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INSIDE

Infectious Triggers of Asthma in Children

ABSTRACT & COMMENTARY

Synopsis: Mycoplasma pneumoniae *may causally contribute to the development of asthma, as well as serve as a trigger for recurrent wheezing.*

Source: Biscardi S, et al. *Mycoplasma pneumoniae* and Asthma in Children. *Clin Infect Dis.* 2004;38:1341-1346.

A PROSPECTIVE STUDY FROM 1999-2001 IN PARIS OF 170 CHILdren 2-15 years of age hospitalized with acute severe asthma included serologic testing of acute and convalescent sera (2-4 weeks later) for IgM and IgG *Mycoplasma pneumoniae* antibodies, and testing of acute serum for *Chlamydia pneumoniae* IgM antibodies. PCR testing was performed for *M. pneumoniae* and *C. pneumoniae* on nasopharyngeal aspirates from 95 children.

By serologic criteria of specific IgM present in either the initial or second serum sample or with a > 4-fold increase in IgG titers, 26 of 51 (50%) children with their first presentation of asthma, and 24 of 119 (20%) children with a history of asthma ($P < 0.01$) were diagnosed with acute *M. pneumoniae* infection. Among children who also had PCR testing, only 7 of 35 (20%) tests among children with their first presentation of asthma, and 5 of 60 tests (8.3%) among children with recurrent asthma, were positive. All children the positive PCR tests also had serologic evidence of *M. pneumoniae* infection. All 4 children with their first episode of asthma and *M. pneumoniae* infection that was untreated, were rehospitalized with another severe asthma attack within 3 weeks, including 2 children requiring intensive care.

C. pneumoniae was diagnosed among children with their first presentation of asthma serologically in 3 of 51 (5.8%) children, and also by PCR for 1 child. Among children with recurrent asthma, *C. pneumoniae* was diagnosed serologically in 4 of 119 (3.4%) children, and also by PCR in 2 children. Using immunofluorescence testing and culture of nasopharyngeal specimens, respiratory syncytial virus was detected in children with initial or recurrent asthma in

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2 (4%) and 14 (12%), respectively, and influenza A or B virus was detected in 0 and 4 (3%), respectively. No adenovirus or parainfluenza viruses were detected. *Bordetella pertussis* was diagnosed in 2 children with their initial presentation of asthma and in 1 child with recurrent asthma. They were unable to test for rhinoviruses.

By comparison, a control group of 113 children with stable asthma and 39 children with allergic rhinitis found serological evidence of acute *M. pneumoniae* infection in 8 of 152 (5.2%) children ($P < 0.005$ compared with each of the other groups), and *C. pneumoniae* in 3 of 120 (2.5%) children (not significant compared with each of the other groups).

Of those children with their first presentation of asthma, 15 of 26 children with acute *M. pneumoniae* infection and all 3 with acute *C. pneumoniae* infection developed recurrence of asthma. Thus, 62% of children with either infection developed recurrent asthma, compared to only 6 of 22 (27%) who did not have an infection ($P < 0.05$). Those with acute infection also had significantly lower serum IgE levels, and less frequent history of allergy or family history of asthma

COMMENT BY HAL B. JENSON, MD, FAAP

This study shows that half of first cases of severe asthma episodes among these children were associated with serological evidence of acute *M. pneumoniae* infections, which are frequently mild or even asymptomatic. Children with acute M. pneumoniae or *C. pneumoniae* infection were also less "allergic" or less destined to develop recurrent asthma. These novel findings suggest that *M. pneumoniae* may play a causal role in the development of recurrent asthma in children. This study also shows that children with untreated *M. pneumoniae* infection during their initial episode of asthma are at increased risk of recurrent severe attacks. These clinical findings substantiate findings from an animal model in mice of asthma, which found that *M. pneumoniae* increased bronchial airway resistance and resulted in persistent *M. pneumoniae* infection at 2 months.

Acute viral infections (eg, rhinoviruses, coronaviruses, respiratory syncytial virus, influenza viruses, and parainfluenza viruses) and chronic infections (eg, *M. pneumoniae*, *C. pneumoniae*, and adenoviruses) are common triggers of asthma exacerbations among children. Chronic *M. pneumoniae* infections, diagnosed by PCR of bronchoalveolar lavage, are frequent among adults with asthma and appear to contribute to repeat severe asthma exacerbations. One impediment to replicating these adult studies in children is the inability to obtain bronchoalveolar lavage specimens. The lower level of *M. pneumoniae* infection diagnosed by PCR in this study reflects the limitations resulting from the necessity to rely on nasopharyngeal aspirates from children. Thus, serological testing for diagnosis of *M. pneumoniae* infection in children is essential.

Acute *M. pneumoniae* infection should be suspected in children presenting with their first episode of severe asthma, especially if their history does not suggest risk for allergic disease or if they require early rehospitalization. It is plausible that macrolide treatment of acute infection may alter the progression to chronic *M. pneumoniae* infection and prevent subsequent recurrent episodes of asthma. The primary obstacles to studying whether the outcome of *M. pneumoniae* infection can be altered by treatment, and to currently recommending or implementing a strategy for routine *M. pneumoniae* testing and treatment, are the lack of rapid, sensitive diagnostic tests and the need to rely on serologic diagnosis, which is time-consuming and often requires a convalescent serum. ■

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VICE PRESIDENT/GROUP PUBLISHER:
Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MARKETING PRODUCT MANAGER:
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MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

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Leslie Hamlin,
Associate Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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Vancomycin and MRSA: How Susceptible is "Susceptible"?

ABSTRACT & COMMENTARY

Synopsis: *A laboratory report indicating susceptibility of MRSA to vancomycin does not guarantee successful therapy with this antibiotic since a significant risk for failure may be present despite MICs within the range considered susceptible.*

Source: Sakoulas G, et al. Relationship of MIC and Bactericidal Activity to Efficacy of Vancomycin for Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia. *J Clin Microbiol.* 2004;42:2398-2402.

