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INSIDE

Staphylococcus lugdunensis: Not Your Father's (or Mother's) Coagulase-Negative Staphylococcus

SPECIAL FEATURE

By Ellen Jo Baron, PhD, D(ABMM)

Staphylococcus lugdunensis, IN CONTRAST TO THE OTHER skin and mucus membrane-colonizing coagulase-negative staphylococci, has virulence factors that closely resemble those of *Staphylococcus aureus* and consequently causes similar aggressively destructive infections. Because diagnostic microbiology laboratories are only just beginning to recognize the importance of this species, some clinically important isolates may go unrecognized.

Lugdunum is Latin for Lyon, France, where the organism was first characterized in 1989.[1] Recent discoveries from French scientists have further differentiated the species.

In one event, a seemingly innocent change in a surgical technique, in which the incision was placed in the shaved pubic area for esthetic concealment, resulted in a dramatic increase in postoperative wound infections due to *S lugdunensis*. The resulting investigation revealed that 22% of incoming surgical patients carried the organism on the skin of the inguinal area.[2] van der Mee-Marquet and associates reviewed previous case reports and found that a preponderance of *S lugdunensis* soft-tissue infections occurred below the waist (73% of all infections). Another recent study showed 69% of a series of *S lugdunensis* infections occurred in the pelvic girdle, all pointing to a perineal, pelvic girdle, or inguinal cutaneous source for the organism.[3] In fact, there appears to be an association between perineal or inguinal skin breaks (vasectomy, femoral arterial catheterization, prostatic cancer) and subsequent development of *S lugdunensis* endocarditis.[4,5] Endocarditis is one of several more serious types of infections, including brain abscess, osteomyelitis, peri-

VOLUME 22 • NUMBER 23 • NOVEMBER 2003 • PAGES 193-204

tonitis, and toxic shock syndrome, caused by this organism.[6,7] The bulk of reports, however, associate *S lugdunensis* with skin and soft-tissue infections, such as breast abscess, furuncles, and others.

Endocarditis due to *S lugdunensis* resembles that caused by *S aureus*, with associated abscess formation and rapid progression. Most cases are community-acquired, which fits with predisposing factors, including vasectomy or other perineal or pelvic girdle site infection.[4,7,8] A recent Stanford case and another report describe endocarditis following angiography.[9,10] These case reports and studies emphasize the need for antimicrobial prophylaxis for "clean" perineal procedures, as several authors have suggested. Only one-fourth of endocarditis patients have prosthetic valves, again more similar to endocarditis caused by *S aureus* than that due to other coagulase negative staphylococci. Three-fourths of patients, however, have pre-existing cardiac abnormalities. Again, unlike endocarditis due to *S epidermidis* and more similar to that due to *S aureus*, symptoms typically present acutely within the first 2-3 weeks, with 50% of patients presenting with hemodynamic instability on admission and 25% of cases showing valvular destruction.[4] The overall mortality rate associated with *S lugdunensis* endocarditis, despite appropriate antibiotics and surgical intervention as needed, is high, with estimates from 50% to 73% in the literature. One key difference between *S aureus* and *S lugdunensis* is the latter's relative susceptibility to penicillins. Most strains are actually penicillin susceptible, in which case of course, penicillin is the drug of choice. Oxacillin (methicillin) resistance is so rare that it motivated a case report (the first to describe infection with a MRSL) when such an isolate caused a bloodstream infection in a neonate in Singapore.[11] Of 59 clinical isolates evaluated in one study, all were susceptible to oxacillin, cephalothin, gentamicin, rifampicin, and vancomycin. Seventy-six percent of isolates were beta-lactamase negative, with penicillin G MICs ≤ 0.13 microgram/mL.[12]

Both *S lugdunensis* and *S aureus* may harbor similar virulence factors such as an accessory gene regulator (agr) and ability to bind extra-cellular matrix protein.[13,14] *S lugdunensis* is also similar to *S aureus* in that it is infrequently recovered as colonizer or contaminant.[12] *S lugdunensis* is most commonly recovered from skin and skin structure infections followed by blood and vascular catheter infections.

Because *S lugdunensis* are typically slide-coagulase (clumping-factor) positive, they may be confused with *S aureus* on initial screening of colonies. Another coagulase-negative staphylococcus, *S schleiferi*, is also typically slide-coagulase positive. The tube coagulase tests for both *S lugdunensis* and *S schleiferi*, however, are negative. Laboratories should have a heightened suspicion for this species from serious infectious sites and sterile body fluids, and should use special tests, such as the pyrrolidonyl peptidase (PYR) test, which is positive, to differentiate this species from *S aureus*.[15] Importantly, if staphylococci are placed immediately into liquid coagulase test tubes, this species may be misidentified as a conventional "coagulase-negative staphylococcus." Physicians may wish to check that their laboratories are aware of detecting this species and have appropriate methods in place.

As laboratories improve their ability to recognize *S lugdunensis*, we are becoming more aware of its role in

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.

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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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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, we disclose that Dr. Deresinski serves on the speaker's bureau of Merck, GlaxoSmithKline, Ortho, Bayer, and Pfizer. Dr. John is a consultant for Cubist, Roche, and BioMerieux, is on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Bayer, and Wyeth, and does research for Merck. Dr. Kemper serves on the speaker's bureau of Virologic, GlaxoSmithKline, Pfizer, and Agouron and is involved in research with Chiron, Merck, Agouron, and Virologic. Dr. Schleis is on the speaker's bureau for Aventis and Bayer and is a consultant for FFF Enterprises, Aventis, and Bayer. Dr. Muder does research for Aventis, and Pharmacia. Dr. Tice is a consultant for Roche, Merck, and ZLB and is on the speaker's bureau of Roche, Ortho, GlaxoSmithKline, and Pharmacia, and does research for Elan, Roche, Merck, Pharmacia, and Becton-Dickinson. Dr. Jenson is on the speaker's bureau of Merck. Dr. Donnelly is a consultant for OrthBioTech, and does research for Janssen, Merck, Novartis, Numico, Pharmacia, and Pfizer. Dr. Smilack reports no speaker's bureau, research, stockholder, or consulting relationships having ties to this field of study.

serious infections and the need for aggressive early medical and surgical intervention. ■

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Corticosteroids for Kawasaki Disease

ABSTRACT & COMMENTARY

Synopsis: *Pulsed-dose intravenous methylprednisolone added to the conventional treatment of IVIG and high-dose aspirin, resulted in faster resolution of fever and lower ESR, CRP, and levels of IgA in children with Kawasaki disease.*

Source: Sundel RP, et al. Corticosteroids in the initial treatment of Kawasaki disease: Report of a randomized trial. *J Pediatr*. 2003;142:611-616.

