Pertussis: A cause of cough in adults as well as children

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Since pertussis has been considered to be primarily a pediatric disease, it is often overlooked as a cause of cough in adults. However, the incidence has been increasing in adolescents and adults, and these persons are the major reservoir for the disease. The first stage of illness is characterized by flu-like symptoms; then patients typically have paroxysms of severe coughing—several short dry coughs, followed by a deep inspiratory effort and the characteristic "whoop." The most common complication of pertussis is pneumonia, but other complications include bronchitis, laryngitis, atelectasis, pneumothorax, subconjunctival hemorrhage, subdural hematoma, and seizures. The diagnosis can be confirmed by isolation of *Bordetella pertussis* in culture; rapid diagnostic tests, such as the direct fluorescent antibody method and polymerase chain reaction; and serological tests to detect antibodies to *B* pertussis. First-line therapy for pertussis includes a macrolide antibiotic. (*J Respir Dis.* 2008;29(4):172-178)

**ABSTRACT:** Since pertussis has been considered to be primarily a pediatric disease, it is often overlooked as a cause of cough in adults. However, the incidence has been increasing in adolescents and adults, and these persons are the major reservoir for the disease. The first stage of illness is characterized by flu-like symptoms; then patients typically have paroxysms of severe coughing—several short dry coughs, followed by a deep inspiratory effort and the characteristic "whoop." The most common complication of pertussis is pneumonia, but other complications include bronchitis, laryngitis, atelectasis, pneumothorax, subconjunctival hemorrhage, subdural hematoma, and seizures. The diagnosis can be confirmed by isolation of *Bordetella pertussis* in culture; rapid diagnostic tests, such as the direct fluorescent antibody method and polymerase chain reaction; and serological tests to detect antibodies to *B* pertussis. First-line therapy for pertussis includes a macrolide antibiotic. (*J Respir Dis.* 2008;29(4):172-178)

Pertussis is a serious respiratory infection that was first described in the 1500s. The original description of the clinical syndrome of pertussis is credited to Guillaume de Baillou during an epidemic in Paris in 1578.¹ Thomas Sydenham first used the term "pertussis," meaning intense cough, in 1670.² The bacterium that causes pertussis was first identified and cultured at the Pasteur Institute by Jules Bordet and Octave Gengou in 1906.³ Originally named *Haemophilus pertussis*, it was renamed *Bordetella pertussis* in honor of Bordet.

In this article, I will review the epidemiology, clinical presentation, diagnosis, and treatment of pertussis.

**Epidemiology**

In the 1930s and 1940s, the annual incidence of pertussis in the United States was approximately 150 per 100,000 population, and the case fatality rate was 4%.⁴ After the development of a whole-cell vaccine and the introduction of infant immunization programs in 1950, the incidence of pertussis and the mortality associated with it decreased to 1 case and less than 0.01 deaths per 100,000, respectively, by the mid-1970s.⁵ Immunization with an acellular pertussis vaccine was started in 1981.⁴ However, lax implementation of policy resulted in epidemic pertussis in many states in 1989 to 1990, 1993, 1996, and 2003. More than 7500 cases were reported to the CDC in 1996, and 11,647 cases were reported in 2003; this was the highest incidence since 1967.²,⁶ There is good evidence that pertussis is underdiagnosed and underreported.² The number of cases per year in the United States has been reported to be as low as 1200 to 4000⁷ and as high as 6000 to 8000.² In developing countries, pertussis is a major cause of morbidity and mortality, and annual rates may reach 200 to 500 per 100,000 persons, with 350,000 deaths among children younger than 5 years.⁸,⁹ An outbreak of pertussis was reported in Afghanistan in 2003.¹⁰

Previously, pertussis was considered to be primarily a disease of infants and young children. In 1992, about 50% of reported cases in the United States occurred in children younger than 1 year, and 75% occurred in children younger than 5 years.⁵ Now, about 67% of cases occur in adolescents and
adults; in these persons, pertussis is not usually recognized as the cause of their cough. These adolescents and adults currently are the major reservoir for the disease and are the usual sources for "index cases" in infants and children.²

Pathophysiology

Pertussis is characterized by a pattern of endemic activity with cyclic periodic epidemics that occur on average every 3 years and last 12 to 18 months. Infection is most common during the late spring and summer.⁵ Pertussis is a highly communicable disease, with attack rates up to 90% in exposed susceptible persons, such as those who have not received a full series of pertussis vaccinations and those whose vaccine-induced immunity has waned.

The organism is acquired by person-to-person contact and enters through the respiratory tract. The incubation period ranges from 5 to 21 days, with an average of 7 days. In the absence of treatment, the infectivity period extends from 7 days after exposure until 3 weeks after the onset of paroxysms of coughing.

B pertussis, the major cause of the pertussis syndrome, is a Gram-negative, pleomorphic, nonmotile coccobacillus. It produces a number of virulence factors. Filamentous hemagglutin (FHA) helps the organism attach to respiratory ciliated epithelial cells. Pertussis toxin (PT) also helps the organism attach to these cells, promotes leukocytosis and lymphocytosis, enhances the immune response, increases host susceptibility to histamine and serotonin, increases insulin activity, and causes a -adrenergic blockade–like effect. Other virulence factors include dermonecrotic toxin, pertactin (pn), tracheal cytotoxin (which causes ciliary stasis), adenylate cyclase (which interferes with phagocytic function), and agglutinogens (especially fimbiae [FM] types 2 and 3). These antigens also are important in the formulations of the different vaccines and their related effects.⁴,¹¹-¹³ Pathologically, the entire respiratory tract is congested, edematous, and infiltrated with cells.⁴ Necrosis of the bronchial epithelium is present along with clumps of organisms in the cilia of the bronchial and tracheal epithelium.¹⁴ The presence of pneumonia is indicated by infiltration of the bronchial walls by polymorphonuclear leukocytes and by the peribronchial collar of mononuclear cells. The alveolar walls are thickened and infiltrated by mononuclear cells. Viscous mucus may fill the bronchi and bronchioles. Atelectasis and bleb formation commonly occur. Edema and hemorrhage may be present in the lung parenchyma.⁴

Clinical manifestations

Clinically, pertussis is divided into 3 stages: catarrhal, paroxysmal, and convalescent. The catarrhal stage lasts for 1 to 2 weeks. Symptoms include congestion and rhinorrhea, low-grade fever, sneezing, lacrimation, conjunctival injection, malaise, anorexia, and slight cough (Table).

