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INSIDE

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HIV Genotyping of Chronically Infected Patients

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor of Medicine, Stanford University School of Medicine

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

Source: Smith D, et al. Clinical Utility of HIV Standard Genotyping Among Antiretroviral-Naive Individuals with Unknown Duration of Infection. *Clinical Infect Dis.* 2007;44:456-458.

Synopsis: *A total of 103 antiretroviral-naïve patients with HIV infection in San Diego County underwent genotyping between January and December 2005. Of the patients, 25% showed evidence of resistance to at least one drug class.*

THIS STUDY FROM THE EXCELLENT GROUP AT UNIVERSITY of California in San Diego had standard population-based HIV genotyping performed on plasma obtained from all antiretroviral (ARV)-naïve patients who received care in publicly funded clinics in San Diego County during the 2005 calendar year. Of the 103 patients who were studied, 26 (25%) had resistance-associated substitutions detected for at least one class of ARV agent; 18% had resistance demonstrated to one drug class, 6% to 2 classes, and 1% demonstrated 3 drug class resistance.

COMMENTARY

Studies of recently infected cohorts of HIV patients have shown the prevalence of transmitted ARV resistance to range from 8.3%-20%. Routine drug resistance testing of populations before initiation of ARV therapy has been estimated to be cost effective when the prevalence of drug resistance is 8%-10%.[1] There have been few studies evaluating the prevalence of ARV resistance in chronically infected antiretroviral naïve HIV patients, so this paper is an important contribution to the literature. It is likely that the resistance observed in this study is due to both de novo infection with

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ARV-resistant virus and to casual use of antiretrovirals not disclosed to the patients' provider. Not surprisingly nnRTI substitutions (K103N in 12 patients and Y181C/I in 4 cases) were common as were NRTI substitutions (including TAMs and M184V). Probably due to reduced fitness in the absence of selective pressure of ARVs, PI substitutions were much rarer with resistance associated substitutions seen in only a few cases.

Due to the high cost of newer ARV agents and the potential for limiting future treatment options in patients placed on sub-suppressive regimens, it seems clear that obtaining baseline genotypic testing of all patients before initiating ARV therapy is now appropriate. While good data on timing of resistance testing in this population are not available, it makes sense to consider obtaining a baseline genotype on ARV-naïve patients when they first come into care and not waiting until just before placing the patient on ARV therapy is contemplated. This is due to the known instability in plasma of many resistance-associated substitutions in the absence of ARV-selective pressure, although "archival" resistant variants may exist as proviral DNA and re-emerge under selective pressure of ARV therapy. ■

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MRSA Decolonization

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Source: Simor AE, et al. Randomized Controlled Trial of Chlorhexidine Gluconate for Washing, Intranasal Mupirocin, and Rifampin and Doxycycline Versus No Treatment for the Eradication of Methicillin-Resistant *Staphylococcus aureus* Colonization. *Clin Infect Dis.* 2007;44:178-185.

Synopsis: *A combination of topical and systemic therapies was associated with successful MRSA decolonization.*

In an open label study, hospitalized adults with MRSA colonization at one or more sites were randomized (3:1) to attempted decolonization or no treatment. Treatment consisted of 7 days of bathing with 2% chlorhexidine gluconate, together with application of 2% mupirocin ointment to the anterior nares 3 times daily and administration of rifampin (300 mg twice daily) and doxycycline (100 mg twice daily). Follow-up cultures were obtained from the anterior nares, perianal area, skin lesions, catheter or other medical device exit sites, as well as any other site from which MRSA had previously been recovered. Among the reasons for exclusion from the study were prior attempts at decolonization within the previous 6 months, known resistance of the MRSA to any of the study drugs (including mupirocin), AST or ALT >5 times the upper limit of normal, and planned surgery in the following 3 months.

Of the 112 patients (from among the 146 randomized), who were followed for at least 3 months, 87 received decolonization treatment and 25 did not. At 3 months, successful decolonization was achieved in 64 (74%) of the treated and 8 (32%; $P = 0.0001$) of those not treated. At 8 months, 54% of those treated continued to have negative MRSA cultures. Initial and follow-up strains differed by PFGE typing in 18% of cases, however, indicating acquisition of a new strain, rather than failure of decolonization. Baseline resistance to mupirocin (approximately 20% of baseline isolates were resistant) was an independent risk factor for treatment failure. Although known mupirocin resistance was a reason for exclusion from the study, this information was often not available until after random-

ization. In addition to resistance at baseline, mupirocin resistance emerged in 5% of isolates obtained from follow-up cultures.

COMMENTARY

The high rate of persistent success of this decolonization procedure is encouraging. While MRSA colonization is associated with an increased risk of infection, evidence that decolonization is associated with a reduction in that risk remains to be demonstrated, except in a few circumstances, such as chronic peritoneal dialysis and some surgical patients. One benefit of decolonization that can be agreed upon, however, is that it allows the hospitalized or institutionalized patient to be removed from isolation.

Rifampin and doxycycline were reported to be well tolerated in this study. Concern must be maintained, however, about the possibility of adverse effects, such as the development of *Clostridium difficile*-associated disease. Furthermore, the polypharmacy to which most hospitalized patients are exposed makes the routine use of rifampin difficult because of its induction of cytochrome P450 enzymes and the resultant increased clearance of a large number of medications that are metabolized by those enzymes.

The high baseline rate of mupirocin resistance seen in this study (despite attempted exclusion of those with known mupirocin resistance prior to randomization) is not without precedent in hospital-acquired MRSA and all but one of the isolates (a USA 400 strain) were hospital strains as determined by multilocus sequence typing. Mupirocin resistance, however, appears to also be a problem in USA 300, the community-acquired MRSA prevalent in the United States. Thus, a gene encoding high-level resistance to mupirocin, *ileS*, carried on a conjugative plasmid, pUSA03 has been detected in 46% of multidrug-resistant strains of USA300, the most prevalent community acquired MRSA in the United States.[1] Alternative anti-MRSA nasal applications that may be considered include triple antibiotic ointment[2] and investigative agents, such as REP8839, an inhibitor of methionyl-tRNA synthetase .[3]

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More Evidence of Vancomycin Impotence

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Source: Stryjewski ME, et al. Use of Vancomycin or First-Generation Cephalosporins for the Treatment of Hemodialysis-Dependent Patients with Methicillin-Susceptible *Staphylococcus aureus* Bacteremia. *Clin Infect Dis.* 2007; 44:190-196.