A PROSPECTIVE, RANDOMIZED TRIAL WAS CONDUCTED among children with Kawasaki disease in Boston between February 1998 and November 2000. Patients were stratified, using a permuted blocks design, by age (< 1 yr, ≥ 1 yr) and sex, and randomly assigned to receive pulsed-dose intravenous methylprednisolone (30 mg/kg; maximum, 1.5 g administered over 3 h) before receiving IVIG. Usual doses of IVIG (2 g/kg, administered over 10 h) and aspirin (20-25 mg/kg administered every 6 h until afebrile for 48 h, then 3-5 mg/kg/24 h as a single dose) were given to all patients.

Of the 39 study subjects, 18 received methylprednisolone with IVIG and aspirin, and 21 received IVIG and aspirin. Children treated with methylprednisolone had lower mean 6:00 pm temperatures (36.3 ± 0.6ºC vs 37.0 ± 0.7ºC; $P = .002$) and maximum daily temperatures (37.1 ± 1.1ºC vs 39.2 ± 1.1ºC; $P = .001$), shorter total duration of fever (0.5 days [range, 0-4 days] vs 2 days [range, 0-8 days]; $P = .009$), and tended to be treated less frequently with acetaminophen during their hospitalization (8/18 [33%] vs 12/21 [57%]; $P = .06$, Fisher's exact test). Because of persistent or recrudescent fever for > 48 hr after the initial IVIG dose, 2 children (11%) in the methylprednisolone group required retreatment with a second dose of IVIG (2 g/kg), compared with 5 children (24%) in the control group. One child (5%) who received methylprednisolone had transient hypertension.

At follow-up, children who received methylprednisolone had lower serum IgA levels at 2 weeks (86.8 ± 45.8 mg/dL vs 139.8 ± 67.7 mg/dL; $P = .02$) and at 6 weeks (53.4 ± 30.4 mg/dL vs 91.8 ± 50.1 mg/dL; $P = .017$); at 6 weeks, they also had lower mean ESR (11.1 ± 5.7 mm/h vs 19.4 ± 12.4; $P = .027$) and lower median CRP (0.03 [range, 0.02-0.12] vs 0.08 [range, 0.02-1.78]; $P =$. 011, Wilcoxon statistic). No other laboratory tests

differed significantly between treatment groups at 2 or 6 weeks. At 6 weeks, the groups were similar in their mean absolute coronary dimensions, coronary Z scores, and change in absolute dimension from baseline. One patient (5%) in each group had at least 1 coronary segment with Z score between 2 and 3; none had a coronary segment with Z score > 3.

COMMENT BY HAL B. JENSON, MD, FAAP

Kawasaki disease is a vasculitis that is distinguished by the target age (children < 5 years of age) and its predilection for affecting coronary arteries. The vasculitis of Kawasaki disease is self-limited, but IVIG and high-dose aspirin hasten resolution and reduce the incidence of coronary artery aneurysms. An early nonrandomized study reported a high rate (11/17) of coronary aneurysms among children with Kawasaki disease treated with oral prednisolone 2-3 mg/kg/24 h for at least 2 weeks followed by 1.5 mg/kg/24 h for an additional 2 weeks. Following the publication of that study in 1979, the use of corticosteroids as primary therapy for Kawasaki disease has been generally viewed as potentially deleterious.

The advent of IVIG and high-dose aspirin has proved to be effective management for Kawasaki disease. Nevertheless, the potential for corticosteroids as an adjunct to IVIG and aspirin in reducing the vasculitis remains attractive. A retrospective review of children with Kawasaki disease treated with a variety of regimens from 1982 to 1998 concluded that corticosteroid-containing regimens were associated with shorter duration of fever and lower prevalence of coronary artery aneurysms.[1] The findings of this newest study of lower ESR and CRP levels may reflect less vasculitis. Higher post-treatment serum levels of IgA have been previously associated with an increased risk of developing coronary artery aneurysms. This study was not blinded, included only 39 patients, and had follow-up for only 6 weeks. However, these results clearly indicate that a larger, double-blind, placebo-controlled, randomized trial of corticosteroids added to the current regimen of IVIG and high-dose aspirin is warranted.

Because the conventional regimen is effective in 90% of patients, and because of the potential adverse events associated with pulse corticosteroids, the role of corticosteroids as part of *primary therapy* is uncertain. Most patients with Kawasaki disease respond quickly and very favorably to IVIG and aspirin. For those patients who fail conventional primary therapy, a second (and third, if necessary) dose of IVIG (2 g/kg) continues to be recommended. The benefit of the addition of corticosteroids as part of *rescue therapy* also is uncertain. Until further studies are completed, parents should be informed of the potential risks as well as benefits if corticosteroids are used as part of the primary or rescue therapy for Kawasaki disease. ■

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Progress in the Control of Nosocomial Legionnaires' Disease

ABSTRACT & COMMENTARY

Synopsis: *Copper silver ionization in potable waters was found to be highly effective in reducing environmental* Legionella *colonization and preventing nosocomial Legionnaires' disease over prolonged time periods.*

Source: Stout JE, Yu VL. Experiences of the first 16 hospitals using copper-silver ionization for *Legionella* control: Implications for evaluation of other disinfection modalities. *Infect Control Hosp Epidemiol*. 2003;24:563-568.