SAKOULAS AND COLLEAGUES EXAMINED THE POTENTIAL relationship between the outcome of treatment of MRSA bacteremia with vancomycin and the relative degree of in vitro inhibition and killing of the individual patient's isolates by this antibiotic. Thirty "susceptible" bloodstream MRSA isolates from 30 patients, 23 of whom had failed therapy with vancomycin, were analyzed to determine their susceptibility or resistance to killing by vancomycin. Bactericidal activity was quantitated after 72 hours of incubation of an original inoculum of 107 to 108 CFU/mL in the presence of vancomycin at a concentration of 16 mg/mL.

In-vitro killing ranged widely from 0.17 $\log_{10}$ to 8.16 $\log_{10}$ CFU/mL at 72 hours. There was no significant correlation of bactericidal activity with the MICs of the organisms—all of which were < 2 mg/mL. Bactericidal activity and MIC did each, however, significantly correlate with outcome. The treatment success rate was 0% in those with < 4.71 $\log_{10}$ killing, 23% in those with 4.71 $\log_{10}$—6.26 $\log_{10}$ killing, and 50% in those with a 72 hour kill of > 6.27 $\log_{10}$ CFU/mL. The treatment success rate was 55.6% in those infected with an isolate with a vancomycin MIC < 0.5 mg/mL and only 9.5% in those with an MIC of 1 to 2 mg/mL ($P = 0.01$). Finally, multivariate analysis demonstrated a statistically significant relationship ($P = 0.01$) between the increased therapeutic efficacy of vancomycin and both lower vancomycin MIC and increased killing in vitro.

COMMENT BY STAN DERESINSKI, MD, FACP

We recently discussed on these pages an analysis of 25 MRSA-infected patients who had microbiologic failure after vancomycin therapy, despite the fact that their bacterial isolates were considered vancomycin susceptible, with MICs of 2 to 4 mg/mL.[1,2] These isolates were demonstrated by population analysis to have heteroreistance to vancomycin—ie the presence of clonal populations with elevated MICs within the larger, more susceptible population.

The current study did not look for heteroresistance, which likely was present in at least some of the cases examined. The major aim here was to examine the relationships between vancomycin MIC, the bactericidal activity of vancomycin against MRSA, and the therapeutic success or failure after treatment with this agent. This investigative group had previously found a relationship between vancomycin MIC and failure of vancomycin therapy in 87 patients by univariate analysis, but MIC did not prove to be an independent predictor in multivariate analysis.[3] The current study found that the efficacy of vancomycin therapy is reduced for MRSA isolates with vancomycin MICs of 1 to 2 mg/mL, values within the range considered to demonstrate susceptibility to this glycopeptide antibiotic since the upper limit is < 4 mg/mL. Furthermore, the extent of in vitro killing of an initial large inoculum by vancomycin at 72 hours also correlated with therapeutic outcome.

The small sample and other aspects of this investigation make it necessary that further larger studies are required to draw firm conclusions. Nonetheless, these results add to the current concern regarding the relative efficacy of vancomycin in the treatment of serious MRSA infections. While it is possible that increasing doses beyond those currently recommended could overcome some of these problems, I believe we are fortunate in having a variety of alternative antistaphylococcal agents available, with more on the horizon.[4] ■

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Which *Nocardia* Species Is It, Anyway?

ABSTRACT & COMMENTARY

Synopsis: *Molecular techniques provide a more rapid and accurate method of* Nocardia *species identification than do classical microbiologic methods. A surprise: of 94 isolates, the most commonly identified species was* Nocardia cyriacigeorgica *and none were* Nocardia asteroides.

Source: Joann L. Cloud, et al. Evaluation of Partial 16S Ribosomal DNA Sequencing for Identification of Nocardia Species by Using the MicroSeq 500 System with an Expanded Database. *J. Clin. Microbiol*. 2004;42:578-584.

THE 16S RIBOSOMAL DNA SEQUENCING IS VERY USEFUL for speciating many microbial pathogens. Workers in Utah, the NIH, and Munster, Germany, combined forces to determine the species of 94 non-repetitive *Nocardia* isolates. A 16S ribosomal DNA sequencing system called MicroSeq 500 was compared to conventional biochemical and susceptibility speciation routines. The "gold standard" was an NIH speciation routine that has been previously described (*J Clin Microbiol*. 2000;38:158-164). The species that are routinely identified by the MicroSeq 500 are shown in the Table.

There are 31 validly named species.of *Nocardia* Results of this study showed the molecular method was more discriminative than the conventional method and identified 10 species. Previously identified human pathogens like *Nocodia africana*, *Nocodia paucivorans*, and *Nocodia pseudobrasiliensis* were not found in this study.

Readers may be most surprised by the species of the most commonly isolated *Nocardia*, *Nocardia cyriacigeorgica*. The conventional analysis would be *Nocardia asteroides*. None of the isolates in this study were identical to the *N. asteroides* type strains. The second most common groups were *Nocardia farcinica* (14) and *Nocardia nova* (16) followed by *N. africana* (11), and *Nocardia veterana* (10). There were 8 isolates identified as *N. asteroides* drug pattern IV and 8 as *Nocardia abscessus*. The MicroSeq identified 14 isolates as *Nocardia* but gave no definitive species.

COMMENT BY JOSEPH J. JOHN, Jr, MD

*Nocardi*a are becoming an ever more important cause of opportunistic infection. Conventional identification has always been fraught with problems, as shown in this current study by Cloud and colleagues. Clinicians remember the species they grew up with, *N. asteroides*, but they will need to expand their minds consistent with the expansion of species within the genus.

As this study shows, we need to expand the identification of the pathogenic species we are seeing clinically. More *N. asteroides* cases will become *N. cyriacigeorgia*. The other important names needing our familiarity include veterna, nova, and farcinica.