Synopsis: *Vancomycin was inferior to cefazolin in the treatment of MSSA bacteremia in chronic hemodialysis patients in a retrospective study.*

A number of retrospective studies have provided evidence that, relative to therapy with semisynthetic penicillins such as nafcillin, vancomycin is inferior in the treatment of bactermic infections due to methicillin-susceptible *Staphylococcus aureus* (MSSA). Vancomycin, however, continues to be used in the treatment of MSSA infections in patients with beta lactam allergies and, often, because of the convenience of infrequent dosing in patients requiring dialysis. In patients with non-life-threatening penicillin allergies, cephalosporins are often used as an alternative to semisynthetic penicillins. Stryjewski et al have now retrospectively examined the efficacy of vancomycin relative to that of a first-generation cephalosporin, cefazolin, in the treatment of 123 adults at the Duke University Medical Center with MSSA bacteremia who were receiving chronic hemodialysis.

Vancomycin therapy was initiated with a 15 mg/kg loading dose, followed by a 500 mg dose after each high-flux dialysis, while cefazolin was given as a 2-gram or 3-gram dose, depending upon whether the next dialysis was scheduled to occur in 2 or 3 days, respectively. Vancomycin recipients were younger (51 years vs 57 years) and also had a significantly higher incidence of the presence of meta-static complications of their infections at the initiation of therapy (36.7% vs 11.7%). Despite this imbalance favoring vancomycin, treatment failure, defined as death or recurrent infection, nonetheless, occurred significantly more frequently in vancomycin recipients (24 of 77; 31.2%) than cefazolin recipients (6 of 46; 13.0%; $P = 0.02$). Among those treated with vancomycin and for whom the data was available, the median vancomycin serum trough

concentration was 13.7 mcg/ml in those who were successfully treated with this glycopeptide antibiotic and 16.8 mcg/ml in those who failed therapy. None of the isolates had a vancomycin MIC > 2 mcg/ml; most were 1 mcg/ml. Hemodialysis access was removed in 67.7% of vancomycin recipients and 75.6% of those treated with cefazolin. Multivariate analysis identified retention of dialysis access and treatment with vancomycin as significant independent risk factors for treatment failure.

COMMENTARY

The role of vancomycin in the treatment of serious infections due to *S. aureus* has been called into serious question. In the case of MSSA infections, the evidence of inferiority vancomycin, relative to beta-lactam therapy, has, in my opinion, achieved critical mass. In addition to this report by Stryjewski and colleagues, eg, Chang and colleagues have reported their prospective observational experience indicating that, relative to treatment with nafcillin, vancomycin therapy was associated with a significantly greater risk of persistent bacteremia and/or relapse.[1]

These results are particularly interesting because of previously identified deficiencies of cefazolin as an antistaphylococcal antibiotic. The efficacy of cefazolin in the treatment of MSSA infections may be less than that of nafcillin, particularly with MSSA isolates that produce type A-lactamase, which is capable of rapid hydrolysis of cefazolin, especially when a high inoculum of organisms is present.[2] The relative inefficacy of vancomycin is thus thrown into even higher relief when the problems with cefazolin are considered.

The role of vancomycin in the treatment of MRSA infections is also questionable,[3] with increasing evidence of diminished efficacy as the susceptibility of this organism diminishes, as evidenced by "MIC creep." Thus, vancomycin may be in the twilight of its career as an antistaphylococcal agent. ■

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Relationship of HCV Infection to Mortality In Families

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP

Source: Hansen AB, et al Mortality in Siblings of Patients Coinfected with HIV and Hepatitis C Virus. *J Infect Dis.* 2007;195:230-235.

Synopsis: *437 siblings of HIV/HCV-coinfected patients, 1856 siblings of HIV-monoinfected patients, and 285,509 siblings of control subjects were studied. Mortality was significantly higher in siblings of HCV-coinfected patients than either siblings of HIV-monoinfected patients or siblings of controls.*

THIS INTERESTING STUDY FROM DENMARK USED data from the comprehensive Danish Civil Registration System to examine mortality in siblings of HIV/HCV-coinfected patients, HIV-monoinfected patients, and controls. Mortality rates of siblings of HIV/HCV coinfected patients (3.4-7.3 deaths/1000 person-years) were strikingly increased at all decades of life from 20-49 years over mortality rates seen in siblings of HIV-monoinfected patients (1.4-1.9 deaths/1000 person-years) and siblings of control subjects (0.8-2.1 deaths/1000 person years).

COMMENTARY

It is estimated that 30% of HIV-infected patients in Western countries are coinfected with hepatitis C virus. Most cohort studies have shown increased liver-related mortality in coinfected patients vs HIV-monoinfected patients. Data are conflicting on the effect of HCV coinfection on non-liver related mortality in HIV patients. This large cohort study conclusively demonstrates strikingly higher mortality in siblings of patients co-infected with HCV and HIV over siblings of either HIV-monoinfected patients or siblings of normal control subjects. A key to the possible explanation is found on examination of the baseline characteristics table of the paper. Not surprisingly 67% of the coinfected patients acquired their HIV infection by injection drug use (IDU). While data on high-risk behavior were not available on the siblings, it seems likely that the siblings of these HIV/HCV-coinfected patients may have also suffered from addiction or made other high-risk lifestyle choices that served to increase their mortality as well as that of their coinfected siblings.

I found the implications of this article to be profoundly disturbing, but not particularly surprising on

further reflection. Practicing where I do now at our county hospital and serving as the medical director of our HIV clinic, I see daily the end results of the tragic lives of so many of our patients. When one talks with so many of our HIV/HCV-coinfected patients it is clear that many of them were severely abused (physically, sexually, verbally, and emotionally) during their childhoods. Infection with these viruses was a predictable consequence as they tried to soothe the pain in their souls with drugs or risky sex. In view of this, it is not surprising that that the HIV-negative siblings of these patients lead the same sorts of tragic lives.