The first 16 hospitals to install silver-copper ionization were surveyed in 1995 and again in 2000 to assess the efficacy of this method of environmental *Legionella* control. The water systems of all hospitals had been colonized with *L pneumophila* prior to installation of copper-silver ionization, and all had experienced cases of nosocomial Legionnaires' disease. Twelve hospitals (75%) had tried other means of *Legionella* control prior to installation of copper-silver ionization and had found them to be unsatisfactory; these included heat-and-flush, hyperchlorination, and UV light, singly or in combination. The duration of operation of copper-silver ionization ranged from 5 to 11 years. After installation, the hospitals reported reduction in the frequency of isolation of *Legionella* from the water system; in 7 (43%), subsequent surveillance cultures were consistently negative, indicating complete eradication of the *Legionella* from the water system. In 15 of the 16 hospitals, no cases of nosocomial Legionnaires' disease occurred after installation of copper-silver ionization. In the remaining hospital, a single case was identified shortly after installation; no cases were identified for the subse-

quent 7-year period.

The mean installation cost was $86,432 (range, $6000-134,000); annual maintenance costs ranged from $240 to $8000. Problems related to water quality were relatively few and consisted primarily of occasional water discoloration.

COMMENT BY ROBERT MUDER, MD

Legionnaires' disease differs from other common causes of nosocomial bacterial pneumonia in that the reservoir of infection is the environment, eg, the hospital water system. Colonization of the hospital water system is highly predictive of the occurrence of nosocomial Legionnaires' disease,[1,2] and elimination of the organism from this reservoir is an effective means of prevention. The 1997 CDC recommendations for the prevention of nosocomial pneumonia recommended 2 methods for control of environmental *Legionella* colonization in hospitals that had experienced nosocomial Legionnaires' disease. These were raising the hot water temperature to 65°C followed by flushing of distal outlets, or hyperchlorination to a chlorine level of 1-2 ppm. The CDC did not recommend copper silver ionization at that time, citing limited experience with that method.[3]

However, both of the recommended methods have some drawbacks. Heating and flushing is fairly labor intensive, and *Legionella* tends to recolonize the system in weeks to months after the procedure. High chlorine levels can be difficult to sustain in the hot water system, and high chlorine levels can accelerate corrosion of pipes. High levels of chlorine may also lead to the formation of potentially carcinogenic chlorinated organic compounds within plumbing systems.

The report by Stout and Yu indicates that copper-silver ionization is effective in controlling *Legionella* colonization and nosocomial Legionnaires' disease over protracted periods of time. In addition, operation of the system was reasonable in terms of effort and cost. However, copper-silver ionization systems do require monitoring and maintenance for continued effectiveness. Periodic monitoring of copper and silver ion concentrations, and periodic culture surveillance for *Legionella* are highly desirable. The copper and silver electrodes need to be descaled periodically and may need to be replaced occasionally. This is well within the capability of most hospital engineering departments and infection control programs, as demonstrated by the fact that 16 diverse hospitals were able to use copper-silver ionization effectively for prolonged periods of time. It should now be considered a proven method of *Legionella* control in hospitals. ■

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Treatment of CAP with Levofloxacin: What Dose? What Duration?

ABSTRACT & COMMENTARY

Synopsis: *Treatment of CAP with 750 mg of levofloxacin daily for 5 days was as effective as a 10-day course of 500 mg daily.*

Source: Dunbar LM, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: A new treatment paradigm. *Clin Infect Dis*. 2003;37:752-760.

Dunbar and colleagues at 70 US sites randomized, after stratification by severity, 530 adults with community-acquired pneumonia (CAP) to receive 1 of 2 regimens of levofloxacin—750 mg daily for 5 days or 500 mg daily for 10 days. A total of 122 patients had relatively mild disease, with pneumonia severity index (PSI) scores ≤ 70. All but 3 of the remaining patients had PSI scores of 71-130. The most frequently encountered among the 158 infectious etiologies identified was *Mycoplasma pneumoniae*, which accounted for 79 (50%), followed by *Streptococcus pneumoniae* (27%) and *Chlamydia pneumoniae* (24%). There were 11 *Legionella pneumophila* infections in the 5-day group and only 3 in the 10-day group.

The clinical success rates among the 390 evaluable patients were similar in the 2 treatment groups at 92.4% and 91.1%, respectively. Defervescence occurred significantly more rapidly in the 750 mg group. The frequency of subsequent clinical relapse did not differ significantly between those receiving 5 days of treatment (4.3%) and 10 days (1.2%). Microbiological efficacy also did not differ between the 2 treatment arms and was ≥ 90% in

each arm for each identified pathogen. Seven cases of pneumococcal bacteremia were detected in each arm, with all but (possibly) 1 being cured.

There were no signicant differences in the frequencies of drug related adverse events.

COMMENT BY STAN DERESINSKI, MD, FACP

This study demonstrates that a 5-day course of 750 mg levofloxacin daily is not inferior to a 10-day course of 500 mg daily. The rationale for the shorter course with a higher dose has sound bases. The antibacterial activity of fluoroquinolones is concentration-dependent, and outcome of infection appears to be most closely linked to the achieved C_{max}/MIC and AUC/MIC, both of which are optimized at higher doses. In addition, the blood levels achieved with the 500 mg daily dose of levofloxacin may be becoming marginally effective in some areas as the MIC of *S pneumoniae* creeps upward. Such marginally effective concentrations may also increase the likelihood of selection of resistant mutants. A CDC study has demonstrated a reduced risk of selection of resistant pneumococci in nasopharyngeal cultures of children given higher-dose, shorter-course amoxicillin than the reverse.[1] This analogy is not perfect, however, since beta-lactams exhibit time-dependent, rather than concentration-dependent, activity. Also, however, in terms of gross tonnage, the shorter course levofloxacin regimen exposes the bacterial ecology to a total of 25% less antibiotic.

Some caveats are warranted. It is reported that 140 of the 530 (26%) randomized patients were not clinically evaluable. With the exception of 3 patients, those with the most severe pneumonia (PSI >130) were not included in this study. In addition, an etiologic agent was apparently identified in only a minority of cases and one-half of these were believed to be due to *M pneumoniae*. The identification of this etiology, as well as *C pneumoniae*, relied on serological testing. However, Dunbar et al neglect to indicate the methodology, whether a central laboratory was used, and what the criteria for diagnosis were. Thus, one could question these diagnoses.

