

# Metronidazole Treats Non-GABHS Tonsillitis

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WASHINGTON — Metronidazole is effective in the treatment of non-β-hemolytic streptococcal tonsillitis, Itzhak Brook, M.D., reported in a poster presentation at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Although group A β-hemolytic streptococcus (GABHS) is one of the major causes

of tonsillitis, other aerobic as well as anaerobic organisms have been isolated from both normal and inflamed tonsils. The exact role of these organisms is uncertain, and some are believed to be part of the normal oropharyngeal flora, said Dr. Brook, professor of pediatrics at Georgetown University, Washington.

The option of using metronidazole (250 mg every 12 hours for 10 days) was offered to 40 children (mean age 9 years) who presented with sore throat and mas-

similar to the 20 who did not with respect to age, race, sex, family size, current clinical findings, and previous antibiotics. Compared with the children who remained untreated, those given metronidazole had significantly lower rates of fevers over 38° C after 1 day (11 vs. 17 children) and after 2 days (3 vs. 9 children), fewer sore throats after 1 day (12 vs. 19) and 2 days (9 vs. 16), and lower rates of tonsillar enlargement after 3 days (11 vs. 16) and 5 days (8 vs. 14). Pharyngeal injection at 2 days also was reduced with metronidazole, Dr. Brook reported at the conference, sponsored by the American Society for Microbiology.

Metronidazole was chosen for this study because it is effective against anaerobic bacteria but has virtually no activity against facultative and aerobic bacteria. These findings add to previous data suggesting a pathogenic role of anaerobes in the acute inflammatory process in the tonsils.

The 20 who got metronidazole were

## Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

**DAPTACEL®**

⌘ only

**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). Children who have had well-documented pertussis (culture positive for *B. pertussis* or epidemiologic linkage to a culture positive case) should complete the vaccination schedule. Pertussis immunization including acellular pertussis vaccine as well as appropriate well-documented pertussis disease is likely to confer immunity, the duration of protection is unknown.<sup>1</sup>

**CONTRAINDICATIONS:** The vaccine is contraindicated in children and adults seven years of age and older. Hypersensitivity to any component of the vaccine or to any of the antigens is a contraindication.

The following events after receipt of DAPTACEL are contraindications to further administration of any pertussis-containing vaccine:<sup>2</sup>

- 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.

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 patients with mild illnesses such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness.<sup>3</sup> However, children with moderate or serious illness should not be immunized until recovered.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis because of the risk of provoking paralysis.<sup>4,5,7</sup>

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

If any of the following events occur within the specified period after administration of a whole-cell pertussis DTP or DTPa vaccine, providers and parents should be alerted to subsequent doses of whole-cell pertussis DTP or DTPa vaccine:<sup>8</sup>

- Temperature of ≥40.5°C (105°F) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent crying lasting ≥3 hours within 48 hours.
- Convulsions with or without fever within 7 days.

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

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.

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>9</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 DTPa vaccines according to the recommended schedule.<sup>10,11</sup>

For infants or children at higher risk for seizures than the general population, 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>12</sup>

Whether to administer DAPTACEL to children with neurologic disorders should 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>

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

Epileptiform Hydrocephalus Solution (11,000), other appropriate agents and equipment must be available for immediate use in case of an anaphylactic or acute hypersensitivity reaction. Health-care providers must be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.<sup>13,14</sup>

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 immunocompromised persons.

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 OR AN ADVERSE REACTION AFTER THE PREVIOUS DOSE OF VACCINE. (See CONTRAINDICATIONS AND ADVERSE REACTIONS.)

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

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 advisable to defer immunization until the patient has been off therapy for one month before the patient should be vaccinated with IM vaccine.<sup>15</sup>

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.

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>16</sup>

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

**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.

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

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

**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.

**ADVERSE REACTIONS:** Over 11,400 doses of DAPTACEL have been administered to infants and toddlers in 6 clinical studies. In all, 3,694 children received a total of 3 doses and 476 children received 4 doses of DAPTACEL. (See Table 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18)

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 fewer rates than infants receiving whole-cell pertussis DTP.

