

# Combo Beats Azithromycin for Resistant AOM

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An amoxicillin/clavulanate combination was significantly more effective than azithromycin in eliminating bacterial acute otitis media, including penicillin-resistant strains, reported Alejandro Hoberman, M.D., of the Children's Hospital of Pittsburgh, and his colleagues.

In a randomized, investigator-blinded

study sponsored in part by GlaxoSmith-Kline, 730 children aged 6-30 months were randomized to receive either a 90-mg amoxicillin and a 6.4-mg clavulanate/kg combination daily in 2 divided doses for 10 days, or a 10-mg/kg dose of azithromycin once daily for 1 day, followed by 5 mg/kg once daily for 4 days.

The study was conducted at 34 centers worldwide, including Bulgaria, Chile, the Dominican Republic, Guatemala, Israel, Peru, Romania, Latvia, Mexico, and the

United States from April 2001 to November 2002.

The increasing evolution of antimicrobial resistance among the pathogens that cause acute otitis media (AOM) and the approval of a large-dose pediatric formulation of amoxicillin/clavulanate prompted the study.

At baseline, 494 (67.7%) of the children had at least one protocol-defined pathogen; 249 in the amoxicillin/clavulanate group and 245 in the azithromycin group.

Of these, 19 (7.6%) children in the amoxicillin/clavulanate group and 38 (15.5%) in the azithromycin group had more than one pathogen at baseline (Pediatr. Infect. Dis. J. 2005;24:525-32). The children without discernible pathogens at baseline (118 in each group) were included in the safety analysis.

In addition, of the 229 total *Streptococcus pneumoniae* isolates (111 children in the amoxicillin/clavulanate group and 118 children in the azithromycin group), 48.5%, 11.4%, and 20.5% were not susceptible to penicillin, amoxicillin, and azithromycin, respectively.

Overall, clinical success rates among children with baseline AOM pathogens were significantly greater in the amoxicillin/clavulanate group (90.5%), compared with the azithromycin group (80.9%).

Clinical success was defined as the lessening or complete resolution of acute ear infection and inflammation, with or without middle-ear effusion, to the extent that no additional antibiotics were needed. Clinical response at 12-14 days after the start of therapy served as the primary end point of the study. Bacteriologic success was defined as the eradication of the initial AOM pathogen with or without a new pathogen, based on a lack of middle-ear fluid.

Bacteriologic success at an "on-therapy" visit 4-6 days after the start of treatment was associated with clinical success at the end of therapy in 96 of 105 children (91.4%) in the amoxicillin/clavulanate group and 80 of 89 (89.9%) in the azithromycin group.

Amoxicillin/clavulanate was significantly more effective than azithromycin against both *S. pneumoniae*, (96.0% vs. 80.4%) and *Haemophilus influenzae*, (96.7% vs. 52.9%). The distribution of pathogens was similar between the two groups. *H. influenzae* was the more common, found in 48.6% of the amoxicillin/clavulanate group and 50.6% of the azithromycin group.

In the subset of 101 amoxicillin/clavulanate patients and 82 azithromycin patients who demonstrated bacteriologic responses after 4-6 days, amoxicillin/clavulanate was significantly more effective than azithromycin against penicillin-resistant *S. pneumoniae*, with eradication in 23 of 25 cases (92.0%) vs. 12 of 22 cases (54.5%), respectively.

Although significantly more children in the amoxicillin/clavulanate group withdrew from the study due to an adverse event, compared with the azithromycin group (21 vs. 7), the total number of adverse events was not significantly different between the two groups (139 vs. 128). ■

## Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed DAPTACEL®

BRIEF SUMMARY: Please consult package insert for full prescribing information.

**INDICATIONS AND USAGE:** DAPTACEL® is indicated for active immunization against diphtheria, tetanus and pertussis in infants and children 6 weeks through 6 years of age (prior to seventh birthday).

**CONTRAINDICATIONS:** This vaccine is contraindicated in children and adults seven years of age and older. Hypersensitivity to any component of the vaccine is a contraindication to further administration.<sup>2</sup>

**Warnings:** An immediate anaphylactic reaction. Because of uncertainty as to which component of the vaccine may be responsible, no further vaccination with diphtheria, tetanus or pertussis components should be carried out. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

**Encephalopathy not attributable to another identifiable cause (e.g., an acute, severe central nervous system disorder occurring within 7 days after vaccination and consisting of major alterations in consciousness, unresponsiveness or generalized or focal seizures that persist more than a few hours, without recovery within 24 hours).** In such cases, DT vaccine should be administered for the remaining doses in the vaccination schedule.

