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INSIDE

Financial Disclosure:

Infectious Disease Alert's Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study. Updates author Carol A. Kemper, MD, FACP, reports no financial relationship relevant to this field of study.

A New Rotavirus Vaccine

ABSTRACTS & COMMENTARY

By Hal B. Jenson, MD, FAAP

Chair, Department of Pediatrics; Director, Center for Pediatric Research, Eastern Virginia Medical School and Children's Hospital of the King's Daughter

Dr. Jenson is on the speaker's bureau for Merck.

Synopsis: *In these 2 studies, the safety and efficacy of 2 new, different formulations of liquid oral rotavirus vaccines were studied in young infants. Both vaccines were highly efficacious in preventing rotavirus disease, especially severe disease. Neither vaccine was associated with an increased risk of intussusception or other severe adverse events. RotaTeq, one of the 2 vaccines studied, was approved by the FDA in February for young infants.*

Sources: Ruiz-Palacios GM, et al. Safety and Efficacy of an Attenuated Vaccine Against Severe Rotavirus Gastroenteritis. *N Engl J Med*. 2006;354:11-22; Vesikari T, et al. Safety and Efficacy of a Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine. *N Engl J Med*. 2006;354:23-33.

OVER 63,000 HEALTHY INFANTS FROM 11 LATIN AMERICAN countries and Finland were randomized to receive either 2 oral doses of a live, attenuated human rotavirus vaccine or placebo at 2 and 4 months of age. The vaccine, developed by GlaxoSmithKline and planned to be marketed as Rotarix, contained 106.5 median cell-culture infective doses of the RIX4414 vaccine strain of G1P[8] specificity. Vaccination was 85% efficacious against severe rotavirus gastroenteritis and rotavirus-associated hospitalization ($P < 0.001$), and was almost 100% against the most severe disease. Hospitalization was reduced by 42% (95% CI, 29-53%; $P < 0.001$). Intussusception occurred in 6 vaccine recipients and 7 placebo recipients within 31 days.

VOLUME 25 • NUMBER 12 • SEPTEMBER 2006 • PAGES 133-144

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Over 68,000 healthy infants 6-12 weeks of age from the United States and other countries were randomized to receive either 3 oral doses of live, pentavalent human-bovine (WC3 strain) reassortant rotavirus vaccine containing human serotypes G1, G2, G3, G4, and P[8] or placebo at 4-10 wk intervals in a blinded study. This vaccine was developed by Merck and licensed in February as RotaTeq. Vaccination reduced hospitalization and emergency department visits related to G1-G4 rotavirus gastroenteritis occurring > 14 days after the third dose by 94.5% (95% CI, 91.2-96.6%). In the first full rotavirus season after vaccination, efficacy against severe rotavirus gastroenteritis was 98% (95.0% CI, 88.3-100%), and efficacy against any rotavirus gastroenteritis was 74.0% (95% CI, 66.8-79.9%). Clinic visits related to G1-G4 rotavirus gastroenteritis were reduced by 86.0% (95% CI, 73.9-92.5%). Intussusception occurred in 12 vaccine recipients and 15 placebo recipients within 1 year after the first dose, including 6 vaccine recipients and 5 placebo recipients within 42 days of any dose (relative risk, 1.6; 95% CI, 0.4-6.4).

COMMENTARY

Rotavirus is the leading cause of severe diarrhea-related illness and death in infants and young children in the United States and worldwide. Every year, rotavirus infection is associated with an estimated 55,000 hospitalizations in the United States and 2 million worldwide. Death from rotavirus is rare in the United States, but in developing countries, rotavirus gastroenteritis has been estimated to cause up to 600,000 deaths annually in children younger than 5 years of age. A safe, effective, and affordable vaccine is a priority for developing countries, where the disease burden is highest.

In 1998, a tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV) was licensed as RotaShield and recommended for routine immunization of infants in the United States. It was withdrawn in October 1999 because of the association with intussusception, which occurred at an increased rate during the 3-14 days after the first dose and 3-7 days after the second dose. The attributable risk for intussusception with the RRV-TV rotavirus vaccine was estimated at approximately 1 per 10,000 vaccine recipients.

Each of these studies were designed and powered to evaluate the safety of these new vaccines with respect to intussusception by including a large sample size sufficient to detect intussusception at the rate that occurred with RRV-TV. Although neither of the new vaccines were associated with intussusception, the safety of the licensed vaccine will be monitored also in a post-licensure study of approximately 44,000 children. The Centers for Disease Control and Prevention (CDC) also evaluates vaccine safety in approximately 80,000 infants every year as part of the Vaccine Safety Datalink Program. In addition, the manufacturer is required to report cases of intussusception and all serious and unexpected adverse events to the FDA within 15 days of receiving notice, and to report all other adverse effects on a monthly basis.

The Advisory Committee on Immunization Practices (ACIP) has already recommended the vaccine for infants in a dosage regimen of 3 oral doses at 2, 4, and 6 months of age. The first dose should be administered by 12 weeks of age, with all 3 doses of vaccine by 32 weeks of age. These age guidelines reflect the design of the safety and efficacy study. There are insufficient data on safety and efficacy outside of these age ranges. The ACIP recommendations will become formal CDC recommendations as soon as they are published in the *Morbidity and Mortality Weekly Report*. ■

Infectious Disease Alert, ISSN 0739-7348, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

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MANAGING EDITOR: Leslie Hamlin.

GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Infectious Disease Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Update on Quinolone-Induced Changes in Glycemic Control

SPECIAL FEATURE

By Thao Tran, Jocelyn Walton, Christine Maddox, and Jessica C. Song

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Thao Tran, Jocelyn Walton, and Jessica C. Song report no financial relationships relevant to this field of study.