The 750 mg dose appeared to be well tolerated. This is not surprising since this dose has received US FDA approval in both skin/skin structure infection and nosocomial pneumonia.

Reference

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Mycoplasma and Acute Chest Syndrome in Sickle Cell Disease

ABSTRACT & COMMENTARY

Synopsis: *A prospective study of 671 episodes of acute chest syndrome in 538 patients with sickle cell anemia found that 51 (9%) had serologic evidence of* Mycoplasma pneumoniae *infection, including 12% of episodes in children < 5 years of age.* Mycoplasma hominis *was cultured in 10 episodes.*

Source: Neumary L, et al. Mycoplasma disease and acute chest syndrome in sickle cell disease. *Pediatrics*. 2003;112: 87-95.

A PROSPECTIVE STUDY OF ACUTE CHEST SYNDROME was performed at 30 centers of children with sickle cell disease (hemoglobin SS, hemoglobin SC, or hemoglobin SB). Acute chest syndrome was defined as a new pulmonary infiltrate (involving at least 1 complete segment consistent with alveolar consolidation, excluding transient atelectasis) associated with chest pain, fever > 38.5°C, tachypnea, wheezing, or cough. The study included a total of 671 episodes among 538 hospitalized patients enrolled from March 1993 through March 1997.

Paired serologies from 598 episodes in 484 patients documented *Mycoplasma pneumoniae* infection in 51 episodes (9%). Infection with *M pneumoniae* was determined by a 4-fold rise in IgG antibody titers between acute and convalescent sera (31 patients), or by a high IgG titer (≥ 1024) in paired serologies and detectable IgM antibodies (20 patients). There were no cases of recurrent infection documented. Of 555 episodes with appropriate samples, cultures for *M pneumoniae* were positive in 2 episodes. In the other 10 episodes, *Mycoplasma hominis* was identified by culture, with serologies that were not consistent with acute *M pneumoniae* infection. A total of 9 patients with *M pneumoniae* had evidence of another pathogen including rhinovirus, respiratory syncytial virus, *Steptococcus pneumoniae*, and *Haemophilus influenzae*. The incidence of *M pneumoniae* was higher in younger patients—12% of 112 episodes in patients < 5 years, 14% of 181 episodes in patients 10-14.9 years, and only 3% of the 207 episodes in children ≥ 15 years of age.

At the time of diagnosis, 98% of all patients had fever, 78% had cough, and 51% were tachypneic. During hospitalization, more than half of these patients

developed multilobar pneumonia, 84% required supplemental oxygen, 82% required transfusion, 6% required assisted ventilation, and 78% were administered bronchodilators. The average hospital stay was 10 days.

The average age of the 10 patients with *M hominis* was higher than those with *M pneumoniae* (18.6 years vs 9.7 years; $P = .004$). The rate of vaso-occlusive crisis was higher (60% vs 39%,) and the duration of hospitalization was longer (13.1 days vs 9.8 days), but these were not statistically significant.

COMMENT BY HAL B. JENSON, MD

This study found that *M pneumoniae*, and less often *M hominis*, is commonly associated with acute chest syndrome in patients with sickle cell disease, including very young children. The incidence of *M pneumoniae* in children younger than 5 years (12%) was similar to that in 5- to 10-year olds (14%). Patients with acute chest syndrome, including children younger than 5 years, should be treated with a broad-spectrum antibiotic regimen that includes a macrolide antibiotic. A common regimen is a broad-spectrum cephalosporin and either erythromycin or azithromycin. *Mycoplasma* also contributes to bronchial hyper-reactivity, as evidenced in 36% of these patients, who had wheezing during their hospitalization, and bronchodilator therapy is usually indicated. Early administration of leukocyte-depleted, matched simple transfusions are indicated in the presence of significant anemia, multilobar pneumonia, any signs of respiratory distress on oxygen, and those at risk for complications. ■

Asymptomatic Lyme Disease

ABSTRACT & COMMENTARY

Synopsis: *Up to 7% of* B burgdorferi *infections in the United States are asymptomatic.*

Source: Steere AC, et al. Asymptomatic infection with *Borrelia burgdorferi*. *Clin Infect Dis*. 2003;37:528-532.

In a study of a vaccine for prevention of Lyme disease in which almost 11,000 subjects were enrolled, 269 subsequently met criteria for the infection. Of 25 patients initially classified as having asymptomatic infection from whom clinical information was subsequently available, only 15 were in fact, asymptomatic and remained so through 20 months of follow-up. Thus, only 7% of *Borrelia burgdorferi* infections were asymptomatic.

COMMENT BY STAN DERESINSKI, MD, FACP

Prior studies have reported rates of asymptomatic seroconversion to *B burgdorferi* to be from 0% to 50%. Steere and associates point out that the major limitation of their analysis was that most patients with asymptomatic seroconversion received antibiotic therapy approximately 4-6 months after the tick transmission season and the subsequent follow-up was only 4-14 months. Thus, the 7% rate reported here can be considered the upper limit of the true likely incidence of asymptomatic infection. Nonetheless, the large sample size and the careful follow-up make this study a powerful one. ■

Human Metapneumovirus Infection in Children

ABSTRACT & COMMENTARY

Synopsis: *Human metapneumovirus was found in 6.4% of respiratory tract specimens collected from children < 5 years of age who had no evidence of other respiratory tract pathogens. Cough, rhinorrhea, and wheezing occurred in approximately two-thirds of patients, and fever occurred in half.*

Source: Esper F, et al. Human metapneumovirus infection in the United States: Clinical manifestations associated with a newly emerging respiratory infection in children. *Pediatrics*. 2003;111:1407-1410.

Respiratory tract specimens (nasopharyngeal swabs, washes, and bronchoalveolar lavage) collected from children < 5 years of age who were negative by direct fluorescent antibody (DFA) tests for the presence of respiratory syncytial virus (RSV), influenza, parainfluenza, and adenovirus antigens were tested for the presence of human metapneumovirus (hMPV) by RT-PCR. From Oct. 30, 2001, to Feb. 28, 2002, 357 specimens from 296 children were tested. From these, hMPV was detected in 16 (5.4%) children who had no evidence of co-infection with another respiratory tract pathogen.

