Chapter 3 — Treatment and Chemoprophylaxis

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Revised June 2000

Pertussis may cause severe illness in young infants and result in complications such as apnea, cyanosis, feeding difficulties, pneumonia, and encephalopathy. Infants and other patients with severe pertussis may require hospitalization for supportive care; for very severe cases, intensive care facilities may be required. Corticosteroids and albuterol (a B_2-adrenergic stimulant) may be effective in reducing paroxysms of coughing but further evaluation is required before their use can be recommended.[1,2] Therapeutic use of pertussis-specific immunoglobulin is currently under investigation.

Antimicrobial agents have had varying effects in reducing pertussis symptoms and clearing *B. pertussis* from the respiratory system, and have been used extensively for treatment and prophylaxis.

ERYTHROMYCIN

Erythromycin, a macrolide antibiotic, has shown substantial *in vitro* and *in vivo* activity against *B. pertussis*.[3-6] Because it has been successful in rapidly clearing *B. pertussis* from the nasopharynx, erythromycin has been the antimicrobial agent of choice for the treatment of pertussis.

Effectiveness of Erythromycin

Studies have shown that *B. pertussis* can no longer be isolated from the nasopharynx of most patients with pertussis following five days of erythromycin therapy.[7-10] In a few studies, culture positive cases were detected up to seven days after commencing treatment.[11,12] Because relapses have been observed after completion of 7-10 days of treatment [2,8,9,13-15] with erythromycin, 14 days of treatment has been recommended.[1,16] More recently, a study by Halperin, et al. indicated that the difference between failure rates (2.7%) after 7 days of erythromycin treatment (n=74) and 14 days of treatment (1.06%, n=94) was not statistically significant.[17]

Erythromycin can be used for two purposes in the control and prevention of pertussis:

1. Treatment to modify clinical symptoms of pertussis by administering to symptomatic patients.
2. Prevention of secondary spread of pertussis by administering to:
    a. Symptomatic patients (treatment) and interrupting infectiousness and transmission by eliminating the organism from the respiratory system.
    b. Asymptomatic contacts (prophylaxis) and interrupting transmission by eliminating any organisms that may have been contracted.

Effectiveness of Treatment on Symptoms

The effect of erythromycin treatment on modifying symptoms of pertussis patients has been minimal. A few studies (both experimental and observational) have shown that

erythromycin may reduce symptoms (e.g., number of whoops, developing cough, duration of cough and paroxysms) if administered in the early stages of the disease (i.e., catarrhal stage and within 2 weeks of paroxysmal cough) (see **Table 3-1**). However, when administered in the later stage of paroxysmal cough, erythromycin usually does not relieve symptoms. Major limitations of these studies have been the small number of patients evaluated.

Effectiveness of Treatment and Chemoprophylaxis on Spread of Pertussis

Several studies have evaluated the impact of erythromycin on the spread of pertussis (see **Table 3-2**). Some studies evaluated the impact of treating the patient on transmission, while others evaluated the impact of prophylaxis of contacts. In one study, randomly selected household contacts of culture-confirmed cases were given either erythromycin estolate or placebo; data suggested duration of the treatment of the index cases did not affect the efficacy of chemoprophylaxis.[18]

Overall, data from the studies suggest that treatment of patients and prophylaxis of contacts are most effective when erythromycin is administered in the early stages of disease (i.e., catarrhal stage and within 2 weeks of paroxysmal cough) or exposure (within 3 weeks of cough onset of primary case), respectively. Data from microbiologic studies have shown that in 80-90% of untreated patients will clear *B. pertussis* clears from the respiratory tract within 3-4 weeks of cough onset; untreated and unvaccinated infants may remain culture-positive for more than six weeks.[6,14]

Dosage, Duration of Therapy, and Recommended Preparation

Results from all studies cited above support the early use of erythromycin as standard treatment for pertussis patients and prophylaxis for contacts.[1,4,16,19,20] The recommended dose of erythromycin for use against pertussis in children is 40 to 50 mg/kg per day and in adults 1 to 2 g/day orally in 4 divided doses for 14 days (maximum 2 g/day).[1,16] Some experts recommend the use of erythromycin estolate, because it achieves higher serum levels compared to erythromycin ethylsuccinate or stearate when equal doses are given.[3,21,22] The antimicrobial agents and dosages used for chemoprophylaxis of contacts are the same as that recommended for treatment of a clinical case.[1,16]

Initiating antimicrobial treatment in the patient after three weeks of paroxysmal cough has limited benefit except in high risk cases (see **Chapter 11: Definitions**); symptoms are not reduced and infectiousness is not interrupted because in a majority of case-patients *B. pertussis* clears from the nasopharynx spontaneously. Chemoprophylaxis in those contacts who have been exposed to a pertussis patient more than three weeks ago also has limited benefit, except in high risk contacts (see **Chapter 11: Definitions**). The challenge in providing effective treatment and chemoprophylaxis of pertussis lies in the early recognition and reporting of cases.