In reality, it is often too late to "save" many of our patients. However, it is not too late to save the next generation and to intervene in meaningful ways to break the familial cycle of abuse, neglect and despair. As American citizens and people of conscious we should do all we can to promote public support of early childhood enrichment programs, child care, emotional support for parents, and, of course, drug and alcohol rehabilitation. In addition to voting, we should make our priorities known to our elected representatives. We should also be generous in our charitable giving. ■

Fever, Rash, and Severe Arthralgias in Travelers Returning from India

CASE REPORT

By Sheela Shenoi, MD, and Albert Shaw, MD

Dr. Shenoi is a Fellow in Infectious Diseases, and Dr. Shaw is an Assistant Professor of Medicine, Section of Infectious Diseases, both at the Yale School of Medicine, New Haven, CT

Drs. Shaw and Shenoi report no financial relationships relevant to this field of study. This article originally appeared in the January 2007 issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, MPH, and peer reviewed by Lin H. Chen, MD. Dr. Bia is Professor of Medicine and Laboratory Medicine; Co-Director, Tropical Medicine and International Travelers' Clinic, Yale University School of Medicine, and Dr. Chen is Assistant Clinical Professor, Harvard Medical School; Director, Travel Resource Center, Mount Auburn Hospital in Cambridge, MA. Dr Bia is a consultant for Pfizer and Sanofi Pasteur, and receives funds from Johnson & Johnson. Dr. Chen reports no financial relationship relevant to this field of study.*

A 56-year-old man, originally from India and with a history of hypertension, had developed bilateral red, swollen ankles while on a recent trip to Bangalore. Five days later, the patient developed severe fever and shaking chills that resolved within 48 hrs. He had stayed in his brother-in-law's house in an urban setting, with several children residing there. He had not been swimming or spent any time in rural areas or farmland, nor had he been in direct contact with animals. He saw a physician, was told that he had a viral syndrome, but was given an unknown antibiotic and pain medication. Two days later, he developed diarrhea with 5 loose bowel movements, with no blood or abdominal pain, so he stopped the antibiotics with resolution of the diarrhea. He arrived back in the United States, and 24 hrs later noticed worsening of the ankle swelling, dizziness, and "red dots" on the upper extremities, prompting emergency evaluation. He reported swelling of fingers in both hands, fatigue and mild discomfort in both ankles, but was otherwise asymptomatic. The patient reported numerous mosquito bites, but took no antimalarial prophylaxis. Of note, the patient's brother-in-law in India had also developed similar symptoms.

In the hospital, the patient was afebrile and examination was significant for peripheral edema 1/3 up the calves with associated erythema and mild tenderness, without effusion or warmth. On the hands, there was mild proximal interphalangeal joint swelling bilaterally without warmth, effusion, or synovial hypertrophy. The heart and lung sounds were within normal limits, and abdominal exam was unremarkable and without hepatosplenomegaly. There was no cervical, axillary, or inguinal lymphadenopathy, and the rash had resolved.

White blood cell count was 3,600 cells /uL with 41% segmented neutrophils, 34% lymphocytes, and 10% eosinophils. Platelets were 151,000/uL with normal hemoglobin. Peripheral blood smears were negative for malaria; urinalysis was unremarkable, and blood cultures were negative. Serum creatine phosphokinase (CK) was elevated at 357 IU with normal serum CK-MB and troponin levels. AST was elevated 70 U/L and ALT was 77 U/L (nl. for both 0 - 35 U/L) with normal serum bilirubin and alkaline phosphatase.

The presumptive diagnosis was chikungunya versus dengue virus infection. The patient was discharged home. At a follow up appointment ~10 days later, the patient reported persistent arthralgias in the ankles without effusion on exam. Fourteen days after discharge, serologies sent to CDC were reported as IgM-positive, IgG-negative for chikungunya virus and IgM-negative, IgG-positive for dengue.

COMMENTARY

The CDC's website (www.cdc.gov/travel/), as well as sites such as the WHO Weekly Epidemiological Record (www.who.int/wer/en/) and ProMED mail www.promedmail.org/pls/promed/) are useful resources. In this case, a relevant outbreak of chikungunya virus involving > 200,000 cases starting early 2005 and peaking in December 2005 had been noted in Reunion (Indian Ocean) with associated cases in Mauritius and Seychelles. More than 340 cases have been documented in France among tourists returning from islands in the Indian Ocean. Cases have also been reported in returning travelers in China and Germany. There have been 12 cases among travelers to the United States, diagnosed serologically at the CDC in 2005-2006. In India, since March 2006, there has been an epidemic of chikungunya virus, with thousands of cases reported in the central states of Maharashtra (home to Mumbai, or Bombay), Andrha Pradesh (home to Hyderabad), and Karnataka (home to Bangalore, where our patient resided during his trip).

The word chikungunya, a Makonde term meaning "that which bends up," was given in reference to the joint pain and contortions associated with severe infections. A classic paper by Robinson et al (1955) described the illness among 115 patients along the border of modern day Tanzania and Mozambique. Since then, it has been considered responsible for multiple epidemics in Africa, southeast Asia, and the Philippines, such as in Peace Corps volunteers in 1986. Retrospective studies attribute many epidemics of fever, rash, and arthralgias from Indonesia (1779) to east Africa, to India, and possibly even to the southwestern United States (1827) to chikungunya infections.

Epidemiological studies done by Robinson, Ross, and Lumsden (1955) during chikungunya outbreaks in Uganda that examined the various mosquito species in an infected village and viral infectivity demonstrated that the most likely vector was the *Aedes aegypti* mosquito, an aggressive daytime feeding species. In recent outbreaks (2/06) among the islands of the Indian Ocean, the vector is *Aedes albopictus* (the Asian tiger mosquito). Serologic studies indicate that > 20% of people in various regions of tropical Africa have evidence of infection. Clinical similarity to dengue may represent under diagnosis and underreporting of chikungunya infections.

