# PEDIATRIC PHARMACOTHERAPY

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## Pneumococcal Conjugate Vaccine

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*Streptococcus pneumoniae* is the most common cause of pediatric bacterial infection. The spectrum of disease associated with this organism varies from mucosal diseases, such as otitis media and sinusitis, to invasive diseases including bacteremia and meningitis. Community-based studies from 1986-1995 revealed an annual incidence of invasive pneumococcal disease in the United States of 10-30 cases per 100,000 persons. The highest risk is in children less than 2 years of age (140-160 cases per 100,000 persons). With the emergence of beta-lactam-resistant *Streptococcus pneumoniae*, the need for prevention of these diseases has become even more important.

Vaccine Development

Prevention of invasive pneumococcal disease in patients at risk has relied for many years on the administration of the 23-valent polysaccharide pneumococcal (23PS) vaccine. Although this vaccine has proved to be effective in adults and older children, it is not immunogenic in children younger than 2 years. The 23PS vaccine does not induce immunologic memory, necessary for efficacy at younger ages. In addition, it does not significantly affect nasopharyngeal colonization.

Recently, a conjugate pneumococcal vaccine was developed to address these problems. The serotypes included in the conjugate pneumococcal vaccine are responsible for about 85% of pneumococcal disease in the United States and about 70% of invasive pneumococcal disease worldwide. The FDA approved the new conjugate pneumococcal 7-valent vaccine, Prevnar® (PCV7) in February, 2000.[1] PCV7 is the first pneumococcal vaccine indicated for active immunization of infants and toddlers against invasive disease caused by *Streptococcus pneumoniae* due to serotypes contained in the vaccine (4, 6B, 9V, 14, 18C, 19F, 23F). These saccharides are coupled to a nontoxic mutant of diphtheria toxin and the protein $CRM_{197}$.[1-8]

Safety and Efficacy Trials

Rennels and colleagues found PCV7 to be both safe and effective in a large clinical trial performed in the United States.[2] In this study, PCV7 was administered to children at 2, 4, 6, and 12 to 15 months of age. The vaccine was immunogenic and was demonstrated to induce a significant amnestic response to every serotype included in its formulation, especially after the fourth, or booster, dose.

The vaccine's efficacy was also evaluated in a recently published clinical trial by Black and coworkers.[3] In this double-blind trial, PCV7 was given to infants at 2, 4, 6, and 12-15 months of age. The study included 37,868 children, of which 18,927 and 18,941 received one or more doses of pneumococcal conjugate and meningococcal conjugate vaccine, respectively. Both groups received their routine immunizations according to the standard American Academy of Pediatrics (AAP) schedule for that time period.

The primary endpoint of this study was development of pneumococcal disease due to vaccine serotypes. All cases of pneumococcal disease that occurred more than 14 days after the third dose were included in the protocol analysis. Intention-to-treat analysis included all cases of invasive pneumococcal disease due to vaccine serotypes in children who received at least one vaccine dose. The secondary efficacy endpoint was development of invasive pneumococcal disease regardless of serotype. Other endpoints included the number of episodes of otitis media, differences between treatment groups in time to diagnosis of otitis media, placement of ventilator tympanostomy tubes, and number of cases of spontaneously draining ruptured tympanic membranes with a culture of vaccine serotypes.

Of all the children included in this study, invasive disease caused by strains included in the vaccine occurred in 40 children, 29 of whom were in the control group. In the intent-to-treat analysis, 52 children, including 49 from the control group, developed invasive disease. The vaccine's effectiveness in preventing disease caused by the serotypes included in the formulation was calculated to be 97.4% and 93.9% for the fully vaccinated and intent-to-treat groups, respectively. The effectiveness in preventing invasive disease caused by all serotypes was 89.1%. In addition, the vaccine provided a 7% reduction in otitis media. The authors concluded that PCV7 is effective in preventing invasive disease caused by *Streptococcus pneumoniae*.

Immunogenicity and safety were evaluated in a subset of patients enrolled in the study. In addition, the effect of concurrent vaccines on immunogenicity was also investigated. The patients received either PCV7 or the combination product containing conjugate Haemophilus b, diphtheria, tetanus toxoid, and whole cell pertussis (DTwP-HbOC). Both groups received the oral polio vaccine (OPV) concurrently. Half of the subjects also received hepatitis B (HepB) vaccine at each visit in the same thigh as the DTwP-HbOC and half received HepB at least two weeks before or after the investigational vaccine. At 12-15 months, patients received the fourth dose of the study vaccine with diphtheria toxoid, tetanus toxoid, and acellular pertussis (DTaP) and conjugate *H. influenzae* type b (HbOC), study vaccine alone, or DTaP and HbOC alone.