The effectiveness of erythromycin is short-term (i.e., during the course of therapy). During an outbreak, repeated exposure to pertussis may necessitate repeated use of chemoprophylactic erythromycin. However, asymptomatic contacts do not always comply with a recommended second or third course of erythromycin. Persons who do not comply with antimicrobial use should be advised to suspect pertussis as soon as they develop cough and to seek health care for early diagnosis and treatment.

Adverse Events and Compliance

Gastrointestinal irritation, including epigastric distress, abdominal cramps, nausea, vomiting, and diarrhea, are the most common adverse effects associated with erythromycin and usually are seen more often after oral administration.[23] Symptoms are dose-related. Some brands with enteric-coated tablets and the ester derivatives (e.g., estolate, ethylsuccinate) may be taken with food to minimize these effects. Hypersensitivity reactions (e.g., skin rashes, drug fever, or eosinophilia), cholestatic hepatitis,[24] and sensorineural hearing loss have occurred occasionally after administration of macrolides; severe reactions such as anaphylaxis are rare. Erythromycin can have adverse interactions frequently with the following drugs, and should be used concomitantly with caution: terfenadine, astemizole, theophylline, carbamazepine, and warfarin. For more information, please refer to the package insert or the Physicians' Desk Reference.

Infantile hypertrophic pyloric stenosis (IHPS) in neonates has been reported following the use of erythromycin; in one case, pyloric stenosis developed in a breast feeding infants whose mother took erythromycin.[25,26] In 1999, a cluster of seven cases of IHPS were reported among neonates (all aged <3 weeks when prophylaxis was started) who had taken erythromycin for prophylaxis after exposure to a pertussis case in the hospital. In the cohort study conducted among infants born in the hospital, erythromycin prophylaxis was associated with having IHPS diagnosis and pyloromyotomy [7 cases out of 157 erythromycin exposed infants vs. zero cases out of 125 infants with no erythromycin exposure; relative risk: infinity (95% CI: 1.7-infinity)].[27] The high case-fatality ratio of pertussis in neonates demonstrates the need to prevent pertussis in this age group. However, unnecessary prophylaxis in neonates should be avoided. Physicians who prescribe erythromycin to newborns should inform parents about the possible risks for IHPS and counsel them about signs of developing IHPS.

There are few data on compliance with erythromycin treatment or chemoprophylaxis. The study by de Serres, et al. indicated that among 309 people who were administered erythromycin, 27% had digestive problems, 6% stopped taking it, and 10% interrupted therapy.[24] Among 17 patients treated with erythromycin in a study in Sweden, only one had vomiting and stopped treatment.[8] An investigation of a nosocomial pertussis outbreak in Seattle found that 27% (5/18) of health care workers placed on erythromycin and 10% (9/86) of health care workers placed on trimethoprim-sulfamethoxazole were

non-compliant with the prescribed regime (taking less than 7 days of medication) due to side effects (M. Curtis, personal communication, 1999). In a Canadian study, 15% of 144 household contacts completed <60% of erythromycin chemoprophylaxis doses (i.e., poor compliance), compared with 8% of 166 household contacts given a placebo.[18]

Treatment and Chemoprophylaxis

a. ***Cases***. Antimicrobial treatment should be initiated as soon as pertussis is suspected in a patient. The antibimicrobial of choice is erythromycin. Initiating treatment ≥3 weeks after cough onset has limited benefit to the patient or contacts. However, treatment is recommended up to six weeks after cough onset in late pregnancy. Please see section for dosage and duration of therapy.

b. ***Contacts.*** If pertussis is highly suspected in patient, chemoprophylaxis of all household and close contacts with erythromycin is recommended regardless of their age and vaccination status. Initiating chemoprophylaxis ≥3 weeks after exposure has limited benefit for the contacts. However, chemoprophylaxis should be considered for high-risk contacts (e.g., infants) up to 6 weeks after exposure. Please see section on adverse reactions in neonates.

Erythromycin Resistance

Resistance of *B. pertussis* to erythromycin was reported first in a case from Yuma County, Arizona in June 1994.[28,29] The strain was isolated from an unvaccinated 2-month-old infant who had paroxysmal cough, whoop, posttussive vomiting, episodes of cyanosis and apnea. Pertussis diagnosis was based on positive culture and DFA. Following 12 days of treatment with erythromycin ethylsuccinate (oral, 50 mg/kg), the condition of the child worsened and a second specimen was found to be still culture-positive. Following another 12 days of erythromycin lactobionate (intravenous, 30 mg/kg/day, increased to 40 mg/kg/day 5 days later) treatment, the condition of the child had not improved and *B. pertussis* was again isolated. Susceptibility testing suggested that the isolate was resistant to erythromycin (agar dilution minimum inhibitory concentration [MIC] >64 ug/mL) and was susceptible to trimethoprim-sulfamethoxazole (TMP-SMZ). The child was begun on TMP-SMZ therapy and the culture result was negative five days later.