Among the alphaviruses, chikungunya is antigenically distinct from the encephalitis viruses, WEE, EEE, and VEE, and is grouped in the Semliki Forest virus antigenic complex.

Chikungunya infections may be asymptomatic, or may appear as an abrupt illness similar in presentation to dengue infection, with fever, headache, myalgias, malaise, and severe polyarticular arthralgias, especially of the small joints and also of those which have been previously injured. Incubation period is 1-8 days. The joints become swollen, without significant effusions, and usually resolve within 1-2 weeks. Often a maculopapular rash erupts over the face and neck in the first few days of the illness, and may later reappear on the trunk, limbs, face, palms, and soles. Petechial lesions have also been frequently reported, though their pathogenesis is unclear. Lymphadenopathy is mild or absent. Conjunctivitis is frequently reported. Rare but serious CNS manifestations such as seizures, and meningoencephalitis have been reported, particularly in children. The acute fevers usually resolve within 3 days, though low-grade temperatures may recur later in the course. *Arthritis is frequently the most prominent symptom, and has been characterized as a symmetric polyarthritis that may affect the MCP joints, wrists, elbows, knees, ankles and MTP joints*.

The differential diagnosis includes non-hemorrhagic dengue, which is often clinically indistinguishable from chikungunya virus infections. Dengue usually has less rash, headache and arthralgia, but more adenopathy, especially long term. There are several additional arboviruses that can cause fever and arthralgias, including O'nyong-nyong, which is antigenically closely related to chikungunya, but is found primarily in Africa.

Laboratory studies reveal relative leukopenia with lymphocytosis, mild thrombocytopenia, and slightly elevated ESR/CRP. A mild elevation in hepatocellular enzymes is often found. As the level of viremia and fever trend down, hemagglutinin inhibition and serum antibodies rise. An antibody capture IgM ELISA is available through CDC (CDC Arboviral Diseases Branch: 970-221-6400; instructions for shipping specimens: www.cdc.gov /ncidod/dvbid/misc/specimen-submission.htm). A reverse transcription PCR (E1 protein and nonstructural protein 1) has been developed which takes less than 48 hours but is not widely available in the United States. Generally, diagnosis is made on clinically grounds.

Many patients recover uneventfully with supportive care, including rest, hydration, acetaminophen

and/or NSAIDS. However, arthritis may be persistent and occasionally incapacitating in adults; 4 months later, up to 50% may have musculoskeletal findings such as morning stiffness, decreased grip strength, tenosynovitis, and periarticular soft tissue swelling, especially involving the proximal interphalangeal joints (Kennedy et al, 1980). Of the 4 patients presented in the CDC case series, one patient's arthralgias persisted for approximately one month, whereas another patient's joint symptoms persisted for up to 5 months. Cardiac involvement, including arrhythmias or cardiomyopathy and heart failure, has been rarely suggested to be associated with chikungunya infections. The development of a live-attenuated vaccine in a phase II trial has been reported, though it is still in trial.

As *Aedes albopictus*, the chikungunya vector in the Indian Ocean outbreak, is prevalent worldwide, including the Americas, there is risk that infected returning travelers may introduce chikungunya into local mosquito populations and cause outbreaks, especially in temperate areas of the United States. Patients with suspicion for infection should be reported and should avoid introduction of the virus to local mosquitoes by staying indoors as much as possible, wearing long sleeves, and using insect repellents during the first week of illness. ■

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Update on Guillain-Barré Syndrome and Menactra® Meningococcal Conjugate Vaccine

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

Sansum-Santa Barbara Medical Foundation Clinic, Santa Barbara, CA

Dr. Scully reports no financial relationship relevant to this field of study. This article originally appeared in the January 2007 issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, MPH, and peer reviewed by Lin H. Chen, MD. Dr. Bia is Professor of Medicine and Laboratory Medicine; Co-Director, Tropical Medicine and International Travelers' Clinic, Yale University School of Medicine, and Dr. Chen is Assistant Clinical Professor, Harvard Medical School; Director, Travel Resource Center, Mount Auburn Hospital in Cambridge, MA. Dr Bia is a consultant for Pfizer and Sanofi Pasteur, and receives funds from Johnson & Johnson. Dr. Chen reports no financial relationship relevant to this field of study.*

Source: CDC. Update: Guillain-Barré Syndrome Among Recipients of Menactra® Meningococcal Conjugate Vaccine- United States, June 2005- September 2006. *MMWR*. 2006; 55:1120-1124.

Synopsis: *This report summarizes the 9 additional reports of Guillain-Barré Syndrome to the Vaccine Adverse Event Reporting System (VAERS) during March through September 2006. There have now been a total of 17 cases. Although the available data suggest a small increased risk for Guillain-Barré Syndrome after Menactra® Meningococcal Conjugate Vaccine (MCV4), the CDC recommends continuing routine vaccination of adolescents, college freshman living in dormitories, and persons increased risk of meningococcal disease.*

In October of 2005, the first reports of 5 cases and the possible association of Guillain-

Barré Syndrome (GBS) and recipients of Menactra® Meningococcal Conjugate Vaccine (MCV4) were reported. In April 2006, 3 additional confirmed cases of GBS within 6 weeks of MCV4 vaccination were reported. This most recent report summarizes 9 additional cases, resulting in a total of 17 GBS cases reported since June of 2005.

Of the 9 new cases, 5 were male and 4 were females. All but 2 patients (ages 43 and 30) were between the ages of 15 to 18. Each of the 9 cases was reviewed by both a CDC medical officer and a clinical investigator from Boston University. Four of the 9 had received MCV4 as the sole vaccination. The other patients had received concurrent vaccines such as Hepatitis A, Hepatitis B, Tdap, and human papillomavirus (HPV) vaccine. One patient, the 43-year-old male, received 6 other concomitant vaccinations with MCV4, including trivalent inactivated influenza vaccine. The range of onset of the adverse event from vaccination with MCV4 was 2-33 days with a mean of 15.7 days. The timing and onset of neurological symptoms after MCV4 vaccination is of concern.

