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Decreased Pneumococcal Meningitis after PCV7 Implementation: Another Vaccine Success Story

ABSTRACT & COMMENTARY

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Dr. Blackburn reports no financial relationships relevant to this field of study. This article originally appeared in the June 2008 issue of Infectious Disease Alert. It was peer reviewed by Connie Price, MD. Dr. Price Reports no financial relationships relevant to this field of study.

Source: Tsai CJ, et al. Changing epidemiology of pneumococcal meningitis after the introduction of pneumococcal conjugate vaccine in the United States. *Clin Infect Dis*. 2008;46:1664-1672.

Synopsis: *After implementation of universal childhood vaccination with the seven-valent pneumococcal conjugate vaccine (PCV7), the incidence of pneumococcal meningitis decreased not only among children, but also among adults.*

Pneumococcal meningitis remains a deadly disease, with a case fatality rate among adults that is still above 20%, and also with permanent neurological sequelae in a substantial minority of survivors.[1] Prevention of this disease, thus, remains an important element of public health policy. Although the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been available for over 25 years, it has proven only adequate in preventing invasive pneumococcal disease in adults, with a protective efficacy of about 55-60%.[2] Furthermore, because children under two years of age do not mount a reliable immunologic response to polysaccharide vaccines, protection of this high-risk group is not achieved with PPV23.

In 2000, a seven-valent pneumococcal conjugate vaccine (PCV7) was licensed in the United States, and recommendations followed shortly thereafter for universal vaccination of children 2-23 months of age.[3] Conjugate vaccines offer several advantages over polysaccharide vaccines, including immunogenicity in young children, better stimulation of the memory T-cell response, and eradication of the carrier state, offering better herd immunity.

Although several studies have subsequently demonstrated sharp declines in invasive pneumococcal disease among the target population of this vaccine (children under two years of age), the data have not convincingly demonstrated a decrease in pneumococcal meningitis among adults.[4] Because this conjugate vaccine would be expected to decrease pneumococcal colonization among children under two, one might expect the overall burden of disease due to the vaccine serotypes to decrease in the population.

Tsai and colleagues undertook a retrospective review of the Nationwide Inpatient Sample (NIS), a large database with patient level information from about 1000 hospitals (a 20% sample of community hospitals) in the United States. Using discharge diagnosis ICD-9 codes, they ascertained the incidence of pneumococcal and other forms of meningitis from 1994-2004, using population-based hospitalization and mortality rates. Universal PCV7 vaccination of children under two was recommended beginning in 2000; although they did not have access to individual patient vaccination status, they used year of illness as a proxy for vaccination status, with 1994-1999 regarded as the baseline (pre-vaccination) period, 2000 as the transitional year, and 2001-2004 as the post-vaccination period.

Hospitalization rates for pneumococcal meningitis decreased 33% among all ages in 2001-2004 compared to 1994-1999. Subgroup analysis showed that the decrease in pneumococcal meningitis hospitalization rates in the post-vaccination period was 66% among children under two and 33% among adults over 65, compared to the pre-vaccination period. In addition, deaths due to pneumococcal meningitis decreased 51% and 44% in these groups, respectively. Significant decreases in pneumococcal meningitis hospitalization rates were also seen in the 2-4 and 18-39 year age groups, and strong trends toward fewer hospitalizations were seen in the other age groups. Overall, Tsai et al estimated that PCV7 prevented 3330 pneumococcal meningitis hospitalizations and 394 deaths in 2001-2004. The median age of patients with pneumococcal meningitis increased from 37 to 46 years in the post-vaccination period due to the more robust impact on younger children. Interestingly, decreases in hospitalization rates for meningococcal, *Haemophilus influenzae*, and other types of meningitis were seen in the post-vaccination period as well.

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PCV7 has been one of the major public health success stories of the past decade. Not only has it resulted in a significant decrease in the incidence of invasive pneumococcal disease among young children (the target population of this vaccine, and the group at highest risk for bacterial meningitis), it has also resulted in significantly lower rates of invasive pneumococcal disease among adults, including pneumococcal meningitis. Probably related, in large part, to decreased colonization rates in vaccinated children, this is a prime example of the advantage of conjugate vaccines over polysaccharide vaccines.