Following this report, surveillance activities were enhanced in Yuma County, in Arizona overall, and two neighboring California counties.[28] None of the 6 isolates (out of 127 specimens cultured) from Yuma, 22 isolates from Arizona, or 13 isolates from California counties was resistant to erythromycin, suggesting that erythromycin resistance was not widespread in the area.

Korgenski and Daly evaluated susceptibility to erythromycin in 47 *B. pertussis* strains isolated between January 1985 and June 1997 at the Primary Children's Medical Center in Salt Lake City, Utah.[30] They determined agar dilution MIC on Regan-Lowe agar. One

(2.2%) isolate showed a MIC of 32 µg/ml and was considered resistant. This isolate was recovered in January 1997. Cross-resistance to clarithromycin and clindamycin was observed. In this study, additional susceptibility tests done with Etest MIC and disk diffusion testing on commercial Regan-Lowe agar suggested that these methods were adequate methods for erythromycin resistance screening for *B. pertussis* isolates. The authors recommended *B. pertussis* isolates be tested for erythromycin susceptibility only when there is therapeutic failure or for surveillance purposes.

Approximately 1000 *B. pertussis* isolates have been evaluated for antimicrobial resistance at the CDC Pertussis Laboratory. Among these, only one was found to be resistant to erythromycin (G. Sanden, unpublished data, 2000). This isolate was forwarded to CDC by the New York City Department of Health in 1994.

Susceptibility testing is not routinely recommended for *B. pertussis* isolates. However, surveillance for resistant organisms is needed. Criteria for assessing treatment failure are:[28]

1. persistence or worsening of the typical symptoms of pertussis disease;
2. initiation of erythromycin therapy within 2 weeks of onset of illness;
3. completion of erythromycin therapy in the recommended dosage, or positive culture after completion of 7 days of a full course antimicrobial therapy; and
4. verification of patient compliance with therapy.

All of the above criteria should be met to consider antimicrobial resistance. Isolates obtained from patients with erythromycin therapy failure should be sent to CDC for further testing. For address and specimen collection and shipping instructions, see **Chapter 2: Diagnosis and Laboratory Methods**.

TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

Based on data from a few studies, TMP-SMZ also appears to be effective in eradicating *B. pertussis* from the nasopharynx,[6,9,31] and it is recommended as an alternative antibiotic treatment for patients who cannot tolerate erythromycin.[16] The recommended dosage for children is trimethoprim 8 mg/kg/day, sulfamethoxazole 40 mg/kg/day in two divided doses for 14 days.[1,16] The recommended dosage for adults is trimethoprim 320 mg/day, sulfamethoxazole 1600 mg/day in two divided doses for 14 days.[1,16] Mild, diffuse skin reactions as a result of hypersensitivity to the sulfonamide component are the most common adverse reactions to TMP-SMZ. Because of the risk of kernicterus (a condition with severe neural symptoms, associated with high levels of bilirubin in the blood), TMP-SMZ should not be given to pregnant women at term, nursing mothers, or infants aged <2 months.

AZITHROMYCIN AND CLARITHROMYCIN

Azithromycin and clarithromycin are two macrolide antibiotics that became available in recent years and are administered often for treatment and prophylaxis against pertussis.

Because of structural differences from erythromycin, azithromycin and clarithromycin are more stable in acid, have improved bioavailability, and may reduce gastrointestinal irritation. An investigation of a nosocomial pertussis outbreak in Seattle found that non-compliance rates among health care workers were 27% (5/18) among those placed on erythromycin, 10% (9/86) among those placed on TMP-SMZ, and 1% (1/102) among those placed on azithromycin (M. Curtis, personal communication, 1999).

Although in vitro studies suggest that *B. pertussis* is susceptible to azithromycin and clarithromycin,[32,33] there are limited data on their effectiveness against pertussis *in vivo*. Aoyama, et al. have studied nine pertussis patients who were administered clarithromycin, 10mg/kg per day, twice a day for 7 days, and eight who were administered azithromycin, 10mg/kg per day, once a day for 5 days.[34] For each patient, two erythromycin-treated patients with pertussis were selected as controls. After one week of treatment, all clarithromycin and azithromycin treated patients, and 16 of 18 patients in the first and 13 of 16 patients in the second erythromycin treatment control groups were culture-negative, respectively. No bacterial relapse was detected in any of the groups. In another study, Bace, et al. evaluated the effectiveness of azythromycin administered for 3 to 5 days to 28 children aged 2 to 15-months who had culture-confirmed clinical pertussis.[35] Bacteriologic eradication was achieved in 27/27 children on day 7, 27/27 on day 14, and 16/17 on day 21. At the end of the observation period, of those tested, one patient had relapse. No control group was included in the study.

