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Summary

The recommendations in this report were developed to broaden the spectrum of antimicrobial agents that are available
for treatment and postexposure prophylaxis of pertussis. They include updated information on macrolide agents other
than erythromycin (azithromycin and clarithromycin) and their dosing schedule by age group.

Introduction

Pertussis is an acute bacterial infection of the respiratory tract that is caused by Bordetella pertussis, a gram-negative bacterium (Box 1).

B. pertussis is a uniquely human pathogen that is transmitted from an infected person to susceptible persons, primarily through aerosolized droplets of respiratory secretions or by direct contact with respiratory secretions from the infected person.

Disease Burden

The Council of State and Territorial Epidemiologists (CSTE) reviewed and approved a standard case definition for pertussis in June 1997 (1,2) (Box 2). The national pertussis surveillance system is passive and relies on physicians to report cases of pertussis to state and local health departments, which then report cases of pertussis weekly to the National Notifiable Diseases Surveillance System (NNDSS). The reports are transmitted to CDC through the National Electronic Telecommunications System for Surveillance (NETSS) and contain demographic data and supplemental clinical and epidemiologic information for each reported pertussis case.

Despite high childhood vaccination coverage levels for pertussis vaccine (3,4), pertussis remains a cause of substantial morbidity in the United States. Pertussis is the only disease for which universal childhood vaccination is recommended

that has an increasing trend in reported cases in the United States. The disease is endemic in the United States with epidemic
cycles every 3--4 years. In the early vaccine years during 1922--1940, an average annual rate of 150 per 100,000 population
was reported (5,6). After introduction of universal vaccination during the 1940s, the incidence of reported pertussis
declined dramatically to approximately one case per 100,000 population.
During the preceding 3 decades, reports of pertussis steadily increased again in the United States, from a nadir of
1,010 cases in 1976 (3) to 25,827 in 2004 (2004 rate: 8.5 cases per 100,000 population)
(7); the number of reported pertussis cases in 2004 was the highest since 1959. Increased awareness and improved recognition of pertussis among clinicians, greater
access to and use of laboratory diagnostics (especially extensive polymerase chain reaction [PCR] testing), and increased
surveillance and reporting of pertussis by public health departments could have contributed to the increase in reported cases
(8). Some of the reported increase might constitute a real increase in the incidence of pertussis
(9). Although infants have the highest incidence of pertussis of any age group, adolescents and adults account for the majority of reported cases.

Clinical Manifestations

The incubation period of pertussis averages 7--10 days (range: 5--21 days)
(6,10) and has been reported to be as long as
6 weeks (11,12). Pertussis has an insidious onset with catarrhal symptoms (nasal

congestion, runny nose, mild sore-throat,
mild dry cough, and minimal or no fever) that are indistinguishable from those of minor respiratory tract infections. Some
infants can have atypical disease and initially have apneic spells and minimal cough or other respiratory symptoms. The catarrhal
stage last approximately 1--2 weeks. The cough, which is initially intermittent, becomes paroxysmal. A typical paroxysm
is characterized by a succession of coughs that follow each other without inspiration. Paroxysms terminate in typical cases
with inspiratory "whoop" and can be followed by posttussive vomiting. Although children are often exhausted after a
coughing paroxysm, they usually appear relatively well between episodes. Paroxysms of cough usually increase in frequency and
severity as the illness progresses and usually persist for 2--6 weeks. Paroxysms can occur more frequently at night. The illness can
be milder and the characteristic whoop absent in children, adolescents, and adults who were previously vaccinated.
Convalescence is gradual and protracted. The severity of illness wanes, paroxysms subside, and the frequency of
coughing bouts decreases. A nonparoxysmal cough can continue for 2--6 weeks or longer. During the recovery period,
superimposed viral respiratory infections can trigger a recurrence of paroxysms.
Patients with pertussis often have substantial weight loss and sleep disturbance
(13). Conditions resulting from the effects
of the pressure generated by severe coughing include pneumothorax, epistaxis, subconjunctival hemorrhage, subdural
hematoma, hernia, rectal prolapse, urinary incontinence, and rib fracture

(14). Some infections are complicated by primary or secondary bacterial pneumonia and otitis media. Infrequent neurologic complications include seizures and hypoxic encephalopathy.

Adolescents and adults with unrecognized or untreated pertussis contribute to the reservoir of B. pertussis in the community. Patients with pertussis are most infectious during the catarrhal stage and during the first 3 weeks after cough onset. Pertussis is highly infectious; the secondary attack rate exceeds 80% among susceptible persons (15,16). Unvaccinated or incompletely vaccinated infants aged <12 months have the highest risk for severe and life-threatening complications and death (5,8,17--25).

Differential Diagnosis

The differential diagnoses of pertussis include infections caused by other etiologic agents, including adenoviruses, respiratory syncytial virus, Mycoplasma pneumoniae, Chlamydia pneumoniae, and other Bordetella species such as B. parapertussis, and rarely B. bronchoseptica (26) or B. holmseii (27). Despite increasing awareness and recognition of pertussis as a disease that affects adolescents and adults, pertussis is overlooked in the differential diagnosis of cough illness in this population (28).