It is hard to say how soon standard clinical micobiological laboratories will choose to use the MicroSeq system. One of the study participants in the Cloud study was the ARUP Institute, a lab that many of our university clinical microbiology now uses. Clinicians will have to decide based on patient characteristics and the need for expanded epidemiologic information how often to ask for speciation. MicroSeq speciation takes only1-3 days, compared to the conventional time of 2-3 weeks. In fast moving specialities like transplantation, patient care may mandate the more rapid and clearly more definitive method of DNA sequencing and correlation of bactericidal activity with the MICs of the organisms—all of which were < 2 mg/mL. ■

Table
Nocardia Species Associated with Human Infections

N. asteroides
N. abscessusa,b
N. asteroides drug group IVa
N. cyriacigeorgicaa,c
N. africanaa
N. beijingensisa
N. brasiliensis
N. brevicatena
N. carnea
N. corynebacteroides
N. crassostreaea
N. farcinica
N. nova
N. otitidiscaviarum
N. paucivoransa
N. pseudobrasiliensis
N. seriolae
N. transvalensis
N. veteranaa
N. vinaceaa

A Widespread Outbreak of *Yersinia pseudotuberculosis* O:3 Infection from Iceberg Lettuce

ABSTRACT & COMMENTARY

Synopsis: *An outbreak of food poisoning by* Yersinia pseudotuberculosis *in Finland in October/November1998 involved 46 cases and was traced to locally grown iceberg lettuce.*

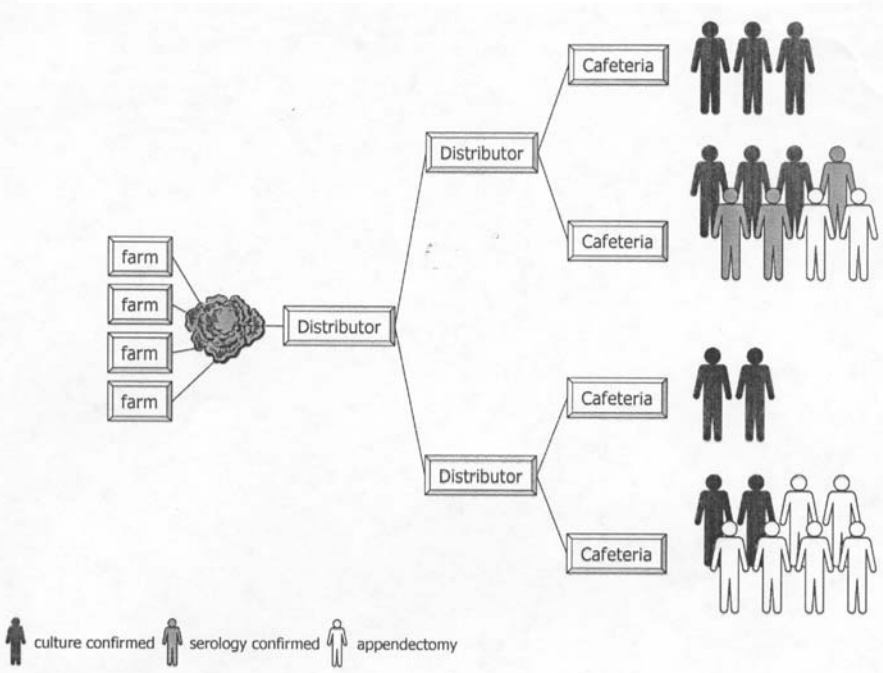
Source: Nuorte JP, et al. A Widespread Outbreak of Yersinia Pseudotuberculosis O:3 Infection. *J Infect Dis*. 2004;189:766-774.

AN OUTBREAK OF INFECTIONS DUE TO *Yersinia pseudotuberculosis* serotype O:3 occurred in Fin-

land from October 15 to November 6, 1998. Locally grown iceberg lettuce was identfied as the source. The infection had come to light because laboratories in Finland routinely screen faecal samples from patients with acute gastroenteritis for this organism and report any isolates to the National Infectious Disease Registry. Of the 47 cases identified, 1 with bacteremia died and 5 others underwent appendectomies. A case-control study was done to determine the factors involved and only Iceberg lettuce emerged as a risk factor, with 71% of cases having eaten this compared with 43% of controls yielding an odds ratio of 3.8 (95% CI,1.3-9.4). There was also an apparent dose-response insofar as 29% of cases ate lettuce more than 5 times a week, compared with 3% of controls (odds ratio, 11.8). Nuorte and colleagues also set about trying to trace the source (see Figure). Although they were unable to isolate the strain in question from the lettuce which were long since gone, they did manage to recover *Y. pseudotuberculosis* from soil, irrigation water, and 2 lettuce from 1 of the farms. Although not incontrovertible, the evidence assembled by Nuorte et al is sufficiently compelling to show that *Y. pseudotuberculosis* can and does cause food-borne infection, can be acquired from fresh produce such as lettuce, and can lead to significant morbidity, including appendectomies.

Figure

Schematic Representation of the Outbreak



COMMENT BY J. PETER DONNELLY, PhD

Although this is the first report of its kind concerning the capacity of *Y. pseudotuberculosis* to cause a food-borne infection outbreak, it may not be the last. In an accompanying editorial, Tauxe (*J Infect Dis*. 2004;189:761-763) points out that there may be little we, as consumers, can do to prevent these. Firstly, it seems unlikely that simple surface contamination of lettuce and other fresh produce by irrigation, washing, or other handling procedures accounts for the risk. Instead, *Yersinia*, like its cousins *Escherichia*, *Shigella*, and *Salmonella*, is quite content to settle in moist soil, and can be taken up through the roots to disseminate throughout the plant including the edible leaves. In our glasshouse world we often forget that bacteria have had a much longer relationship with plants than with animals, and human variants may still have the capacity to rekindle ancient links when the opportunity arises. With globalization, the risk that contaminated fresh produce will cross borders and even continents is greater than ever before. So local inhabitants and those further afield may experience similar problems. Personally, I avoid eating lettuce in restaurants because of the risk of surface contamination. It seems now that I might have to reconsider lettuce as part of my domestic diet if these enteric bacteria are, in fact, the tip of the iceberg. Consumer confidence in safe foods is being continually shaken by events. Perhaps it is now time to employ a similar trace-back procedure as Nuorte et al attempted with some success, and to implement tests for the weak links in the chain. This might offer a more durable solution than reaching for the irradiation, at least here in Europe. The Finns have to be commended for sustaining laboratory surveillance, for freeing sufficient resources to get to the bottom of the outbreak, and for showing us how to investigate similar events when they occur on our own patch. ■

Treatment of Bacteremia Due to ESBL-Producing *Klebsiella pneumoniae*

ABSTRACT & COMMENTARY

Synopsis: *A carbapenem (most often imipenem) was found in a prospective observational study to be the optimal choice for therapy of bacteremia due to ESBL-producing* Klebsiella pneumoniae.

