Top Findings in Pediatric Infectious Disease

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TORONTO — Advances in the fight against human bocavirus, infant botulism, and severe rotavirus gastroenteritis were among the topics selected as the top new findings in pediatric infectious disease at the annual meeting of the Infectious Diseases Society of America.

"There has been a lot of activity in pediatric infectious diseases, with some important observations over the past year that will likely have an impact on clinical practice," said Dr. Joseph W. St. Geme III of Duke University, Durham, N.C., who, along with Dr. Janet Englund of the University of Washington, Seattle, presented the past year's top findings in pediatric infectious disease.

Human Bocavirus

"One of the major problems in pediatrics continues to be respiratory tract infections," said Dr. St. Geme. Along these lines, Dr. John C. Arnold and his colleagues assessed the prevalence and clinical spectrum of the recently identified human bocavirus (HBoV) among nearly 1,500 children aged 0-18 years who were treated for respiratory tract infection over a 20-month period at the Children's Hospital, San Diego (Clin. Infect. Dis. 2006;43:283-8).

The investigators screened by polymerase chain reaction 1,474 nasal scraping specimens that had been collected and frozen, and they found HBoV DNA in 5.6% of the specimens. The researchers noted that the peak infection rate was between March and May in both 2004 and 2005 and that 63% of the patients were younger than 12 months.

Evidence of underlying disease, including asthma, bronchopulmonary dysplasia, neuromuscular disease, and trisomy 21, was present in roughly one-third of the patients.

The most common symptoms were cough (present in 85% of cases), rhinorrhea, and fever. Clinical evidence of lower respiratory tract HBoV infection was present in 62% of the children, and nearly half of the patients had hypoxemia. Approximately 19% of HBoV-infected patients had paroxysmal cough, which led to further testing for pertussis.

Based on the findings, "it's clear that more widely available diagnostic testing for human bocavirus will be a priority in terms of establishing a better understanding of the epidemiology and clinical manifestations," said Dr. St. Geme.

Influenza in Young Children

"In contrast to a new virus that we can't diagnose, influenza is an old virus that we can diagnose," said Dr. Englund while presenting a paper on the burden of influenza in young children by Dr. Catherine Poehling of Vanderbilt University, Nashville, Tenn., and her colleagues at the Center for Disease Control and Prevention's New Vaccine Surveillance Network (N. Engl. J. Med. 2006;355:31-40).

The investigators used population-based surveillance to assess the disease burden of influenza among children younger than 5 years who were seeking medical care for acute respiratory tract infection or fever at clinics, emergency departments, and hospitals in three U.S. counties. They collected outpatient data during two influenza seasons—2002-2003 and 2003-2004 (when influenza vaccine was recommended for all children between 6 and 23 months)—and inpatient data from 2000 to 2004.

The average annual rate of hospitalization associated with influenza was 0.9 per 1,000 children in 2000-2004. The estimated burden of outpatient visits associated with influenza was 50 clinic visits and 6 emergency department visits per 1,000 children during the 2002-2003 season and 95 clinic visits and 27 emergency department visits per 1,000 children during the 2003-2004 season.

Of particular interest, Dr. Englund noted, was the fact that only 28% of the inpatient population and 17% of the outpatient population with laboratory-confirmed influenza received a discharge diagnosis of influenza by the treating physician, "despite the availability of on-site testing." Of even more concern, she added, "is that fewer than half of the children in the ICU setting had a diagnosis of influenza made during their hospitalization."

'One of the major problems in pediatrics continues to be respiratory tract infections,' including the recently discovered human bocavirus.

The take-home message is that "influenza is underrecognized and underappreciated, even by pediatricians," noted Dr. Englund. Increasing awareness and adopting and promoting broader universal vaccination strategies "has the potential to decrease the outpatient burden."

Infant Botulism

Infant botulism, caused by ingestion of *Clostridium botulinum* bacteria, which then germinate and produce toxins in a baby's large intestine, is the most common form of human botulism in the United States; 80-110 cases occur per year. A rare but serious and potentially fatal condition, infant botulism typically requires hospitalization for 4-6 weeks and often requires mechanical ventilation. Although adults with botulism poisoning can be treated effectively with an equine-derived botulism antitoxin, the treatment is not used in infants because of the risk of serious side effects, such as anaphylaxis and serum sickness.

For this reason, the development and successful testing in infants of a human-derived botulism antitoxin called BIG-IV (Human Botulism Immune Globulin-Intravenous) by Dr. Stephen S. Arnon of the California Department of Health Services and his colleagues in the Infant Botulism Treatment and Prevention Program was "tremendously important," according to Dr. St. Geme. In the first of two studies included in the published paper, 122 infants (age range, 21-313 days) with laboratory-confirmed infant botulism were randomized to receive BIG-IV or placebo within 3 days of hospital admission. Infants who received BIG-IV had significantly shorter hospital stays, compared with the placebo group (mean 5.7 vs. 2.6 weeks), and shorter durations of intensive care (5.0 vs. 1.8 weeks), mechanical ventilation (4.4 vs. 1.8 weeks), and tube or intravenous feeding (10.6 vs. 3.6 weeks). Both type and frequency of adverse events were similar in the two groups.