Prevention

Vaccination of susceptible persons is the most important preventive strategy against pertussis. Universal childhood
pertussis vaccine recommendations have been implemented since the mid-1940s. For protection against pertussis during childhood,
the Advisory Committee on Immunization Practices (ACIP) recommends 5 doses of diphtheria and tetanus toxoid and
acellular pertussis (DTaP) vaccine at ages 2, 4, 6, 15--18 months, and 4--6 years
(29). Childhood vaccination coverage for
pertussis vaccines has been at an all-time high
(4). However, neither vaccination nor natural disease confers complete or
lifelong protective immunity against pertussis or reinfection. Immunity wanes after 5--10 years from the last pertussis vaccine
dose (3,8,30--34). Older children, adolescents, and adults can become susceptible to pertussis after a complete course
of vaccination during childhood.
During spring of 2005, two Tetanus Toxoid and Reduced Diphtheria Toxoid and Acellular Pertussis vaccines
adsorbed (Tdap) formulated for adolescents and adults were licensed in the United States
(BOOSTRIX®, GlaxoSmithKline
Biologicals, Rixensart, Belgium and ADACEL, Sanofi Pasteur, Toronto, Ontario, Canada). ACIP voted to recommend a single dose
of Tdap for adolescents aged 11--18 years in June 2005 and adults aged 19--64 years in October 2005.

Treatment of Pertussis

Maintaining high vaccination coverage rates among preschool children, adolescents, and adults and minimizing exposures
of infants and persons at high risk for pertussis is the most effective way to prevent pertussis. Antibiotic treatment of
pertussis and judicious use of antimicrobial agents for postexposure prophylaxis will eradicate
B. pertussis from the nasopharynx of

infected persons (symptomatic or asymptomatic). A macrolide administered early in the course of illness can reduce
the duration and severity of symptoms and lessen the period of communicability
(35). Approximately 80%--90% of patients
with untreated pertussis will spontaneously clear
B. pertussis from the nasopharynx within 3--4 weeks from onset of cough
(36); however, untreated and unvaccinated infants can remain culture-positive for >6 weeks
(37). Close asymptomatic contacts
(38) (Box 3) can be administered postexposure chemoprophylaxis to prevent secondary cases; symptomatic contacts should
be treated as cases.
Erythromycin, a macrolide antibiotic, has been the antimicrobial of choice for treatment or postexposure prophylaxis
of pertussis. It is usually administered in 4 divided daily doses for 14 days. Although effective for treatment (Table 1)
and postexposure prophylaxis (Table 2), erythromycin is accompanied by uncomfortable to distressing side effects that result

in poor adherence to the treatment regimen. During the last decade, in vitro studies have demonstrated the effectiveness
against B. pertussis of two other macrolide agents (azithromycin and clarithromycin) (57--64). Results from in vitro studies
are not always replicated in clinical studies and practice. A literature search and review was conducted for in vivo studies and
clinical trials that were conducted during 1970--2004 and used clarithromycin or azithromycin for the treatment and prophylaxis
of pertussis (Table 3). On the basis of this review, guidelines were developed to broaden the spectrum of macrolide
agents available for pertussis treatment and postexposure prophylaxis and are presented in this report to update previous
CDC recommendations (71). Treatment and postexposure prophylaxis recommendations are made on the basis of existing
scientific evidence and theoretical rationale.

Recommendations

I. General Principles

A. Treatment. The macrolide agents erythromycin, clarithromycin, and azithromycin are preferred for the treatment
of pertussis in persons aged >1 month. For infants aged <1 month, azithromycin is preferred; erythromycin and
clarithromycin are not recommended. For treatment of persons aged
>2 months, an alternative agent to macrolides is

trimethoprim-sulfamethoxazole (TMP--SMZ) (Table 4).

The choice of antimicrobial for treatment or prophylaxis should take into account effectiveness, safety (including the potential for adverse events and drug interactions), tolerability, ease of adherence to the regimen prescribed, and cost. Azithromycin and clarithromycin are as effective as erythromycin for treatment of pertussis in persons aged >6 months, are better tolerated, and are associated with fewer and milder side effects than erythromycin. Erythromycin and clarithromycin, but not azithromycin, are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with other drugs that are metabolized by this system. Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (1--2 doses per day) and shorter treatment regimens (5--7 days). Erythromycin is available as generic preparations and is considerably less expensive than azithromycin and clarithromycin.

B. Postexposure prophylaxis. A macrolide can be administered as prophylaxis for close contacts of a person with pertussis if the person has no contraindication to its use. The decision to administer postexposure chemoprophylaxis is made after considering the infectiousness of the patient and the intensity of the exposure, the potential consequences of severe pertussis in the contact, and possibilities for secondary exposure of persons at high risk from the contact (e.g., infants aged <12 months). For postexposure prophylaxis, the benefits of administering an antimicrobial

agent to reduce the risk for pertussis and its complications should be weighed against the potential adverse effects of the drug. Administration of postexposure prophylaxis to asymptomatic household contacts within 21 days of onset of cough in the index patient can prevent symptomatic infection. Coughing (symptomatic) household members of a pertussis patient should be treated as if they have pertussis. Because severe and sometimes fatal pertussis-related complications occur in infants aged <12 months, especially among infants aged <4 months, postexposure prophylaxis should be administered in exposure settings that include infants aged <12 months or women in the third trimester of pregnancy. The recommended antimicrobial agents and dosing regimens for postexposure prophylaxis are the same as those for treatment of pertussis (Table 4).