Source: Paterson DL, et al. Antibiotic Therapy for *Klebsiella pneumoniae* Bacteremia: Implications of Production of Extended-Spectrum B-Lactamases. *Clin Infect Dis.* 2004;39:31-37.

Paterson and colleagues performed a prospective, observational study of 440 patients with 455 episodes of bacteremia due to *Klebsiella pneumoniae* who were managed at 12 centers in Asia, Africa, Europe, and the Americas in 1996-1997. Antibiotic choice was at the discretion of the treating physicians. Eighty-five (19%) of the episodes were due to an ESBL-producing *K. pneumoniae*; 20 (24%) of these episodes ended with the patient's death. The mortality rate was 14% in those who received early antibiotic therapy with in vitro activity against the isolated pathogen and 64% ($P = 0.001$) in those whose antibiotics lacked such activity. Administration of a carbapenem (mostly imipenem) was associated with significantly lower mortality at 14 days than was administration of other antibiotics with in vitro activity against the infecting pathogen. Multivariate analysis demonstrated that use of a carbapenem during the 5 days after the onset of bacteremia with an ESBL-producing *K. pneumoniae* was independently associated with lower mortality (OR, 0.09; 95% CI, 0.01-0.65; $P = 0.09$) and was superior to monotherapy with other agents. There was no difference in the incidence of superinfections.

COMMENT BY STAN DERESINSKI, MD, FACP

Extended spectrum beta lactamases (ESBL) are enzymes whose evolution from standard plasmid mediated enzymes, such as TEM and SHV, has resulted in their ability to hydrolyze 3rd generation cephalosporins and aztreonam, but not cephamycins or carbapenems. ESBLs, of which more than 200 genetically distinct types have been identified, have been found in most of the Enterobacteriaciae, but are most highly prevalent in *K. pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*. It is currently recommended by the NCCLS, that all isolates of these 3 species, with an MIC > 2.0 mg/mL, be tested against cefpodoxime, ceftazidime, aztreonam, cefotaxime, or ceftriaxone, and examined for the presence of an ESBL.[1] The sensitivity of screening for ESBLs in enteric bacteria is further increased by testing with more than 1 of these 5 antibiotics. For instance, the production of an ESBL with relative specificity for cefotaxime (CTX-M) would be missed by screening with ceftazidime. The NCCLS recommends that ESBL production be confirmed by testing both cefotaxime and ceftazidime alone and in combination with clavulanic acid, which, like tazobactam and sulbactam, inhibits most ESBLs, resulting in increased susceptibility to the cephalosporin.

Such phenotypic confirmatory testing does not, however, detect all ESBLs. The presence of these enzymes maybe masked by, for example, the presence of an *AmpC* β-lactamase, since the hydrolysis of third generation cephalosporins by *AmpC* is not inhibited by clavulanic acid. The coexistence of inhibitor-resistant TEM or hyperproduction of TEM or SHV β-lactamases in ESBL-producing organisms may also lead to false-negative phenotypic screening tests.

The NCCLS recommends that all isolates confirmed to produce an ESBL be reported as resistant to all penicillins, cephalosporins and to aztreonam. There is controversy, however, regarding the potential efficacy of cefepime against infections caused by ESBL-producers.

In contrast to monobactams and third generation cephalosporins, carbapenems, such as imipenem, are resistant to hydrolysis by these enzymes and thus retain their activity against ESBL-producers. While non-β-lactam antibiotics are not affected by ESBLs, the large plasmids which carry the genes for these enzymes often carry genes encoding resistance to other antibiotics, including fluoroquinolones and aminoglycosides.[2]

While third generation cephalosporins are ineffective in the treatment of these infections, the role of cefepime, a putative fourth generation cephalosporin, remains incompletely understood. In a recent randomized trial of treatment of nosocomial pneumonia in intensive care patients, cefepime failed in 4 of 13 patients infected with an ESBL-producing organisms while no failures were observed in 10 patients treated with imipenem.[3] Nonetheless, successes have been reported elsewhere.

This study has a number of drawbacks, not the least of which is its lack of randomization. Furthermore, as Peterson et al point out, they did not collect information about antibiotic dosing. Systematic underdosing of a particular antibiotic could bias the results against that agent. Nonetheless, these results

provide a large database of use to the clinician faced with therapeutic choices in the hospital setting. ■

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More Antibiotic Resistance—Now Syphilis

ABSTRACT & COMMENTARY

Synopsis: Treponema pallidum *strains resistant to azithromycin are prevalent in San Francisco, Seattle, Baltimore, and Dublin.*

Source: Lukehart SA, et al. Macrolide Resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med.* 2004;351:154-158.

AZITHROMYCIN THERAPY FAILED IN A PATIENT IN San Francisco with a primary syphilitic chancre which subsequently resolved after administration of a single dose of benzathine penicillin. Sequencing of the 23S rRNA genes of *Treponema pallidum* from 2 San Francisco patients who had failed azithromycin therapy revealed the presence of a mutation (A→G in a position cognate to A2058 in *E. coli*) identical to that previously associated with macrolide resistance in a single isolate (*T. pallidum,* Street 14 strain). This mutation was subsequently identified in 4 isolates in Dublin, Ireland, and 2 in Seattle.

Screening of convenience samples identified the A→G mutation in 15 of 17 (88%) samples from Dublin, 12 of 55 (22%) from San Francisco, 3 of 23 (13%) from Seattle, and 2 of 19 (11%) from Baltimore. While the mutation was present in only 4% of samples from 1999 through 2002 in San Francisco, this prevalence increased to 37% in 2003. Therapeutic studies in a rabbit model of infection confirmed the relevance of the mutation to treatment failure with macrolide therapy.

■ COMMENT BY STAN DERESINSKI, MD, FACP

Previous studies demonstrated the effectiveness of azithromycin in the treatment of syphilis. Because of the convenience of a single oral dose (2 grams), its use has been increasingly utilized. Prior to this study, initiated by the identification of a series of cases in San Francisco,[1] only one macrolide resistant *T. pallidum*, called Street 14, had been identified.[2] The emergence of azithromycin resistance is undoubtedly related to the widespread use of this antibiotic , primarily for respiratory tract infection.