Of the 302 subjects recruited for this study, 272 completed the three dose primary series, and 211 received the 12-15 month booster doses. Immunologic responses to all seven pneumococcal serotypes occurred. There was a drop in antibody concentration for all serotypes before the booster dose. One month following the booster, all geometric means of antibody concentrations (GMCs) were above 1 ug/mL. There were no significant differences in GMCs of pneumococcal serotypes between subjects who received HepB vaccination concurrently or 2 weeks apart from the pneumococcal vaccine. Antibody titers to HepB and poliovirus types 1, 2, and 3 were present in 92.6%, 95.2%, 100% of patients, respectively. Although GMCs were higher when PCV7 was administered alone as opposed to administration with DTaP and HbOC, differences in the proportion of subjects with antibody concentrations above 1 ug/mL for all seven serotypes were not greater than 10%. The authors concluded that PCV7 is immunogenic and the differences observed in GMCs when PCV7 was administered concurrently with DTaP and HbOC were not clinically significant.

Simultaneous administration with other vaccines

In clinical trials, PCV7 has been administered simultaneously with DTP-HbOC, DTaP, HbOC, HepB, OPV, inactivated polio vaccine (IPV), measles mumps rubella (MMR) and varicella vaccines. In infants, enhanced antibody response to HbOC was observed. Some suppression of response to HbOC was observed at the fourth dose; however, 97% of children achieved titers > 1 ug/ml. Responses to pertussis antigens were inconsistent, but the clinical significance of this is unknown. Three months after two doses of IPV were administered concomitantly with PCV7, response to poliovirus types 2 and 3 were consistent with controls; however, titers for poliovirus type 1 were lower. Immunogenicity data for MMR and varicella vaccines administered with PCV7 are not yet available.

Adverse effects

PCV7 is contraindicated in patients with known hypersensitivity to diphtheria toxoid or latex. It should not be given to individuals with thrombocytopenia or coagulation disorders that would contraindicate intramuscular injection.[1]

In clinical trials, fever > 38.0° C, irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhea, and rash or hives were reported more frequently in the PCV7 group within two to three days of vaccination than in controls. Within 48 to 72 hours of vaccination, patients may also experience edema, pain or tenderness, redness, inflammation or skin discoloration, mass, or local hypersensitivity at or around the injection site.[1-3]

Dosing and administration

PCV7 should be given intramuscularly (IM) using a dose of 0.5 ml. Preferred sites are the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in toddlers and young children. For infants, the recommended immunization series consists of three doses at two month intervals followed by a fourth dose at 12-15 months of age. For previously unvaccinated older infants and children who are beyond the age of the routine infant schedule, the following schedule should be used.[8]

**Table 1. PCV7 Dosing**

| Age | Primary Series | Booster Dose† |
|---|---|---|
| 2-6 mo | 3 doses, 6-8 wk apart | 1 dose at 12-15 mo of age |
| 7-11 mo | 2 doses, 6-8 wk apart | 1 dose at 12-15 mo of age |
| 12-23 mo | 2 doses, 6-8 wk apart | |
| >24 mo‡ | 1 dose | |

†Booster doses to be given at least 6 to 8 weeks after the final dose of the primary series.
‡The AAP is not recommending universal immunization of low and moderate risk children in this age group at this time.

Two doses of PCV7 are recommended for children 24 to 59 months old at high risk of invasive pneumococcal infection who have not been immunized previously with PCV7. These children also should receive 23PS to expand serotype coverage. High-risk children should be given vaccines at the earliest possible opportunity (Tables 2 and 3).

**Table 2. Children at High or Moderate Risk of Invasive Pneumococcal Infection**

High Risk (attack rate >150 cases/100,000 people/yr)
1. Sickle-cell disease, congenital or acquired asplenia, or splenic dysfunction
2. Infection with human immunodeficiency virus

Presumed High Risk (attack rate not calculated)
1. Congenital immune deficiency: some B or T-lymphocyte deficiencies, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), or phagocytic disorders (excluding chronic granulomatous disease)
2. Chronic cardiac disease (particularly cyanotic congenital heart disease and cardiac failure)
3. Chronic pulmonary disease (including asthma treated with high-dose oral corticosteroids)
4. Cerebrospinal fluid leaks
5. Chronic renal insufficiency (e.g. nephrotic syndrome)
6. Diseases associated with immunosuppressive therapy or radiation and solid organ transplantation
7. Diabetes mellitus

Moderate Risk (attack rate >20 cases/ 100,000 people/yr)
1. All children 24-35 mo old
2. Children 36-59 mo old attending out-of-home care
3. Children 36-59 mo old who are of Native American, Alaskan Native, or African American descent

**Table 3. Recommendations for Pneumococcal Immunization for Children at High Risk**

| Age | Previous Doses | Recommendations |
|---|---|---|
| <23 mo | None | PCV7 as in Table 1 |
| 24-59 mo | 4 doses PCV7 | 1 dose of 23PS at 24 mo, at least 6-8 wk after last dose of PCV7; 1 dose of 23PS, 3-5 y after the first dose of 23PS |
| 24-59 mo | 1-3 doses PCV7 | 1 dose of PCV7, 1 dose of 23PS, 6-8 wk after the last dose of PCV7; 1 dose of 23PS, 3-5 y after the first dose of 23PS |
| 24-59 mo | 1 dose 23PS | 2 doses of PCV7, 6-8 wk apart, beginning at least 6-8 wk after last dose of 23PS; 1 dose of 23PS, 3-5 y after the first dose of 23PS |
| 24-59 mo | None | 2 doses of PCV7, 6-8 wk apart; 1 dose of 23PS, 6-8 wk after the last dose of PCV7; 1 dose of 23PS, 3-5 y after the first dose of 23PS |