C. Special considerations for infants aged <6 months when using macrolides for treatment or postexposure prophylaxis. The U.S. Food and Drug Administration (FDA) has not licensed any macrolide for use in infants aged <6 months. Data on the safety and efficacy of azithromycin and clarithromycin use among infants aged <6 months are limited.

Data from subsets of infants aged 1--5 months (enrolled in small clinical studies) suggest similar microbiologic effectiveness of azithromycin and clarithromycin against pertussis as with older infants and children. If not treated, infants with pertussis remain culture-positive for longer periods than older children and adults (36,72). These limited data support the use

of azithromycin and clarithromycin as first-line agents among infants aged 1--5 months, based on their in vitro
effectiveness against B. pertussis, their demonstrated safety and effectiveness in older children and adults, and more convenient
dosing schedule.

For treatment of pertussis among infants aged <1 month (neonates), no data are available on the effectiveness
of azithromycin and clarithromycin. Abstracts and published case series describing use of azithromycin among infants aged
<1 month report fewer adverse events compared with erythromycin
(73); to date, use of azithromycin in infants aged <1
month has not been associated with infantile hypertrophic pyloric stenosis (IHPS). Therefore, for pertussis, azithromycin is
the preferred macrolide for postexposure prophylaxis and treatment of infants aged <1 month. In this age group, the risk
for acquiring severe pertussis and its life-threatening complications outweigh the potential risk for IHPS that has been
associated with erythromycin (74). Infants aged <1 month who receive a macrolide should be monitored for IHPS and other
serious adverse events.

D. Safety. A comprehensive description of the safety of the recommended antimicrobials is available in the package
insert, or in the latest edition of the Red Book: Pharmacy's
Fundamental Reference. A macrolide is contraindicated if there is history
of hypersensitivity to any macrolide agent (Table 5). Neither erythromycin nor clarithromycin should be
administered concomitantly with astemizole, cisapride, pimazole, or terfenadine. The

most commonly reported side effects of

oral macrolides are gastrointestinal (e.g., nausea, vomiting, abdominal pain and cramps, diarrhea, and anorexia) and rashes;

side effects are more frequent and severe with erythromycin use.

II. Specific Antimicrobial Agents

1. Azithromycin. Azithromycin is available in the United States for oral administration as azithromycin

dihydrate (suspension, tablets, and capsules). It is administered as a single daily dose. Recommended regimen:

Infants aged <6 months: 10 mg/kg per day for 5 days.

Infants and children aged

>6 months: 10 mg/kg (maximum: 500 mg) on day 1, followed by 5 mg/kg per day

(maximum: 250 mg) on days 2--5.

Adults: 500 mg on day 1, followed by 250 mg per day on days 2--5.

Side effects include abdominal discomfort or pain, diarrhea, nausea, vomiting, headache, and dizziness. Azithromycin should be prescribed with caution to patients with impaired hepatic function. All patients should be cautioned not to

take azithromycin and aluminum- or magnesium-containing antacids simultaneously because the latter reduces the rate

of absorption of azithromycin. Monitoring of patients is advised when azithromycin is used concomitantly with

agents metabolized by the cytochrome P450 enzyme system and with other drugs for which the pharmacokinetics change

(e.g., digoxin, triazolam, and ergot alkaloids). Drug interactions reactions similar to

those observed for erythromycin

and clarithromycin have not been reported. Azithromycin is classified as an FDA Pregnancy Category B drug

(75).

2. Erythromycin. Erythromycin is available in the United States for oral administration as erythromycin base (tablets

and capsules), erythromycin stearate (tablets), and erythromycin ethylsuccinate (tablets, powders, and liquids).

Because relapses have been reported after completion of 7--10 days of treatment with erythromycin, a 14-day course

of erythromycin is recommended for treatment of patients with pertussis or for postexposure prophylaxis of close contacts

of pertussis patients (76).

Recommended regimen:

Infants aged <1 month: not preferred because of risk for IHPS. Azithromycin is the recommended antimicrobial agent.

If azithromycin is unavailable and erythromycin is used, the dose is 40--50 mg/kg per day in 4 divided doses. These

infants should be monitored for IHPS.

Infants aged >1 month and older children: 40--50 mg/kg per day (maximum: 2 g per day) in 4 divided doses for 14 days.

Adults: 2 g per day in 4 divided doses for 14 days

Gastrointestinal irritation, including epigastric distress, abdominal cramps, nausea, vomiting, and diarrhea, are the most common adverse effects associated with oral administration of erythromycin. Symptoms are dose-related. Some formulations with enteric-coated tablets and the ester derivatives (e.g., ethylsuccinate) can be taken with food to minimize these side effects. Hypersensitivity reactions (e.g., skin rashes, drug fever, or eosinophilia), cholestatic hepatitis, and sensorineural hearing loss have occurred after administration of macrolides; severe reactions such as anaphylaxis are rare.

An increased risk for IHPS has been reported in neonates during the month after erythromycin administration. In one case, pyloric stenosis occurred in a breastfeeding infant whose mother took erythromycin. 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 after exposure to a pertussis patient. In a cohort study, erythromycin prophylaxis was causally associated with IHPS (seven cases out of 157 erythromycin exposed infants versus zero cases out of 125 infants with no erythromycin exposure (relative risk: infinity [95% confidence interval = 1.7--infinity]).