Until more data from clinical studies evaluating new macrolides become available, the CDC recommends erythromycin as the antimicrobial agent of choice for treatment of and prophylaxis against pertussis. The American Academy of Pediatrics states that because of *in vitro* susceptibilities, clarithromycin (15-20 mg/kg/day orally in two divided doses; maximum 1 g/d, for 10-14 days), and azithromycin (10-12 mg/kg per day orally in one dose; maximum 500 mg/d, for 5-7 days) also are likely to be effective and, thus, are alternatives for patients who cannot tolerate erythromycin.[1]

OTHER ANTIMICROBIALS

Although ampicillin and amoxicillin exhibit satisfactory *in vitro* activity against *B. pertussis*,[36] *in vivo* they have been found to be ineffective in clearing *B. pertussis* from nasopharynx. In several studies, patients who received erythromycin were culture-negative sooner than those treated with ampicillin or amoxicillin.[10,11,37,38] Failure to clear *B. pertussis* from the nasopharynx with amoxicillin or ampicillin may be related to their poor penetration into respiratory secretions and thus not achieving high levels in the respiratory secretions.[39]

In addition, due to their potential harmful side effects in children, tetracyclines, chloramphenicol and fluoroquinolones are not recommended for treatment or prophylaxis of pertussis. Cephalosporins are also not suitable for the treatment of pertussis; the MIC of *B. pertussis* to the cephalosporins is unacceptably high.[4] Therefore none of these other

antimicrobial agents should be used for the treatment of pertussis.

Table 3-1. Results from studies that evaluated the effectiveness of erythromycin treatment on reducing symptoms of pertussis patients.

Author & Year	Setting	Type of study	Case definition	Comparison groups	Sample size	Erythromycin treatment	Effect of treatment on symptoms	Vaccination status
Bass,[10] 1969	New Orleans, LA	Randomized	Clinical pertussis and culture (+) or DFA (+)	4 therapy (erythromycin, chloramphenicol, oxytetracycline, ampicillin) and 1 untreated control group	10 patients in each group	50 mg/day, 4 divided doses, ≥7 days	Duration of catarrhal, paroxysmal and convalescent stages were similar between the groups.	Only 2 children had 3 doses of DTP (both in oxytetracycline group)
Baraff,[11] 1978	Los Angeles, CA	Experimental	Cough lasting >1 w* and cyanosis, or vomiting or whoop, and cx (+)	Those who received erythromycin vs those who were not treated (onset not reported)	7 untreated, 18 treated patients	Estolate: 40 mg/kg/day (duration not reported)	Mean duration of hospitalization similar in two groups: treatment group 7.3 d, vs control group 8.5 d.	Not controlled for
Bergquist,[8] 1987	Sweden	Randomized open	>1 yr age, suspected pertussis evident for <14 d. 25/38 already had whoops	Same as cases, untreated	17 treated with erythromycin, 21 untreated controls	Ethylsuccinate: 25 mg/kg twice daily for 10 days	Number of whoops between day 1 and 14: 50% reduction in the treatment group ($p<0.02$) and doubled in the control group ($p<0.05$).	Not reported
Steketee,[40] 1988	Wisconsin	Observational, retrospective cohort	Respiratory illness and culture, DFA, or serology positive in an institutional setting	Treatment within 1 w vs >1 week of any respiratory symptoms in seropositive patients or untreated patients	40 treated <1 w, 43 treatment started >1 w	Erythromycin base or ethylsuccinate: 40 mg/kg/d orally, divided into 4 daily doses for 14 d	43% (17/40) of early treated patients and 19% (8/43) of late treated patients did not develop cough (RR= 2.28; 95% CI, 1.14-4.54). Duration of cough longer and significantly higher proportion of severe symptoms in late treatment group.	Few unvaccinated residents, not controlled for in the analysis.
Farizo,[41] 1992	U.S.	Analysis of national surveillance data	Cases of pertussis reported to CDC during 1980-1989	Cases who started prophylaxis <0-7 d, 8-14 d, and >14 d of cough onset compared to untreated group (controlled for age)	>700 in each group	All treated people received oral erythromycin therapy for ≥10 days	Percentage of those coughed ≥28 d was lower in the group treated <0-7 d after cough onset compared to untreated group ($p<0.01$). The highest percentage of patients with long cough was in the group treated >14 d of cough onset.	Not controlled for
Bortolussi, 1995 [42]	Canada	Observational prospective, HH study	Culture (+) index cases	Persons who began treatment <1 w of cough onset vs >21 d of cough onset	189 patients in all ages	Dosage and duration not reported	Mean duration of cough and paroxysms 38 and 28 d in early treatment group vs 57 and 44 d in late treatment group.	>90% of children had 3 doses
Halperin,[17] 1997	Canada	Prospective, randomized, controlled, clinical trial	NP aspirate culture (+)	Those who received 7 days of erythromycin vs. those who received 14 days of erythromycin	87 treated for 7 days, 106 treated for 14 days	7 or 14 days of erythromycin estolate, 40 mg/kg/d in 3 divided doses, max of 1 g/d	No difference in the bacteriologic persistence ($p=0.98$) or bacteriological relapse ($p=0.77$) between the 7 and 14 day treatment groups	Not reported.