Lukehart and colleagues point out that there have, to date, been no failures among 100 patients with early syphilis treated with azithromycin in a randomized trial. This trial excludes HIV-infected patients, and is being performed at 4 sites (Madagascar; Birmingham, Alabama; Chapel Hill, North Carolina; and Indianapolis, Indiana) that did not include those utilized in this study.

No documented resistance of *T. pallidum* to penicillin has been identified, and penicillin remains the antibiotic of choice for the treatment of syphilis at all stages.[3] Despite the lack of resistance, I have the impression that we are seeing more non-HIV infected patients with latent syphilis who remain seropositive at high titers despite receipt of recommended doses of penicillin. Whether this is the result of resistance or of host factors (or both) can only be conjectured. ■

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Cows Harbor Expanding Serotypes of Pathogenic *Escherichia coli*

ABSTRACT & COMMENTARY

Synopsis: The *E. coli* geneticists are working on ways to facilitate rapid diagnosis, and in time, to purge eae positive strains from bovine reservoirs.

Source: Stephen R, et al. First Isolation and Further Characterization of Enteropathogenic *Escherichia coli* (EPEC) O157:H45 Strains from Cattle. *BMC Microbiol*. 2004;4(1):10. www.biomedcentral.com/1471-2180/4/10.

ENTEROPATHOGENIC *Escherichia coli* (EPEC) CAUSE of infantile diarrhoea, and represent 1 of the at least 6 different categories of diarrheagenic *E. coli*. Most of the EPEC strains belong to a series of O antigenic groups known as EPEC O serogroups: O26, O55, O86, O111, O114, O119, O125, O126, O127, O128, O142 and O158. Readers are probably most familiar with 0111 group but these others can be pathogenic for humans.

The hallmark of EPEC pathogenesis is the presence of attaching-and-effacing (A/E) lesions on intestinal cells characterized by microvillus destruction, intimate adherence of strains to the intestinal epithelium, formation of a pathogenic entity called a pedestal, and aggregation of polarized intracellular actin. The genetic determinants for the production of A/E lesions are located on a so called pathogenicity island that contains the genes *n* (*eae*), a type III secretion system, a number of secreted proteins (ESP) and the translocated intimin receptor (Tir). Characterization of *eae* genes in the strains from this study revealed the existence of different *eae* variants. Many genetic variants of the *eae* gene have been identified and several intimins are probably responsible for different host- and tissue-cell tropism. In epithelial culture cells, EPEC strains produce various characteristic adherence patterns. Localized adherence is mediated by a large EPEC adherence factor (EAF) plasmid which also encodes a bundle-forming pili (BFP).

In this study from Switzerland, *E. coli* 0157:H45 were isolated from either "fattening" cattle or from cows positive for Shiga toxin genes. The *eae* gene was present in all strains so these were considered EPEC strains. Ten of 11 strains were positive for heat-stable enterotoxin and the same number showed adherence and effacement with fluorescent actin staining. These strains resemble both typical EPEC strains because they have the large virulence plasmid but have some genetic connection with atypical EPEC strains because they have astA genes.

COMMENT BY JOSEPH F. JOHN Jr, MD

The genetics of enteropathogenic *E. coli* have become extremely complicated and full characterization of isolates can occur only in a research microbiology laboratory. What the general clinical microbiology laboratory can determine is by use of sorbitol in lactose positive Gram-negative bacilli, so called sorbitol-positive *E. coli*, that strongly suggest the strains may be enteropathic.

This article works its epidemiology a bit back-to-front by noting that O157:045 strains have not been found in animals to date and realizing the novelty of the discovery in these Swiss cows. There are likely other serotypes of EPEC lurking out there in animal reservoirs.

Animal husbandry, itself, is facing new challenges of public pressure for organic farming and vegetarian palates. What the public needs is to know that any herd suspicious of harboring enteropathic strains be clearly tested so that the public can be duely warned. The *E. coli* geneticists, in the meantime, are working on ways to facilitate rapid diagnosis, and in time, to purge eae positive strains from bovine reservoirs. ■

ICAAC/IDSA/ASTMH 2003

CONFERENCE COVERAGE

*The following is a summary of selected abstracts from 3 meetings. The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) met in Chicago September 14-17, 2003. The Infectious Disease Society of America (IDSA) met in San Diego October 9-12, 2003. The American Society of Tropical Medicine and Hygiene met in Philadelphia December 3-7, 2003.—**Stan Deresinski, MD, FACP***

Blood- and Tissue-Dwelling Protozoa

Trypanosomiasis

Forty-four HIV-infected patients were found to be coinfected with *Trypanosoma cruzi* at one Sao Paulo clinic. During follow-up, 46% developed manifestations of the parasitic infection, including 4 with reactivation acute

myocarditis, 3 with meningoencephalitis, and 1 with skin lesions. Two additional subjects who remained asymptomatic had organisms detected on direct microscopic examination of blood. Others developed progressive cardiomyopathy or megaesophagus (*ASTMH 778*).

Bushmeat

The African bushmeat trade is believed to have played a critical role in the introduction of HIV infection into humans from primates. It has also been identified as important in outbreaks of Ebola virus infection in humans. A survey of bushmeat markets in 8 major urbanized areas throughout Liberia found that the most preferred species were cane rat, water chevrotain, giant pangolin, black duiker, brush-tailed porcupine, bush buck, and giant forest hog (*ASTMH 547*).

Cestodes

Echinococcus

Three patients with progressive human alveolar echinococcosis had responses to ongoing treatment with IV amphotericin B (*ASTMH 389*).

Intestinal Parasites

Cyclospora cayetanensis infections were common but usually asymptomatic among residents of San Carlos Island, Venezuela (*ASTMH 337*).

Examination of blended fruit drinks collected from street vendors and small restaurants in Mexico detected *Trichuris trichiura* ova in 13 of 27. *E histolytica* cysts were found in 7 samples, *Ascaris lumbricoides* ova in 4, and *G lamblia* cysts in 1 (*ASTMH 494*).