The high case-fatality ratio of pertussis in neonates underscores the importance of preventing pertussis among exposed infants. Health-care providers who prescribe erythromycin rather than azithromycin to newborns should inform parents

about the possible risks for IHPS and counsel them about signs of IHPS.

Erythromycin is contraindicated if there is history of hypersensitivity to any macrolide agent. Erythromycin should not be administered concomitantly with astemizole, cisapride, pimazole, or terfenadine. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QTc interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have been observed after concomitant use of erythromycin with these drugs.

Erythromycin is an inhibitor of the cytochrome P450 enzyme system (CYP3A subclass). Coadministration of erythromycin and a drug that is primarily metabolized by CYP3A can result in elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Drugs that are metabolized by CYP3A include alfentanil, bromocriptine, cyclosporine, carbamazepine, cilostazol, disopyramide, dihydroergotamine, ergotamine, lovastatin and simvastatin, methylprednisolone, quinidine, rifabutin, vinblastine, tacrolimus, triazolo-benzodiazepines (e.g., triazolam and alprazolam) and related benzodiazepines, and sildenafil. In addition, reports exists of drug interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including zidovudine, hexobarbital, phenytoin, and valproate, theophylline, digoxin, and oral anticoagulants.

Erythromycin is classified as an FDA Pregnancy Category B drug (76). Animal reproduction studies have failed to demonstrate a risk to the fetus, but no adequate or well-controlled studies in humans exist.

3. Clarithromycin. Clarithromycin is available in the United States for oral administration as granules for oral
suspension and tablets.
Recommended regimen:

Infants aged <1 month: not recommended.
Infants and children aged
>1 month: 15 mg/kg per day (maximum: 1 g per day) in 2 divided doses each day for 7 days.
Adults: 1 g per day in two divided doses for 7 days.

The most common adverse effects associated with clarithromycin include epigastric distress, abdominal cramps,
nausea, vomiting, and diarrhea. Hypersensitivity reactions (e.g., skin rashes, drug fever, or eosinophilia), hepatotoxicity, and
severe reactions such as anaphylaxis are rare. Because of its similarity to erythromycin, both chemically and
metabolically, clarithromycin should not be administered to infants aged <1 month because it is unknown if the drug can be
similarly associated with IHPS. The drug is contraindicated if there is history of hypersensitivity to any macrolide agent. Similar
to erythromycin, clarithromycin should not be administered concomitantly with astemizole, cisapride, pimazole, or
terfenadine. Clarithromycin inhibits the cytochrome P450 enzyme system (CYP3A subclass), and coadministration of clarithromycin

and a drug that is primarily metabolized by CYP3A can result in elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Clarithromycin can be administered without dosage adjustment in patients with impaired hepatic function and normal renal function; however, drug dosage and interval between doses should be reassessed in the presence of impaired renal function. Clarithromycin is classified by FDA as a Pregnancy Category C drug (76). Animal reproduction studies have shown an adverse effect on the fetus; no adequate or well-controlled studies in humans exist.

4. Alternate agent (TMP--SMZ). Data from clinical studies indicate that TMP--SMZ is effective in eradicating B. pertussis from the nasopharynx (64,77,78). TMP--SMZ is used as an alternative to a macrolide antibiotic in patients aged >2 months who have contraindication to or cannot tolerate macrolide agents, or who are infected with a macrolide-resistant strain of B. pertussis. Macrolide-resistant B. pertussis is rare. Because of the potential risk for kernicterus among infants, TMP--SMZ should not be administered to pregnant women, nursing mothers, or infants aged <2 months.

Recommended regimen (79):

Infants aged <2 months: contraindicated.

Infants aged >2 months and children: trimethoprim 8 mg/kg per day, sulfamethoxazole 40 mg/kg per day in 2
divided doses for 14 days.
Adults: trimethoprim 320 mg per day, sulfamethoxazole 1,600 mg per day in 2 divided doses for 14 days.

Patients receiving TMP-SMZ might experience gastrointestinal adverse effects, hypersensitivity skin reactions, and
rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis, blood dyscrasias, and hepatic necrosis. TMP--SMZ is
contraindicated if there is known hypersensitivity to trimethoprim or sulfonamides. TMP--SMZ should be prescribed with caution to
patients with impaired hepatic and renal functions, folate deficiency, blood dyscrasias, and in older adults because of the
higher incidence of severe adverse events. Patients taking TMP--SMZ should be instructed to maintain an adequate fluid intake
to prevent crystalluria and renal stones. Drug interactions must be considered when TMP--SMZ is used concomitantly
with drugs, including methotrexate, oral anticoagulants, antidiabetic agents, thiazide diuretics, anticonvulsants, and
other antiretroviral drugs. TMP--SMZ is classified by FDA as a Pregnancy Category C drug
(76). Animal reproduction studies have indicated an adverse effect on the fetus; no adequate or well-controlled studies in humans exist.
5. Other antimicrobial agents. Although in vitro activity against
B. pertussis has been demonstrated for other
macrolides such as roxithromycin and ketolides (e.g., telithromycin)

(60), no published data exist on the clinical effectiveness of these agents.