* m = month; w = week; and d=day.

Table 3-2. Results from studies that evaluated the effectiveness of erythromycin treatment and prophylaxis on reducing spread of disease.

Author & Year	Setting	Type of study	Case definition	Treatment of index case	Comparison groups	Erythromycin Prophylaxis	Effect of prophylaxis on secondary spread	Vaccination status
Altemeier, 1977 [43]	TN	Case report	Index case: a cx (+), hospitalized, symptomatic neonate	Not treated at the time of exposure	7 neonates exposed to the index case prior to his treatment	50 mg/kg/day of erythromycin IM x 5 days	None developed symptoms (two were culture (+) prior to prophylaxis)	N/A
Halsey,[15] 1980	CO	Case report	Index case: a culture (+), hospitalized, symptomatic neonate	E. ethylsuccinate: 55 mg/kg/d.* But infant was still culture(+) at the time of exposure	One infant exposed to the index case for 3 days during culture (+) stage	Ethylsuccinate 55 mg/kg/day	Three days after erythromycin prophylaxis began, contact became symptomatic and culture (+). After 8 more days of treatment, he became culture (-)	One dose of DTP
Grob,[44] 1981	Britain	Randomized, placebo controlled, double blind	Index case: culture (+) secondary case: not specified	29/40 index cases treated with erythromycin, dosage and duration not reported	HH** contacts (31unvaccinated , 60 vaccinated) prophylaxed or received placebo	50 mg/kg/day 4 divided doses x 14 days. Prophylaxis began 13 ± 8 days.	Unvaccinated contacts: 20% (4/20) treated, vs 18% (2/11) untreated contacts had pertussis. Could not separate effect of treatment of index from effect of prophylaxis.	None of the vaccinated children had pertussis.
Spencely,[45] 1981	Britain	Randomized	Index case: diagnosed pertussis; 2^{ndary} case: respiratory symptoms of more than trivial duration	17 cases - 8 had erythromycin, 2 received other antibiotics; dosage and duration not reported	HH contacts prophylaxed (11) or received placebo (9)	125 mg or 250 mg 4 times a day for 10 days for children aged < or ≥2 yrs, respectively	82% (9/11) treated and 22% (2/9) untreated children had pertussis. More erythromycin group was already experiencing symptoms at trial onset.	9 contacts were unvaccinated, 5 had 2 doses.
Granstrom 1987 [46]	Sweden	Retrospective review of cases	Index case: pregnant women with serology or culture (+) pertussis	250-500 mg x 3 doses a day x 10 d. Received 3 ± 3 days before delivery.	28 newborns prophylaxed with erythromycin. 4 did not receive.	Erythromycin 40 mg/kg/d, 3 times a day. 22 for 10 d, 6 for 5 d. All mothers nursed their infants.	None of the infants developed symptoms or laboratory evidence of pertussis.	N/A
Biellik,[47] 1988	Marshfield WI	Case-control, HH study	Acute cough illness ≥14 d or ≥7 d and paroxysms or paroxysmal cough causing sleep disturbance on ≥2 nights	Not reported	HHs with 2^{nd} cases vs HH without 2^{nd} cases	Erythromycin, dosage and duration not reported	Average interval between onset of illness in 1^{st} case and initiation of therapy: 24 d (HH with 2^{nd} cases) vs 11 d (HH with no 2^{nd} cases) ($p<0.001$). Average interval between onset of illness in 1^{st} case and initiation of prophylaxis: 23 d (HH with 2^{nd} cases) vs 14 d (HH with no 2^{nd} cases) ($P<0.02$). Similar number of contacts given prophylaxis, number of contacts and 1^{st} cases completed ≥10 d treatment	Similar vaccination status.

* m = month; w = week; and d=day. ** HH = household.

Table 3-2 (Continued). Results from studies that evaluated the effectiveness of erythromycin treatment and prophylaxis on reducing spread of disease.

