Experts Differ on Treatment for Group A Strep

BY LAIRD HARRISON

EXPERT ANALYSIS FROM A PEDIATRIC UPDATE

LAS VEGAS - What's the treatment of choice for group A streptococcal tonsillo-

In 2009, attendees at this pediatric update sponsored by the American Academy of Pediatrics California District 9 were advised that cephalexin

was the best first-line treatment. But those who returned this year heard a conflicting recommendation - for amoxicillin taken in one dose per day. Both recommendations differ from the AAP Red Book.

"Amoxicillin is my favorite," said Dr. Christopher J. Harrison, a pediatrician who is an infectious disease specialist at Children's Mercy Hospital in Kansas City, who presented this year.

While the AAP Red Book, Centers for Disease Control and Prevention, and other organizations still recommend penicillin as the first line of treatment, recent studies have shown it to be less effective than amoxicillin, said Dr. Harrison, citing an article that compared the two regimens in 152 children (Pediatrics 1999;103:47-51).

One problem with penicillin is that the generic versions taste bad, he said, so patients are less likely to take the full course. "The taste has always been an issue," said Dr. Harrison. Amoxicillin tastes better. So he recommends amoxicillin 50 mg/kg up to 1 g, taken once per day - an approach shown to be effective in one study (Arch. Dis. Child. 2008;93:474-8).

The standard recommendation for amoxicillin is 750 mg four times a day, but administering a drug three to four times a day is hard for families, he said. "That's not something that our parents are going to get done."

So Dr. Harrison prescribes the amoxicillin all in one dose per day. "The single big dose - or twice a day - is actually pharmacokinetically better than what we used to do," he said. Fewer, larger



Cephalosporins should be used as second-line treatments because of the resistance.

DR. HARRISON

risk of bacterial

doses result in a longer period of time in which the serum level of the drug is at a high concentration. The longer time at a higher concentration is helpful in eradicating bacteria that can protect themselves in biofilm, he said.

He also cited studies showing that cephalosporins, such as cephalexin, are more effective than penicillin.

But he agreed with the Red Book recommendation that these drugs should be used as second-line treatments because of the risk that the bacteria might develop resistance to them. He also pointed out that the cephalosporins, while more successful in eradicating the bacteria, have never been shown to directly prevent rheumatic fever.

Asked to comment, Dr. Michael E. Pichichero, a pediatrician who is an infectious disease specialist at the University of Rochester (N.Y.) Medical Center, stuck to the position he articulated at last year's meeting: that cephalexin is the best first-line treatment. He uses two 15mg doses per kilogram per day.

He cited his own research, including a study to which he contributed published in Clinical Pediatrics (2008;47:549-54), which found that children treated with first-generation cephalosporins are much less likely to experience symptomatic relapses than children treated with amoxicillin, which in turn works better than penicillin.

'Cephalexin tastes good," he said. "It can be used twice a day. It doesn't kill the normal flora. And it's no more expensive." The possibility that the use of cephalexin as a first-line treatment might lead to more resistant strains of streptococcus "has never been shown," he said. "It's hypothetical."

Dr. Pichichero pointed out that there are reasons to eradicate the bacteria be-Continued on following page

RotaTeq®

[Rotavirus Vaccine, Live, Oral, Pentavalent]

BRIEF SUMMARY OF PRESCRIBING INFORMATION

DOSAGE AND ADMINISTRATION

FOR ORAL USE ONLY. NOT FOR INJECTION. The vaccination series consists of 3 ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 weeks of age.

A demonstrated history of hypersensitivity to the vaccine or any component of the vaccine. Infants who develop symptoms suggestive of hypersensitivity after receiving a dose of RotaTeq should not receive further doses of RotaTeq.

Infants with Severe Combined Immunodeficiency Disease (SCID) should not receive RotaTeq, Post-marketing reports of gastroenteritis, including severe diarrhea and prolonged shedding of vaccine virus, have been reported in infants who were administered RotaTeq and later identified as having SCID.

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WARNINGS AND PRECAUTIONS
Immunocompromised Populations: No safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to infants who are potentially immunocompromised including: Infants with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; Infants on immunosuppressive therapy (including high-dose systemic corticosteroids). RotaTeq may be administered to infants who are being treated with topical corticosteroids or inhaled steroids; Infants with primary and acquired immunodefficiency states, including HIV/AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. There are insufficient data from the clinical trials to support administration of RotaTeq to infants with indeterminate HIV status who are born to mothers with HIV/AIDS; Infants who have received a blood transfusion or blood products, including immunoglobulins within 42 days.