Other antimicrobial agents such as ampicillin, amoxicillin, tetracycline, chloramphenicol, fluoroquinolones (e.g., ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin), and cephalosporins exhibit various levels of in vitro inhibitory activity against B. pertussis, but in vitro inhibitory activity does not predict clinical effectiveness. The clinical effectiveness of these agents for treatment of pertussis has not been demonstrated. For example, both ampicillin and amoxicillin were ineffective in clearing B. pertussis from nasopharynx (80). Poor penetration into respiratory secretions was proposed as a possible mechanism for failure to clear B. pertussis from the nasopharynx (81). The minimum inhibitory concentration of B. pertussis to the cephalosporins is unacceptably high (82). In addition, tetracyclines, chloramphenicol, and fluoroquinolones have potentially harmful side effects in children. Therefore, none of the above antimicrobial agents are recommended for treatment or postexposure prophylaxis of pertussis.

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The recommendations in this report were developed to broaden the spectrum of antimicrobial agents that are available
for treatment and postexposure prophylaxis of pertussis. They include updated information on macrolide agents other
than erythromycin (azithromycin and clarithromycin) and their dosing schedule by age group.

Introduction

Pertussis is an acute bacterial infection of the respiratory tract that is caused by Bordetella pertussis, a gram-negative bacterium (Box 1).

B. pertussis is a uniquely human pathogen that is transmitted from an infected person to
susceptible persons, primarily through aerosolized droplets of respiratory secretions or by direct contact with respiratory secretions
from the infected person.

Disease Burden

The Council of State and Territorial Epidemiologists (CSTE) reviewed and approved a standard case definition for
pertussis in June 1997 (1,2) (Box 2). The national pertussis surveillance system is passive and relies on physicians to report cases
of pertussis to state and local health departments, which then report cases of pertussis weekly to the National Notifiable
Diseases Surveillance System (NNDSS). The reports are transmitted to CDC through the National Electronic
Telecommunications System for Surveillance (NETSS) and contain demographic data and supplemental clinical and epidemiologic information
for each reported pertussis case.

Despite high childhood vaccination coverage levels for pertussis vaccine
(3,4), pertussis remains a cause of
substantial morbidity in the United States. Pertussis is the only disease for which universal childhood vaccination is recommended
that has an increasing trend in reported cases in the United States. The disease is endemic in the United States with epidemic
cycles every 3--4 years. In the early vaccine years during 1922--1940, an average annual rate of 150 per 100,000 population

was reported (5,6). After introduction of universal vaccination during the 1940s, the incidence of reported pertussis
declined dramatically to approximately one case per 100,000 population.

During the preceding 3 decades, reports of pertussis steadily increased again in the United States, from a nadir of
1,010 cases in 1976 (3) to 25,827 in 2004 (2004 rate: 8.5 cases per 100,000 population)
(7); the number of reported pertussis cases in 2004 was the highest since 1959. Increased awareness and improved recognition of pertussis among clinicians, greater
access to and use of laboratory diagnostics (especially extensive polymerase chain reaction [PCR] testing), and increased
surveillance and reporting of pertussis by public health departments could have contributed to the increase in reported cases
(8). Some of the reported increase might constitute a real increase in the incidence of pertussis
(9). Although infants have the highest incidence of pertussis of any age group, adolescents and adults account for the majority of reported cases.

Clinical Manifestations

The incubation period of pertussis averages 7--10 days (range: 5--21 days)
(6,10) and has been reported to be as long as
6 weeks (11,12). Pertussis has an insidious onset with catarrhal symptoms (nasal congestion, runny nose, mild sore-throat,
mild dry cough, and minimal or no fever) that are indistinguishable from those of minor respiratory tract infections. Some
infants can have atypical disease and initially have apneic spells and minimal cough or

other respiratory symptoms. The catarrhal stage last approximately 1--2 weeks. The cough, which is initially intermittent, becomes paroxysmal. A typical paroxysm is characterized by a succession of coughs that follow each other without inspiration. Paroxysms terminate in typical cases with inspiratory "whoop" and can be followed by posttussive vomiting. Although children are often exhausted after a coughing paroxysm, they usually appear relatively well between episodes. Paroxysms of cough usually increase in frequency and severity as the illness progresses and usually persist for 2--6 weeks. Paroxysms can occur more frequently at night. The illness can be milder and the characteristic whoop absent in children, adolescents, and adults who were previously vaccinated.

Convalescence is gradual and protracted. The severity of illness wanes, paroxysms subside, and the frequency of coughing bouts decreases. A nonparoxysmal cough can continue for 2--6 weeks or longer. During the recovery period, superimposed viral respiratory infections can trigger a recurrence of paroxysms.

Patients with pertussis often have substantial weight loss and sleep disturbance (13). Conditions resulting from the effects of the pressure generated by severe coughing include pneumothorax, epistaxis, subconjunctival hemorrhage, subdural hematoma, hernia, rectal prolapse, urinary incontinence, and rib fracture (14). Some infections are complicated by primary or secondary bacterial pneumonia and otitis media. Infrequent neurologic complications include seizures and hypoxic encephalopathy.