**Warnings:** The decision to administer or delay vaccination because of a current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. According to the ACP, all vaccines can be administered to persons with mild illness such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness.<sup>1,2</sup> However, children with moderate or serious illness should not be immunized until recovered.<sup>4,5,6,7</sup>

**Warnings:** The stopper to the vial of this product contains dry natural latex rubber that may cause allergic reactions.

**Warnings:** If any of the following events occur within the specified period after administration of a whole-cell pertussis DTP or DTap vaccine, providers should evaluate the risks and benefits of subsequent doses of whole-cell pertussis DTP or DTap vaccines:<sup>2</sup>

- Temperatures  $\geq 40.5^{\circ}\text{C}$  ( $105^{\circ}\text{F}$ ) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent crying lasting  $\geq 3$  hours within 48 hours.
- Convulsions with or without fever within 3 days.

**Warnings:** When a decision is made to withhold pertussis vaccine, immunization with DT vaccine should be continued.<sup>4</sup>

**Warnings:** Because of the risk of hemorrhage, DAPTACEL® should not be given to children with any coagulation disorder, including thrombocytopenia, which would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

**Warnings:** Studies suggest that, when given whole-cell pertussis DTP vaccine, infants and children with a history of convulsions in first-degree family members have a 2.4-fold increased risk for neurologic events.<sup>8</sup> However, ACP has concluded that a history of convulsions or other central nervous system disorders in parents or siblings is not a contraindication to pertussis vaccination and that children with such family histories should receive DTP vaccines according to the recommended schedule.<sup>1,2,4</sup>

**Warnings:** For infants or children at higher risk for seizures, an appropriate antiepileptic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing an acellular pertussis component (including DAPTACEL®) and for the following 24 hours, to reduce the possibility of post-vaccination fever.<sup>2,9</sup>

**Warnings:** Whether to administer DAPTACEL® to children with proven or suspected underlying neurologic disorders must be decided on an individual basis. An important consideration includes the current local incidence of pertussis. The ACP has issued guidelines for such children.<sup>10</sup>

**Warnings:** Precautions: General: Care is to be taken by the health-care provider for the safe and effective use of this vaccine.

**Warnings:** Epinephrine Hydrochloride Solution (1:1,000), other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Health-care providers must be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.<sup>11</sup>

**Warnings:** Before an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. The expected immune response to DAPTACEL® may not be obtained in immunosuppressed persons.<sup>4</sup> Pertussis-containing vaccines are not contraindicated in persons with HIV infection.<sup>1</sup>

**Warnings:** IT IS EXTREMELY IMPORTANT WHEN A CHILD RETURNS FOR THE NEXT DOSE IN THE SERIES THAT THE PARENT OR GUARDIAN SHOULD BE QUESTIONED CONCERNING ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE OF VACCINE. (See CONTRAINDICATIONS AND ADVERSE REACTIONS.)

**Warnings:** Drug Interactions: As with other intramuscular (IM) injections, use with caution in patients on anticoagulant therapy.

**Warnings:** Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy is to be soon discontinued, it seems reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.<sup>4</sup>

**Warnings:** If DAPTACEL® is administered to persons with an immunodeficiency disorder, on immunosuppressive therapy or after a recent injection of immune globulin, an adequate immunologic response may not occur.

**Warnings:** For information regarding simultaneous administration with other vaccines refer to DOSAGE AND ADMINISTRATION. If passive immunization is needed for tetanus or diphtheria prophylaxis, Tetanus Immune Globulin (Human) (TIG), or Diphtheria Antitoxin, if used, should be given in a separate site, with a separate needle and syringe.<sup>3</sup>

**Warnings:** Carcinogenesis, Mutagenesis, Impairment of Fertility: DAPTACEL® has not been evaluated for its carcinogenic or mutagenic potential or impairment of fertility.

**Warnings:** Pregnancy Category C: Animal reproduction studies have not been conducted with DAPTACEL®. It is not known whether DAPTACEL® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. DAPTACEL® is NOT recommended for use in a pregnant woman.

