely to be used by burn patients that have been reported in the medical literature. In addition, dosing and level monitoring recommendations for vancomycin, gentamicin, and colistin will be highlighted in this review.

Pharmacokinetics

Therapeutic drug monitoring in burn patients relies on plasma drug concentrations, volume of distribution (Vd), absorption, metabolism, clearance (total, renal, non-renal), and half-life in order to predict the dosage necessary to produce maximum efficacy and minimal toxicity. Unfortunately, the altered physiologic state of burn patients, along with inter-individual variations in this population, cause the relevant pharmacokinetic parameters to change significantly.[1]

There is no one single factor that solely influences the pharmacokinetics of antimicrobial agents. Factors such as the size and depth of the burn, presence of sepsis, time since burn injury, as well as the age, serum protein level, and fluid status of the patient, can influence the pharmacokinetics of antimicrobial agents.[1]

Absorption of medication is affected in burn patients as a result of the change in blood flow, intestinal permeability,[2] and dermal injury.[3] Medications administered subcutaneously or intramuscularly during the acute phase display decreased extent of absorption, whereas increased absorption may be observed with percutaneous and oral administration of medications.[3]

The distribution of a medication depends on its chemical/pharmacokinetic properties, such as water solubility and protein binding. During the hypermetabolic phase, patients exhibit lower albumin levels and increased α-1 acid glycoprotein levels.[1-4] Consequently, the extent of protein binding can be decreased for certain drugs, but increased with other medications. In general, an inverse relationship exists between the degree of protein binding and the fraction of free drug available to the tissues. Alterations in the fraction of free drug can result in significant changes in the dose of drug required to produce the same effect.

The Vd represents a key parameter in determining the loading dose of drugs that require rapid administration to achieve target unbound concentrations.[2] Changes in protein binding, free fraction of drug, and fluid/electrolyte status can lead to significant changes in Vd.

During the hypermetabolic phase, phase II metabolism (conjugation of medications) appears to be unaffected, whereas phase I metabolism (metabolism by cytochrome P450 enzymes) may be decreased.[3,4] The effect of the change in metabolism may be offset by the increase in the hepatic blood flow to the liver.

Burn patients display increased elimination of medications as a direct consequence of increased clearance, both renal and non-renal. During the hypermetabolic phase, ele-vated GFRs allow for enhanced drug delivery to the kidneys.[2-4] The changes in drug delivery and possible increases in free drug can cause more of the drug to be cleared from the kidney. Moreover, increased non-renal clearance may be attributed to the loss of drug through wounds.[3]

Changes in Vd and clearance ultimately effect the half-life of the drug.[2] Changes in half-life may necessitate a change in dosing frequency in order to maintain therapeutic concentrations.

Dosing of Antimicrobial

There is limited data regarding the pharmacokinetics of different antimicrobial agents in patients who have suffered a burn injury. Developing optimal antimicrobial therapeutic regimens for burn patients can pose a tremendous challenge to practitioners, given that the degree and type of burn injury varies with each patient. The published studies and case reports generally included 10 or fewer patients, and included patients with widely varying total body surface areas covered by the burns. Because of the numerous variables influencing the pharmacokinetics of antimicrobials in burn patients, individualization of antimicrobial therapy is critical for this patient population. *Table 1* summarizes the most relevant case reports, studies, reviews, and recommendations for dosing modifications.[2-10]

Aminoglycosides represent the best studied antimicrobials in the setting of burn injuries. One study conducted by Zaske et al demonstrated the need for higher doses of gentamicin. Patients in this study required doses of 7.4-11.2 mg/kg/d of gentamicin compared to 3-5 mg/kg/d in non-burn patients.[1,11] Increased mortality rates have been shown to be associated with gram negative septicemia,[1] and rapid attainment of therapeutic aminoglycoside levels has been shown to improve outcomes.[11] Weinbren proposed using a loading dose of 5 mg/kg of gentamicin and monitoring the peak level after the first dose, followed by a second level seven hours later.[1] A seven-hour