Trematodes

Liver Flukes

Seventeen cases of opisthorchiasis or clonorchiasis were diagnosed by stool examination in immigrants in St. Paul over a 6-year period. Half of the cases were identified at initial refugee screening, while the remainder were not detected until as long as 14 years after arrival in the United States. While the majority of patients came from Southeast Asia, more recent cases have occurred in individuals from the former Soviet Union and 1 from Latin America. *Eosinophilia* was present in 88% but was often mild (*ASTMH 151*).

Schistosomiasis

Among individuals tested by the US State Department over a 5-year period, 70 (60%) had serological evidence by immunoblotting of infection with *Schistosoma mansoni*, 4 (3.4%) with *S haematobium*, 1 (1.1%) with *S japonicum*, and 17 (15%) were reactive to both *S mansoni* and *S haematobium*. Most of these infections were acquired in Africa; the individual with *S japonicum* seropositivity had been in the Philippines (*ASTMH 700*).

Viral Infections

Muructu Fever

Muructu virus is a group C virus of the family *Bunyaviridae*. Eight patients with muructu fever were identified in Iquitos, Peru, in the Amazonian region. The patients were aged 16-45, and all presented with fever, chills, and arthralgia. Most had headache and ocular pain. All markedly improved or completely recovered within 14 days of onset (*ASTMH 141*).

Yellow Fever

Ribavirin administration beginning 24-48 hours after exposure was therapeutically effective in a hamster model of yellow fever virus infection (*ASTMH 364*).

Miscellaneous

In a randomized trial, a 5-day course of amoxicillin/clavulanate 2000 mg/125 mg b.i.d. was superior to placebo in reducing episodes of infection after third mandibular molar removal (*ICAAC L-1384*).

In a randomized, blinded, placebo-controlled trial, the administration of doxycycline and rifampin for 3 months to patients with Alzheimer's disease was associated with significant reduction in decline in cognitive function. Serological and PCR studies suggest that the benefit was not related to any effect on *C pneumoniae* (*IDSA 516*).

Infliximab administration to 7 children with Kawasaki syndrome refractory to IVIG plus aspirin and/or corticosteroids was associated with resolution of fever within 24 hours, as well as marked clinical improvement and normalization of C-reactive protein levels (*IDSA 803*).

C-reactive protein was elevated 4-fold or more in 15 of 15 children with classical PFAPA syndrome (periodic fever with lymphadenopathy, pharyngitis, and aphthous stomatitis). The erythrocyte sedimentation rate was > 40 mm/h in only 1 of 11 tested (*IDSA 897*).

Smallpox vaccination was associated with an increase in C-reactive protein (*IDSA 815*).

Investigators demonstrated silencing of antibiotic

resistance genes in vivo in the absence of antibiotic administration. Thus, expression of mRNA was switched off, despite the presence of apparently intact promoters and resistance genes (*ICAAC C1-174a*).

An outbreak of staphylococcal scalded skin syndrome affected 13 neonates (*ICAAC K-1439*).

S pneumoniae was a rare cause of bacteremia in adults with sickle cell disease in France (*ICAAC L-119*).

Preterm infants immunized with DTPa-HBV-IPV/Hib at the chronological ages of 2, 4, 6, and 18-20 months developed antibody responses similar to that observed in full-term infants (*ICAAC L-186a*).

A retrospective cohort study found that the use of vancomycin was significantly associated with the subsequent isolation of ciprofloxacin-resistant *Klebsiella* spp. (*ICAAC K-697*).

A single 40-mg dose of atorvastatin significantly inhibited neutrophil chemotaxis in healthy volunteers without affecting serum lipid concentrations (*ICAAC N-1518*). ■

CME Questions

4. Which of the following is a trigger of asthma exacerbations in children?
a. Rhinoviruses
b. Influenza viruses
c. Respiratory syncytial virus
d. Mycoplasma pneumoniae
e. All of the above

5. Which of these nocardia species is not a human pathogen?
a. *N. asteroides*
b. *N. cyriacigeorgia*
c. *N. farcinica*
d. *N vinacea*

6. What is the characteristic intestinal lesion of enteropathogenic *E. coli*
a. Pseudomembrane formation
b. Elongation of microbilus structure
c. Attachment and effacaement of microvillus surfaces
d. Multiple punctate ulceration

Answers: 4. (e); 5. (d); 6. (c)

In Future Issues:

Nipah is Back

UPDATES

By Carol A. Kemper, MD, FACP

Multivitamins delay progression to AIDS

Source: Fawzi WW, et al. *N Engl J Med.* 2004;351:23-32.

An 8-year study conducted in Dar es Salaam, Tanzania, has found that daily multivitamins (vitamins B, C and E) can delay progression of HIV disease in African women. Between 1995-1997, a total of 1078 pregnant women with HIV were enrolled in this double-blind, placebo-controlled trail initially comparing MVI (vitamin B,C, and E), vitamin A, the combination of MVI and vitamin A, and placebo. None of the women had access to antiretroviral therapy.

The study was later modified so that the women received MVI during all pregnancies, and then after delivering they resumed their previously assigned blinded therapy. The women also received standard doses of folic acid and iron during their pregnancies. Vitamin A was later dropped from the study when safety analyses suggested it increased the risk of neonatal transmission of HIV.

During a median of 71 months of follow-up, 67 of 271 women who received MVI developed World Health Organization (WHO) Stage 4 AIDS or died (a primary outcome), compared with 83 of 267 women who received placebo (24.7% vs 31.1%, relative risk 0.71; $P = .04$). MVI also resulted in a statistically significant slower progression to (WHO) Stage 3 disease, as well as significantly higher CD4 counts and significantly lower viral loads. MVI also significantly reduced the frequency of a number of other complications, including oral ulcers, angular cheilitis, difficult or painful swallowing, dysentery, rash, fatigue, and acute upper respiratory infection. In comparison, women assigned to receive vitamin A alone had no apparent benefit, and may have had an increased risk of certain symptoms, such as angular cheilitis and difficult or painful swallowing. The addition of vitamin A to MVI actually appeared to diminish the effect of MVI—suggesting that the administration of vitamin A should be avoided in patients with HIV.