WITHIN THE PAST FEW MONTHS, GATIFLOXACIN (Tequin®) has received some attention in the medical community due to reports of serious hypoglycemia and hyperglycemia.[1] Gatifloxacin is an 8-methoxyfluoroquinolone that exhibits in vitro activity against numerous Gram-positive and Gram-negative aerobes, as well as anaerobes and some atypical organisms.[2] To date, over 20 published cases of dysglycemia (hypoglycemia or hyperglycemia) have been reported with gatifloxacin.[3] Because of these events, Bristol-Myers Squibb has ceased production of this antibiotic.[4] A few months prior to its discontinuation, the prescribing information added a new contraindication in patients with diabetes mellitus, as well as updated warnings and precautions to identify other risk factors for dysglycemia, such as concomitant antidiabetic medications, renal insufficiency, and older age.[5]

Pathophysiology for Quinolone-Induced Dysglycemia

While gatifloxacin is known to cause both hypoglycemia and hyperglycemia, hypoglycemic events appear to be more commonly associated with use of this agent.[6-10] Much of the available evidence explaining the pathophysiology of gatifloxacin-induced hypoglycemia has been extrapolated from in vitro studies performed on mouse pancreatic islet cells.[6] Chimeric pancreatic islets were isolated and placed in buffers containing different concentrations of glucose, as well as one of the following quinolones: gatifloxacin, levofloxacin, or temafloxacin. KATP (adenosine triphosphate-sensitive potassium channel) currents regulating insulin secretion were recorded. Inhibitory effects on these ATP-dependent K+ channels depolarize pancreatic cells, which allow for the opening of voltage-gated calcium channels. The entrance of calcium into the cell promotes insulin secretion, leading to the adverse side effects associated with hypoglycemia.[6,7]

The 3 tested quinolones exhibited varying degrees of effects on insulin release. Astunori and colleagues observed that gatifloxacin and temafloxacin stimulated insulin secretion, whereas levofloxacin caused no significant effects. Increasing doses of gatifloxacin also increased insulin secretion, thereby suggesting a dose- dependent augmentation of insulin secretion.[6]

The exact pathogenesis of gatifloxacin-associated hyperglycemia has yet to be fully elucidated, but it is hypothesized that it may trigger the vacuolation of pancreatic beta cells, which decreases insulin levels.[7] Of note, a recently published case report highlighted the development of diabetes after gatifloxacin therapy.[10] A 57-year-old man developed new-onset diabetes 3 weeks after receiving a 10-day course of gatifloxacin. His fasting blood glucose concentrations from the previous years ranged from 103 to 116 mg/dL. Bhasin and colleagues noted a temporal relationship between the administration of gatifloxacin and the onset of diabetes, as the patient's blood glucose concentration was 992 mg/dL within 3 weeks of completing gatifloxacin therapy. In addition, Bhasin et al stated that the usual onset of type 2 diabetes is a more gradual process than the one displayed by their patient.

Hypoglycemia Associated with Gatifloxacin and Other Quinolones

Although the incidence of serious dysglycemia during gatifloxacin therapy is rare, the possibility of life-threatening effects on the central nervous system raises concern.[9] The updated product labeling (prior to discontinuation) warned of decreased serum glucose usually occurring within 3 days of initiating the medication, while hyperglycemia was noted to occur after the third day of administration.[2,7] Serious complications have included seizures, hypoglycemic coma, altered level of consciousness, and hyperosmolar non-ketotic hyperglycemic coma. Most of these events were reversible (within 1-2 days), but a few resulted in fatal outcomes.[5] Patients without a history of diabetes nor on glucose-altering medications may also be at risk, as one study found no significant difference in the risk of experiencing dysglycemia between diabetic patients receiving treatment and patients not taking diabetic medications.[7]

Hypoglycemia appears to be more common in older patients and those with renal insufficiency.

Both populations have decreased renal function, which may reduce the clearance of the medication. Gatifloxacin is primarily excreted through the kidneys, of which 80% is eliminated unchanged in the urine.[8] Patients with impaired renal function will subsequently have increased exposure to gatifloxacin, possibly leading to hypoglycemia.

The true incidence of gatifloxacin-related dysglycemia is difficult to estimate, as the FDA's process for monitoring adverse events (Adverse Events Reporting System) is limited by under-reporting.[7] The package labeling referred to 2 earlier studies in which no clinically significant changes in glucose tolerance and homeostasis were found in non-insulin dependent patients controlled with diet and exercise. Only transient, modest increases in serum insulin, and decreases in glucose concentrations, were reported after the first dose of gatifloxacin. Additionally, it was found that patients on glyburide experienced clinically insignificant decreases in serum insulin.[2]

Park-Wyllie and colleagues analyzed data from the National Ambulatory Medical Care Survey and from the National Hospital Ambulatory Medical Care Survey (1995-2002), in order to conduct 2 separate nested case-control studies to assess the odds of gatifloxacin-associated hypo- and hyperglycemia.[7] Park-Wyllie et al examined dysglycemic events necessitating hospitalization within 30 days of administration of quinolones (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin), macrolides, and second-generation cephalosporins (cefaclor, cefuroxime axetil) in a population of approximately 1.4 million Ontario, Canada residents over the age of 65. The percentages of diabetic patients were 92% and 62%, respectively, in the hypo- and hyperglycemia nested case-control studies.

The adjusted odds ratio for hypoglycemia in the gatifloxacin group as compared to macrolide-treated patients was 4.3 (95% CI, 2.9 to 6.3). Levofloxacin use was also shown to increase the risk of hypoglycemia relative to macrolides (adjusted odds ratio 1.5, 95% CI, 1.2 to 2.0), though to a lesser degree than observed with gatifloxacin. Of note, no increased odds of hypoglycemia were reported after treatment with either ciprofloxacin or moxifloxacin. Interestingly, aside from gatifloxacin (adjusted odds ratio 16.7, 95% CI, 10.4 to 26.8), there were no statistically significant differences in the odds of hyperglycemia for the other quinolones or second-generation cephalosporins (compared to macrolides).[7]

The results from a retrospective study conducted by Frothingham and colleagues[3] support the observations reported in the Canadian nested, case-control studies. Frothingham et al analyzed spontaneous adverse event reports associated with the use of ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin in the United States during the time from November 1997 to September 2003. Of 568 dysglycemic events, 80% were attributed to gatifloxacin. Furthermore, 68% of the fatal dysglycemic events were associated with gatifloxacin treatment.