**Warnings:** Geriatric Use: This product is NOT recommended for use in adult populations.

**Warnings:** Pediatric Use: SAFETY AND EFFECTIVENESS OF DAPTACEL® IN INFANTS BELOW 6 WEEKS OF AGE HAVE NOT BEEN ESTABLISHED. (See DOSAGE AND ADMINISTRATION.)

**Warnings:** THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE OR OLDER. Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) is to be used in individuals 7 years of age or older.

**Warnings:** ADVERSE REACTIONS: Over 11,400 doses of DAPTACEL® have been administered to infants and toddlers in 6 clinical studies. In all, 3,699 children received a total of 3 doses and 476 children received 4 doses of DAPTACEL®.<sup>12,13,14,15,16,17,18</sup>

**Warnings:** In the Sweden Efficacy Trial, information on systemic and local reactions were recorded on a standard diary card kept for 14 days after each dose, and follow-up telephone calls were made 1 and 14 days after each injection. Telephone calls were made monthly to monitor the occurrence of severe events and/or hospitalizations for the 2 months after the last injection. As shown in Table 1, the 2,587 infants who enrolled to receive DAPTACEL® at 2, 4, and 6 months of age had similar rates of reactions within 24 hours as recipients of DT and significantly lower rates than infants receiving whole-cell pertussis DTP.<sup>12,13</sup>

**Warnings:** TABLE 1.2.13

PERCENTAGE OF INFANTS FROM SWEDEN IN EFFICACY TRIAL WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 24 HOURS POST-DOSE 1, 2 AND 3 OF DAPTACEL® COMPARED WITH DT AND WHOLE-CELL PERTUSSIS DTP VACCINES

EVENT	Dose 1 (2 MONTHS)			Dose 2 (4 MONTHS)			Dose 3 (6 MONTHS)		
	DAPTACEL® N = 2,587	DT N = 2,574	DTP N = 2,102	DAPTACEL® N = 2,563	DT N = 2,555	DTP N = 2,040	DAPTACEL® N = 2,549	DT N = 2,538	DTP N = 2,001
Local Tenderness	8.0*	8.4	59.5	10.1*	10.3	60.2	10.8*	10.0	50.0
Redness $\geq 2$ cm	0.3*	0.3	6.0	1.0*	0.8	5.1	3.7*	2.4	6.4
Swelling $\geq 2$ cm	0.9*	0.7	10.6	1.6*	2.0	10.0	6.3*	3.9	10.5
Systemic Fever $\geq 38^{\circ}\text{C}$ (100.4°F)	7.8*	7.6	72.3	19.1*	18.4	74.3	23.6*	22.1	65.1
Fretfulness†	32.3	33.0	82.1	39.6	39.8	85.4	35.9	37.7	73.0
Anorexia	11.2*	10.3	39.2	9.1*	8.1	25.6	8.4*	7.7	17.5
Drowsiness	32.7*	32.0	56.9	25.9*	25.6	50.6	18.9*	20.6	37.6
Crying $\geq 3$ hours	1.7*	1.6	11.8	2.5*	2.7	9.3	1.2*	1.0	3.3
Vomiting	6.9*	6.3	9.5	5.2*	5.8	7.4	4.3	5.2	5.5

N = Number of evaluable subjects \*p < 0.001 DAPTACEL® versus whole-cell pertussis DTP †p < 0.0001 DAPTACEL® versus whole-cell pertussis DTP ‡p < 0.0001 DAPTACEL® versus DT §p < 0.0001 DAPTACEL® versus DT ¶Rectal temperature

|| Statistical comparisons were not made for this variable DT: Swedish National Biologics Laboratories DTP: Aventis Pasteur Inc. In patients who received DAPTACEL® the incidence (per 1,000 doses) of local reactions was  $\geq 40^{\circ}\text{C}$  (104°F) within 48 hours of vaccination was 0.39 following dose 1 and dose 3 and the incidence of persistent crying  $\geq 3$  hours within 24 hours of vaccination was 1.16 and 0.39 following dose 1 and 2, respectively.