Vaccine virus transmission from vaccine recipient to non-vaccinated contacts has been reported.

Vaccine virus transmission from vaccine recipient to non-vaccinated contacts has been reported Gastrointestinal Illness: No safety or efficacy data are available for administration of RotaTeq to infants Gastrointestinal Illness: No safety or efficacy data are available for administration of Nota leg to infants with a history of gastrointestinal disorders including infants with a citive acute gastrointestinal illness; infants with chronic diarrhea and failure to thrive, and infants with a history of congenital abdominal disorders, abdomina surgery, and intussusception. Caution is advised when considering administration of RotaTeg to these infants.

Intussusception: Following administration of a previously licensed live rhesus rotavirus-based vaccine, an increased risk of intussusception was observed. In REST* (n=69,625), the data did not show an increased risk intussusception for RotaTeg when compared to placebo. In post-marketing experience, cases of intussusception have been reported in temporal association with RotaTeg.

have been reported in temporal association with RotaTeq.

Shedding and Transmission: Shedding of vaccine virus was evaluated among a subset of subjects in REST 4 to 6 days after each dose and among all subjects who submitted a stool antigen rotavirus positive sample at any time. RotaTeq was shed in the stools of 32 of 380 (8.9%, 95% C1 (6.2%, 12.3%)] vaccine recipients tested after dose 1; 0 of 249 [0.0%, 95% C1 (0.0%, 1.5%)] vaccine recipients tested after dose 2; and in 1 of 385 [0.3%, 95% C1 (-0.1%, 1.4%)] vaccine recipients after dose 3. In phase 3 studies, shedding was observed as early as 1 day and as late as 15 days after a dose. Transmission of vaccine virus strains from vaccines to non-vaccinated contacts has been observed post-marking. The potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural virus. Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient close contacts such as: Individuals with malignancies or who are otherwise immunocompromised; individuals with primary immunodeficiency; or individuals receiving immunosuppressive therapy.

Febrile Illness: Febrile illness may be reason for delaying use of RotaTeq except when, in the opinion of the physician, withholding the vaccine entails a greater risk. Low-grade fever (<100.5°F [38.1°C]) itself and mild upper respiratory infection do not preclude vaccination with RotaTeq.

Incomplete Regimen: The clinical studies were not designed to assess the level of protection provided by only one or two doses of RotaTeq.

Limitations of Vaccine Effectiveness: RotaTeq may not protect all vaccine recipients against rotavirus. Post-Exposure Prophylaxis: No clinical data are available for RotaTeq when administered after exposure

ADVERSE REACTIONS

Clinical Studies Experience: 71,725 infants were evaluated in 3 placebo-controlled clinical trials including 36,165 infants in the group that received RotaTeq and 35,560 infants in the group that received placebo. Parents/guardians were contacted on days 7, 14, and 42 after each dose regarding intussusception and any other serious adverse events. The racial distribution was as follows: White (69% in both groups); Hispanic-American (14% in both groups); Black (8% in both groups); Multiracial (5% in both groups); Saian (2% in both groups); Native American (RotaTeq 2%, placebo 1%), and Other (<1% in both groups). The gender distribution was 51% male and 49% female in both vaccination groups. Because clinical trials are conducted under conditions that may not be typical of those observed in clinical practice, the adverse reaction rates presented below may not be reflective of those observed in clinical practice.

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Serious Adverse Events: Serious adverse events occurred in 2.4% of recipients of RotaTeq when compared to 2.6% of placebo recipients within the 42-day period of a dose in the phase 3 clinical studies of RotaTeq. The most frequently reported serious adverse events for RotaTeq compared to placebo were: bronchiolitis (0.6% RotaTeq vs. 0.7% Placebo), gastroenteritis (0.2% RotaTeq vs. 0.3% Placebo), pneumonia (0.2% RotaTeq vs. 0.2% Placebo), Rever (0.1% RotaTeq vs. 0.1% Placebo), and urinary tract infection (0.1% RotaTeq vs. 0.1% Placebo).