Table 1

Pharmacokinetic Changes Effect on Antimicrobials[2-10]

Medication	Time after burn injury	Volume of Distribution	Clearance	Renal Clearance	Non-renal Clearance	Half life	Dose Adjustment
Aztreonam	5-9 days	↑	no change	no change			Yes
Ceftazidime	2-21 days	↑	↑	no change	↑	↑	Yes
Cefepime	2-14 days	↑	↑				Adjust based on CrCl
Imipenem	5-25 days	no change	no change			no change	Adjust based on CrCl
Piperacillin	6-21 days	↑	↑			↑	Unknown
Ticarcillin	not reported	↑	↑	↑	↑	no change	Yes
Piperacillin-Tazobactam	7-21 days	↑		no change			Use high dose (4.5g Q 6-8 hrs.)
Ticarcillin-Sulbactam	not reported	↑					Use high dose (5.2g Q 8-12 hrs.)
Amikacin	6-38 days	no change				—	Yes
Gentamicin	not reported	no change	↑			—	Yes
Tobramycin	4-35 days	no change	↑			↓	Yes
Vancomycin	12-199 days	↑	↑	↑	no change	↓	Yes
Daptomycin	not reported		↑				Yes (10-12 mg/kg/d)
Ciprofloxacin	3-5 days	↑	↑	↑	no change	no change	No
Enoxacin	not reported	↓					Unknown
Levofloxacin	not reported	↓*	↑				High dose (750 mg Qday)
Fluconazole	3-4 days	↓*	↑			↓*	Adjust based on CrCl

* Not statistically significant

level below 1 μ/mL allowed for a repeat dose of 5 mg/kg; a level in excess of 1 μg/mL delayed the administration of a repeat 5 mg/kg dose until the level dropped below 1 μg/mL.[1]

Vancomycin levels may be decreased in patients with burn injuries. This phenomenon occurs as a result of increased drug clearance and shortened half life.[4] Garrelts and Peterie reported that achievement of therapeutic Vancomycin concentrations required a dose increase of 78%.[2] Total daily doses of vancomycin have ranged between 2-6 g/day, and may be divided in 6-8 hour dosing intervals.[1,11] Continuous infusion of vancomycin has been suggested to maintain appropriate drug levels. However, while this regimen has been shown to be safe, it does not result in improved achievement rates of therapeutic levels over intermittent dosing.[1] Therapeutic level monitoring of vancomycin will guide the necessity of an increase in dosage.

Clearance of beta-lactams is increased in burn patients.[2] Routine level monitoring of this class of drugs does not occur in clinical practice and, as a result, dose adjustment of β-lactams should be based on the patient's response to treatment. Maximum doses should be used to compensate for increased drug clearance. Patients with impaired renal function should be dosed based on their creatinine clearances for those medications requiring renal dose adjustment.

At present, no pharmacokinetic studies of colistin in burn patients have been reported in the medical literature. However, since colistin undergoes renal elimination, a higher dose of colistin may be needed. David and Gill

reported a case of potential subtherapeutic dosing of colistin in a patient with resistant Acinetobacter.[12] The authors hypothesized that resistance to colistin developed as a result of subtherapeutic drug levels secondary to the increased clearance of colistin. The report concluded with the recommendation of checking colistin levels three to five days after the start of therapy, aiming for a peak level (drawn 30 minutes after infusion) of 10-15 mg/L.[12]

Conclusion

As a population, burn patients exhibit large inter- and intra-patient variability. As a result, the pharmacokinetics, as well as dose requirements of antimicrobials may be ever changing. Therapeutic drug monitoring helps to individualize therapy to the patient, as well as accommodate the patient's changing status. Aminoglycosides and vancomycin levels are commonly monitored; monitoring of colistin levels can be of benefit to patients with burn injury. ■

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CME Questions

1. Which of the following is correct?

a. Chagas disease is caused by *Trypanosoma brucei.*
b. Chagas disease is transmitted by mosquitoes.
c. Chagas disease can be transmitted by blood;
d. All blood banks in the United States currently screen for Chagas disease.