Conclusion

Recent reports have suggested that the use of gatifloxacin, especially in elderly and diabetic patients, may lead to severe hypoglycemia or hyperglycemia, warranting in-hospital treatment. Ciprofloxacin and moxifloxacin appear to be safe for diabetic patients, whereas levofloxacin use may be associated with a slightly higher risk of hypoglycemia. At present, no cases of dysglycemia have been attributed to gemifloxacin, one of the newer quinolones available in the United States. Quinolones have become the most commonly prescribed class of antibiotics, with nearly half prescribed for non-approved diagnoses.[11] Consequently, since there may be a slightly higher risk of hypoglycemia associated with levofloxacin use, compared with other quinolones on the US market, healthcare providers should discuss how to detect changes in blood glucose with patients who may be at risk for dysglycemic events. ■

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Utility of Follow-Up Imaging Studies in Spine Infections

ABSTRACT & COMMENTARY

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Dr. Winslow is a consultant for Bayer Diagnostics, and on the speaker's bureau for GlaxoSmithKline and Pfizer.

Synopsis: *A retrospective cohort analysis of 79 patients with spine infection who underwent baseline and 4-8 week follow-up imaging was conducted. Twenty-seven (34%), 38 (48%), and 14 (18%) patients were judged to have images graded as improved, equivocal, or worse respectively. Absence of microbiological treatment failure was seen in 100%, 89%, and 56% of patients respectively.*

Source: Kowalski TJ, et al. Do Follow-Up Imaging Examinations Provide Useful Prognostic Information in Patients with Spine Infection? *Clin Infect Dis*. 2006;43:172-179.

This paper presents the results of a retrospective cohort analysis from the Mayo Clinic of 79 patients with bacterial spine infection who underwent baseline and follow-up imaging studies with MRI. Thirty-five infections (44%) were due to *Staphylococcus aureus*, 9 (11%) due to coagulase-negative staphylococci, and 16 (20%) were culture-negative. Twenty-seven (34%), 38 (48%), and 14 (18%) of follow-up imaging studies were judged as improved, equivocal, or worse, respectively. One year survival free of microbiologically-confirmed treatment failure was 100%, 89%, and 56% across these same groups. In another analysis, looking across radiographic strata, only 3 (6%) of 52 patients who were judged to have had clinical improvement at time of follow-up imaging experienced treatment failure. Elevated levels of inflammatory biomarkers were present in 2 of these 3 patients.

COMMENTARY

I recently finished a 2-month stint as the attending physician on ID consult service at our county hospital, which included the first 2 weeks of July with a bright, young, brand new first-year ID fellow, and 2 excellent medical residents. As always, one of the toughest questions the ID attending is usually asked is, "How long should you treat XYZ infection?" With the exception of a handful of diseases where the pathophysiology is relatively homogenous (such as bacterial endocarditis due to a particular organism), most of us fall back on the wisecrack answer most commonly attributed to the legendary Max Finland at Boston City Hospital, "Long enough." After using that answer almost daily followed by the equally unhelpful answer ("clinical experience") to the follow-up question of how do you know how long is "long enough," I was glad to see this article in *CID* which helps answer this question for bacterial spinal infections.

The study does have some limitations, including its retrospective nature and the fact that only staphylococcal and culture-negative infections were included in the series. However, Kowalski and colleagues used a reasonable and simple grading scale for assessing improvement, equivocal, and worsening MRI findings in which signal abnormality and abscess size in the paraspinal/psoas musculature and/or epidural space were considered. A somewhat arbitrary set of criteria for interpretation of biomarker improvement (25% reduction in ESR or CRP from baseline or final value of ESR < 40 mm/h and CRP < 1 mg/dL), but this seemed helpful and congruent with the prognostic information gleaned from follow-up MRI imaging. Using similar inflammatory biomarker criteria provides sensitivity for predicting treatment failure, but has low specificity since many patients who are cured do not experience normalization of ESR and/or CRP in the first 4-8 weeks of treatment.[1] Despite this limitation, this study shows that only one patient in the cohort's relapse/treatment failure would have been

missed by relying on serial biomarkers of inflammation in the absence of follow-up imaging. Kowalski et al postulate that a cost-effective approach derived from this study would be to order follow-up imaging only on those patients who are at high risk for treatment failure based on clinical status and inflammatory biomarker response.

Magnetic resonance imaging is a relatively new imaging technology which is exquisitely sensitive for use in assessing the brain, spinal cord, and axial skeleton, and has appropriately become the imaging technique of choice for infections involving these structures.[2] Ironically, one limitation of MRI is its exquisite sensitivity and the fact that the scan does not rapidly return to normal following an adequate course of antimicrobial therapy. This retrospective study sheds some light on how to best use MRI (in conjunction with ESR, CRP, and, yes, "clinical judgment" is still in the equation) in managing spinal infections due to staphylococci. ■

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Myopathy Associated with Daptomycin Use

SPECIAL FEATURE

By Heather Baker, Jennifer Murphy, Jessica C. Song

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Heather Baker, Jennifer Murphy, and Jessica C. Song report no financial relationships relevant to this field of study.

Introduction

DAPTOMYCIN IS A CYCLIC LIPOPEPTIDE ANTIBIOTIC which was initially approved by the Food and Drug Administration (FDA) for the treatment of complicated skin and skin-skin structure infections in September 2003.[1] More recently, the FDA issued an approval letter to Cubist Pharmaceuticals for the indication of the treatment of *Staphylococcus aureus* bacteremia, including right-sided endocarditis caused by methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*.[2]

Of note, earlier phase-1 and phase-2 clinical trials in the 1980s and early 1990s utilized multiple daily dosing regimens of daptomycin. However, because of the apparent propensity of daptomycin to cause myopathy, Eli Lilly voluntarily discontinued clinical development of this agent in 1991.[3] However, because of the relative lack of treatment options for life-threatening Gram-positive infections, the renewed clinical development of daptomycin was licensed to Cubist Pharmaceuticals in 1997.[3] Subsequent animal studies indicated that increasing the dosing interval appeared to minimize the frequency and severity of myotoxic effects of this drug.[3,4]

This article will: 1) review the mechanism of myopathy induction by daptomycin; 2) review the literature reports of myopathy associated with daptomycin; and 3) review the potential interaction between daptomycin and statins (HMG CoA Reductase Inhibitors).