**PERCENTAGE OF INFANTS FROM SWEDEN 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.**

**TABLE 1**

**TABLE 2**

**TABLE 3**

**TABLE 4**

**TABLE 5**

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**TABLE 48**

**TABLE 49**

**TABLE 2**<sup>18,19</sup>  
**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 AT 2, 4, 6 AND 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
<b>Local</b>								
Redness	12.7*	44.4	20.6*	57.5	22.2*	51.8	36.5*	55.7
Any	12.7	13.9	7.8*	22.6	10.0*	17.3	27.9	36.1
≥10 mm	0.3*	3.7	0.3*	5.7	1.6	1.9	21.9	20.6
≥35 mm	0.3*	23.1	4.3*	32.1	4.7*	25.0	18.6*	28.9
Any	1.9*	15.7	2.2*	21.7	3.8*	14.4	15.9*	25.8
≥10 mm	0.2*	6.5	0.1*	5.7	0.0*	18.1	11.3	15.5
≥25 mm	10.2*	37.0	7.5*	51.9	8.8*	46.1	23.9*	86.6
Any	0.2*	13.0	0.1*	13.0	0.2*	13.5	1.0*	6.6
≥10 mm	0.0*	4.6	0.3*	7.5	0.0*	4.8	0.3*	12.4
<b>Systemic</b>								
Fever†	12.0*	43.7	7.7*	50.0	14.8*	53.2	14.5*	67.9
Any	12.0	17.0	1.0	11.7	1.0	11.7	1.0	17.9
≥38°C (100.4°F)	0.3	0	0	1.0	0	1.1	0	0
Any	0.0†	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	16.0	22.2	9.0*	16.0	11.6*	23.1	17.6*	41.2
Moderate + Severe	1.5	3.7	0.8	2.8	1.3	1.9	2.0*	13.4
Severe	0	0	0	0	0	0	0	0
Drowsiness	4.2	5.8	21.8*	33.0	14.4*	32.7	13.3*	29.9
Moderate + Severe	7.7	8.3	2.8*	7.5	1.3*	1.0	1.0*	6.2
Severe	0.3	0	0	0	0	0	0	0
Crying ≥3 hours	0.3	0	0	0	0	0	0	0

N = Number of evaluable subjects † DTP: whole-cell pertussis DTP vaccine (Aventis Pasteur Limited) ‡ Significantly less

reactogenic than whole-cell DTP vaccine, p<0.05. \* Moderate + Severe with gentle pressure at injection site; Severe = cries

when leg is moved. † Temperature measurements were axillary. ‡ Number of evaluable subjects for DAPTACEL/DTP = 307/103,

298/102, 257/94 and 207/78 at 2, 4, 6 and 18 months, respectively. § Sustained cry for more than 30 minutes; Severe = persistent crying/irritability 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 BRISQ Study was designed, in part, to assess the safety of DAPTACEL in infants at 2, 4 and 6 months of age, and routinely

concurrently given childhood vaccines (Aerobacterium influenzae type A vaccine, OPV and hepatitis B). The incidence of

redness, swelling, pain or tenderness at the injection site after each dose was 12.9%, 10.7%, 12.5%, 17.8% and 15.9% - 30.5%

respectively. Fever ≥38°C (100.4°F) was observed in 9.9% - 11.9% of subjects. One anaphylactic reaction occurred within 24 hours post

dose 2 (N = 321).

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>19</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>

Although-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may

occur in cases of tetanus toxoid. 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>20</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 associated with some vaccines containing tetanus toxoid:

neurological complications:<sup>22,23</sup> idiopathic coxial lesion, brachial plexus neuropathies;<sup>24</sup> paralysis of the radial nerve;<sup>25</sup> paralysis of the

reticular nerve, accommodation paresis and EEG disturbances with encephalopathy (with or without permanent intellectual or motor

impairment).<sup>26-28</sup> In the differential diagnosis of polyradiculopathy following administration of a vaccine,<sup>29</sup>

tetanus toxoid should be considered as a possible etiology.<sup>30</sup>

**DOSAGE AND ADMINISTRATION:** JUST BEFORE USE, SHAKE THE VIAL WELL until a uniform, cloudy suspension results. WITHDRAW

0.5 mL (0.15 mL DOSE). Administer the vaccine intramuscularly (IM). In children younger than 1 year of age, use the

anterolateral aspect of the thigh providing the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is

large enough for IM injection. The vaccine should not be injected into the gluteal area or areas where there may be a large

nerve trunk.

Do NOT administer this product intravenously or subcutaneously.

**Immunization Series:** A 0.5 mL dose of DAPTACEL is approved 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 10th 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

has not been fully demonstrated.<sup>27</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 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 at birth.<sup>31</sup>

• Persistence 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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