Clinical information was obtained by chart review. The most common clinical findings of hMPV infection were cough (11 of 16 [69%]), rhinorrhea (11 of 16 [69%]), fever (10 of 16 [63%]), and wheezing (8 of 16 [50%]). Five patients (31%) developed hypoxia (oxygen saturation of ≤ 90%). Chest radiographs were obtained from 14 children, which showed abnormal findings including peribronchial cuffing, prominent hilum, and

focal infiltrates. All hMPV infections occurred during a 6-week period in January and February 2002, although only 59% of specimens were from this period. No hMPV was detected in isolates obtained in November or December 2001.

COMMENT BY HAL B. JENSON, MD

The prevalence of hMPV is unknown, but hMPV has been found in Great Britain, Australia, Hong Kong, and Canada. This study shows that, during the winter of 2001, hMPV was present in the United States and accounted for approximately 5% of respiratory illnesses not caused by RSV, influenza viruses, parainfluenza viruses, or adenoviruses among children < 5 years of age. The detection of hMPV during a confined 6-week span during the 4-month study period strongly suggests a seasonal pattern. Additional studies incorporating active surveillance are necessary to define the epidemiology of hMPV in the general population, including the presence and transmission of hMPV among asymptomatic children and adults.

The clinical manifestations reported in this study and others reflect a wide spectrum of disease in children, with both upper and lower respiratory tract symptoms. Common diagnoses in hospitalized children with hMPV infection include pneumonia, asthma exacerbation, and acute bronchiolitis. In addition to the 16 cases with hMPV infection alone, this study reported 2 cases of co-infection, with influenza A, and 1 case of nosocomial infection. Co-infection may contribute to the severity of clinical illness. The possibility of nosocomial transmission underscores the need for developing sensitive diagnostic tests for hMPV. ■

Duration of Antiviral Immunity After Smallpox Vaccination

ABSTRACT & COMMENTARY

Synopsis: *More than 90% of individuals studied maintain measurable humoral or T-cell mediated immunity against vaccinia virus for as long as 75 years after smallpox vaccination.*

Source: Hammarlund E, et al. Duration of antiviral immunity after smallpox vaccination. *Nature Med*. 2003;9:1131-1137.

HAMMARLUND AND COLLEAGUES AT THE UNIVERSITY of Oregon examined a group of individuals who had received smallpox vaccination 1-75 years previously in order to determine the duration and magnitude of immunity against vaccinia virus. The in vitro studies performed included the quantification of virus-specific CD4+ and CD8+ lymphocyte responses as well as of neutralizing antibody.

More than 90% of volunteers who had been vaccinated 1-75 years previously had evidence of substantial humoral and/or cellular immunity against vaccinia. While antiviral T-cell responses declined slowly over time with a half-life of 8-15 years, antibody responses remained stable for 1-75 years after vaccination.

COMMENT BY STAN DERESINSKI, MD, FACP

The duration of immunity after receipt of vaccinia has been a matter of some discussion. Often accepted is a duration of only 3-5 years, and this was the figure that was used in the structuring of the vaccination program recently held in abeyance by the United States. Mack, however, cites a number of epidemiological studies that suggest the period of protection is many years longer, with at least 90-95% protection against lethal infection for more than 20 years after vaccination.[1] This is consistent with the long-term immunity induced by other live attenuated virus vaccines.

The nationwide smallpox vaccination program was recently halted. The vaccine had been offered to the approximately 2.5 million health care professionals and technicians working in US hospitals. Based on previous estimates of risk, at least 7-8 vaccine-related deaths were expected.[2,3] The vaccine was offered regardless of prior vaccination—more than 90% of Americans older than 35 have been vaccinated against smallpox, mostly as infants. However, by the end of March 2003, only 25,645 public health and health care workers in the United States had been vaccinated. Many health care workers opted out of the program for a number of reasons, including the reports of the occurrence of myocarditis and cardiac deaths in a small number of vaccine recipients. For many health care workers who chose to not be vaccinated, it is likely that their calculus was something like the following: While the risk of an attack is unknowable, there have been no cases. There is some risk from vaccination. Postexposure vaccination, especially combined with vaccinia immune globulin, is quite effective in prevention of severe disease.

The program also proved costly in terms of dollars. In April, the Association of State and Territorial Health Officials estimated the average cost of a single vaccination to be $249, with the cost ranging from $79 in Tennessee to more than $1000 in Hawaii and Alaska. Randy Cohen in his column on ethics in the *New York Times Sunday Magazine* (Jan 19, 2003, page 18) point-

ed out another aspect of this issue. "Financing an expensive smallpox vaccination program necessarily means neglecting many pressing medical problems, both here and abroad. In our era of tight budgets, deciding how to allocate health care resources is a question with both moral and political implications." In other words, is it moral to spend large amounts of money on a problem, which we may never confront, or on ones, such as malaria and diarrheal illness, that kill children every day? ■

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2. Bozzette SA. A model for a smallpox vaccination policy. *N Engl J Med*. 2003;348:416-425.
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HIV, FUO, and *Bartonella*

ABSTRACT & COMMENTARY

Synopsis: Bartonella *is a cause of unexplained fever in HIV-infected patients.*

Source: Koehler JE, et al. Prevalence of *Bartonella* infection among human immunodeficiency virus-infected patients with fever. *Clin Infect Dis*. 2003;37:559-566.

KOEHLER AND COLLEAGUES AT UNIVERSITY OF Califonia in San Francisco and the CDC examined the prevalence of *Bartonella* infection in patients with persistent or recurrent fever of at least 2 weeks duration. Patients who had received tetracycline, a macrolide, or a rifamycin in the previous 2 weeks were excluded, as were HIV-infected patients with a history of *Mycobacterium avium* complex (MAC) infection. In addition, HIV-infected patients must have had a negative MAC blood culture within the previous 4 weeks.