Adolescents and adults with unrecognized or untreated pertussis contribute to the

reservoir of
B. pertussis in the community. Patients with pertussis are most infectious during the catarrhal stage and during the first 3 weeks after cough onset. Pertussis
is highly infectious; the secondary attack rate exceeds 80% among susceptible persons (15,16). Unvaccinated or incompletely vaccinated infants aged <12 months have the highest risk for severe and life-threatening complications and death
(5,8,17--25).

Differential Diagnosis

The differential diagnoses of pertussis include infections caused by other etiologic agents, including adenoviruses,
respiratory syncytial virus, Mycoplasma
pneumoniae, Chlamydia pneumoniae, and other
Bordetella species such as B.
parapertussis, and rarely B. bronchoseptica
(26) or B. holmseii (27). Despite increasing awareness and recognition of pertussis as a disease that
affects adolescents and adults, pertussis is overlooked in the differential diagnosis of cough illness in this population
(28).

Prevention

Vaccination of susceptible persons is the most important preventive strategy against pertussis. Universal childhood
pertussis vaccine recommendations have been implemented since the mid-1940s. For

protection against pertussis during childhood,
the Advisory Committee on Immunization Practices (ACIP) recommends 5 doses of diphtheria and tetanus toxoid and
acellular pertussis (DTaP) vaccine at ages 2, 4, 6, 15--18 months, and 4--6 years
(29). Childhood vaccination coverage for
pertussis vaccines has been at an all-time high
(4). However, neither vaccination nor natural disease confers complete or
lifelong protective immunity against pertussis or reinfection. Immunity wanes after 5--10 years from the last pertussis vaccine
dose (3,8,30--34). Older children, adolescents, and adults can become susceptible to pertussis after a complete course
of vaccination during childhood.

During spring of 2005, two Tetanus Toxoid and Reduced Diphtheria Toxoid and Acellular Pertussis vaccines
adsorbed (Tdap) formulated for adolescents and adults were licensed in the United States
(BOOSTRIX®, GlaxoSmithKline
Biologicals, Rixensart, Belgium and ADACEL, Sanofi Pasteur, Toronto, Ontario, Canada). ACIP voted to recommend a single dose
of Tdap for adolescents aged 11--18 years in June 2005 and adults aged 19--64 years in October 2005.

Treatment of Pertussis

Maintaining high vaccination coverage rates among preschool children, adolescents, and adults and minimizing exposures
of infants and persons at high risk for pertussis is the most effective way to prevent

pertussis. Antibiotic treatment of

pertussis and judicious use of antimicrobial agents for postexposure prophylaxis will eradicate

B. pertussis from the nasopharynx of

infected persons (symptomatic or asymptomatic). A macrolide administered early in the course of illness can reduce

the duration and severity of symptoms and lessen the period of communicability

(35). Approximately 80%--90% of patients

with untreated pertussis will spontaneously clear

B. pertussis from the nasopharynx within 3--4 weeks from onset of cough

(36); however, untreated and unvaccinated infants can remain culture-positive for >6 weeks

(37). Close asymptomatic contacts

(38) (Box 3) can be administered postexposure chemoprophylaxis to prevent secondary cases; symptomatic contacts should

be treated as cases.

Erythromycin, a macrolide antibiotic, has been the antimicrobial of choice for treatment or postexposure prophylaxis

of pertussis. It is usually administered in 4 divided daily doses for 14 days. Although effective for treatment (Table 1)

and postexposure prophylaxis (Table 2), erythromycin is accompanied by uncomfortable to distressing side effects that result

in poor adherence to the treatment regimen. During the last decade, in vitro studies have demonstrated the effectiveness

against B. pertussis of two other macrolide agents (azithromycin and clarithromycin)

(57--64). Results from in vitro studies

are not always replicated in clinical studies and practice. A literature search and review was conducted for in vivo studies and clinical trials that were conducted during 1970--2004 and used clarithromycin or azithromycin for the treatment and prophylaxis of pertussis (Table 3). On the basis of this review, guidelines were developed to broaden the spectrum of macrolide agents available for pertussis treatment and postexposure prophylaxis and are presented in this report to update previous CDC recommendations (71). Treatment and postexposure prophylaxis recommendations are made on the basis of existing scientific evidence and theoretical rationale.

Recommendations

I. General Principles

A. Treatment. The macrolide agents erythromycin, clarithromycin, and azithromycin are preferred for the treatment of pertussis in persons aged >1 month. For infants aged <1 month, azithromycin is preferred; erythromycin and clarithromycin are not recommended. For treatment of persons aged >2 months, an alternative agent to macrolides is trimethoprim-sulfamethoxazole (TMP--SMZ) (Table 4).

The choice of antimicrobial for treatment or prophylaxis should take into account effectiveness, safety (including the potential for adverse events and drug interactions), tolerability, ease of adherence

to the regimen prescribed, and

cost. Azithromycin and clarithromycin are as effective as erythromycin for treatment of pertussis in persons aged

>6 months, are better tolerated, and are associated with fewer and milder side effects than erythromycin. Erythromycin and

clarithromycin, but not azithromycin, are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with

other drugs that are metabolized by this system. Azithromycin and clarithromycin are more resistant to gastric acid, achieve

higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (1--2 doses per

day) and shorter treatment regimens (5--7 days). Erythromycin is available as generic preparations and is considerably less

expensive than azithromycin and clarithromycin.