Using data from the Healthcare Cost and Utilization Project (HCUP) and the Vaccine Safety Datalink (VSD), the background incidence rate for GBS among patients aged 11-19 years was estimated at 0.11 per 100,000 person-months. The rate of GBS was estimated to be 0.20 per 100,000 person-months in 11-19 year olds who had received MCV4. However, in a separate VSD analysis, a total of 126,506 doses of MCV4 were delivered between March 2005 and September 2006, and no cases within 6 weeks of vaccination were observed in recipients aged 11-19 years (0.2 cases would have been expected). Two cases of GBS were reported among an equal number of 11- to 19-year-olds receiving preventive care who had not received MCV4 vaccination.

Campylobacter jejuni, a cause of bacterial gastroenteritis, is a known precipitating factor for GBS. It is unlikely that *C. jejuni* played a role in these recent reports.

COMMENTARY

Menactra®, a quadrivalent (A, C, Y, and W135) meningococcal conjugate vaccine (MCV4), was licensed in the United States on January 14, 2005. Each 0.5-ml dose of MCV4 contains 4 mg each of capsular polysaccharide from *Neisseria meningitidis* serogroups A, C, Y, and W135 conjugated to 48 g of diphtheria toxoid. The MCV4 vaccine is approved for ages 11 to 55 years old. In February of 2005, the Advisory Committee on Immunization Practices (ACIP) recommended that in addition to the previous recommendations for first year college students living in dormitories and other high risk groups, MCV4 be given at the preadolescent visit (ages 11-12 years) or prior to high school at 15 years if not previously vaccinated.[1]

The serogroups responsible for most cases in the United States are serogroups B, C, and Y. No vaccines for serogroup B are readily available except in New Zealand. Serogroup B accounts for a significant amount of disease in Europe and America and often occurs in infants, a group at high risk of invasive disease and little immunologic maturity.[2] In the meningitis belt of sub-Saharan Africa, epidemics secondary to serogroup A and more recently W-135 predominate. In the United Kingdom, high rates of serogroup C led to a campaign to immunize all infants and children with a serogroup C conjugate vaccine.

Unfortunately, it may take several years of monitoring to more clearly define the risk association of GBS and MCV4. In May of 2006, in response to a vaccine shortage of MCV4, the CDC and the Advisory Committee on Immunization Practices (ACIP) recommended deferral of vaccination of children aged 11 to 12 years. These vaccine shortages have now been resolved and as of November 3, 2006, the routine vaccination of children 11 to 12 years old should resume.[3] Further monitoring will be essential as we resume full-scale vaccination of these adolescents.

An updated fact sheet for health care workers on GBS and Menactra is available at www.cdc.gov/nip/vacsafe/concerns/gbs/Menactra.htm. Patients with prior history of GBS should not receive MCV4. Any provider who suspects GBS or any other adverse event after MCV4 is encouraged to report online at www.vaers.hhs.gov or by fax at 877-721-0366. ■

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Preventing Nosocomial Infection in Cardiac Surgery by Topical Oro-Nasal Decontamination

ABSTRACT & COMMENTARY

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Dr. Pierson reports no financial relationship relevant to this field of study.

This article originally appeared in the January 2007 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and nurse planner Leslie A. Hoffman, PhD, RN. It was peer reviewed by William Thompson, MD. Dr. Hoffman reports no financial relationship relevant to this field of study; she works at the Department of Acute/Tertiary Care in the School of Nursing at the University of Pittsburgh. Dr. Thompson reports no financial relationship relevant to this field of study. He is Associate Professor of Medicine at the University of Washington in Seattle.*

Source: Segers P, et al. *JAMA*. 2006;296:2460-2466.

Synopsis: *In adult patients undergoing elective cardiac surgical procedures, perioperative decontamination of the nasopharynx and oropharynx with chlorhexidine solution substantially reduced nosocomial infections and nasal carriage of* S aureus*, and was associated with a mean reduction in hospital stay of 0.8 days.*

Segers and colleagues of the University of Amsterdam conducted this randomized, double-blind clinical trial at a 480-bed community hospital that performs 1200 cardiac surgical procedures annually. They sought to determine whether the routine application of the disinfectant chlorhexidine to the nasopharynx and oropharynx of patients undergoing cardiac surgery would decrease the incidence of nosocomial infection, nasal carriage of *Staphylococcus aureus*, and the duration of hospital stay.

All patients over 18 years of age who underwent sternotomy for electively-scheduled cardiac procedures and gave consent during the 25-month study period were included. They were randomized to receive 0.12% chlorhexidine gluconate both as a nasal gel and as a 10-mL mouth rinse or an apparently identical placebo. Application of the experimental solutions began on hospital admission and continued 4 times daily until the nasogastric tube was removed postoperatively, usually the day after surgery. Nosocomial infections were diagnosed using accepted criteria from the Centers for Disease Control and Prevention (CDC), and nasal surveillance cultures for *S. aureus* were performed at fixed intervals. All patients underwent perioperative skin cleansing and administration of intravenous cefuroxime according to institutional protocols.

In this study, 991 patients were randomly administered chlorhexidine decontamination or placebo. The overall incidence of nosocomial infection was 19.8% in the chlorhexidine group as compared to 26.2% in the placebo group (absolute risk reduction [ARR], 6.4%; 95% confidence interval [CI], 1.1%-11.7%; $P = 0.002$). The most severe infections—lower respiratory tract infections and deep surgical site infections—were significantly less common in the active treatment group: ARR, 6.5% and 3.2%, respectively, $P = 0.002$ for each. The number needed to treat in order to prevent 1 nosocomial infection was 16. In addition, *S. aureus* nasal carriage was reduced by 57.5% in the patients who received chlorhexidine, as compared with 18.1% in the placebo group ($P < 0.001$). Total hospital stay for patients treated with chlorhexidine gluconate was 9.5 days, compared with 10.3 days in the placebo group (ARR, 0.8 days; 95% CI, 0.24-1.88; $P = 0.04$). One patient in the active treatment group experienced temporary discoloration of the teeth; there were no other reported adverse effects.