Of the 382 patients studied, 95% of whom were HIV infected, 68 (18%) had evidence of *Bartonella* infection as determined by indirect fluorescent antibody testing, culture, or PCR. Nineteen patients (5%) had serological titers > 1:64—levels previously associated with active *Bartonella* infection. Twelve patients had organism identification by either culture or PCR of blood and/or tissue. When the 12 patients were carefully examined, cutaneous bacillary angiomatosis was detected in 6. In a nested, case-control study, only bacillary angiomatosis and elevated alkaline phosphatase level were significantly associated with *Bartonella* infection.

COMMENT BY STAN DERESINSKI, MD

Eighteen percent of persistently or intermittently febrile HIV-infected patients with previous negative MAC blood cultures had evidence of infection with either *B henselae* or *B quintana*, although only a minority of these had direct evidence (culture or PCR) of the presence of the organism. At the same time, only 14% of the cohort proved to have disseminated MAC infection, making it less prevalent than bartonellosis, but this likely was the result of selection bias since patients with positive MAC cultures in the 4 weeks before study entry were excluded. Two percent of the patients proved to have disseminated histoplasmosis.

One can certainly question the relevance of the diagnosis of active *Bartonella* infection based on a single serological test. Koehler et al cite studies indicating that the background prevalence of *Bartonella* antibodies in an afebrile population is 4-7%. It is possible that higher titers might be expected in HIV-infected patients as a consequence of the polyclonal increase in gamma globulin levels commonly seen in this population.

Despite such caveats, this study clearly demonstrates that *Bartonella* infection is a cause of "fever of unknown origin" in AIDS-infected patients with advanced immunodeficiency—the median cell count of the *Bartonella* patients in this study was only 35/mm^3. The problem is in diagnosis. While antibody testing for *Bartonella* is readily available through a number of commercial laboratories, PCR is less readily available and the performance of these tests may not be as good as those used here. Blood culture can be obtained with a little cooperation from your laboratory. In this study, 10 mL of blood was cultured by lysis-centrifugation with inoculation for 3 weeks. Nonetheless, the diagnosis of this infection is important since it is treatable. ■

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. **At the end of the testing period, you must complete the eval-**

uation form provided and return it in the reply envelope provided in order to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

CME Questions

10. A 3-year-old boy presents with fever, cough, rhinorrhea, and wheezing. Chest x-ray shows scattered, diffuse infiltrates. DFA testing for respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses, and adenoviruses is negative. What is the likelihood of human metapneumovirus infection?

a. < 1%
b. 5%
c. 50%
d. 80%
e. > 95%

11. The proportion of *B burgdorferi* infections in the United States that are asymptomatic is approximately:

a. 1%.
b. 7%.
c. 15%.
d. 35%.

12. Which of the following is correct?

a. *Bartonella quintana*, but not *Bartonella henselae*, was found to be a cause of fever in HIV-infected patients.
b. *Bartonella* infection was found to be a cause of fever in HIV infected patients with CD4 counts > 350 cells/mm^3.
c. *Bartonella* bacteremia can readily be detected with standard blood culture techniques.
d. Both *Bartonella quintana* and *Bartonella henselae* were found to cause fever in HIV-infected patients.

CME Answers: 10(b); 11(b); 12(d)

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Infectious Disease Alert*. Send your questions to: Christie Messina—Reader Questions, *Infectious Disease Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. ■

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1. Publication Title	2. Publication No.	3. Filing Date
Infectious Disease Alert	0 7 3 9 - 7 3 4 8	10/01/03
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$249.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Robin Salet — Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*: Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Christine Messina, same as above

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Full Name	Complete Mailing Address
Thomson American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

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13. Publication Name: Infectious Disease Alert — 14. Issue Date for Circulation Data Below: October 2003

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1391	1260
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	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	4	3
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c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			1067	990
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	22	19
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h. Copies Not Distributed			276	225
i. Total *(Sum of 15g. and h.*			1391	1260
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			96	96

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2003 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Brenda L. Mooney, Publisher — Date: 9/30/03

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IDSA Conference Coverage

UPDATES

By Carol A. Kemper, MD, FACP

Management of Lipodystrophy in HIV: A Mini-Update

Source: Abstracts of the Fifth International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. July 8-11, 2003. Paris.

Several recent abstracts from the Fifth International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, which was held just prior to the Second IAS Conference on HIV Pathogenesis and Treatment in Paris, highlighted recent advances in the management of lipoatrophy/lipodystrophy in patients with HIV infection. Preliminary reports have suggested that rosiglitazone may improve insulin resistance, thereby facilitating improved glucose use and lipid metabolism. A randomized, double-blind, placebo-controlled study of rosiglitazone in HIV-infected patients with lipoatrophy/dystrophy found significant increases in insulin sensitivity, increased body fat, and increased levels of adiponectin in treated patients compared with controls (*Hadigan C. Oral Abstract 12*). By 3 months of therapy, body fat had increased 15% in the treatment group compared with 5% in the placebo group. Increased levels of cholesterol were also observed in treated subjects. In a second smaller open-label study, improved insulin resistance, increases in subcutaneous body fat, and decreases in visceral fat were observed in 4 patients with lipodystrophy receiving 3 months of rosiglitazone (*Visnegarwala F. Poster Abstract 74*).

Recombinant growth hormone (rGH) has become increasingly popular on the West Coast for the treatment of lipodystrophy. In one larger study, 555 patients were randomized to receive either rGH 6 mg daily or 6 mg every other day or placebo for 8 weeks (*Kottler. Poster Abstract 93*). Increased body weight and lean body mass were observed in both of the treatment groups compared with placebo recipients, although the effects appeared to be greater in patients receiving daily rGH. Trunk fat increased disproportionately to limb fat, thereby increasing the trunk:limb fat ratio. This is exactly the opposite of what would be hoped for in patients with limb lipoatrophy.

Two smaller studies found progressive increases in body fat in patients after switching from d4T to another reverse transcriptase inhibitor. Increases in body fat by both DEXA and computed tomographic scanning were observed in one group of patients 48 weeks after switching from d4T to either abacavir or zidovudine (*McComsey G. Poster Abstract 90*); virologic control was reportedly maintained. Similar effects were observed in patients enrolled in the MITOX study in Sydney: Limb fat increased 36% in patients switched from either a d4T- or zidovudine-containing regimen to an abacavir-containing one. Incremental increases in fat accumulation were observed throughout the 2-year period of observation, suggesting that a long period of time is required to reverse the process.