Pathophysiology for Daptomycin-Induced Myotoxicity

Several clinical studies and case reports have examined the possible causes and options for controlling myopathy. Unlike other causes of myopathy, daptomycin-associated myotoxicity appears to be specific for skeletal muscle.[4] No myofiber lesions were detected during microscopic evaluation of canine cardiac muscle at doses as high as 75mg/kg daily.[4] Moreover, studies in animals, as well as humans have shown that muscle-related adverse effects associated with daptomycin are readily reversible, with no resulting fibrosis of the skeletal muscle.[4,5]

Creatine phosphokinase (CPK) is an important marker for both the diagnosis, as well as in monitoring the course of myopathy. When skeletal muscle is injured, CPK leaks into the blood and is commonly associated with muscle weakness.[6] CPK release by skeletal muscle has been attributed to numerous events, including surgical trauma, IM injections, physical activity, and bacterial or viral infection.[5] Consistent with daptomycin's characteristics and mechanism of action, membrane disturbances can lead to cellular release of CPK, with corresponding elevations of CPK in plasma. Clinical studies have shown that 2.8% of patients experience CPK elevations,[7] and some case reports have described CPK elevations as high as 21,243 U/L (normal 0-200).[8]

Dosing Frequency of Daptomycin

The dosing frequency of daptomycin has been implicated in the development of myopathy and CPK elevations. In Phase I studies, 2 of 5 subjects dosed at 4mg/kg q12h experienced myopathy, with CPK levels 10 times the upper limit of normal.[5] In contrast, Oleson and colleagues demonstrated in animals that once-daily dosing of daptomycin resulted in significantly fewer skeletal muscle effects, with 5 times more muscle degeneration seen in dogs dosed at intervals of 8h compared to every 24h (*see Chart A*).[4]

Oleson et al evaluated fractionated versus once-daily dosing regimens and the subsequent effects on skeletal muscle, along with serum CPK levels. The highest elevations in CPK were observed in animals that received fractionated regimens. Similar CPK values were seen in both the high-dose and low-dose once-daily regimens, despite the 3-fold increase in daily dose. However, a 4-fold increase in CPK was seen in the fractionated regimen versus once-daily regimen, despite the same total overall dose. Of further significance, muscle fiber lesions seen upon microscopic evaluation were higher in the fractionated regimens of daptomycin compared to the once-daily regimen. Chart A illustrates these results.

The dosing regimen of 75 mg/kg q24h resulted in plasma daptomycin concentrations well below the trough achieved with fractionated dosing for 12 hours prior to the next dose administration. It was postulated by researchers that this could allow for repair of myofibers damaged during previous dosing.[4]

Although the dosing interval plays a major role in the development of myopathy, the C_{max} is unlikely to be responsible for the acquisition of this adverse effect. In the study conducted by Oleson et al, a dosing regimen of 25 mg/kg q8h resulted in a CPK value of 3996 U/L, whereas dosing once daily at 75 mg/kg yielded a CPK value of 991 U/L, even though the C_{max} was twice that of the fractionated regimen.[4]

Case Studies in Specific Patient Populations

In a Phase I study conducted by Cubist Pharmaceuticals, 2 subjects experienced elevations in CPK to values no more than 2.5 times the upper limit of normal. The subject who experienced the highest CPK elevation (477 U/L) had engaged in significant physical activity the day prior to serum sampling, to which the elevation was attributed. In both subjects, CPK levels returned to normal within 2 days, despite continued therapy with daptomycin. However, this study population consisted solely of those with normal hepatic and renal function and those who were free from prescription medication use for at least 30 days prior to initiation of the study.[5]

In contrast, several case reports have described substantial elevations in CPK with severe corresponding myopathy. A 45-year-old female with refractory AML (acute myeloid leukemia) received 6 mg/kg daptomycin daily after failing both vancomycin and linezolid therapy for *E. faecium* bacteremia. Her CPK values increased from 108 U/L to 996 U/L within 10 days of initiating daptomycin, and she subsequently developed rhabdomyolysis. Of note, this patient was also taking Amphotericin B lipid complex and had developed bacterial sepsis, both of which are known to be precipitating factors for the development of rhabdomyolysis.[1]

In another case report, a patient with diabetes, hypertension, and peripheral vascular disease experienced rhabdomyolysis while on 6 mg/kg daptomycin once daily. After experiencing severe muscle weakness with a CPK level of 21,243 U/L (10 days after start of therapy), daptomycin therapy was withdrawn and a diagnosis of acute renal failure secondary to rhabdomyolysis was made. In this case, no other medications or disease states thought to cause rhabdomyolysis were involved.[8]

In addition to renal dysfunction and rhabdomyolysis, a case report of possible hepatotoxicity associated with daptomycin has been filed. This patient was also taking simvastatin, which was discontinued upon initiation of daptomycin, per the manufacturer's recommendations. Even without concomitant use of medications known to cause myopathy, this patient's CPK value rose to 20,771 U/L after 9 days of treatment with 6.5 mg/kg daptomycin once daily.[9]

Finally, a 26-year-old SLE (systemic lupus erythematosus) patient who failed quinupristin/dalfopristin due to severe myalgia, also experienced myopathy while on daptomycin, with a CPK elevation of 492 U/L (day 15 of therapy). This patient continued treatment with a normalization of her CPK level within 3 days of the end of therapy. Although this patient also had SLE, the inflammation and release of CPK was attributed solely to daptomycin.[10]

FDA Briefing Document on Daptomycin

In the FDA-reviewed document prepared by the manufacturer, the incidence of significant CPK elevations was examined between daptomycin and comparator regimens (nafcillin/oxacillin, vancomycin).[11] Also examined was the relationship between CPK elevations and prior or concomitant therapy with statins, a medication

Chart A

CPK Elevations and Myopathy•

Dose Regimen	CPK (U/L)	Number of Sites with Myofiber Degeneration
25 mg/kg q24h	994 ± 1401	3/28
75 mg/kg q24h	991 ± 421	8/28
25 mg/kg q8h	3996 ± 3151	15/28
5 mg/kg q24h	157 ± 30	4/28
5 mg/kg q8h	483 ± 553	21/28

• Derived from Table 1 from Pharmacokinetics and Myopathy Findings[4]

Chart B

CPK Elevations with HMG-CoA Reductase Inhibitor Therapy•

	Comparator Regimen (%)	Daptomycin Regimen (%)
Overall Study	1/116 (.95)	11/120 (9.2)
Patients who had CPK > 500 and treatment with HMG Co-A reductase inhibitor	0/1 (0.0)	4/11 (36.4)

• Rates of CPK Elvations Greater than 500

class known to cause myotoxicity. Below is a summary of the manufacturer's findings (*see Chart B*).