2. Which of the following is correct with regard to ICU patients without known severe immunocompromise?

a. Detection of CMV viremia is an unequivocal indication for initiation of therapy with gancilcovir.
b. The finding that CMV viremia occurs in one-third of patients indicates that all ICU patients should receive antiviral prophylaxis.
c. The detection of CMV viremia is an indication of the presence of end organ disease in all.
d. There is an associate between detection of CMV viremia and increased risk of death.

3. Which of the following is correct?

a. During the hypermetabolic phase of burn injury, metabolism by cytochrome P450 enzymes is increased.
b. During the hypermetabolic phase of burn injury, blood flow to the liver is increased.
c. In burn patients, the clearance of antibiotics is significantly decreased.
d. During the acute phase of burn injury, serum albumin levels are increased.

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Coverage of Australian Conference

UPDATES

By Carol A. Kemper, MD, FACP

Tamiflu-Resistant Influenza A Increasing

ProMED-mail post, September 5, 2008; www.promedmail.org

RESISTANCE TO OSELTAMIVIR (tamiflu^{R}) has increased in Influenza A isolates around the world at an alarming rate. Levels of resistance now range from 13% in Chile to 100% (10 of 10 isolates) in Australia. Oseltamivir-resistant strains were initially recognized in Norway, and previously occurred with less than 1% frequency. As reported in *Infectious Disease Alert* in April 2008, the level of resistance to oseltamivir in 437 isolates of Influenza A/H1N1 identified in 10 European countries from November 2007-January 2008 was 14%. All of the isolates carried the same amino acid substitution (H274Y) of the neuraminidase, which is known to cause high level oseltamivir resistance. At that time, the oseltamivir-resistant strains remained sensitive to zanamivir (Relenza) and amantadine/rimantidine.

Recent reports document the death of a 67-year-old man due to oseltamivir-resistant Influenza A. He was receiving treatment for chronic lymphocytic leukemia, but remained stable. He presented with bilateral pneumonia and rapidly deteriorated, requiring ventilatory support. Respiratory specimens were positive for Influenza A/H1N1, and he was started on oseltamivir on the sixth hospital day. Despite this, he developed progressive respiratory failure and ultimately succumbed to his illness. Remarkably, by the 13th day of his hospitalization, the laboratory reported sequencing results confirming the H274Y mutation. His isolate was also resistant to amantadine. He had no known contact with any person with influenza.

Studies suggest that the transmission of this strain is not correlated with treatment with oseltamivir; the strain seems to be appearing in countries where use of this agent is not frequent, suggesting that selective pressure is not responsible for circulation of this strain. Even more puzzling are reports that this mutation may diminish the replicative capacity of the organism, making it less virulent, although this is controversial. Obviously, this infection proved fatal for this modestly immunosuppressed man.

Clinicians in the United States should be aware that this strain is now being reported from the United States and Canada, and that oseltamivir may not be effective. Persons with serious respiratory or influenza-like illness should be tested for influenza using newer, rapid screening EIA techniques. Cultures of respiratory secretions are essential for epidemiologic purposes, and your public health department can assist in identifying isolates.

Utility of Newer TB Blood Tests

Pai M, et al. Systematic review: T-cell-based assay for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med*. 2008; 149:177-184.

NEWER GAMMA-INTERFERON-BASED assays for detection of an immune system response to latent infection from *M. tuberculosis* (LTBI) have many potential benefits over standard tuberculin skin testing (TST). Such assays eliminate the need for two-step skin testing, decreasing personnel time and office visits. In addition, these assays do not cross-react with BCG vaccination, giving them an advantage over TST in BCG vaccinated populations. One of these products, the Quantiferon-TB Gold assay (Cellestis, Victoria, Australia), has been approved by the FDA, and is already being utilized for screening of health care workers. Cellestis also makes a second gamma-interferon-based assay called the QuantiFERON-TB Gold In-Tube test. Another gamma-interferon-based assay, previously available only in Europe, now approved for use in the United States is the T-SPOT.TB test (Oxford Immunotec, Oxford, United Kingdom).