Deaths: Across the clinical studies, 52 deaths were reported. There were 25 deaths in the RotaTeq recipients compared to 27 deaths in the placebo recipients. The most commonly reported cause of death was sudden infant death syndrome, which was observed in 8 recipients of RotaTeq and 9 placebo recipients.

Intussusception: In REST, 34,837 vaccine recipients and 34,788 placebo recipients were monitored by active surveillance to identify potential cases of intussusception at 7.14, and 42 days after each dose, and every 6 weeks thereafter for 1 year after the first dose. For the primary safety outcome, cases of intussusception occurring within 42 days of any dose, there were 6 cases among RotaTeq recipients and 5 cases among placebo recipients (see Table 1). The data did not suggest an increased risk of intussusception recipients.

Table 1: Confirmed cases of intussusception in recipients of RotaTeq as compared with placebo recipients during REST

	RotaTeq (n=34,837)	Placebo (n=34,788	
Confirmed intussusception cases within 42 days of any dose	6	5	
Relative risk (95% CI) [†]	1.6 (0.4, 6.4)		
Confirmed intussusception cases within 365 days of dose 1	13	15	
Relative risk (95% CI)	0.9 (0.4, 1.9)		
†Relative risk and 95% confidence interval based upon group s	equential design stonning criteri	a employed in REST	

Among vaccine recipients, there were no confirmed cases of intussusception within the 42-day period after the first dose, which was the period of highest risk for the rhesus rotavirus-based product (see Table 2).

Table 2: Intussusception cases by day range in relation to dose in REST

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	Dos	se 1	Dose 2		Dose 3		Any Dose	
Day Range	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
1-7	0	0	1	0	0	0	1	0
1-14	0	0	1	0	0	1	1	1
1-21	0	0	3	0	0	1	3	1
1 //2	n	1	4	1	2	2	6	E .

All of the children who developed intussusception recovered without sequelae with the exception of a 9-month-old male who developed intussusception 98 days after dose 3 and died of post-operative sepsis. There was a single case of intussusception among 2,470 recipients of RotaTeq in a 7-month-old male in the phase 1 and 2 studies (716 placebo recipients).

Hematochezia: Hematochezia reported as an adverse experience occurred in 0.6% (39/6,130) of vaccine and 0.6% (34/5,560) of placebo recipients within 42 days of any dose. Hematochezia reported as a serious adverse experience occurred in <0.1% (4/36,150) of vaccine and <0.1% (7/35,536) of placebo recipients within 42 days of any dose.

Seizures: All seizures reported in the phase 3 trials of RotaTeq (by vaccination group and interval after dose) are shown in Table 3

Table 3: Seizures reported by day range in relation to any dose in the phase 3 trials of RotaTeq					
Day range	1-7	1-14	1-42		
RotaTeg	10	15	33		
Placeho	5	8	24		

Seizures reported as serious adverse experiences occurred in <0.1% (27/36,150) of vaccine and <0.1% (18/35,536) of placebo recipients (not significant). Ten febrile seizures were reported as serious adverse experiences, 5 were observed in vaccine recipients and 5 in placebo recipients.

Kawasaki Disease: In the phase 3 clinical trials, infants were followed for up to 42 days of vaccine dose Kawasaki disease was reported in 5 of 36,150 vaccine recipients and in 1 of 35,536 placebo recipients with unadjusted relative risk 4.9 (95% Cl 0.6, 239.1).

Most Common Adverse Events

Solicited Adverse Events: Detailed safety information was collected from 11,711 infants (6,138 recipients of RotaTeq) which included a subset of subjects in REST and all subjects from Studies 007 and 009 (Detailed Safety Cohort). A Vaccination Report Card was used by parents/guardians to record the child's temperature and any episodes of diarrhea and vomiting on a daily basis during the first week following each vaccination. Table 4 summarizes the frequencies of these adverse events and irritability.

Table 4: Solicited adverse experiences within the first week after doses 1, 2, and 3 (Detailed Safety Cohort)

	Dose 1		Dose 2		Dose 3	
Adverse experience	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
	n=5,616	n=5,077	n=5,215	n=4,725	n=4,865	n=4,382
Elevated temperature [‡]	17.1%	16.2%	20.0%	19.4%	18.2%	17.6%
	n=6,130	n=5,560	n=5,703	n=5,173	n=5,496	n=4,989
Vomiting	6.7%	5.4%	5.0%	4.4%	3.6%	3.2%
Diarrhea	10.4%	9.1%	8.6%	6.4%	6.1%	5.4%
Irritability	7.1%	7.1%	6.0%	6.5%	4.3%	4.5%
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Temperature ≥100.5°F [38.1°C] rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures.