Author & Year	Setting	Type of study	Case definition	Treatment of index case	Comparison groups	Erythromycin prophylaxis	Effect of treatment or prophylaxis on secondary spread	Vaccination status
Steketee, 1988 [40]	Wisconsin	Observational, retrospective cohort	Respiratory illness and culture, DFA, or serology positive in an institutional setting	Erythromycin base or ethylsuccinate: 40 mg/kg/d orally, divided into 4 daily doses for 14 d	Wards whose residents prophylaxed <2 w of cough onset of 1st case vs wards prophylaxed ≥4 w of 1st case	Same as treatment for all residents of exposed wards	AR in wards prophylaxed early: 16% (13/125 residents) vs late-75% (85/113 residents)	Few unvaccinated residents, in the analysis vaccination status not controlled for.
Sprauer,[4 8] 1988	Maricopa Co., AZ	Observational, retrospective cohort	Culture (+), ≥14 d cough or paroxysmal cough of ≥7 d. Secondary case: onset 7-28 d after 1st case	Receiving 5 d of continuous erythromycin, dosage not reported	HHs (17) with 2nd cases vs HHs (20) without 2nd cases	≥10 d of erythromycin after exposure	More 1st cases in HHs with no 2nd transmission received treatment (100% vs 76%) (p<0.05). Median interval to treatment of 1st case: 11 d in HH with no 2nd cases, 21 d in HH with 2nd cases (p=0.057). Percentage of contacts receiving prophylaxis <3 w of 1st case: 97% in HH with no 2nd cases, 47% in HH with 2nd cases (p<0.001). Median interval from 1st cases to prophylaxis: 16 d in HH with no 2nd cases, 22 d in HH with 2nd cases (p<0.001).	Vaccination status similar between groups
Fisher,[49] 1989	Philadelphia	Observational	Culture (+) or DFA (+) or serology (+)	Erythromycin, 14 d	None. Results from culture specimens taken on 3 occasions (0, 18 d and 2 m later) were compared	Erythromycin, 14 d	Administration of erythromycin to all residents eliminated culture (+) cases and halted the spread of infection. No resident had a positive culture or DFA test result at the end of 14 days of treatment or 2 months later.	
Wirsing von Konig,[50] 1995	Germany	HH study, nested in a vaccine efficacy trial	Primary case: ≥21 d paroxysmal cough and lab (culture, serology) confirmation; secondary case: ≥7 d paroxysmal cough and lab confirmation, onset ≥7 d after primary case	Erythromycin, dosage and duration not reported	HH contacts whose index cases have been treated (265) or not treated (151)	Erythromycin, dosage and duration not reported	AR in child contacts (6-47 mo, unvaccinated) of treated 1st cases: 51% (55/109) vs untreated 1st cases: 64% (41/64) (p>0.05). AR in adult contacts of treated 1st case: 20% (31/156) vs untreated 1st cases: 36% (31/87) (p<0.05).	Not reported for contacts

* m = month; w = week; and d=day. ** HH = household.

Table 3-2 (Continued). Results from studies that evaluated the effectiveness of erythromycin treatment and prophylaxis on reducing spread of disease.

Author & Year	Setting	Type of study	Case definition	Treatment of index case	Comparison groups	Erythromycin prophylaxis	Effect of treatment or prophylaxis on secondary spread	Vaccination status
DeSerres,[24] 1995	Canada	Retrospective cohort, HH study	Primary case: culture (+) or CDC sporadic case definition; secondary case: ≥2 w cough	Not reported	Contacts (940) in HHs with prophylaxis vs without prophylaxis	Varied. Adults: 250-500 mg x 3 times a day; children 40-50 mg/kg/day, 10-14 days	2nd AR: HH with prophylaxis: 17%; HH without prophylaxis: 25% (RR=0.69; 95% CI, 0.52-0.93). 2nd AR: prophylaxis used before onset of 2nd case: 4% vs after 2nd case: 35% (p<0.001). Compared to 2nd AR among HH prophylaxed ≤21 d, 2nd AR doubled when prophylaxis was given >21 d after onset of cough in the primary case or not given at all.	Vaccination status was not a factor in 2nd AR
Schmitt,[51] 1996	Germany	Blinded, prospective follow-up of HH contacts	Index case: ≥21 d spasmodic cough and culture or serology (+); secondary case: onset 7-28 d after onset of cough in the 1st case	Erythromycin, dosage not reported	Unvaccinated contacts whose index cases have been treated vs not treated	Erythromycin, dosage and duration not reported	AR in unvaccinated HH contacts whose index cases have been treated: 51% vs index case not treated: 64% (p=0.08).	67% of unvaccinated contacts received prophylaxis.
Halperin,[18] 1999	Canada	Randomized, double-blind, placebo-controlled	a) cx (+), b) cx (+) or paroxysmal cough ≥2 w, c) cx (+) or cough ≥2 w and (whoop, paroxysm, vomiting, apnea or cyanosis)	Erythromycin for 7 or 14 d	HH contacts of randomly selected culture confirmed cases. Contacts were given placebo.	10 days of erythromycin estolate, 40 mg/kg/d in 3 divided doses, maximum of 1 g/d	Fewer post-tussive vomiting or whoop in the erythromycin treatment group; respiratory symptoms, nasal congestion, cough or paroxysmal cough similar in both groups. Efficacy in preventing cx(+) pertussis=67.5% (95% CI: 7.6%-88.7%). No significant difference in 2nd AR when only contacts who were asymptomatic before prophylaxis were examined.	Not reported.