While most of these women were poor, they were not malnourished but had fairly reasonable diets for Africans. For this reason, Fawzi and colleagues believe that the additive benefit of MVI could be measured. In other words, while the effect of MVI may not be apparent in HIV-infected individuals living in theUnited States, who by comparison have diets rich in nutrients, supplemental MVI made enough of a difference in these womens' African diet to help maintain gastrointestinal mucosal integrity, local and cellular immunity, and cytokine responses. In addition, both vitamin C and E are excellent anti-oxidants. Given an estimated retail cost of $15 per person each year, the use of MVI may be a relatively inexpensive stopgap measure for HIV-infected individuals living in third world countries with limited access to anti-retrovirals. ■

Tenofovir Decreases Atazanavir Levels

Source: Taburet AM, et al. *Antimicrob Agents Chemother.* 2004;48:2091-2096.

Atazanavir (ATV), an azapeptide protease inhibitor with a distinct resistance profile, functions as a CYP3A substrate. Hence, ATV concentrations in the blood stream can readily be boosted with low-dose ritonavir. In healthy volunteers, the addition of 100 mg ritonavir daily to 300 mg ATV daily leads to a 3- to 4-fold increase in the area under the curve (AUC) in the bloodstream, and the half-life of ATV increases from 6.5 hours to 15-18 hours. However, a number of factors may lower ATV concentrations, including autoinduction, diminished absorption in the presence of a fatty meal, and the co-administration of tenofovir (TNF).

Following a 2-week course of ATV plus RTV, 11 HIV-infected patients additionally received 300 mg TNF per day. Peak concentrations, AUC, and t1/2 were measured at week 2 and week 6. With the addition of TNF, there was a significant decrease in the 24-hour AUC for ATV (~27% decrease), and both the Cmin and Cmax values dropped by about one-third, although there was significant individual variability. The half-life remained unchanged, suggesting that TNF had no effect on ATV clearance. Although the exact mechanism of the interaction between the 2 drugs remains unclear, Taburet and colleagues speculate that absorption of ATV could be impaired in the gut by the co-administration of TNF, possibly through the induction of P-glycoprotein transport mechanisms. Although staggering the administration of the 2 agents may diminish this effect, further information is needed before these 2 drugs should commonly be used together. ■

Breakthrough Chickenpox in Vaccinated Kids

Source: Vasquez M, et al. *JAMA.* 2004,291:851-855.

BREAKTHROUGH VARICELLA IN previously vaccinated kids is not uncommon. The occurrence of several recent outbreaks of chickenpox in heavily vaccinated preschool groups led Vasquez and colleagues to re-evaluate the effectiveness of varicella vaccine in a large group of children who developed chickenpox (matched by age and site of clinical care), compared to children without chickenpox. In this case-control study, 339 children with chickenpox were compared with 669 control subjects who had not had chickenpox (aged 13 months or older). All cases were confirmed by PCR of active lesions.

Overall, 36% of case patients had a history of varicella vaccination compared with 70% of uninfected controls. Chickenpox was significantly more likely to be more severe in unvaccinated children; 45% vs 87% of unvaccinated vs vaccinated children with chickenpox had mild disease. Interestingly, the rash was more likely to be predominately vesicular in unvaccinated children compared with those who had been vaccinated (58% vs 30%). Overall, the vaccine was 97% effective during the first year post-vaccination, but decreased to 86% by the second year, and to 81% by 7-8 years following vaccination. Vaccine efficacy was significantly lower if the vaccine was administered before 15 months of age (73%), although the earlier administration of vaccine still protected against more severe infection.

These data provides continuing evidence for the overall benefit of varicella vaccine—if not so much for the prevention of chickenpox but for a reduction in the risk of more severe disease. If the objective is to reduce rates of breakthrough infection, then the administration of vaccine should be delayed until at least 15 months of age, and consideration should be given to a booster dose later in life. However, shifting the timing of vaccination to slightly older babies leaves them vulnerable to infection for those additional few months, and some children may not return for vaccination. Probably the best bet is to offer vacation to kids (ie, moms) as they present for care at about ≥ 1 years of age, with a good explanation that vaccination does not prevent infection: ~14-27% of kids still get chickenpox but they are much more likely to have milder disease. ■

Find the VRSA in the MRSA: Get an Etest!

Source: *MMWR Morb Mortal Wkly Rep*. 2004;53(15):322-323.

ROUTINE AUTOMATED SUSceptibility testing of methicillin resistant *Staphylococcus aureus* (MRSA) may fail to detect vancomycin resistance (MIC >32 mg/mL). The Centers for Disease Control & Prevention is alerting physicians and micro labs, following discovery of a third case of vancomcyin-resistant *S. aureus* (VRSA) infection in the United States, that initially escaped detection. The patient was a resident of a long-term care facility, who developed a urinary tract infection with MRSA. Susceptibility testing by MicroScan (Dade Behring, Deerfield, IL) showed a vancomycin MIC = 4 mg/mL. Further testing by Etest (AB Biodisk North America, Inc, Piscataway, NJ) demonstrated vancomycin resistance with an MIC > 256 mg/mL.

After first being tested by the New York Public Health Department, the isolate was forwarded to the CDC, where MicroScan and Vitek (bioMerieux, Hazelwood, MI) methods failed to detect vancomycin resistance. Using NCCLS guidelines, broth microdilution testing confirmed vancomycin resistance with an MIC = 64 mg/mL. Further tests confirmed that the isolate contained both mecA and VanA genes—encoding methicillin and vancomycin resistance, respectively, but was unrelated to the 2 earlier VRSA isolates identified in Michigan and Pennsylvania last year. The isolate was also susceptible to linezolid, quinopristine-dalfopristine, minocycline, rifampin, trimethoprim-sulfamethoxazole, and chloramphenicol.

There is increased concern that commonly employed automated methods for susceptibility testing in microbiology laboratories may fail to detect vancomycin intermediate and resistant MRSA strains. The CDC recommends that micro labs should include a non-automated MIC method (broth microdilution,agar dilution, or agar-gradient diffusion) when setting up *S. aureus* isolates, especially MRSA isolates, for automated testing.