One case of whole limb swelling and generalized symptoms, with resolution within 24 hours, was observed following dose 2 of DAPTACEL®. No episodes of anaphylaxis or encephalopathy were observed. No seizures were reported within 3 days of vaccination with DAPTACEL®. Over the entire study period, 6 seizures were reported in the DAPTACEL® group, 9 in the DT group and 3 in the whole-cell pertussis DTP group, for overall rates of 2.3, 3.5 and 1.4 per 1,000 vaccinations, respectively. One case of infantile spasms was reported in the DAPTACEL® group. There were no instances of invasive bacterial infection or death.<sup>12,13</sup>

Rates of serious adverse events that are less common than those reported in the Sweden Efficacy Trial are not known at this time. Table 2 summarizes the safety results from the Phase II Study in Canada in children who were immunized at 2, 4, 6 and 17-18 months of age with DAPTACEL®. Local and systemic adverse events were consistently less common in DAPTACEL® recipients at 2, 4 and 6 months of age than in those who received whole-cell pertussis DTP vaccine. Following the fourth dose, the same trends were observed, except for rates of severe redness and swelling which did not differ between the 2 vaccine groups. Rates of local reactions of redness and swelling were increased following the fourth dose compared with the first 3 doses as was mild tenderness but there was no increase in severe tenderness.

TABLE 2.13.14  
PERCENTAGE OF CHILDREN FROM PHASE II STUDY IN CANADA WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 72 HOURS OF VACCINATION WITH DAPTACEL® AND WHOLE-CELL PERTUSSIS DTP VACCINE AT 2, 4, 6 AND 17-18 MONTHS OF AGE

EVENT	Dose 1 (2 MONTHS)		Dose 2 (4 MONTHS)		Dose 3 (6 MONTHS)		Dose 4 (18 MONTHS)	
	DAPTACEL® N = 324	DTP N = 108	DAPTACEL® N = 321	DTP N = 106	DAPTACEL® N = 320	DTP N = 104	DAPTACEL® N = 301	DTP N = 97
Local Redness								
Any $\geq 10$ mm	12.7*	44.4	20.6*	57.5	22.2*	51.9	36.5*	55.7
$\geq 25$ mm	1.2*	13.9	7.8*	22.6	10.0*	17.3	27.9	36.1
Swelling	0.3*	3.7	0.3*	5.7	1.6	1.9	21.9	20.6
Any $\geq 10$ mm	4.3*	23.1	4.3*	32.1	4.7*	25.0	18.6*	28.9
$\geq 25$ mm	1.9*	15.7	2.2*	21.7	3.8*	14.4	15.9*	25.8
Tenderness†	0.3*	6.5	0*	5.7	0.9*	4.8	11.3	15.5
Any Moderate + Severe	10.2*	37.0	7.5*	51.9	8.8*	48.1	23.9*	86.6
Severe	0.9*	13.0	1.2*	20.8	1.3*	17.3	3.0*	52.6
Severe	0*	4.6	0.3*	7.5	0*	4.8	0.3*	13.4
Systemic Fever‡								
Any $\geq 37.5^{\circ}\text{C}$ (99.5°F)	12.0*	43.7	7.7*	50.0	14.8*	53.2	14.5*	67.9
$\geq 38^{\circ}\text{C}$ (100.4°F)	0.7	1.9	0*	7.8	1.2*	11.7	1.9*	17.9
$\geq 40.0^{\circ}\text{C}$ (104°F)	0.3	0	0	1.0	0	1.1	0	0
Irritability¶								
Any	41.0*	65.7	41.4*	68.9	40.9*	67.3	36.9*	79.4
Moderate + Severe	9.0*	18.5	6.9*	22.6	5.0*	22.1	5.0*	24.7
Severe	0	1.9	0.3	0	0	1.0	0	2.1
Anorexia‡								
Any	16.0	22.2	9.0*	16.0	11.6*	23.1	17.6*	41.2
Moderate + Severe	1.5	3.7	0.9	2.8	1.3	1.9	2.0*	13.4
Severe	0	0	0.3	0	0	0	0	2.1
Drowsiness§								
Any	43.2	52.8	21.8*	33.0	14.4*	32.7	13.3*	29.9
Moderate + Severe	7.7	8.3	2.8*	7.5	1.3	0	1.0*	6.2
Severe	0	0	0.3	0	0	0	0	0
Crying $\geq 3$ Hours	0.6	0.9	0.3	0.9	0	1.0	0	1.0