COMMENTARY

Nosocomial infections occur in as many as 20% of patients who undergo cardiac surgery, and are an important cause of mortality, morbidity, prolongation of hospitalization, increased antibiotic utilization, and excess costs. The source of these infections is often the patient's own organisms, the suppression of which by means of topical decontamination would seem a logical and practical strategy for reducing their incidence.

This was a study in patients undergoing elective cardiac surgery, whose ICU stays were generally short. Whether beneficial effects of routine naso- and oropharyngeal decontamination with chlorhexidine similar to those obtained in this study would be observed in medical ICU patients or in a general surgical ICU population is not known at this point.

The treatment as used in this study was both safe and inexpensive. The reported daily cost for

the decontamination regimen employed was $7.20. With an average duration of decontamination of 2 days, the cost to prevent one nosocomial infection was estimated to be $230. Costs would undoubtedly be higher using the prepackaged commercial kits for oral hygiene and decontamination that are currently being marketed in the United States; an estimation of the cost to prevent one infection, assuming clinical effectiveness similar to the efficacy demonstrated by Segers et al and using actual current costs in your hospital, would be a worthwhile exercise prior to widespread adoption of this treatment. ■

CME Questions

25. Which of the following is correct?

A. MRSA rarely is resistant to mupirocin.
B. While some hospital strains of MRSA may be resistant to mupirocin, community-acquired MRSA are never resistant to this drug.
C. Almost one-fifth of MRSA follow-up isolates in the study by Simor and colleagues were the result of acquisition of a new strain, rather than failure of decolonization.
D. In the study by Simor and colleagues, decolonization was demonstrated to significantly decrease the risk of invasive MRSA infections.

26. Which of the following is correct with regard to the report by Stryjewski and colleagues?

A. Vancomycin was more effective than cefazolin in the treatment of MSSA bacteremia in chronic hemodialysis patients.
B. Vancomycin failure was associated with lower vancomycin trough concentrations when compared to cases in which vancomycin was successful.
C. Cefazolin may be inactivated by at least some strains of MSSA.
D. Retention of hemodialysis access and treatment with vancomycin were independent predictors of treatment failure.

27. Which of the following is correct?

A. Chikungunya is a Swahili word meaning "that which causes diarrhea."
B. Chikungunya virus is a flavivirus.
C. Chikungunya infections are limited to Southeast Asia.
D. Severe persisting joint pain is commonly observed in patients with Chikungunya fever.

Answers: 25.(c) 26.(d) 27. (d)

CME Objectives

The objectives of *Infectious Disease Alert* are:

• To discuss the 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; and

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

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In Future Issues:

IVIG in Sepsis.

UPDATES

By Carol A. Kemper, MD, FACP

The First 80 Hours in TB Treatment

Source: Gumbo T, et al. Isoniazid's bactericidal activity ceases because of the emergence of resistance, not depletion of Mycobacterium tuberculosis in the log phase of growth. *J Infect Dis* 2007;195:194-201.

In patients with M. tuberculosis infection, the emergence of chromosomally mediated resistance to INH is a stochastic process, meaning it is the sum of the product of the spontaneous mutation rate (10^{-6}) and the total bacterial load. In other words, if a patient has a small pulmonary infiltrate, with an estimated bacterial load of 10^{+4}, the risk of INH-resistant organisms being present is about 1 in 100 (10^{-2}). However, in a patient with a large cavitary infiltrate, with an estimate bacterial load of 10^{+9}, the potential number of INH-resistant organisms is closer to 1000 (10^{+3}). This rate of spontaneous mutation may occur in the absence of selective pressure, and may therefore be present prior to initiation of treatment, although it is well below the levels of detectability for most laboratories (> 1% of colonies).

For this reason, the information from Gumbo and colleagues is especially important. While clinicians have long believed that antimicrobial killing of TB stops at about 3-4 days of INH therapy because of depletion of organisms in the exponential growth phase, Gumbo and colleagues' data suggests otherwise. During the first 3 days of INH therapy, a rapid decline in colony counts (~ 2 logs) was observed, due entirely to the killing of INH-susceptible organisms. At that point, the number of organisms started to increase again, largely due to the exponential phase growth of the small INH-resistant population, which began to outnumber the declining INH-susceptible population.

Increases in both the low-level and high-level INH-resistant population were observed at various daily dosages of INH. Similar data was observed for either fast or slow acetylators (INH half-life 1.8 vs 4.2 hrs) - bacterial growth resumed at about 80 hours.

Resistance was primarily due to typical katG mutations, a single point mutation in the catalase-peroxidase gene, and the induction of multidrug resistant efflux pumps.

These data are important to consider in the context of the activity of other antimycobacterial agents. While cidal activity during the first 2 days is largely due to INH, rifampin and pyrazinamide affect a much slower decline in bacterial colony counts, beginning at about day 3 to day 14. Critically, this is just the point where killing from INH wanes. Administration of moxifloxacin is associated with about a one-third log reduction between days 0 and 2, and then a 0.24 log drop between days 2 and 7. The age-old practice of starting TB therapy one drug at a time is no longer advisable. Based on these data, one can see why. ■

More on XDR-TB: A Looming Crisis

Source:ProMED-mail, January 28, 2007; promed@promedmail.org

An increasing amount of lay press is illuminating the emergence of an exceptionally drug-resistant strain of M. tuberculosis (XDR-TB) (resistant to 6-10 second line agents) in South Africa - and the growing controversy surrounding that government's response.

Since XDR-TB was first detected in 53 persons (52 HIV+ patients quickly died) in KwaZulu-Natal Province in South African in May 2005, at least 300 additional cases have been identified in 39 hospitals in 8 other provinces in S. Africa. Experts at the WHO, and a spokesman for a consortium of South African and American AIDS researchers have expressed alarm that not enough is being done to identify and isolate cases, and that the infection is quickly spreading, threatening the large number of HIV-infected South Africans (estimated to exceed 20% of the population).

Active cases probably represent the tip of the iceberg, and many more persons have likely been exposed. Because of cross-border traffic of migrant workers and refugees, it is feared the infection has crossed into Mozambique, Swaziland, Lesotho and Zimbabwe-nations that have even fewer health care dollars to deal with this looming disaster. Experts are concerned that, since learning about the first outbreak in May 2005, the South African government is doing too little too late to identify and isolate cases. Sadly, treatment for many is not an option, given the extreme drug-resistant profile.