B. Postexposure prophylaxis. A macrolide can be administered as prophylaxis for close contacts of a person with

pertussis if the person has no contraindication to its use. The decision to administer postexposure chemoprophylaxis is made

after considering the infectiousness of the patient and the intensity of the exposure, the potential consequences of severe pertussis

in the contact, and possibilities for secondary exposure of persons at high risk from the contact (e.g., infants aged <12

months). For postexposure prophylaxis, the benefits of administering an antimicrobial agent to reduce the risk for pertussis and

its complications should be weighed against the potential adverse effects of the drug. Administration of postexposure

prophylaxis to asymptomatic household contacts within 21 days of onset of cough in

the index patient can prevent symptomatic infection. Coughing (symptomatic) household members of a pertussis patient should be treated as if they have pertussis. Because severe and sometimes fatal pertussis-related complications occur in infants aged <12 months, especially among infants aged <4 months, postexposure prophylaxis should be administered in exposure settings that include infants aged <12 months or women in the third trimester of pregnancy. The recommended antimicrobial agents and dosing regimens for postexposure prophylaxis are the same as those for treatment of pertussis (Table 4).

C. Special considerations for infants aged <6 months when using macrolides for treatment or postexposure prophylaxis. The U.S. Food and Drug Administration (FDA) has not licensed any macrolide for use in infants aged <6 months. Data on the safety and efficacy of azithromycin and clarithromycin use among infants aged <6 months are limited.

Data from subsets of infants aged 1--5 months (enrolled in small clinical studies) suggest similar microbiologic effectiveness of azithromycin and clarithromycin against pertussis as with older infants and children. If not treated, infants with pertussis remain culture-positive for longer periods than older children and adults (36,72). These limited data support the use of azithromycin and clarithromycin as first-line agents among infants aged 1--5 months, based on their in vitro effectiveness against B. pertussis, their demonstrated safety and effectiveness in older children and adults, and more convenient

dosing schedule.

For treatment of pertussis among infants aged <1 month (neonates), no data are available on the effectiveness of azithromycin and clarithromycin. Abstracts and published case series describing use of azithromycin among infants aged <1 month report fewer adverse events compared with erythromycin (73); to date, use of azithromycin in infants aged <1 month has not been associated with infantile hypertrophic pyloric stenosis (IHPS). Therefore, for pertussis, azithromycin is the preferred macrolide for postexposure prophylaxis and treatment of infants aged <1 month. In this age group, the risk for acquiring severe pertussis and its life-threatening complications outweigh the potential risk for IHPS that has been associated with erythromycin (74). Infants aged <1 month who receive a macrolide should be monitored for IHPS and other serious adverse events.

D. Safety. A comprehensive description of the safety of the recommended antimicrobials is available in the package insert, or in the latest edition of the Red Book: Pharmacy's Fundamental Reference. A macrolide is contraindicated if there is history of hypersensitivity to any macrolide agent (Table 5). Neither erythromycin nor clarithromycin should be administered concomitantly with astemizole, cisapride, pimazole, or terfenadine. The most commonly reported side effects of oral macrolides are gastrointestinal (e.g., nausea, vomiting, abdominal pain and cramps, diarrhea, and anorexia) and rashes; side effects are more frequent and severe with erythromycin use.

II. Specific Antimicrobial Agents

1. Azithromycin. Azithromycin is available in the United States for oral administration as azithromycin dihydrate (suspension, tablets, and capsules). It is administered as a single daily dose.

Recommended regimen:

2. Erythromycin. Erythromycin is available in the United States for oral administration as erythromycin base (tablets and capsules), erythromycin stearate (tablets), and erythromycin ethylsuccinate (tablets, powders, and liquids).

Because relapses have been reported after completion of 7--10 days of treatment with erythromycin, a 14-day course of erythromycin is recommended for treatment of patients with pertussis or for postexposure prophylaxis of close contacts of pertussis patients (76).

Recommended regimen:

Gastrointestinal irritation, including epigastric distress, abdominal cramps, nausea, vomiting, and diarrhea, are the most common adverse effects associated with oral administration of erythromycin. Symptoms are dose-related. Some formulations with enteric-coated tablets and the ester derivatives (e.g., ethylsuccinate) can be taken with food to minimize these side effects. Hypersensitivity reactions (e.g., skin rashes, drug fever, or eosinophilia), cholestatic hepatitis, and sensorineural hearing loss have occurred after administration of macrolides; severe reactions such as anaphylaxis are rare.

An increased risk for IHPS has been reported in neonates during the month after erythromycin administration. In one case, pyloric stenosis occurred in a breastfeeding infant whose mother took erythromycin. 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 after exposure to a pertussis patient. In a cohort study, erythromycin prophylaxis was causally associated with IHPS (seven cases out of 157 erythromycin exposed infants versus zero cases out of 125 infants with no erythromycin exposure (relative risk: infinity [95% confidence interval = 1.7--infinity]).

The high case-fatality ratio of pertussis in neonates underscores the importance of preventing pertussis among exposed infants. Health-care providers who prescribe erythromycin rather than azithromycin to newborns should inform parents about the possible risks for IHPS and counsel them about signs of IHPS.