Differences between these assays were discussed in an accompanying editorial.[1] The QuantiFERON-TB Gold assay uses whole blood cells, with an undetermined number of white blood cells, and provides quantitation of the total amount of interferon-gamma produced in the supernatant. The T-SPOT.TB test utilizes peripheral blood mononuclear cells and provides quantitation of the level of interferon-gamma produced per PBMC. Both assays can be processed within one day, although the first is somewhat less complicated to perform in the lab. There is no potential for boosting with either assay. Both assays make use of an internal positive control, with a sample well containing a potent nonspecific stimulator of interferon-gamma production. Thus, the failure of the positive control in these assays provides information about the ability of the test subject's T cell function.

Pai et al compared the sensitivity and specificity of the three assays for detection of TB infection based on a meta-analysis of data reported from 38 published studies. To assess the relative specificity of the assays, the study sample had to comprise healthy, low-risk persons without known exposure to TB. To assess the sensitivity of the assays, the data had to be based on individuals with confirmed active tuberculosis. The data was extracted by one of the investigators, and confirmed separately by a second.

The pooled specificity of both QuantiFERON-TB assays was 99% for non-BCG-vaccinated subjects and 96% for BCG vaccine recipients. The pooled specificity of the T-SPOT.TB test was slightly lower at 93%. The specificity of all three assays compared favorably with TST, which also had a high specificity (97%) in non BCG-vaccinated patients; but provided variable and poorer results in BCG recipients. Hence, the risk of false-positives with any of the newer assays is low, and compares favorably with TST, which still provides excellent specificity in most patients, except those who have received BCG.

The sensitivity of the three assays was more variable: pooled sensitivities for the QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube assays were 78% (95% CI, 73% to 82%) and 70% (CI, 63% to 78%), respectively. In contrast, the pooled specificity of the T-SPOT.TB test was 90% (95% CI, 86% to 93%).

Any of these assays, including standard TST, provide variable sensitivity, depending on the population tested, and whether screening for LTBI or active TB infection. All three gamma-interferon-based assays and TST have diminished sensitivity in persons with immune system suppression, especially those with T cell dysfunction. For example, the utility of the QuantiFERON-Gold assay was evaluated in 242 persons with suspected active TB at the San Francisco Public Health Department, 45 of whom were diagnosed with active TB (82% culture-confirmed).[2] QuantiFERON-Gold results were positive in 55%, negative in 38%, and indeterminate in 7%, providing a sensitivity of 60% for this group, with a negative predictive value of 86%. Patients with extra-pulmonary disease were more likely to have falsely-negative results compared with those with pulmonary disease (35% vs 4%, $p < .05$). QuantiFERON-Gold results were positive in only one of three HIV-infected patients with active TB.

Thus, the interferon-based assays are highly specific for detection of LTBI, irrespective of prior BCG vaccination. In immune-competent persons, all three assays are sensitive for the detection of LTBI, and somewhat less sensitive for detection of active TB, although various studies suggest the T-SPOT.TB test may have slightly greater sensitivity. The tests perform differently in patients with cellular immune suppression where, again, the T-SPOT.TB may be somewhat more sensitive. Clinicians should be mindful that a negative interferon-gamma assay does not rule-out a diagnosis of TB, similar to our experience with skin testing.

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Ebola Vaccination of Great Apes

Dolgin E. Baiting Ebola. *The Scientist*. 2008;22:22.

Scientists and primate biologists have teamed up in Leipzig, Germany, to create a novel vaccine delivery system for delivering a newly developed live-attenuated Ebola vaccine to chimps and gorillas. Ebola is just as deadly for apes and humans, and in 2006, is estimated to have claimed the lives of approximately 5,000 gorillas in a 2,700 square meter area in central Africa.