The Director of South Africa's National TB Program, Dr. Lindiwe Mvusi, disagrees with these concerns, contending that sufficient hospital beds are available, and new facilities are under construction.

The cost of routine TB treatment in Africa is estimated at about $15 dollars per case; about 10 times the health dollars available per person in some countries. However, the estimated cost of treating a single case of MDR-TB, including isolation, is about $150 per person. Some countries do not even have sufficient laboratory support to manage this problem, especially when you consider that one laboratory technician can process about 20 sputum specimens for AFB smear and culture per day. ■

Hemorrhaging Doctors and Nurses

Source: Mullan F. Doctors and Soccer players - African Professionals on the Move. *N Engl J Med.* 2007; 356:440-442.

This article briskly states another pressing problem for African health care: the loss of their educated health care professionals. A prime example of the "leaky" medical system is Ghana, which has attempted to ramp up the number of trained physicians and the quality of their education, hoping to retain at least some portion of their trained physicians. But the more dollars are pored into improving the quality of medical education, the more trained professionals are lost to the United States, the United Kingdom and Canada. Although Ghana has considerable natural resources, and a larger health care budget than most African nations, it is estimated to have only 13 physicians per 100,000 population, about one-twentieth the number of physicians per person in the United States. At least 20% of the physician work force is practicing outside of Ghana, leaving only about 2,600 doctors inside the country. The situation for nurses is even worse: attempts to establish a training facility for medical assistants failed because too few nurses were available to apply - they had all emigrated.

A major factor cited in this migration was money - a physician can make 6 times the salary in London as in Africa. Various creative measures to retain physicians, such as free cars, subsidized housing, and pay increases are being attempted but may fall short of the anticipated income and life-style of a medical practice in the United States or the United Kingdom. Other considerations, such as academic camaraderie, access to sub-specialty training, and the opportunity to practice a higher standard of medical care may be important factors, and must be compensated for if physicians are to be retained.

What went unstated in this article was the wish for a safer life for physicians and their families. Physicians, especially those who do not refrain from politic activity or social activism, have been run out of their country, or escaped corrupt and violent regimes, and are unable to return. I know of one Kaiser physician from Nigeria who expressed a wish to return to his country one day should the political situation change. And while a medical education may presently be a ticket out of Africa, it is possible these individuals would have found other opportunities to exit. ■

Improving TB Screening of Immigrants

Source: Varkey P, etal. The Epidemiology of Tuberculosis Among Primary Refugee Arrivals in Minnesota Between 1997 and 2001. *J Travel Med.* 2007; 14:1-8.

The emergence of increasingly drug-resistant forms of TB is prompting re-examination of TB screening practices of immigrants and refugees in the United States. By 2002, more than 50% of active TB cases in the United States occurred in foreign-born persons.

Minnesota, which has a long tradition of sponsoring immigrants and refugees, has one of the largest populations of Ethiopians and other Africans in the United States, and the third largest Southeast Asian population. (People are often surprised to learn that my medical school classmates and I lived on the inexpensive and delicious Vietnamese food around the University Medical Center in Minneapolis in the early 1980s). From 1979 to 2004, Minnesota accepted over 75,000 refugees. By 1998, 70% of MN TB cases were foreign born, compared with 41% for the rest of the nation.

In order to assess the adequacy of current public health screening procedures for refugees, these authors examined information available for 13,866 refugees who entered MN between 1997 and 2001. All persons were screened with skin testing, and chest radiographs were performed in those with a positive skin test, symptoms consistent with active TB, or an overseas exam or history of active, treated, or old TB. Of those with a documented skin test result, 51% were positive. Of these, 74% were from Africa, 58% were male, and 62% were 19 to 64 years of age.

Chest radiograph results could be located for 88% of those with a positive skin test, 70% of which were normal, 12% were abnormal but inconsistent with TB, 7% as abnormal but without any other information, 5% consistent with "old" TB, 0.8% non-cavitary disease, and 0.1% cavitary disease. Chest radiographs were missing or not performed for about 10% of patients with a positive skin test.

Of those with a positive skin test, 49% received treatment for latent tuberculosis. The remainder was not treated because of age > 35 years, refusal, loss to follow-up, or prior treatment was completed overseas. No data were available on compliance with treatment or successful completion of appropriate therapy.

Refugees have a peculiar status in the United States - because of their political status, many do not receive appropriate screening and vaccination before entry into the country, although they are "encouraged" to get a health care screening within 90 days of arrival. But many do not have ready access to good public health care systems and fall through the cracks. As a result, refugee status is an independent predictor of failure to diagnosis and promptly treat TB. In this survey of refugees entering MN from 1997 to 2001, half of those with positive skin tests did not received appropriate therapy for latent TB. This finding is especially important when rates of reactivation TB are examined across the United States, most of which occur in foreign-born persons. Thus far, INH remains the standard of treatment for TB exposure and latent TB. However, the increasing frequency of drug-resistant strains may diminish the effectiveness of INH for these purposes. Even in our own Santa Clara County, the rate of INH resistance has dramatically risen to 17%, largely because of the presence of a significant Southeast Asian population. ■

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.

Higher HDL Cholesterol in Statin Therapy, Key to Slowing Atherosclerosis?

Aggressive statin therapy is associated with slowed progression and even regression of atherosclerosis. A new study suggests that, when monitoring statin therapy, increases in HDL cholesterol may be as important as decreases in LDL cholesterol in preventing disease progression. Researchers from the Cleveland Clinic reviewed 4 large studies from United States, North America, Europe and Australia in which 1,455 patients with angiographic coronary disease underwent serial intravascular ultrasonography while receiving aggressive statin therapy for 18 or 24 months. During therapy, mean LDL levels dropped from 124.0 mg/dl to 87.5 mg/dl, and mean HDL levels increased from 42.5 mg/dl to 45.1 mg/dl, and LDL to HDL ratios were reduced from a mean of 3 to 2.1 ($P < 0.001$ for all). These changes were accompanied by a small, but statistically significant decrease in atheroma volume as measured by intravascular ultrasound. The largest decrease in atheroma volume was associated with patients with LDL cholesterol less than the mean of 87.5 mg/dl, and percentage increases in HDL cholesterol of greater than 7.5%. The authors conclude that when treating with statins, decreases of LDL cholesterol and increases in HDL cholesterol are independently associated with regression of atheroma volume. They also note that these changes were not associated with reductions in clinical events or improved clinical outcomes and that more research is needed (*JAMA*. 2007; 297:499-508).