In the daptomycin-treated patients who experienced CPK elevations (n = 11), 4 had prior or current treatment with statins, namely simvastatin and atorvastatin. Of the 11 patients who developed CPK elevations, 6 required discontinuation of daptomycin therapy, but it is unclear if this included patients who were also being treated with statins.[11]

Of interest is the dose of statin therapy that led to elevations in CPK. While not reported in the FDA briefing document, the manufacturer has stated in the package insert that patients stable on 40mg of simvastatin while taking 4mg/kg daptomycin did not show an increase in adverse muscle effects.[12]

Recommendations for Appropriate Use of Daptomycin

Current manufacturing recommendations include weekly CPK monitoring, as well as discontinuing daptomycin therapy if CPK levels exceed 10 times the normal level, or if myopathy symptoms are present with a CPK level above 1,000U/L.[12]

The manufacturer also recommends consideration be given to holding medications known to cause myopathy while on daptomycin therapy, including statins.

Post-marketing case reports have led to recommendations for patient-specific monitoring, including obtaining more frequent CPK levels for critically ill patients and those patients who are also taking myopathy-causing drugs.[1] ■

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Linezolid-Resistant Coagulase-Negative Staphylococci

ABSTRACT & COMMENTARY

By Robert Muder, MD

Hospital Epidemiologist, Pittsburgh VA Medical Center

Dr. Muder does research for Aventis and Pharmacia.

Synopsis: *In one university medical center, 4% of all coagulase-negative staphylococci were linezolid resistant. A case-control study found that admission to a particular unit and prior receipt of linezolid were significant, independent risk factors for isolation of a linezolid-resistant isolate. PFGE analysis found that 84% of linezolid-resistant isolates were genetically related.*

Source: Potoski BA, et al. Epidemiological Profile of Linezolid-Resistant Coagulase-Negative Staphylococci. *Clin Infect Dis*. 2006;43:165-171.

AT THE UNIVERSITY OF PITTSBURGH MEDICAL CENTER, laboratory-based surveillance of coagulase-negative staphylococci found that 4% were linezolid resistant. MIC's to linezolid were generally > 256 ug/mL; the isolates were all susceptible to vancomycin and daptomycin. In a case-control study, prior receipt of linezolid (OR, 20.6; 95% CI, 5.8-73) and location on a particular hospital unit (OR, 12.4; 95% CI, 3.4-45) were independently associated with isolation of a linezolid resistant strain. The identified unit served as a the receiving unit for an intensive care unit that had an unusually high level of linezolid use, approximately 8 times higher than that of the facility as a whole. PFGE analysis showed that 21/25 (84%) resistant strains were genetically related. Strains of susceptible coagulase negative staphylococci were genetically diverse.

COMMENTARY

Resistance to linezolid among staphylococci has been rare in prior studies; less than 0.1% of isolates of coagulase negative staphylococci have been resistant in prior studies. The study by Potoski and colleagues demonstrates a markedly higher rate of linezolid resistance among coagulase negative staphylococci in their facility. Although prior receipt of linezolid was a significant independent risk factor, it is of note that most resistant strains were genetically related, and that admission to a particular ward was also a significant risk factor. This demonstrates that both antimicrobial exposure and patient-to-patient transmission are likely to be important in the epidemiology of linezolid resistance of coagulase negative staphylococci.

More importantly, coagulase negative staphylococci and *S. aureus* can exchange resistance genes. The study by Potoski et al did not examine the mechanism of linezolid resistance in coagulase negative staphylococci, and it is not known whether or not linezolid resistance is transferable among staphylococcal species. However, this report suggests that possibility that linezolid resistance could become widely disseminated among *S. aureus* isolates. Should this happen, the arsenal of antimicrobial agents effective against MRSA would be further restricted. ■

Refugees with Eosinophilia: Diagnostic Considerations

ABSTRACT & COMMENTARY

By Michele Barry, MD, FACP

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Dr. Barry is a consultant for the Ford Foundation, and receives funds from Johnson & Johnson.

Synopsis: *Many refugees arriving in the United States have persistent eosinophilia diagnosed, and often are referred to travelers' clinics for diagnostic work-up. What does one consider in planning such a workup?*

Source: Seybolt LM, et al. Diagnostic Evaluation of Newly Arrived Asymptomatic Refugees with Eosinophilia. *Clin Infect Dis*. 2006;42:363-367.

SEYBOLT AND COLLEAGUES PERFORMED A RETROSPECTIVE analysis of refugees seen as part of a 2-visit health evaluation at Boston Medical Center from October 1998 through May 2002. Eosinophilia was defined as an absolute eosinophil count of > 450 cells/μL. Demographic data was abstracted along with results of stool examinations for ova and parasites, and serologic studies for antibodies to *Strongyloides stercoralis*, schistosomal, and filarial species. Eosinophilia was present in 12% of asymptomatic, newly arrived refugees screened. Pathogens were identified in stool samples of 29% of 265 patients. Serologic testing was performed in only 45% of patients but, of these results, schistosoma serology was positive in 22% (15 patients) *S. stercoralis* in 39% (45 patients), and filarial serology in 18 (51%) of 35 patients tested. Most subjects with pathogens identified were children, and more than half were male. The most common stool parasite isolated was

one not associated with eosinophilia (ie, *Giardia lamblia*), suggesting that serological testing aimed at looking for other sources of eosinophilia should be performed, even if the presence of pathogens in stool samples is documented.