Other Adverse Events: Parents/guardians of the 11,711 infants were also asked to report the presence of other events on the Vaccination Report Card for 42 days after each dose. Fever was observed at similar rates in vaccine (N-6,138) and placebo (N-5,573) recipients (42.6% vs. 42.8%). Adverse events that occurred 4 a statistically higher incidence (i.e., 2-sided p-value <0.05) within the 42 days of any dose among recipients are shown in Table 5.

Table 5: Adverse events that occurred at a statistically higher incidence within 42 days of any dose among

recipients of hota red as col	inpared with placedo recipients		
Adverse event	RotaTeq	Placebo	
	N=6,138	N=5,573	
	n (%)	n (%)	
Diarrhea	1,479 (24.1%)	1,186 (21.3%)	
Vomiting	929 (15.2%)	758 (13.6%)	
Otitis media	887 (14.5%)	724 (13.0%)	
Nasopharyngitis	422 (6.9%)	325 (5.8%)	
Dranahaanaam	CC /1 10/ \	40 (0.70/)	

Safety in Pre-Term Infants: RotaTeq or placebo was administered to 2,070 pre-term infants (25 to 36 weeks gestational age, median 34 weeks) according to their age in weeks since birth in REST. All pre-term infants were followed for serious adverse experiences; a subset of 308 infants was monitored for all adverse experiences. There were 4 deaths throughout the study, 2 among vaccine recipients (1 SIDS and 1 motor vehicle accident) and 2 among placebo recipients (1 SIDS and 1 unknown cause). No cases of intussusception were reported. Serious adverse experiences occurred in 5.5% of vaccine and 5.8% of placebo recipients. The most common serious adverse experience was bronchiolitis, which occurred in 1.4% of vaccine and 2.0% of placebo recipients. Parents/guardians were asked to record the child's temperature and any episodes of vomiting and diarrhea daily for the first week following vaccination. The frequencies of these adverse experiences and irritability within the week after dose 1 are summarized in Table 6.

	Dose 1		Dose 2		Dose 3	
Adverse event	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
	N=127	N=133	N=124	N=121	N=115	N=108
Elevated temperature [‡]	18.1%	17.3%	25.0%	28.1%	14.8%	20.4%
	N=154	N=154	N=137	N=137	N=135	N=129
Vomiting	5.8%	7.8%	2.9%	2.2%	4.4%	4.7%
Diarrhea	6.5%	5.8%	7.3%	7.3%	3.7%	3.9%
Irritability	3 9%	5.2%	2 0%	4.4%	Q 1%	5 A%

Temperature ≥100.5°F [38.1°C] rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures.

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Post-Marketing Experience: The following adverse events have been identified during post-approval use of Rota feg from reports to the Vaccine Adverse Event Reporting System (VAERS). Reporting of adverse events following immunization to VAERS is voluntary, and the number of doses of vaccine administered is not known; therefore, it is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to vaccine exposure using VAERS data. In post-marketing experience, the following adverse events have been reported following the use of Rota feg: Gastrointestinal disorders-Intussus ception (including death), Hematochezia. Gastroenteritis with vaccine viral shedding in infants with Severe Combined Immunodeficiency Disorder (SCID). Skin and subcutaneous tissue disorders-Urticaria. Infections and infestations Kawasaki disease. Transmission of vaccine virus strains from vaccine recipient to non-vaccinated contacts.

Reporting Adverse Events: Parents or guardians should be instructed to report any adverse events to their health care provider. Health care providers should report all adverse events to the US Department of Health and Human Services' Vaccine Adverse Events Reporting System (VAERS). VAERS accepts all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967 or report online to www.vaers.hhs.gov.

DRUG INTERACTIONS

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Immunosuppressive therapies including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines.

Concomitant Vaccine Administration: In clinical trials, RotaTeq was administered concomitantly with diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliovirus vaccine (IPV), H. influenzae type b conjugate (Hib), hepatitis B vaccine, and pneumococcal conjugate vaccine. The safety data available are in the ADVERSE REACTIONS section. There was no evidence for reduced antibody responses to the vaccines that were concomitantly administered with RotaTeq.