Citalopram Useful for Depression in CDA Patients

Major depression affects up to one quarter of patients hospitalized with coronary artery disease and these patients have a worse prognosis than non-depressed patients. A new study from Canada compares the efficacy of citalopram vs interpersonal psychotherapy in reducing depressive symptoms among these patients. The study randomized 284 patients with CAD and major depression to 12 weeks of interpersonal psychotherapy plus clinical management vs clinical management only, and a second randomization compared 12 weeks of citalopram 20-40 mg/day vs placebo. The main outcomes were scores on objective depression scales. Citalopram was superior to placebo in reducing depression scores ($P = 0.005$), but interpersonal psychotherapy was ineffective, being no better than clinical management. The authors conclude that citalopram administered in conjunction with weekly clinical management was effective in treating depression whereas there was no evidence of value for interpersonal psychotherapy. The authors suggest that citalopram or sertraline (based on previous studies) should be considered as first-step treatment for patients with CAD and major depression (*JAMA*. 2007;297:367-379). An accompanying editorial agrees that citalopram and sertraline are safe and effective for treatment of depression in patients with coronary heart disease, and suggests physicians should actively screen for signs and symptoms of depression in these patients. However, there is not yet

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) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

any evidence that treating depression in this patient population reduces subsequent cardiac events (*JAMA*. 2007;297:411-412).

When to Stop Anticoagulation Before Surgery?

For patients on warfarin who have been bridging therapy with low molecular weight heparin (LMWH) prior to surgery, when is the best time to stop anticoagulation? A new study suggests that the evening before surgery is too late. Researchers in Ontario, Canada, looked at 80 patients who were scheduled for surgery or invasive procedures and were bridged with LMWH. All 20 patients had normal renal function and were given enoxaparin 1 mg/kg of body weight twice daily with the last dose administered the evening before surgery. Blood anti-factor Xa heparin levels were measured shortly before surgery, an average of 14 hours after the last dose. Two-thirds of patients had anti-Xa heparin levels of 0.5 U/ml or higher shortly before their invasive procedure. Patients with higher BMIs were more likely to have higher levels as were patients with lower creatinine clearances. The authors conclude that preoperative bridging with twice daily enoxaparin results in high residual anti-Xa heparin levels if the last dose is given the evening before surgery. They recommend that the last dose be given the morning on the day prior to surgery (*Ann Int Med.* 2007;146:184-187).

Drug Warnings: Ranibizumab and Bevacizumab

Both of Genentech's anti-angiogenic agents, ranibizumab (Lucentis) and bevacizumab (Avastin), have been the subject of new warnings from the company and the FDA. Ranibizumab, which is used for the treatment of neovascular (wet) macular degeneration, has been associated with increased risk of stroke in elderly patients. The drug, which is administered as an monthly intraocular injection, was found to be associated with a 1.2% risk of stroke at the recommended dose of 0.5 mg compared to a 0.3% risk associated with the lower-than-recommended 0.3 mg dose ($P = 0.02$) at an average follow-up of 230 days. Patients who had a history of stroke were at the highest risk. Bevacizumab, which is approved for treatment of non-small cell lung cancer and metastatic colorectal cancer, was recently found to be associated with increased risk of gastrointestinal perforation and potentially fatal pulmonary hemorrhage. Gastrointestinal perforation was seen as a complication of patients treated for colorectal cancer, while pulmonary hemorrhage was seen in patients receiving chemotherapy plus bevacizumab for lung cancer. Other bleeding complications seen in bevacizumab-treated patients including GI hemorrhage, subarachnoid hemorrhage and hemorrhagic stroke.

Growth Hormone Treatment, More Harm Than Good

The January 16, 2007, *Annals of Internal Medicine* includes a review of the safety and efficacy of growth hormone in the healthy elderly. The review was undertaken because growth hormone is widely recommended and sold as an anti-aging agent in this population. The authors reviewed 31 articles, which included a total of 220 participants who received growth hormone. The mean age was 69 and patients were generally overweight. Treatment duration mean was 27 weeks. Growth-hormone-treated patients compared to placebo- treated patients were noted to have decreases in overall fat mass and increases in overall lean body mass, but weight did not change significantly. Total cholesterol decreased, although not significantly, after adjustment for body composition changes. Bone density and other lipid levels did not change. Those treated with growth hormone were significantly more likely to experience soft tissue edema, and arthralgias, carpal tunnel syndrome, and gynecomastia as well as a slightly increased rate of diabetes and impaired fasting glucose. The authors conclude that growth hormone use in the elderly is associated with small changes in body composition and an increased rate of adverse events and cannot be recommended (*Ann Int Med*. 2007; 146:104-115).

FDA Actions

The FDA has warned against unsupervised use of topical anesthetic products for cosmetic procedures. The agency has received multiple reports of adverse events associated with patients applying excess amounts of topical agents containing lidocaine, tetracaine, benzocaine, and prilocaine. Two women who used topical anesthetics with lidocaine and tetracaine died after applying the creams to their legs and wrapping their legs in plastic to increase absorption. Healthcare professionals are cautioned to prescribe topical anesthetics with caution in the lowest concentration consistent with pain relief goals and to advise patients in their safe use.

The FDA has approved Roche's orlistat for over-the-counter use to facilitate weight loss. The drug, available in prescription form under the trade name "Xenical," blocks absorption of fat by inhibiting pancreatic lipase thus preventing triglyceride absorption in the small bowel. The over-the-counter version will be available as a 60 mg dose, half the prescription dosage. Orlistat over-the-counter will be marketed as "Alli." ■