The most effective Ebola vaccine for apes is a live-attenuated vaccine — if it can be appropriately delivered to the animals. Hypodermic darts are only effective if you can actually find the animals, and using bait risks wasting much of the vaccine on the forest floor. What you really need is some way of getting the animals to eat every last drop of the vaccine, absorbing the virus through cheek epithelial cells where it can quickly stimulate a vigorous immune system response.

But how to deliver a 6 cm. slug of vaccine-impregnated bait to a chimp? Candy! Like children, chimps and other apes love sweets. The scientists set out to perform an (non-randomized) experiment with paraffin-coated bait (to withstand the tropical heat) at the Leipzig zoo. The test baits (sans vaccine) were colored red, yellow, or orange, and flavored with banana, mango, or fig. One gorilla quickly ate all of the baits at once, with no apparent preference. But the chimps went crazy for the mango-flavored baits, which seemed to be a consistent hit.

The next step is to test the sample baits in the wild. There is some concern that placement of the baits is key — lest other forest creatures like rodents sample the baits before the apes get a chance to find them. The stability of the attenuated virus is also a concern, especially if the product does not end up in the right hands and mouths. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Gender Differences with Anticoagulation Discontinuation

In this issue: Some women with DVT may stop warfarin after six months; Vytorin and cancer; preventing recurrent stroke; and FDA news.

When is it safe to stop anticoagulation after an unprovoked venous thromboembolism? A new study suggests that women with minimal risk factors may safely stop anticoagulation after 6 months of therapy, although the same may not be true for men. Canadian researchers randomized 646 patients with a first, unprovoked major venous thromboembolism and followed them for 4 years. Data were collected for 69 potential predictors of recurrent venous thromboembolism while patients were taking oral anticoagulants and a multi-variable analysis of predictor variables was performed. Men had a 13.7% annual risk of recurrence after discontinuing oral anticoagulation and there was no combination of clinical predictors that could identify a low-risk subgroup of men. In women, 52% had zero or one of the following risk factors: hyperpigmentation, edema or redness of either leg, d-dimer ≥ 250 mcg/L while taking warfarin, body mass index ≥ 30 kg/m^2, or age ≥ 65 years. These women had an annual risk of recurrent thromboembolism of 1.6% (95% CI, 0.3% to 4.6%). Women who had two or more of these risk factors had an annual risk of 14.1%. The authors conclude that women with zero or one risk factor may safely discontinue oral anticoagulant therapy after 6 months of therapy following their first unprovoked venous thromboembolism; however, this conclusion does not apply to men (*CMAJ* 2008;179:417-426). An accompanying editorial points out that patients with the first episode of unprovoked venous thromboembolism have a high rate of recurrence if they stop anticoagulation therapy — about 10% in the first year. Current guidelines from the American College of Chest Physicians recommend lifetime therapy for patients with a first episode of proximal deep venous thrombosis or pulmonary embolism provided that good anticoagulant monitoring is achievable and indefinite treatment is consistent with patient preferences. This study identifies a large group of women who may safely stop anticoagulation after 6 months although the authors do recommend further validation (*CMAJ* 2008; 179:401-402).

FDA Announces Vytorin Investigation

The news keeps getting worse for Merck/Schering-Plough, the distributor of Vytorin®: The FDA has announced that it will investigate a report from the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) of the possible association between the use of Vytorin and increased incidence of cancer. The SEAS trial was designed to see if Vytorin, a combination of simvastatin and ezetimibe, would reduce cardiovascular events in patients with aortic stenosis. In a July press