* m = month; w = week; and d=day. ** HH = household.

REFERENCES

1. American Academy of Pediatrics. Pertussis. In: Peter G, ed. 1997 Red Book: Report of the Committee on Infectious Diseases. 24th ed. Elk Grove Village, IL: American Academy of Pediatrics, 1997:394-407.

2. Broomhall J, Herxheimer A. Treatment of whooping cough: The facts. Arch Dis Child 1984;59:185-7.

3. Bass JW. Erythromycin for treatment and prevention of pertussis. Ped Infect Dis J 1986;5:154-7.

4. Hoppe JE. State of art in antibacterial susceptibility of *Bordetella pertussis* and antibiotic treatment of pertussis. Infection 1998;26:242-6.

5. Hoppe JE, Haug A, Botzenhart K. Susceptibility of *Bordetella pertussis* and *Bordetella parapertussis* to 24 antibiotics. Chemotherapy 1987;33:250-4.

6. Kwantes W, Joynson HM, Williams WO. *Bordetella pertussis* isolation in general practice: 1977-79 whooping cough epidemic in West Glamorgan. J Hyg Camb 1983;90:149-58.

7. Nelson JD. Antibiotics in pertussis. Pediatrics 1969;44:474-6.

8. Bergquist S, Bernander S, Dahnsjo H, et al. Erythromycin in the treatment of pertussis: A study of bacteriologic and clinical effects. Ped Infect Dis J 1987;6:458-61.

9. Henry RL, Dorman DC, Skinner J, et al. Antimicrobial therapy in whooping cough. Med J Aust 1981:27-8.

10. Bass JW, Klenk EL, Kotheimer JB, et al. Antimicrobial treatment of pertussis. J Pediatr 1969;75:768-81.

11. Baraff LJ, Wilkins J, Wehrle PF. The role of antibiotics, immunizations, and adenoviruses in pertussis. Pediatrics 1978;61:224-30.

12. Edelman K, Nikkari S, Ruuskanen O, et al. Detection of *Bordetella pertussis* by polymerase chain reaction and culture in the nasopharynx of erythromycin-treated infants with pertussis. Ped Infect Dis J 1996;15:54-7.

13. Henry R, Dorman D, Skinner J, et al. Limitations of erythromycin in whooping cough. Med J Aust 1981;2:108-9.

14. Riitta H. The effect of early erythromycin treatment on the infectiousness of whooping cough patients. Acta Paediatr Scand 1982;298(Suppl):10-12.

15. Halsey N, Welling MA, Lehman RM. Nosocomial pertussis: a failure of erythromycin treatment and prophylaxis. Am J Dis Child 1980;134:521-2.

16. Centers for Disease Control and Prevention. Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures; Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1991;40(RR-10):1-28.

17. Halperin SA, Bortolussi R, Langley JM, et al. Seven days of erythromycin estolate is as effective as fourteen days for the treatment of *Bordetella pertussis* infections. J Pediatr 1997;100:65-71.

18. Halperin SA, Botolussi R, Langley JM, et al. A randomized, placebo-controlled trial of erythromycin estolate chemoprophylaxis for household contacts of children with culture-positive *Bordetella pertussis* infection. Pediatrics 1999;104:e42.

19. Lambert H. Antimicrobial drugs in the treatment and prevention of pertussis. J Antimicrobial Chemotherapy 1979;5:329-36.

20. Bass JW. Pertussis: Current status of prevention and treatment. Ped Infect Dis J 1985;4:614-9.

21. Ginsburg CM. Pharmacology of erythromycin in infants and children. Ped Infect Dis J 1986;5:124-9.

22. Hoppe JE, Erythromycin Study Group. Comparison of erythromycin estolate and erythromycin ethylsuccinate for treatment of pertussis. Ped Infect Dis J 1992;11:189-93.

23. Eichenwald HF. Adverse reactions to erythromycin. Ped Infect Dis J 1986;5:147-50.

24. De Serres G, Boulianne N, Duval B. Field effectiveness of erythromycin prophylaxis to prevent pertussis within families. Ped Infect Dis J 1995;14:969-75.