Erythromycin is contraindicated if there is history of hypersensitivity to any macrolide agent. Erythromycin should not be administered concomitantly with astemizole, cisapride, pimazole, or terfenadine. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QTc interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have been observed after concomitant use of erythromycin with these drugs.

Erythromycin is an inhibitor of the cytochrome P450 enzyme system (CYP3A subclass). Coadministration of erythromycin and a drug that is primarily metabolized by CYP3A can result in elevations in drug concentrations that could increase

or prolong both the therapeutic and adverse effects of the concomitant drug. Drugs that are metabolized by CYP3A
include alfentanil, bromocriptine, cyclosporine, carbamazepine, cilostazol, disopyramide, dihydroergotamine, ergotamine,
lovastatin and simvastatin, methylprednisolone, quinidine, rifabutin, vinblastine, tacrolimus, triazolo-benzodiazepines (e.g.,
triazolam and alprazolam) and related benzodiazepines, and sildenafil. In addition, reports exists of drug interactions of
erythromycin with drugs not thought to be metabolized by CYP3A, including zidovudine, hexobarbital, phenytoin, and
valproate, theophylline, digoxin, and oral anticoagulants.

Erythromycin is classified as an FDA Pregnancy Category B drug
(76). Animal reproduction studies have failed
to demonstrate a risk to the fetus, but no adequate or well-controlled studies in humans exist.

3. Clarithromycin. Clarithromycin is available in the United States for oral administration as granules for oral
suspension and tablets. Recommended regimen:

The most common adverse effects associated with clarithromycin include epigastric distress, abdominal cramps,
nausea, vomiting, and diarrhea. Hypersensitivity reactions (e.g., skin rashes, drug fever, or eosinophilia), hepatotoxicity, and
severe reactions such as anaphylaxis are rare. Because of its similarity to erythromycin, both chemically and
metabolically, clarithromycin should not be administered to infants aged <1 month because it is unknown if the drug can be
similarly associated with IHPS. The drug is contraindicated if there is history of

hypersensitivity to any macrolide agent. Similar to erythromycin, clarithromycin should not be administered concomitantly with astemizole, cisapride, pimazole, or terfenadine. Clarithromycin inhibits the cytochrome P450 enzyme system (CYP3A subclass), and coadministration of clarithromycin and a drug that is primarily metabolized by CYP3A can result in elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Clarithromycin can be administered without dosage adjustment in patients with impaired hepatic function and normal renal function; however, drug dosage and interval between doses should be reassessed in the presence of impaired renal function. Clarithromycin is classified by FDA as a Pregnancy Category C drug (76). Animal reproduction studies have shown an adverse effect on the fetus; no adequate or well-controlled studies in humans exist.

4. Alternate agent (TMP--SMZ). Data from clinical studies indicate that TMP--SMZ is effective in eradicating B. pertussis from the nasopharynx (64,77,78). TMP--SMZ is used as an alternative to a macrolide antibiotic in patients aged >2 months who have contraindication to or cannot tolerate macrolide agents, or who are infected with a macrolide-resistant strain of B. pertussis. Macrolide-resistant B. pertussis is rare. Because of the potential risk for kernicterus among infants, TMP--SMZ should not be administered to pregnant women, nursing mothers, or infants aged <2 months.

Recommended regimen (79):

Patients receiving TMP-SMZ might experience gastrointestinal adverse effects, hypersensitivity skin reactions, and rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis, blood dyscrasias, and hepatic necrosis. TMP--SMZ is contraindicated if there is known hypersensitivity to trimethoprim or sulfonamides. TMP--SMZ should be prescribed with caution to patients with impaired hepatic and renal functions, folate deficiency, blood dyscrasias, and in older adults because of the higher incidence of severe adverse events. Patients taking TMP--SMZ should be instructed to maintain an adequate fluid intake to prevent crystalluria and renal stones. Drug interactions must be considered when TMP--SMZ is used concomitantly with drugs, including methotrexate, oral anticoagulants, antidiabetic agents, thiazide diuretics, anticonvulsants, and other antiretroviral drugs. TMP--SMZ is classified by FDA as a Pregnancy Category C drug (76). Animal reproduction studies have indicated an adverse effect on the fetus; no adequate or well-controlled studies in humans exist.

5. Other antimicrobial agents. Although in vitro activity against B. pertussis has been demonstrated for other macrolides such as roxithromycin and ketolides (e.g., telithromycin) (60), no published data exist on the clinical effectiveness of these agents.

Other antimicrobial agents such as ampicillin, amoxicillin, tetracycline, chloramphenicol, fluoroquinolones (e.g., ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin), and cephalosporins exhibit

various levels of in vitro inhibitory activity against B. pertussis, but in vitro inhibitory activity does not predict clinical effectiveness. The clinical effectiveness of these agents for treatment of pertussis has not been demonstrated. For example, both ampicillin and amoxicillin were ineffective in clearing B. pertussis from nasopharynx (80). Poor penetration into respiratory secretions was proposed as a possible mechanism for failure to clear B. pertussis from the nasopharynx (81). The minimum inhibitory concentration of B. pertussis to the cephalosporins is unacceptably high (82). In addition, tetracyclines, chloramphenicol, and fluoroquinolones have potentially harmful side effects in children. Therefore, none of the above antimicrobial agents are recommended for treatment or postexposure prophylaxis of pertussis.

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References

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