Although some physicians may be inclined to dismiss progressive changes in body habits as superficial, studies suggest that lipoatrophy may significantly adversely affect compliance with HIV medications. Two-thirds of patients in one survey indicated their willingness to give up one year of life from HIV therapy if it meant avoiding lipodystrophy. Although avoiding regimens with the potential for lipoatrophy/dystrophy may not always be possible, consideration should be given to switching regimens that are resulting in progressive lipodystrophy whenever possible. Although the above data looks promising, we're a long way from knowing how to effectively reverse this condition in affected individuals. ■

Yersiniosis Outbreak From Chitterlings

Source: Jones TF. *Emerg Infect Dis*. 2003;9(8):1007-1009.

Yersiniosis is an uncommon cause of food-borne disease and generally accounts for only a small number of sporadic cases of infection in the United States. An outbreak of Yersiniosis limited solely to black infants in Tennessee therefore prompted an investigation as to the cause. During a 3-month period from November 15, 2001, to February 15, 2002, 12 cases of Yersinia infection occurred in infants younger than 1 year of age in Tennessee. All of the patients were black and had presented to local medical centers with severe diarrhea, and all of them had positive stool cultures for *Y enterocolitica*.

A case-controlled study was conducted to identify a potential cause.

Ten infants (who could be located) and their caregivers and 51 controls were interviewed. Of the 10 cases, 8 (80%) had reported fever, 7 (70%) reported blood stools, 7 (70%) reported vomiting, and 4 (40%) required hospitalization. Interestingly, 6 of the cases occurred within days of Thanksgiving, Christmas, or New Year's. Chitterlings had been prepared in the homes of every one of the case patients compared with only 35% of controls. (Chitterlings are that part of the pig small intestine that is often fried and served with special sauce, especially around the holidays.) At least 4 different brands of chitterlings were purchased at 5 different grocery stores. Ten to 80 pounds of raw intestines (possibly contaminated with feces) were prepared at any one time, with several hours of thawing, cleaning, and cooking in and around the sink and kitchen area. The caregivers variously described washing children's bottles in the sink, handling children and their bottles and pacifiers while doing food prep, and small children in and around the food prep area.

Nine of the Yersinia isolates from the children were available for analysis. All were identified as serotype 0:3 biotype 4 (swine are the major reservoir for serotype 0:3, which has largely replaced serotype 0:8 as the most common serotype in human infections). Pulsed-field gel electrophoresis revealed 7 distinct patterns; 1 pattern was shared by 3 infants, 1 pattern was shared by 2 infants, and 1 infant had 2 distinct isolates. Of 13 samples of chitterlings purchased by Jones and associates from various stores in Tennessee, 2 tested positive for *Y enterocolitica*, and 5 were positive for various species of Salmonella.

These data suggest that no one common source is responsible for these cases; simply exposure to the food prep area was sufficient exposure for these small children. None of the infants actually ate the chitterlings. Jones states that attempts to educate the public about the risk of preparing chitterlings in this traditional fashion around the holidays have been unsuccessful, despite the risk to smaller family members. ■

Compassionate-Use Daptomycin Now Available

Newer antimicrobial agents in development for the treatment of VRE and MRSA infections include daptomycin, oritavancin, and tigecycline, as well as ramoplanin for potential decolonization of the intestinal tract of VRE. Daptomycin (Cidecin®, Cubist Pharmaceuticals), a lipopeptide, is rapidly cidal against a range of Gram-positive organisms, including those resistant to vancomycin and methicillin, as well as *Staphylococcus pneumoniae*.[1] The activity of daptomycin in vitro against *S aureus* and enterococcus is similar to linezolid and quinupritistin-dalfopristin.[2] In a murine model of chronic foreign body infection due to *S aureus*, a low dose of daptomycin was similarly effective to vancomycin, although emergence of decreased susceptibility was observed in some animals treated with daptomycin.[3] In an experimental model of endocarditis due to MRSA, daptomycin plus rifampin was more effective in reducing vegetation bacterial colony counts > vancomycin plus rifampin > rifampin alone > daptomycin alone.[4]

Daptomycin appears to be relatively safe and well tolerated. The half-life in serum is ~ 9 hours, and 54% of the drug is excreted unchanged in the urine within 24 hours of administration. Protein binding is ~ 92%. Dose-escalation studies suggest that once-daily dosages up to 8 mg/kg are well tolerated. In ~ 1400 patients treated with daptomycin in various clinical trials, daptomycin was discontinued in ~ 1.5% of patients due to adverse events. Common side effects in up to 3-6% of patients include headache, nausea, vomiting, abdominal pain, diarrhea, constipation, injection site reactions, rash, edema, and abnormal liver function tests. Overall, daptomycin is likely to prove to be a very useful agent against resistant Gram-positive organisms, although more comparative studies are needed, especially in infections resulting in endocarditis and osteomyelitis.

Daptomycin is presently being reviewed by the FDA for the treatment of skin and soft-tissue infections due to Gram-positive organisms. It was also recently made available on a compassionate-use basis for the treatment of serious and life-threatening infections due to Gram-positive bacteria in patients intolerant or refractory to currently available therapies. Patients with renal impairment (creatinine clearance < 40 mL/min) or those receiving hemodialysis or peritoneal dialysis are not eligible for the compassionate-use protocol. (For more information, contact the Daptomycin Study Hotline at 888-327-8630.) ■

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PHARMACOLOGY WATCH

Generic Paxil Scheduled to Hit Market this Fall

A generic form of paroxetine (Paxil—GlaxoSmithKline) will soon be on the market. The drug marks the second SSRI antidepressant to go generic after fluoxetine (Prozac) last year. US sales of Paxil reached $2.23 billion last year, and the approval of a generic is a blow to GSK's bottom-line but is welcome news to consumers. Generic paroxetine will be launched by Canadian drugmaker Apotex almost a year earlier than most analysts had anticipated because of continued legal wrangling over patents. If generic companies launch a drug that is later found in violation of the branded drugs patents, they are liable for treble damages, a threat that has impeded generic competition in the past. In this case, Apotex feels it has a strong legal basis for defending any claims by GSK, a pattern that is being seen more frequently among generic companies in the last year. Generic paroxetine should be available this fall in 4 different dosing strengths.