USE IN SPECIFIC POPULATIONS

Pediatric Use: Safety and efficacy have not been established in infants less than 6 weeks of age or greater than 32 weeks of age. Dat are available from clinical studies to support the use of RotaTeq in pre-term infants according to their age in weeks since birth. Data are available from clinical studies to support the use of RotaTeq in infants with controlled gastroesophageal reflux disease.

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NONCLINICAL TOXICOLOGY

nent of Fertility: RotaTeq has not been evaluated for its carcinogenic or

PATIENT COUNSELING INFORMATION

Information for Parents/Guardians: Parents or guardians should be given a copy of the required vaccine information and be given the "Patient Information" appended to the Prescribing Information. Parents and/or guardians should be encouraged to read the patient information that describes the benefits and risks associated with the vaccine and ask any questions they may have during the visit.

For more detailed information, please read the Prescribing Information and Patient Product Information

MERCK & CO., INC. Whitehouse Station, NJ 08889, USA

*Rotavirus Efficacy and Safety Trial 21004743(2)(301)-RTO

Children With IBD May Be at Risk for Hepatitis B

BY HEIDI SPLETE

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY

SAN ANTONIO – Approximately half of children being treated with infliximab for inflammatory bowel disease did not have immunity to hepatitis B, based on data from 100 children.

Patients with inflammatory bowel disease (IBD) treated with infliximab who lack immunity to hepatitis B virus are at risk for severe liver disease if exposed to

Major Finding: Among children being treated with infliximab for IBD, 51% had no immunity to hepatitis B and were at increased risk for liver complications.

Data Source: A prospective, single-center study of 100 children with IBD.

Disclosures: Dr. Moses had no financial conflicts to disclose.

the virus in the community, noted Dr. Jonathan Moses of the Cleveland Clinic.

To determine the degree of hepatitis B virus (HBV) immunity, Dr. Moses and his colleagues conducted a prospective study of 100 consecutive children who were being treated with infliximab for IBD at a single center; 91 of the children (91%) had Crohn's disease. The mean duration of infliximab therapy was 38 months, and the mean dose was 7 mg/kg.

Blood samples were taken at a routine visit for infliximab infusion. The samples were tested for three markers: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs). Patients

Continued from previous page

sides preventing rheumatic fever. "We know that treating results in a reduction in contagion," he said. "And it prevents sequelae like abscesses of the lymph nodes."

The question of which antibiotic to use was not the only group A strep controversy Dr. Harrison discussed. He also spoke highly of new rapid tests for strep, citing a recent study in Clinical Pediatrics (2010;49:1050-2) that found that several of the new tests had sensitivity and specificity above 95%.

Based on this research, he doesn't think everyone needs to order a throat culture in the case of a negative result with a rapid test. "It's not really a necessary thing, in my personal opinion, for everyone, although it's recommended."

The exception? In an area with rheumatic fever or some other special cause for concern, the throat culture is still advisable.

Dr. Harrison disclosed that he has had a financial relationship with Glaxo-SmithKline Vaccine Group. Dr. Pichichero said that he had no relevant financial disclosures.

with anti-HBs levels of 10 mIU/mL or higher were considered immune.

Regardless of vaccination history, 49% of the children were immune to HBV and 51% were not. The mean concentration of anti-HBs levels in the immune children was 295.6 mIU/mL.

The children were aged 5-18 years (mean, 13 years) at the time of diagnosis with IBD. The mean age at which the blood sample for this study was taken

was 18 years. Approximately 60% of the patients were boys, and most were white.

Vaccination data were available for 87 patients, 91% of whom had been vaccinated. Most of these patients received the hepatitis B vaccine as part of their routine childhood immunization schedules, so they had a 5- to 10-year gap between the time they received hepatitis B vaccination and the time they started infliximab for IBD, Dr. Moses said.

Factors related to HBV immunity, including body mass index percentile and Crohn's disease location, were similar between the two groups. Patients with immunity were slightly older at the time of IBD diagnosis.

A booster dose of HBV vaccine had been given to 20 patients, and the full vaccination series had been started in 7 patients at the time of the study presentation at the meeting.