N = Number of evaluable subjects # DTP: whole-cell pertussis DTP vaccine (Aventis Pasteur Limited) \* Significantly less reactive than whole-cell DTP vaccine, p < 0.05 † Moderate = sustained cry with gentle pressure at injection site; Severe = cries when leg is moved ‡ Temperatures measured were axillary § Number of evaluable subjects for DAPTACEL®/DTP = 301/103, 298/102, 257/94 and 207/79 at 2, 4, 6 and 18 months, respectively ¶ Moderate = more difficulty with settling, even with cuddling; Severe = persistent crying/screaming and inability to console ‡ Moderate = missed one or two feeds; Severe = little or no intake for more than two feeds § Moderate = sleeping much more than normal; Severe = sleeping most of the time with difficulty arousing

The US Bridging Study was designed, in part, to assess the safety of DAPTACEL® in infants at 2, 4 and 6 months of age, with routinely recommended, concurrently given childhood vaccines (*Haemophilus influenzae* type b vaccine, OPV and hepatitis B). The incidence of redness, swelling, pain or tenderness at the injection site after each dose was 12.5%, 19.7%, 14.3%, 17.8%, and 15.9% - 30.5% respectively. Fever  $\geq 38^{\circ}\text{C}$  (100.4°F) was observed in 9.9% - 11.9% of subjects. One afebrile seizure occurred within 24 hours post dose 2 immunization (n = 321).<sup>12</sup>

Additional adverse reactions evaluated in conjunction with pertussis, diphtheria and tetanus vaccination are as follows:

- As with other aluminum-containing vaccines, a nodule may be palpable at the injection sites for several weeks. Sterile abscess formation at the site of injection has been reported.<sup>4,9</sup>

- Rarely, anaphylactic reactions (i.e., hives, swelling of the mouth, difficulty breathing, hypotension or shock) have been reported after receiving preparations containing diphtheria, tetanus and/or pertussis antigens.<sup>4</sup>

At-risk-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid vaccine. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although the evidence is inadequate to accept or reject a causal relation.<sup>2,5</sup>

A review by the Institute of Medicine (IOM) found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré syndrome.<sup>21</sup> The following illnesses have been reported as temporally associated with some vaccines containing tetanus toxoid: neurological complications<sup>22-23</sup> including coxal lesion, brachial plexus neuropathies,<sup>24</sup> paralysis of the radial nerve,<sup>25</sup> paralysis of the recurrent nerve, acute encephalopathy and EEG disturbances with or without permanent intellectual or motor function impairment.<sup>25,26</sup> In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.<sup>26</sup>

**DOSE AND ADMINISTRATION:** JUST BEFORE USE, SHAKE THE VIAL WELL until a uniform, cloudy suspension results. WITHDRAW AND INJECT 0.5 mL DOSE. Administer the vaccine intramuscularly (I.M.). In children younger than 7 years (i.e., infants), the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is usually large enough for I.M. injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.<sup>1</sup>

Do NOT administer this product intravenously or subcutaneously.

**Immunization Series:** A 0.5 mL dose of DAPTACEL® is appropriate for administration as a 4 dose series at 2, 4 and 6 months of age, at intervals of 6-8 weeks and at 17-20 months of age. The customary age for the first dose is 2 months of age, but it may be given as early as 6 weeks of age and up to the seventh birthday. The interval between the third and fourth dose should be at least 6 months. It is recommended that DAPTACEL® be given for all doses in the series because no data on the interchangeability of DAPTACEL® with other DTP vaccines exist. At this time, data are insufficient to establish the frequency of adverse events following a fifth dose of DAPTACEL® in children who have previously received 4 doses of DAPTACEL®.<sup>27</sup> DAPTACEL® may be used to complete the immunization series in infants who have received 1 or more doses of whole-cell pertussis DTP. However, the safety and efficacy of DAPTACEL® in such infants have not been fully demonstrated.<sup>2</sup>

**PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DAPTACEL® OR ANY OTHER PERTUSSIS-CONTAINING VACCINES.** DAPTACEL® should not be combined through reconstitution or mixed with any other vaccine. If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use) should be given as needed to complete the series. Pre-term infants should be vaccinated according to their chronological age from birth.<sup>1</sup>

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with DAPTACEL®. There is no need to start the series over again, regardless of the time between doses.

**STORAGE:** DAPTACEL® should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date.

**REFERENCES:**

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