Although Tsai et al did not have access to individual patient vaccination status, and could not control for the possibility of increased PPV23 vaccination rates among adults in 2001-2004, the declines in pneumococcal meningitis incidence occurred in sharp drops centered around the 2000-2001 period, lending weight to the hypothesis that the decreases described in the article were indeed due to PCV7, which came into widespread use in 2000. Although most other types of meningitis decreased over the study period as well, these seemed to be part of longer trends, dating back years prior to the implementation of PCV7; this renders an uncontrolled, confounding effect occurring in 2000 that decreased all causes of meningitis less likely.

Along with enthusiasm for the decrease in the seven PCV7 serotypes circulating in the community, and the

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resultant salutary effect on invasive pneumococcal disease, there has been concern that the increase in non-vaccine serotypes might negate the benefit of the vaccine.[5] The data presented by Tsai et al suggest that despite this potential for serotype replacement, this has not affected the vaccine's impact on overall morbidity and mortality to date. This, however, does remain an issue that will require close monitoring in the years to come. ■

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Should We Be Screening for Hepatitis C?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Dr. Scherger reports no financial relationships relevant to this field of study. This article originally appeared in the May 15, 2008 issue of Internal Medicine Alert. It was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Roberts reports no financial relationships relevant to this field of study.

Synopsis: *Among veterans with risk factors for hepatitis C, a screening program yields results of limited value.*

Source: Mallette C, et al. Outcome of screening for hepatitis C virus infection based on risk factors. *Am J Gastroenterol*. 2008;103:131-137. Summary review by Essential Evidence Plus:Daily POEM: Screening for hepatitis C has minimal benefit (NNS = 4000). Wiley Subscriptions Services. April 10, 2008.

HEPATITIS C IS THE MOST COMMON VIRAL HEPATITIS leading to chronic liver disease. Most patients with antibodies to hepatitis C do not develop liver disease even with positive RNA viral levels. The Centers for Disease Control and Prevention recommends screening high-risk patients for hepatitis C (HCV) infection. The U.S. Preventive Services Task Force found insufficient evidence to support this recommendation. The current treatment for HCV is toxic and expensive, and the long-term successful outcome as measured by clearing of the viral levels is less than 50%. Given all this, should we be screening high-risk patients and who should we be referring for evaluation and treatment?

Two large VA studies have been published this year on outcomes of screening high-risk patients (Mallette, et al and Groom, et al).[1] In the Mallette study review here, veterans at the Providence, RI Veterans Affairs Medical Center (VA) were given a questionnaire to assess for risk of hepatitis C. High-risk factors were: serving in Vietnam, receiving blood products before 1992, intravenous drug or cocaine use, 5 or more alcoholic drinks per day for 10 or more years, 10 or more lifetime sexual partners, any male homosexual experience, blood exposure, hemodialysis, tattoo, current HIV or hepatitis B, or history of unexplained liver disease. Between October 1998 and May 2004, 25,701 patients were assessed and 8,471 had at least one risk factor. Of them, 5646 agreed to be tested, and 412 patients had a positive HCV test (7.3%). Of these, 260 were new diagnoses, and the authors used this number to support the screening program.

What happened to these 260 patients? One hundred forty-eight could not be reached for further evaluation, reflecting the nature of this population with high levels of drug use and alcoholism. Among the 112 that did undergo a complete evaluation, about half (57) were treatment candidates. Only 18 underwent a full course of treatment, and 6 had a sustained virologic response (less than 1 in 4000 screened). While the authors support the use of the screening program, the reviewers for Daily POEM (Wiley Subscription Services) consider screening for hepatitis C of minimal benefit. The results from a similar study at the Minneapolis VA by Groom, et al, yielded similar results.[1]

■ COMMENTARY

Screening, evaluation, and treatment of hepatitis C is highly controversial. Given the high prevalence of this condition in the population, whether to screen or not and whom to evaluate and treat are vitally important questions. Enormous amounts of money are being spent on

hepatitis C in a health care system strapped for funds.