25. SanFilippo JA. Infantile hypertrophic pyloric stenosis related to ingestion of erythromycin estolate: a report of five cases. J Pediatr Surg 1976;11:177-80.

26. Stang H. Pyloric stenosis associated with erythromycin ingested through breastmilk. Minnesota Med 1986;69:669-70, 682.

27. Honein MA, Paulozzi LJ, Himelright IM, Lee B, Cragan JD, Patterson L, Correa A, Hall S, Erickson JD. Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. Lancet 1999;354:2101-5.

28. Centers for Disease Control and Prevention. Erythromycin-resistant *Bordetella pertussis*--Yuma County, Arizona, May-October 1994. MMWR 1994;43:807-10.

29. Lewis K, Saubolle MA, Tenover FC, et al. Pertussis caused by an erythromycin-resistant strain of *Bordetella pertussis.* Ped Infect Dis J 1995:14:388-91.

30. Korgenski EK, Daly JA. Surveillance and detection of erythromycin resistance in *Bordetella pertussis* isolates recovered from a pediatric population in the intermountain west region of the United States. J Clin Microbiol 1997;35:2989-91.

31. Hoppe JE, Halm U, Hagedorn HJ, et al. Comparison of erythromycin ethylsuccinate and co-trimoxazole for treatment of pertussis. Infection 1989;17:227-31.

32. Hardy DJ, Hensey DM, Beyer JM, et al. Comparative in vitro activities of new 14-, 15-, and 16-membered macrolides. Antimicrobial Agents and Chemotherapy 1988;32:1710-19.

33. Hoppe Je, Eichhorn A. Activity of new macrolides against *Bordetella pertussis* and *Bordetella parapertussis*. Euro J Clin Microb Infect Dis 1989;8:653-4.

34. Aoyama T, Sunakawa K, Iwata S, et al. Efficacy of short-term treatment of pertussis with clarithromycin and azithromycin. J Pediatr 1996;761-4.

35. Bace A, Kuzmanovic N, Zrnic T. Pertussis: Simple and short therapy with azithromycin (abstract 6.04). In 4th International Conference on Macrolides, Azalides, Streptogramins, Ketolides, 1998:58.

36. Hoppe JE, Haug A. Antimicrobial susceptibility of *Bordetella pertussis* (Part I). Infection 1988;16:126-30.

37. Islur J, Anglin CS, Middleton PJ. The whooping cough syndrome: A continuing pediatric problem. Clin Pediatr 1975;14:171-6.

38. Trollfors B. Effect of erythromycin and amoxycillin on *Bordetella pertussis* in the nasopharynx. Infection 1978;6:228-30.

39. Hoppe JE, Haug A. Treatment and prevention of pertussis by antimicrobial agents (Part II). Infection 1988;16:148-52.

40. Steketee RW, Wassilak SGF, Adkins WN, et al. Evidence of a high attack rate and efficacy of erythromycin prophylaxis in a pertussis outbreak in a facility for developmentally disabled. J Infect Dis 1988;157:434-40.

41. Farizo KM, Cochi SL, Zell ER, et al. Epidemiological features of pertussis in the United States, 1980-89. Clin Infect Dis 1992;14:708-719.

42. Bortolussi R, Miller B, Ledwith M, et al. Clinical course of pertussis in immunized children. Ped Infect Dis J 1995;14:870-4.

43. Altemeier WA, Ayoub EM. Erythromycin prophylaxis for pertussis. Pediatrics 1977;59:623-5.

44. Grob PR. Prophylactic erythromycin for whooping-cough contacts (letter). Lancet 1981;I:772.

45. Spencely M, Lambert HP. Prophylactic erythromycin for whooping-cough contacts (letter). Lancet 1981;I:772.

46. Granstrom G, Sterner G, Nord CE, et al. Use of erythromycin to prevent pertussis in newborns of mothers with pertussis. J Infect Dis 1987;155:1210-4.

47. Biellik RJ, Patriarca PA, Mullen JR, et al. Risk factors for community- and household-acquired pertussis during a large-scale outbreak in central Wisconsin. J Infect Dis 1988;157:1134-41.

48. Sprauer MA, Cochi SL, Zell ER, et al. Prevention of secondary transmission of pertussis in households with early use of erythromycin. Am J Dis Child 1992;146:177-81.

49. Fisher MC, Long SS, McGowan KL, Kaselis E, Smith DG. Outbreak of pertussis in a residential facility for handicapped people. J Pediatr 1989;114:934-9.

50. Wirsing von Konig CH, Postels-Multani S, Bock HL, et al. Pertussis in adults: Frequency of transmission after household exposure. Lancet 1995;346:1326-9.

51. Schmitt HJ, Wirsing von Konig CH, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA 1996;275:37-41.