Fortunately, aggressive screening of family members and fellow patients and employees of the LTCF failed to identify any secondary cases. ■

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.*

The Importance of Publishing Negative Clinical Studies

Sources of funding for pharmaceutical research has come under scrutiny in the last decade as academic and government sources of funding have become increasingly scarce and the pharmaceutical industry has become the main source of research dollars. But the issue of objectivity has been raised, and some have even suggested that negative studies, that is studies that show a drug in an unfavorable light, may never be published. The American Medical Association has recently tackled this issue and has asked the department of Health and Human Services to establish a public registry of all clinical trials in United States. The registry would include information regarding the design of the study and the questions to be addressed. The registry would also contain data about the study results, both positive and negative. Some members of Congress have indicated interest in pursuing legislation to create such a registry, and even large pharmaceutical companies such as Merck and GlaxoSmithKline support the concept. But despite the AMA's valid concerns, several negative studies have been newsworthy in the last 2 months. This issue of *PharmWatch* highlights a few of those.

Cognitive Effects of Estrogen Therapy

Two studies in the *Journal of the American Medical Association* suggest that estrogen alone therapy may be associated with a decline in cognitive function in post-menopausal women and may increase the risk of dementia. Both studies are follow-ups from the Women's Health Initiative Memory Study (WHIMS) which had previously shown that estrogen plus progesterone therapy increases the risk of dementia in postmenopausal women. The first study was a follow-up of nearly 3000 women randomized in a double-blind fashion to conjugated estrogen, conjugated estrogen plus progesterone, or placebo. In the estrogen alone wing, 28 women taking estrogen developed probable dementia vs 19 assigned to placebo (HR, 1.49; 95% CI, 0.83-2.66). Similar rates were noted in the estrogen plus progesterone wing. When data were pooled for both estrogen and estrogen plus progesterone, the overall hazard ratio for dementia was 1.76 (95% CI, 1.19-2.60; P = .005). Increased risk of mild cognitive impairment was also noted in the estrogen alone group and the estrogen plus progesterone group. When the data were pooled, the hazard ratio for mild cognitive impairment was 1.25 (95% CI, 0.97-1.60). This study showed that there is no difference between estrogen alone vs estrogen plus progesterone therapy in the risk of dementia or mild cognitive impairment, and in fact, both therapies increase the risk of both these end points (*JAMA*. 2004;291:2947-2958). The second study asked whether estrogen alone alters global cognitive function in postmenopausal

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) 262-5416. E-mail: leslie.hamlin@thomson.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.

women. During a mean 5.4 years of follow-up, nearly 3000 women were randomized to 0.625 mg of conjugated estrogen or matching placebo per day. The women were assessed annually with the Modified Mini-Mental State Examination. The data showed that testing scores were 0.26 units lower among women assigned to conjugated estrogen compared to placebo (P = .04). When the data for estrogen alone was pooled with estrogen plus progesterone, the decrease was 0.21 (P = .006). The adverse effect of hormone therapy was more pronounced in women with low baseline cognitive function. The authors conclude that for women age 65 and older, hormone therapy, including estrogen alone therapy, had an adverse effect on cognition (*JAMA*. 2004;291:2959-2968). As pointed out in the accompanying editorial (*JAMA.* 2004;291:3005-3007), this study did not look at women who took estrogen in the years immediately following menopause. Previous observational data have suggested that there is a critical period just after menopause during which estrogen may be neuro-protective (*JAMA*. 2002;288:2123-2129). However, these current studies seem to conclusively show that neither estrogen nor estrogen plus progesterone are neuroprotective for older women.

Vitamin Therapy and Restenosis

Vitamin therapy to lower homocysteine levels has been touted as an effective way to prevent restenosis after coronary angioplasty. A new study, however, suggests that vitamin combination may actually increase the risk of restenosis in these patients. In a double-blind, placebo-controlled study from Germany and the Netherlands, 636 patients who had undergone successful coronary stenting were randomized to a combination of 1 mg of folic acid, 5 mg of vitamin B, and 1 mg of vitamin B12 intravenously, followed by daily oral doses of the 3 vitamins for 6 months; or to placebo. In a follow-up, the mean luminal diameter was significantly smaller in the vitamin group and placebo group (P = .008), and the extent of luminal loss was greater (P = .004). The restenosis rate was also higher in the vitamin group than the placebo group (34.5% vs 26.5%, P = .05). A higher percentage of patients in the vitamin group also required target vessel revascularization (P = .05). The authors conclude that contrary to previous findings, the administration of folate, vitamin B-6, and vitamin B12 after coronary stenting, may increase the risk of in-stent stenosis (*NEJM*. 2004;350:2673-2681).

Echinacea and the Common Cold

Echinacea purpurea, the commonly prescribed herbal remedy, may have no effect on the common cold, according to a new study. In this randomized, double-blind, placebo-controlled trial, 128 patients with early symptoms of the common cold were randomized to 1 mg of Echinacea or lactose placebo 3 times per day for 14 days or until cold symptoms were resolved, whichever came first. No statistically significant difference was observed between treatment groups for either a total symptom score (P range for symptoms = .29-.90) or mean individual symptom scores (P range = .09-.93). The time toward resolution of symptoms is not statistically significant between the 2 groups (*Arch Intern Med.* 2004;164:1237-1241). The authors admit, however, that testing different preparations and dosing ranges of Echinacea may be needed to confirm these findings.

Effects of Paxil in Children Under 18

GlaxoSmithKline has been accused of suppressing negative data about its antidepressant paroxetine (Paxil), showing that it is broadly ineffective in children and adolescents, and could increase the risk of suicidal behavior. The accusation comes in the form of a lawsuit from New York Attorney General Eliot Spitzer, who filed the suit in early June accusing the company of fraudulently suppressing the data. In response, Glaxo has published several studies on its web site, and states that these studies had previously been published in journals or presented at scientific meetings. The company also reiterates that paroxetine is not approved for treatment of patients 18 years or younger, and states that they do not promote off-label use of their products. The British firm has released data from 9 pediatric trials, as well as the bibliography of public communications derived from the studies, and letters to United States physicians summarizing the data. As mentioned earlier, GlaxoSmithKline, has stated publicly, it's support of the American Medical Association's proposal to create a national registry of all proposed pharmaceutical studies. More information is available at www.gsk.com/media.

FDA Actions

Schering has received approval from the FDA to market a new low dose estrogen patch for the treatment of osteoporosis. The patch, which is dime sized, is applied once a week, and delivers 14 micrograms per day of estradiol. It will be marketed this summer under the trade name Menostar. ■