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release, the company reported on preliminary data which showed that the trial did not show benefit for the primary endpoint of aortic-valve related major cardiovascular events, but did show that a larger percent of subjects treated with Vytorin were diagnosed with, and died from, all types of cancer compared to placebo during the 5-year study. There was improvement in the secondary endpoint of ischemic events (15.7% vs 20%) but no benefit in other secondary endpoints. The number of cancers was 105 (11.1%) in the Vytorin group vs 70 (7.5%) in the control group (P = 0.01), and the number of cancer deaths was 39 (4.1%) in the Vytorin group vs 23 (2.5%) in the control group (HR 1.67; 95% CI, 1.00 to 2.79; P = 0.05). The FDA is also looking at interim data from two large ongoing trials of Vytorin, the Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) which, so far, have not shown an increased risk of cancer associated with Vytorin. The SHARP trial should be completed in 2010, while the IMPROVE-IT trial should be finished in 2012. Initial data from the SEAS trial were presented in the recent news conference; full results were published at www.nejm.org (DOI: 10.1056/NEJMao0804602) on Sept. 2, 2008. The FDA says its investigation will take at least 6 months from the date of publication.

PRoFESS Trial Shows No Stroke Benefit

The recently published PRoFESS trial failed to show benefit of two strategies for preventing recurrent strokes. In the first arm of the study, the angiotensin-receptor blocker (ARB) telmisartan was compared to placebo in more than 20,000 patients with ischemic stroke. Patients were randomized to telmisartan 80 mg daily or placebo and followed for a mean follow-up of 2.5 years. Mean blood pressure was 3.8/2.0 mmHg lower in the telmisartan group; however, there was no difference in the rate of recurrent stroke (8.7% telmisartan vs 9.2% placebo [HR 0.95; 95% CI, 0.87 to 1.01; P = 0.11). The rate of new onset diabetes was 1.7% in the treatment group and 2.1% in the placebo group (P = 0.10). The authors conclude that therapy with telmisartan initiated soon after an ischemic stroke did not significantly lower the rate of recurrent stroke, diabetes, or major cardiovascular events. The second wing of the study compared aspirin plus 200 mg of extended release dipyridamole (Persantine®) twice daily vs clopidogrel (Plavix®) 75 mg daily in the same patient group. After a mean of 2.5 years of follow-up recurrent stroke occurred in 9% of patients receiving aspirin and dipyridamole and 8.8% of patients receiving clopidogrel (HR 1.01; 95% CI, 0.92 to 1.11). The secondary outcomes of stroke, myocardial infarction, or death from vascular causes occurred in 13.1% of both groups. The authors conclude that there is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke (*N Engl J Med*, published on-line at www.NEJM.org, Aug. 27, 2008).

FDA Actions

The FDA has issued a warning regarding the use of simvastatin in patients who are taking amiodarone. More than 20 mg of simvastatin plus amiodarone puts patient at higher risk for rhabdomyolysis since amiodarone inhibits CYP 3A4, one of the enzymes that metabolizes simvastatin. The simvastatin labeling has contained a warning regarding concomitant use with amiodarone since 2002; however, the FDA continues to receive reports of rhabdomyolysis associated with use of the two drugs. Physicians are also urged to tell their patients to report any unexplained muscle pain, tenderness, or weakness while taking the drugs. Other risks for rhabdomyolysis associated with statins include advanced age, uncontrolled hypothyroidism, and renal impairment.

There should be plenty of flu vaccine this fall. The FDA has announced the approval of six manufactures including GlaxoSmithKline, ID Biomedical, MedImmune, Novartis, Sanofi Pasteur, and CSL Limited. The vaccine will again be a trivalent vaccine comprised of two influenza A viruses and one influenza B virus. All three strains are new this year, an unusual occurrence as usually only one or two strains are updated each year.

The FDA issued an alert in October 2007 regarding exenatide (Byetta®) and the risk of acute pancreatitis. Since then, 6 more cases of hemorrhagic or necrotizing pancreatitis have been reported to the FDA associated with use of the drug, including two deaths. Exenatide is an injectable incretin mimetic used to treat type 2 diabetes. The FDA is recommending that exenatide should be stopped immediately if pancreatitis is suspected. Currently there is no patient profile which would predict increased risk of pancreatitis. Amylin Pharmaceuticals, the manufacture of exenatide, is working with the FDA on new labeling regarding the risk of hemorrhagic or necrotizing pancreatitis. ■