New Study Questions CHD and C pneumoniae

An association between *Chlamydia pneumoniae* infection and coronary heart disease has been suggested by several lines of evidence; however, a new, large, multicenter study fails to confirm this association. Nearly 8000 adults with a recent myocardial infarction and positive *C pneumoniae* titers were randomized to 12 weeks of azithromycin (600 mg/d for 3 days then 600 mg/wk through week 12) or placebo. The primary outcomes were death from any cause, nonfatal reinfarction, coronary revascularization, or hospitalization for angina. After a median of 14 months of follow-up, there was no significant risk reduction with azithromycin vs placebo (any primary event 7% risk reduction with azithromycin, P =.23). Adverse reactions to the study drug occurred in 13.2% of patients randomized to azithromycin and were generally mild—predominately diarrhea. The study represents the largest antibiotic trial to date for the eradication of *C pneumoniae*, and although there were indications that there might be an early benefit, this was not sustained at 14 weeks. The authors suggest that there's no justification for the use of antibiotics in treating patients with coronary disease (*JAMA*. 2003;290:1459-1466).

Warfarin Patients: Limit Cranberry Juice

Cranberry juice may increase the risk of hemorrhage in patients taking warfarin according to British researchers. The British Committee on Safety of Medicines recommended patients taking warfarin should limit or avoid drinking cranberry juice until they can sort out 5 reports of hemorrhage associated with the combination, including 1 death. In all cases, increases in INR were noted when patients who had been stabilized on warfarin started drinking cranberry juice. The committee postulates that the juice inhibits cytochrome P450 activity, thus slowing metabolism of warfarin. Cranberry juice has been touted in recent years for its antioxidant proper-

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. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. 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.

ties as well as its purported ability to prevent or treat urinary tract infections.

Therapeutic Magnets Put to Test

A randomized double-blind trial has finally put therapeutic magnets to the test for the treatment of foot pain. Researchers at the Mayo Clinic randomized 101 adults with the diagnosis of plantar heel pain to treatment with cushioned insoles with bipolar magnets and sham magnets. The insoles were worn daily for 8 weeks. The main outcome was reported average daily for pain and the effect of the insoles on work performance and enjoyment. Again, at 8 weeks no significant difference was noted between the 2 groups, with both groups reporting significant improvements in foot pain (33% improvement nonmagnetic group, 35% improvement magnetic group [P = .78]). The authors conclude that embedded bipolar magnets to add nothing to cushioned insoles and the treatment of plantar heel pain (*JAMA*. 2003;290:1474-1478).

St. John's wort Might Block Certain Medications

St. John's wort, the popular herbal product that is widely used to self-treat depression may significantly reduce the effectiveness of at least 50% of all marketed medications. A new study looked at the effect of St. John's wort on cytochrome P450 (CYP) enzymes. Twelve healthy volunteers (6 men and 6 women) were given St. John's wort for 14 days. Participants were given dextromethorphan and alprazolam before and after administration of St. John's wort to assess plasma pharmacokinetics. After 14 days use of St. John's wort, a 2-fold decreased area under the curve for alprazolam plasma concentration and a 2-fold increase in alprazolam clearance was found as well as an elimination half-life that decrease from 12.4 h to 6.0 h suggesting a significantly induced activity of CYP 3A4 (all findings significant at $P <$ .001). Dextromethorphan metabolism, a measure of CYP 2D6, was unchanged. The effect of St. John's wort on CYP 3A4 is quite significant, however, since at least 50% of all medications currently on the market are at least partially metabolized by this enzyme. This, coupled with 2 recent multicenter double-blind, placebo-controlled studies questioning the effectiveness of St. John's wort for the treatment of depression, should alert clinicians to question their patients about their use of herbal medications, especially St. John's wort (*JAMA*. 2003;290:1500-1504).

Parathyroid Hormone and Alendronate Offer No Improved Osteoporosis Treatment

Parathyroid hormone and alendronate in combination offer no advantage and may in fact be less effective than either drug alone in treating osteoporosis according to 2 studies in the Sept. 25 issue of *New England Journal of Medicine*. In a study of 83 men with low bone density, 28 were randomized to receive alendronate 10 mg/d, 27 received parathyroid hormone 40 mg subcutaneously daily, while 28 men received both. The bone mineral density of the lumbar spine, proximal femur, radial shaft, and total body was measured every 6 months and trabecular bone mineral density of the lumbar spine was measured at baseline and 30 months. The most effective treatment was parathyroid hormone alone ($P < 0.001$ for both comparisons), and it appeared that alendronate impaired the ability of parathyroid hormone to increase bone mineral density at the lumbar spine and femoral neck. In the second study, 238 postmenopausal women with low bone mineral density at the hip or spine were randomly assigned to daily treatment with parathyroid hormone 100 mg/d (119 women), alendronate 10 mg/d (60 women), or both (59 women). After 12 months of follow-up, bone mineral density was assessed at the spine and hip. Bone mineral density increased in all treatment groups, but the volumetric density of trabecular bone in his spine increase substantially more in the parathyroid hormone group than either of the other groups. The authors suggest that there is no evidence of synergy between parathyroid hormone and alendronate and there may be evidence that alendronate reduces the anabolic effects of parathyroid hormone in the study group (*N Engl J Med*. 2003;349:1207-1215, 1216-1226).

FDA Actions

Barr laboratories has received approval to market an extended-cycle birth control pill that cuts the number of a women's menstrual cycles from 13 to 4 per year. Marketed under the trade name "Seasonale," the product is a 91-day ethinyl estradiol/levonorgestrel oral contraceptive regimen that includes 84 days of active hormones and 7 days of placebo. The new product seems to be as effective as other oral contraceptives; however, the label does note that the longer interval between menstrual periods may allow for unintended pregnancies to go undetected for longer period of time. ■