In a subsequent open-label study that included 382 infants in 37 states, BIG-IV treatment within 3 days of admission significantly shortened mean length of hospital stay, compared with treatment within 4-7 days of admission: 2.0 vs. 2.9 weeks (N. Engl. J. Med. 2006; 354:462-71).

Rotavirus Vaccine

Two phase III trials of live, attenuated rotavirus vaccines for severe rotavirus gastroenteritis were among this year's most important pediatric infectious disease studies, said Dr. Englund. The vaccines—an oral pentavalent human-bovine reassortant rotavirus vaccine (RotaTeq) and a two-dose oral monovalent human rotavirus vaccine (Rotarix)—were independently studied in large, multicenter trials that included more than 60,000 children each (N. Engl. J. Med. 2006; 354:11-22; N. Engl. J. Med. 2006;354:23-33). Compared with placebo, both vaccines demonstrated significant efficacy in reducing severe gastroenteritis and hospital admissions associated with rotavirus, and both reduced all diarrhea-associated hospital admissions by approximately half, which suggested that a high proportion of the diarrhea-associated admissions in the study areas were linked to rotavirus, noted Dr. Englund.

Both vaccines also had good safety profiles. In particular, there was no evidence of an increased intussusception risk following vaccine administration as had been reported with the first-generation rotavirus vaccine (RotaShield) that was on the market in the late 1990s.

Perhaps the most important outcome of both of these studies "is that they set the standard now for what all vaccine manufacturers are going to do or have the ability to do in the future," said Dr. Englund.

As a result of the positive data coming out of these large trials, the Advisory Committee on Immunization Practices (ACIP) issued a recommendation in the summer of 2006 that all U.S. infants be immunized against rotavirus with three doses of the already Food and Drug Administration–approved RotaTeq vaccine, administered at 2, 4, and 6 months.

Because the rotavirus burden is highest in underdeveloped countries, "efforts should be made to conduct clinical trials in these regions and to determine ways to pay for the vaccine, which is relatively expensive," Dr. Englund noted. "Such efforts are worthwhile considering the vaccine has the potential to prevent 5% of childhood deaths worldwide."

Mumps Vaccination Update

Mumps also made its way into the infectious disease news this year. In response to outbreaks of the disease in early 2006 in the Midwestern United States, the ACIP updated its 1998 criteria for mumps immunity and mumps vaccination recommendations. Among the key changes, Dr. St. Geme noted, were the criteria for acceptable presumptive evidence of immunity for school-age children and adults at high risk, including those who work in health care facilities, international travelers, and college students. "Previously, documentation of adequate vaccination for these populations was one dose of a live mumps virus vaccine; now it's two doses," he said.

Also, routine vaccination with two doses of a live mumps virus vaccine is recommended for health care workers born during or after 1957 without other evidence of immunity. One dose is recommended for health care workers born before 1957 without other evidence of immunity. In outbreak settings, a second dose of a live mumps virus vaccine should be considered for children ages 1-4 years and adults at low risk, within a 28-day interval. For health care workers born before 1957 without other evidence of immunity, two doses should be seriously considered (MMWR 2006;55:1-2).

Live Attenuated Influenza Virus Vaccine

The theoretical potential of secondary transmission of influenza has been a concern related to the use of the live attenuated influenza virus vaccine (FluMist). In previous studies, shedding of vaccine viruses has not been associated with viral transmission to close contacts.

In an effort to estimate the probability of transmission in a "worst-case scenario," Dr. Timo Vesikari of the University of Tampere (Finland) and colleagues conducted a trial in a day care setting, said Dr. Englund. "This study was designed by the authors to maximize opportunity for transmission by including young children without immunity and without prior exposure or minimum exposure to influenza in a close-contact setting," she said.

The study included 197 children between 9-36 months of age from 52 different day care center rooms who were randomized 1:1 to receive the vaccine or placebo. Nasal swabs were taken at regular intervals to determine postvaccination viral shedding, genotype and phenotype of shed viruses, and the probability of secondary transmission of the vaccine influenza strains (Pediatr. Infect. Dis. J. 2006; 25:590-5).

Of the 98 children who received the vaccine, 80% shed at least one vaccine influenza strain. All of the vaccine virus isolates retained their cold adaptation and temperature sensitivity characteristics. There was one confirmed transmission of a vaccine strain to a placebo recipient, but the child did not exhibit any signs or symptoms of clinically significant influenza. The probability of secondary transmission of influenza from one vaccinated child was calculated to be approximately 0.58%.

"This study showed that, even in the worst conditions and despite the high rate of viral shedding following vaccination, there is a low potential for secondary transmission of influenza," said Dr. Englund. ■