Indications for use of PCV7 and 23PS in children 24 months or older at moderate or lower risk remain under investigation. All children 24 to 59 months old, even those not in high or moderate risk groups, may benefit from the administration of a single dose of PCV7 or 23PS. The 23PS is an acceptable alternative, although an enhanced immune response and probable reduction of nasopharyngeal carriage favor use of PCV7.

## Cost

Each 0.5 mL dose of PCV7 costs $56.65. The cost for the complete vaccination series is $229.60 per child when the vaccine is initiated in infancy. This pricing makes PCV7 the most expensive component of the routine immunization schedule. It is currently available without cost to financially qualified patients through local health departments.

## Summary

Invasive pneumococcal disease remains one of the leading causes of mortality in children. The recent release of a conjugate vaccine that will induce immunologic memory in children as young as 2 months of age should have a significant impact on the incidence and severity of pneumococcal disease.

## References


1. Wyeth-Lederle Vaccines. Prevnar [Pneumococcal 7-valent conjugate vaccine (Diphtheria $CRM_{197}$ protein)] package insert. Philadelphia, PA, 2000
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3. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000;19:187-195.
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6. ACIP Prevnar coverage recommendation included prioritization plan. F-D-C Reports "The Pink Sheet" 1999;61(44):13.

7. Eskola J, Anttila M. Pneumococcal conjugate vaccines. Pediatr Infect Dis J 1999;18:543-51.
8. American Academy of Pediatrics Committee on Infectious Disease Policy Statement: Recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar®), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. June, 2000.

## Pharmacology Literature Review

Caffeine citrate for apnea of prematurity

Caffeine is known to reduce both the frequency and duration of apneic episodes and, unlike theophylline, requires only one dose per day. The authors of this study conducted a multi-center trial to demonstrate the efficacy of a newly-marketed product, Cafcit®. Eighty-five patients were given a loading dose of 10 mg/kg intravenously, followed by 2.5 mg/kg/day given orally or intravenously. As anticipated, caffeine citrate was significantly more effective than placebo in reducing apneic episodes within the first week of therapy. Erenberg A, Leff RA, Haack DG, et al. Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo-controlled study. **Pharmacotherapy 2000;20:644-52.**

Effect of ibuprofen on hemodynamics

Ibuprofen is currently being investigated as an alternative to indomethacin for the closure of patent ductus arteriosus (PDA) in preterm neonates. In this study, 17 neonates were studied with ultrasound to evaluate the effect of ibuprofen (10 mg/kg IV) on cerebral and renal blood flow. In the four control infants without a PDA, ibuprofen had no effect on hemodynamics. In the remaining infants, all with a documented PDA, ibuprofen caused an increase in blood flow velocity in both the cerebral and renal arteries. The authors postulate that the increase was consistent with decreased shunting as the PDA closed, and not a result of a direct effect on peripheral vessels. Romagnoli C, De Carolis MP, Papacci P, et al. Effects of prophylactic ibuprofen on cerebral and renal hemodynamics in very preterm neonates. **Clin Pharmacol Ther 2000;67:676-83.**

Lamotrigine tolerability in children

Lamotrigine has been found to be a very effective anticonvulsant as a single agent or adjunctive therapy. In this review, the authors compile the reports of lamotrigine toxicity in children. Common lamotrigine adverse effects are dizziness, tremor, ataxia, diplopia, and nausea. The incidence of rash, including Stevens-Johnson syndrome, appears to be higher in children than adults and is more common in patients also receiving valproic acid. The authors conclude their review with recommendations for dose and slow dose titration. Messenheimer JA, Giorgi L, Risner ME. The tolerability of lamotrigine in children. **Drug Safety 2000;22:303-12.**

Montelukast adverse effects

Montelukast, an leukotriene antagonist, has been shown to be a useful therapy in the management of patients with asthma. The author of this brief review summarizes the literature published to date on montelukast adverse effects in children, concluding that the drug is well tolerated in this age group. Price D. Tolerability of montelukast. **Drugs 2000;59 (Suppl 1):35-42.**

## Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 7/28/00:

1. Oxcarbazepine (Trileptal®) was added to the Formulary, restricted to the epilepsy service for use in patients unable to tolerate carbamazepine.

2. Zonisamide (Zonegran®) was also added, restricted to the epilepsy service.

3. Tenecteplase (TNKase®) was added for the management of patients with an acute myocardial infarction.

4. Intranasal mometasone furoate (Nasonex®) was also added to the Formulary.

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