I am the medical director of the indigent care program for San Diego County and am responsible for the medical policies, including screening and referral for evaluation and treatment of hepatitis C patients. We support hepatitis C screening of at-risk patients, mainly because we think that this knowledge is important to reduce risk of spread through sexual relations and the use of blood products. Our local liver clinics are willing to treat any patients with a positive viral load, which is about 50% of antibody positive patients. However, based on the toxicity, expense, and limited success of treatment, we only support referral of patients with a positive ALT level (at least 50% above normal). This is because 85% of HCV patients will not develop hepatitis, and waiting for early evidence of disease does not significantly change the outcome. Similar policies are used by other public health agencies in an effort to be cost effective.

Much has been learned about the treatment of chronic HCV, and the treatment regimens will improve with time and experience. However, mass evaluation and treatment of HCV today is not the best use of limited health care resources. We need to be selective in our use of screening and treatment. Many of the veterans in these studies voted with their feet and did not pursue evaluation and treatment. I think we need to stay very selective in our screening, evaluation, and treatment of HCV. If I were HCV positive and had a normal ALT, I would sit tight and not undergo a liver biopsy or treatment at this time. ■

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1. Groom H, et al. *J Clin Gastroenterol.* 2008;42:97-106.

Midlife Contraception

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim. This article originally appeared in the May 29, 2008 issue of Internal Medicine Alert. It was peer reviewed by Gerald Roberts, MD. Dr. Roberts reports no financial relationships relevant to this field of study.

Source: Kaunitz AM. *N Engl J Med*. 2008;358:12:1262-1270.

THE MEAN AGE OF ATTAINMENT OF MENOPAUSE IN American women—51 years—has not meaningfully changed over more than a century. During late reproductive life, pregnancy has more adverse consequences than in younger women. The therapeutic abortion rate of post-40 women is higher than any other age group except adolescents. Hence, midlife contraceptive decisions might be weighed differently than at other periods of reproductive life.

Kaunitz reviews multiple factors that impact contraceptive decisions after age 40. DVT risk after age 39 is more than 4-fold greater than in adolescent women, exaggerated further in obese women, in whom progestin-only oral contraceptives might logically be preferred. Older women who smoke should not be prescribed oral contraceptives, and Kaunitz recommends similar restrictions for midlife women with hypertension or diabetes.

Data on risk for breast cancer in association with oral contraceptives is largely reassuring, although data sets usually contain few women over age 45 to study. Oral contraceptives improve bone mineral density, and are associated with reduced risk for ovarian, endometrial, and colon cancer.

No method of discontinuation of contraception has proven ideal in all women. Kaunitz suggests continuing oral contraceptives, if well tolerated, into the early-mid 50s, after which pregnancy risk upon discontinuation is very low. The ideal candidate for midlife oral contraceptives is the lean, slender, nonsmoker. ■

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.

CDC Adds Shingles Vaccine to List for Adults 60 Plus

In This Issue: Shingles vaccine added to CDC list of vaccines for adults 60 and older; CDC recommends Tdap for postpartum women; new study suggests sequential therapy with antibiotics for *H. pylori* may be more effective than standard therapy; FDA Actions.

The Centers for Disease Control and Prevention (CDC) have added shingles vaccine to the list of routine vaccines recommended for adults. Shingles vaccine (Zostavax) is recommended for adults 60 years of age or older even if they have a history of having shingles. The recommendation is based on data showing that the vaccine reduces the occurrence of shingles by 50% in those over the age 60. For the group age 60 to 69, the vaccine reduces the occurrence by 64%. Over 95% of adults have been infected by varicella-zoster virus during their lifetime, most developing chickenpox during childhood. After the acute infection the virus lies dormant in a nerve ganglion until it reactivates as shingles. Most children now receive varicella vaccine as part MMRV or individually with the chickenpox vaccine (Varivax). Shingles becomes more common over the age of 50 with as many as one third of the population developing shingles during their lifetime and one third of those may develop complications such as postherpetic neuralgia (PHN). The vaccine is also effective at preventing PHN (66% reduction). If the vaccine is given to older adults, it is more likely the virus will attenuate the severity of shingles rather than preventing shingles itself. In those older than 80, efficacy of preventing shingles was only 18%; however, there was still efficacy at preventing PHN (39% reduction). A comprehensive of review of this topic may be found at MMWR web site www.cdc.gov/mmwr.