COMMENTARY

Eosinophilia in a refugee population is common and often reflects tissue-invasive helminths rather than the diagnosis of an atopic or allergic skin condition, commonly seen in US populations. Eosinophilia has been assessed in a traveler's population, and is a poor marker of parasitic diseases.[1] However, refugees who have had prolonged exposure to helminths and different economic settings have an increased risk of contracting parasitic infections, and so eosinophilia becomes an important diagnostic clue. Seybolt et al have attempted to demonstrate that serologic testing for schistosoma species, filaria species, and strongyloidiasis might be of benefit in diagnosing patients with more severe eosinophilia.

Not all patients in this report received a serologic evaluation, nor do Seybolt et al present follow-up data; thus, no conclusions as to cost-effectiveness of serologic testing or even resolution of eosinophilia can be made. Furthermore, cross-reactivity of antibody testing and persistent presence of antibodies in patients with past infections may have confounded their results.

However, despite these limitations, this paper remains an excellent reminder that not all asymptomatic eosinophilia can be identified by stool examinations for ova and parasites, and serologic testing for *S. stercoralis*, schistosoma, and filarial species should be appropriately obtained for patients from regions where these pathogens are endemic. Nutman, in an accompanying editorial, suggests that when cost is an issue for refugee populations such as Southeast Asians in which strongyloidiasis and hookworm are common, single dose ivermectin and/or albendazole treatment may be empirically indicated.[2,3] ■

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CME Questions

7. What is the recommended regimen for the newly FDA-licensed live pentavalent human-bovine (WC3 strain) reassortant rotavirus vaccine (marketed as RotaTeq)?

a. 3 doses at birth, 6-8 weeks, and 12 weeks of age
b. 2 doses at 4 and 8 weeks of age
c. 2 doses at birth and 6-8 weeks, with a booster at 1 year of age
d. 3 doses at 2, 4, and 6 months of age
e. First dose at 2 years, with a booster 2-4 mo later

8. Which of the following is correct?

a. Gatifloxacin use has been associated with the development of both hypoglycemia and hyperglycemia.
b. The use of fluoroquinolones other than gatifloxacin has never been associated with the development of hypoglycemia.
c. Gatifloxacin causes hypoglycemia as a result of the reduction of metabolism of several oral hypoglycemic agents.
d. Macrolide antibiotics are more likely to cause hypoglycemia than is gatifloxacin.

9. Daptomycin use has been associated with which of the following is correct?

a. Acute renal failure
b. Seizures
c. Myopathy
d. Peripheral neuropathy

Answers: 7. (d); 8. (a); 9. (c)

CME Objectives

The objectives of *Infectious Disease Alert* are:

• To discuss diagnosis and treatment of infectious diseases;

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

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

• To 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:

HEPA Filtrations and Fungal Infections

UPDATES

By Carol A. Kemper, MD, FACP

Furry Friends in Hospitals

DiSalvo H, et al. *Am J Infect Control*. 2006;34:301-307.

THE INTRODUCTION OF THERAPY animals and pets in the health care setting has created unique opportunities and challenges for infection control personnel—problems that DiSalvo and colleagues point out can be blurred by confusion between various animal programs. For example, the "Furry Friends Foundation" at Santa Clara Valley Medical Center (SCVMC) allows pet visitation in certain areas of the hospital, a program which is distinct from other animals allowed in the facility.

There are 3 categories of animals allowed at our hospital: service animals, therapy animals, and pet visitation animals, each of which has their own purpose, restrictions and policies. Only service animals (generally trained dogs) are regulated by Federal and State laws. Service animals are defined by the American with Disabilities Act as "an animal individually trained to perform (essential) tasks for people with disabilities." An organization such as a hospital cannot require proof of a person's disability or proof of the service animal's training. As such, service animals can go anywhere in the facility.

In contrast, hospitals can define policies and restrictions for therapy pets (also generally dogs) and pet visitation animals. Therapy dogs are used for specific purposes, eg, to stimulate physical or mental rehabilitation, and are used in certain areas of the facility, eg, the burn unit, physical therapy, etc. Pet visitation is just what it sounds like; volunteers bring their own pets to the hospital for recreation and entertainment. While SCVMC only allows pet visitation in the day rooms of their facility, a neighboring hospital has elected to allow them on the medical and surgical floors but restricts them from ICUs and isolation rooms. Infection Control programs can require animals in both of these latter categories to pass certain physical and behavioral evaluations. Specific clearance may be required for stool ova and parasites, vaccinations, and a physical and behavioral evaluation by a licensed vet. The owner may be required to take basic animal training classes or exhibit knowledge about good infection control practices, such as (enthusiastic) hand washing.

Pet programs are a positive addition to the hospital and should be associated with minimal risk, as long as IC programs adopt good policies and regulations, and make clear the differences between animal groups. ■

Culture Conversion Key Measure in MDR-TB

Source: Holtz TH, et al. *Ann Intern Med*. 2006;144:650-659.

SPUTUM CULTURE CONVERSION FOR patients with multidrug resistant tuberculosis (MDR-TB) is generally believed to be the simplest marker of treatment success, and is especially useful in areas with limited resources and access to specialized radiographic techniques. However, medical correlates of sputum conversion and outcome have not been well-defined in clinical trails.

Holtz and colleagues examined the time to sputum mycobacterial conversion in Latvian patients with pulmonary MDR-TB. This retrospective cohort analysis assessed 167 civilians with pulmonary MDR-TB, or at least with combined resistance to INH and rifampin, each of whom received individualized therapy through a DOTS-Plus Strategy. DOTS-Plus was introduced in 1998, and provides directly observed therapy with second line TB drugs tailored to the individual's isolate. Patients first receive empirical, individualized regimens, using anywhere from 4 to 8 agents, including the use of at least one injectable, taking into consideration any previous therapy. Once the results of susceptibility studies are available in 3 to 8 weeks, the therapy is modified as appropriate to include at least 5 or more drugs to which the patient's isolate is susceptible. When appropriate, the injectable agent (generally an aminoglycoside) is continued until culture conversion, at which time it is continued for another 2 to 3 months. The remaining oral regimen is continued for another 12 to 18 months, depending on the patient's status. Adjuvant surgical management was done for patients with advanced disease not responding to therapy.