Pertussis, Tetanus, and Diphtheria Vaccines for Pregnant Women

The CDC through their Advisory Committee on Immunization Practices has also issued new recommendations for the pertussis, tetanus, and diphtheria vaccine for women during and after pregnancy. Mothers are an identified source of pertussis infections in infants where the rates for complications and fatalities are the highest. Women who have not received the tetanus, reduced diphtheria, and acellular pertussis (Tdap[Adacel]) vaccine previously should be vaccinated postpartum before they leave the hospital or soon as possible after discharge. They may receive it as soon as two years after their most recent diphtheria and tetanus (Td) vaccination. They can also receive diphtheria tetanus vaccination during pregnancy if needed or defer it to receive the Tdap

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: iris.young@ahcmedia.com.

immediately postpartum. Currently the Tdap vaccine is not recommended during pregnancy although health-care providers "should weigh the theoretical risks and benefits before choosing to administer Tdap vaccine to pregnant women." The full text of the CDC's recommendations can also be found online at www.cdc.gov/mmwr.

Standard therapy for eradicating *H. pylori* infections fails in up to one quarter of patients. A new study published online as an early release article in *The Annals of Internal Medicine* suggests that sequential therapy with antibiotics may be more effective than standard therapy which generally consists of triple drug regimens including a proton pump inhibitor and clarithromycin with either amoxicillin or a imidazole for 7 to 14 days. In a meta-analysis of 10 randomized controlled trials involving 2747 patients, eradication rates were 93.4% for sequential therapy (95% CI, 91.3%-95.5%) and 76.9% for standard triple therapy (CI, 71.0%-82.8%). Sequential therapy is more complicated for the patient, involving five days of a proton pump inhibitor with an antibiotic followed by five days of a proton pump inhibitor with two other antibiotics. The median rates of adherence were 97.4% for sequential therapy and 96.8% for standard therapy. Both treatments had similar side effect profiles. The authors state that most of the studies were conducted in Italy and there was evidence of publication bias. Despite this they conclude that 10-day sequential therapy appears superior to standard triple therapy for eradication of *H. pylori* infection (published early release *Ann Int Med.* 20th May 2008, print 17 June 2008).

FDA actions

The FDA has proposed broad new labeling requirements for prescription drugs regarding their use during pregnancy and breast-feeding. This labeling information is directed at physicians and other health-care professionals. The new labeling would eliminate the letter categories from the pregnancy section of prescription labeling. The new format would include sections called "Fetal Risk Summary" which would describe what is known about the effects of the drug on the fetus and the strength of the data. This section would be required to include "risk conclusions" for the possibility of fetal harm based on available data. Another section, called "Clinical Considerations" would include information about the effects of the drug if it is taken prior to pregnancy as well as information on the risk of the disease being treated to the mother and baby. The third section under the heading "Data" would describe details regarding data on use of the drug in humans and animals that were used to develop the Fetal Risk Summary. The section on lactation is similar in format as that for pregnancy. Newly approved drugs will need to follow this format while previously approved drugs will be phased in over time.

The FDA has approved lubiprostone for the treatment of the irritable bowel syndrome with constipation (IBS-C) in adult women aged 18 over. The drug was previously approved in 2006 for chronic idiopathic constipation. There is currently no prescription drug therapy available in this country for IBS-C after the withdrawal of Novartis' tegaserod (Zelnorm) last year. The safety and efficacy of lubiprostone was demonstrated in two studies involving 1154 patients of which 92% were women. The drug is not approved for use in men due to lack of data demonstrating efficacy. The dose is 8 µg twice a day orally with food and water. Lubiprostone is manufactured by Sucampo pharmaceuticals and will be jointly marketed Takeda Pharmaceuticals under the trade name "Amitiza."

The FDA is reminding health-care professionals and patients that HFA propelled albuterol inhalers will no longer be available in the United States after December 31, 2008. These inhalers contain chlorofluorocarbon (CFC)-propelled inhalants which are thought to harm the Earth's ozone layer. New inhalers use hydrofluroalkane (HFA) as a propellant, and three have already been approved by the FDA including ProAir HFA, Proventil HFA, and Ventolin HFA. In addition levalbuterol is available in an HFA formulation (Xopenex HFA). Some patients have complained about the HFA propellant, noting the spray has a softer feel. Patients must also prime and clean HFA-propelled albuterol inhalers to avoid build- up of medication in the device. ■