During this study, sputum cultures were obtained monthly, and culture conversion was defined as the date of the first of 2 consecutive negative cultures. Patients frequently missed obtaining monthly sputum cultures, although generally this was fewer than 5.

At baseline, 78% of the patients were men; the median age was 43 years for men and 39 years for women. The majority (74%) had received first or second line therapy for TB in the past and were resistant to a median of 5 agents (range, 2 to 10). One-third had bilateral cavitary disease, and 53% were smear positive. Sputum culture conversion was achieved in 129 of 167 (77%), with a median time of 60 days (range, 4 to 462 days). Among those who converted, 16% converted by one

month of treatment, 39% by 2 months, and 60% by 4 months. Treatment outcome was best for patients who attained sputum conversion by the second month of therapy.

Fourteen patients had initial sputum conversion, followed by positive cultures; 2 of these patients had 7 or more sequential positive monthly cultures, although 13 of these ultimately responded to treatment. The ability to tolerate and comply with the regimen was important; 76% of patients adherent to a full course of treatment had culture conversion. Fourteen patients had initial sputum conversion, followed by positive cultures. Two of these patients had 7 or more positive monthly cultures, although 13 of these ultimately responded to treatment. Of the 129 patients who achieved sputum conversion, 14 (11%) were subsequently lost to follow-up, 5 (4%) died, and 2 (1%) had treatment failure.

Failure of treatment was associated with prior treatment for TB, a history of incarceration, high initial colony counts (4+ smears), bilateral cavitary disease, resistance to 6 or more drugs, and specific resistance to pyrazinamide or kanamycin. Of the 38 patients who failed to respond, 8 (21%) died. Although cavitary disease was considered a poor prognostic factor, 67% of patients who completed a full course of therapy were ultimately cured.

A limitation of this project was the lack of information on how many patients required modifications in their regimens and how often resistance to agents that were initially susceptible was detected in follow-up specimens. However, this study shows that aggressive and individualized intervention using the DOTS-Plus Strategy with multiple antituberculous agents was successful in this hard-to-treat cohort of patients with MDR-TB (with resistance to a median number of 5 drugs!). Three-fourths (77%) of patients responded to treatment, and 65% were considered cured. In those who did respond, sputum culture conversion occurred at a median of 60 days, not much longer than that described for patients with a fully susceptible organism. Monthly sputum cultures were a simple and effective method for monitoring response to therapy. ■

Investigation of MDR-HIV in NYC

CDC. *MMWR Morb Mortal Wkly Rep*. 2006;55:793-796.

You may recall reports of the 46-year-old NYC man with rapidly progressive HIV/AIDS who was infected with a strain of multi-drug resistant, dual tropic HIV (meaning, it utilized both CCR5 and CXCR4 co-receptors for entry in to CD4 lymphocytes). The man developed acute primary HIV infection in December 2004, with rapid progression to AIDS within one month of infection.

A broad public health investigation was conducted to identify sexual contacts of the index case and to define the prevalence of this strain of HIV in the New York area. The investigation was focused in 3 different directions: contact investigation; examination of newly diagnosed MDR HIV cases in NYC; and attempts to match the index case genotype with laboratory sequences. The first problem encountered was the patient's lifestyle. He reported multiple partners, many of whom were anonymous. Fourteen names were provided, 10 of whom were known to be HIV+ before 2004; none of the 10 had a genotype matching the index case. The remaining 4 persons refused testing or could not be located.

A second effort was made to alert physicians and laboratories in the NYC area to report all newly diagnosed cases of MDR-HIV. A total of 189 MDR HIV-1 isolates belonging to 134 patients were identified. An attempt to match persons in the registry with their isolate was made, and the medical records of 121 individuals were examined for date of infection, previous genotype data, and treatment history. Five persons had MDR-HIV and had been infected between 2002 to 2004, 2 of whom had never received therapy.

A third and broader attempt to identify the prevalence of this strain of MDR HIV was also made by comparing the index case's pol gene against sequence libraries at the CDC, the NY State Department of Health, and 3 large commercial laboratories in the United States, 2 in Canada, and one in Europe. In addition, 28 labs conducting HIV genotyping on NYC residents were alerted to match the index pol genotype against sequences in their databases. Isolates belonging to 3 men with > 90% homology to the index case isolate were identified (one in Connecticut and 2 in NYC). The men were contacted, and all reported sexual activity at the same time and at similar venues as the index case. Unfortunately, there was insufficient data to determine the aggressiveness of their disease, although all 3 were reportedly stable on antiretroviral therapy.

It is quite remarkable that despite an extensive and labor-intensive effort by numerous public health departments, the CDC, the Aaron Diamond Research Center, and dozens of laboratories, only a handful of cases with MDR-HIV similar to the index case were identified in the NYC area, and none of these appear to have resulted in rapidly progressive disease. But the *MMWR* points out that at least 6400 MSM in NYC have never been tested for HIV, and many more may be at risk. Many HIV+ individuals have not been genotyped, at least not before initiating HIV therapy. Therefore, the actual prevalence of this particular strain of MDR-HIV in NYC is unknown. This case reinforces current recommendations to obtain baseline genotype testing in any newly diagnosed or treatment-naïve HIV+ individual. ■

INFECTIOUS DISEASE ALERT®

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

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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.

Raloxifene's Role for Estrogen- and Age-Related Problems

What is the role of raloxifene for the treatment of osteoporosis and breast cancer prevention? Raloxifene is a selective estrogen-receptor modulator similar to tamoxifen. There has been considerable interest in the drug in the role of treatment for osteoporosis and, perhaps, breast cancer prevention, especially in light of the Women's Health Initiative findings on conjugated estrogen/progesterone. A new study does little to clarify the issue, however, suggesting, like previous studies, that raloxifene has benefits, but also significant risks associated with its use.

As part of the Raloxifene Use for The Heart (RUTH) trial, more than 10,000 postmenopausal women with CHD or multiple risk factors for CHD were randomized to raloxifene 60 mg daily or placebo and followed for a median of 5.6 years. The 2 primary outcomes were coronary events and the rate of breast cancer. Raloxifene had no effect on the risk of primary coronary events (533 vs 553 events; HR, 0.95; 95% CI, 0.84 -1.07) but was associated with a reduced risk of invasive breast cancer (40 vs 70 events; HR, 0.56; 95% CI, 0.38-0.83). However, the all-cause death rate was the same in both groups, and raloxifene use was associated with an increased rate of fatal stroke (59 vs 39 events; HR, 1.49; 95% CI, 1.00-2.24) and venous thromboembolism (103 vs 71 events; HR 1.44: 95% CI, 1.06-1.95). The drug was associated with a reduced risk of clinical vertebral fractures (64 vs. 97 events: HR, 0.65; 95% CI, 0.47-0.89) (*N Engl J Med*. 2006;355:125-137). In an accompanying editorial, Marcia L. Stefanik, PhD, from the Stanford University Medical School reviews risk benefit profiles of raloxifene for women.

Reviewing data from the RUTH trial, as well as other studies, the author suggests that a key issue in contemplating raloxifene use is balancing the benefits of reduction in the risk of breast cancer and vertebral fractures with the increase risk of venous thromboembolism and fatal stroke. She suggests that raloxifene should be contemplated in women with an increased risk of breast cancer, but asks" What level of breast cancer risk would justify the use of raloxifene for prevention of breast cancer for a given person . . ." and suggest that the answer to that question is currently unknown. She also states that, "For now, there's no magic bullet that can reduce the risks of major health problems related to estrogens and aging without introducing other potentially serious health concerns." (*N Engl J Med*. 2006;355:190-192).

The Truth About Multivitamins

More than half of the adult population in the United States takes multivitamins on a regular basis, yet little is known about the benefits or lack of benefits of vitamins. The National Institutes of Health has published a "State-of-the-Science Conference Statement" on multivitamin/mineral

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

supplements and chronic disease prevention as an early release article on the *Annals of Internal Medicine* web site on August 1. The statement deals with the current patterns of vitamin use, nutrient intake of vitamin users and nonusers, the efficacy of single vitamins and minerals, the efficacy of multivitamins, the safety of multivitamins, and where future research is needed. Regarding single vitamins and minerals, the results have been disappointing.

Beta-carotene was found to cause an increase in lung cancer incidence and deaths in smokers and male asbestos workers and no benefit in preventing other types of cancers. Other cancer preventative studies have shown no benefit from beta-carotene and, some have even suggested, increase rate of stroke and CVD in women smokers. Vitamin A has not been the subject of individual trials but, when paired with beta-carotene or zinc, there is no impact on the incidence of cancer.

Four trials have looked at vitamin E, and the results have been mixed. The largest was the Women's Health Study, which suggested a decrease rate of cardiovascular deaths with vitamin E but no decrease in the incidence of CVD events. Vitamin B_6 was looked at, and 2 small studies showed no benefit regarding cognitive decline in elderly men and women. Folic acid with or without vitamin B_{12} has been shown to decrease the rate of neural tube defects in women of childbearing age, but was not shown to prevent cognitive decline in older adults. Selenium was found to decrease the rate of liver cancer in Chinese patients who were at risk, and there may be some benefit in reducing the rate of lung, prostate, and colorectal cancer. Calcium has been shown to increase bone mineral density in post menopausal women, and calcium coupled with vitamin D has been shown to decrease the risk for hip and non-vertebral fractures. Calcium and vitamin D may increase risk of kidney stones, and has not been shown to reduce the risk of colorectal cancer.

The use of multivitamins and mineral supplementation (MVM) has been studied in 5 randomized, controlled trials. Although the study methodology was quite variable, there is a suggestion that MVM may decrease risk of cancer. No studies have shown any benefit as far as cardiovascular disease, and the benefit for cataract prevention is mixed. Progression of macular degeneration may be slowed by certain multivitamins, and may represent the single most important benefit from multivitamins. The conference statement also stated that the FDA should be given more oversight over the vitamin industry, and that more rigorous randomized controlled studies should be done of individual vitamins, minerals, and MVM, including safety of these products, as well as the interactions with nutrients and medications (www.annals.org 1 August 2006, to be published in print 5 September 2006).

Statins and Hepatitis C

Statins may be effective therapy for hepatitis C infections, and may even be used in combination with interferon to inhibit replication of the hepatitis C virus, according to new study. Japanese researchers recently evaluated the effect of various statins with or without interferon on hepatitis C replication. The synthetic statin fluvastatin was the strongest inhibitor of HCV replication, while atorvastatin and simvastatin were less effective. Lovastatin's effect was relatively weak, while pravastatin displayed no anti-HCV activity. The authors suggest that statins, especially fluvastatin, could be "potentially useful as new anti-HCV reagents" in combination with interferon (*Hepatology*. 2006;44:117-125).

Preventing Hot Flashes

Gabapentin may be as effective as estrogen in preventing hot flashes in postmenopausal women, based upon a recent study. In a randomized, double-blind, placebo-controlled trial on 60 postmenopausal women randomized to conjugated estrogen 0.625 mg daily, gabapentin titrated to 2400 mg daily, or placebo for 12 weeks. The primary outcome, the hot flash composite score, was no different between estrogen or gabapentin (72% improvement vs 71%), with placebo reducing symptoms by 54%. No differences were seen in severity of hot flashes or depression symptoms, although side effects were slightly higher in the gabapentin group (*Obstet Gynecol*. 2006;108:41-48). The authors acknowledge that this is a small study with a significant placebo effect. However, in light of the Women's Health Initiative findings, non-estrogen alternatives for heart flashes are welcome.

FDA News

The FDA is opening the door to allow Duramed's Plan B emergency contraceptive to be available over-the-counter to women 18 and older. Previously the FDA had tabled the OTC application indefinitely, but new FDA leadership is more receptive. The drug is currently available only by prescription. ■