The paroxysmal stage lasts 1 to 4 weeks and consists of paroxysms of severe coughing—5 or more short dry coughs without an inspiration, followed by a deep inspiratory effort resulting in the characteristic "whoop." Paroxysms of coughing and a whoop may not be noted in infants younger
than 3 to 6 months; these infants may have apneic spells instead. The cough paroxysms result in the production of large amounts of mucus and may be associated with cyanosis, choking, and exhaustion. Post-tussive emesis is common.

The paroxysmal episodes may be triggered by various stimuli, such as feeding, sucking, crying, light, and stretching. Adolescents and adults describe a sudden feeling of strangulation followed by uninterrupted coughs, a feeling of suffocation, a bursting headache, diminished awareness, and then a gasping breath—usually without a whoop. The convalescent stage usually starts 4 to 6 weeks after the onset of disease and is characterized by a gradual decrease in the frequency and severity of the paroxysmal episodes. A nonparoxysmal cough may persist for several months. The duration of the illness in uncomplicated cases is 6 to 20 weeks.2,4,11

The severity of pertussis and the incidence of complications vary inversely with age. The most frequent and troublesome complication is the development of pneumonia, which occurs in 0.8% to 2% of cases and is caused by either *B. pertussis* or another respiratory pathogen. Other respiratory complications include otitis media, bronchitis, laryngitis, atelectasis, asphyxia, bronchiectasis, pneumothorax, interstitial and subcutaneous emphysema, pulmonary hypertension, rupture of the diaphragm, development of a unilateral hyperlucent lung (Swyer-James-MacLeod syndrome), and activation of latent tuberculosis.15-17

Nonrespiratory complications may be caused by the pressure effects of severe cough. Complications include subconjunctival hemorrhage, rectal prolapse, herniation, epistaxis, rib fracture, umbilical hernia, hemolytic uremic syndrome, syndrome of inappropriate antidiuretic hormone secretion, and ulceration of the frenulum of the tongue.4,11,15,18 CNS complications occur in up to 14% of cases.19 These include seizures, encephalitis, squint, deafness, cerebral edema, subdural hematoma, and spinal epidural hematoma.

The case fatality rate is 1.3% in infants younger than 1 month, 0.3% to 0.6% in infants aged 2 to 11 months, 0.3% in children aged 1 to 4 years, and less than 0.1% in children aged 5 years and older.5,20,21 Pertussis is an occasional cause of sudden infant death.2

**Diagnosis**

Pertussis should be suspected in any patient who has pure or predominant complaint of cough, especially if the following are absent: fever, malaise or myalgia, exanthema or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales. Apnea or cyanosis (before onset of cough) is a clue in infants younger than 3 months.

Leukocytosis (white blood cell count of 15,000/μL to 100,000/μL) associated with absolute lymphocytosis is characteristic in the catarrhal stage. This is caused by the effect of PT, which appears to reduce L-selectin expression by the T cells and thus prevents their homing to the lymphoid tissues.22 Extreme leukocytosis and thrombocytosis are associated with a severe course and increased risk of death.2

There are no characteristic radiographic features of pertussis. The most frequent abnormalities are atelectasis, perihilar infiltrates or edema, hilar lymphadenopathy, and consolidation.2,4 Isolation of *B. pertussis* in culture is the only way to diagnose pertussis with absolute certainty. The nasopharynx is the optimal site for specimen collection. The specimen is obtained by aspiration of mucus or by use of a flexible swab (made of Dacron) held in the posterior nasopharynx for 15 to 30 seconds (or until coughing).2,4 During the catarrhal stage, 95% to 100% of cultures are positive. During the paroxysmal stage, there is a rapid decline in positive culture findings from 94% in the third week of illness to 44% in the fourth week and less than 20% thereafter.4 Given the problems of culturing *B. pertussis*, various rapid diagnostic methods that do not involve culture have been developed. The direct fluorescent antibody test detects the presence of *B. pertussis* organisms, whether viable or not, in respiratory secretions. It has variable sensitivity and low specificity, and it requires experienced personnel for interpretation.2,4 Polymerase chain reaction assays to detect specific portions of the *B. pertussis* genome in nasopharyngeal secretions are rapid and specific with a sensitivity similar to that of culture, especially if performed during the first weeks of the disease.2,23-27

Serological tests to detect antibodies to *B. pertussis* also can be used for diagnosis. The most sensitive method is demonstration of an acute to convalescent rise in levels of antibodies to the whole *B. pertussis* organism (agglutinins) or to specific *B. pertussis* antigens (including FHA and PT).4
The sensitivity of an enzyme-linked immunosorbent assay to detect a convalescent rise in levels of IgA and IgG antibodies to FHA, PT, or both is 88%, compared with 45% for neutralizing antibodies to PT and 33% for IgM antibodies. However, the need to wait 4 to 6 weeks to obtain convalescent specimens limits the clinical utility of serological diagnosis.\(^4,28,29\)

**Treatment**

The goals of therapy are to limit, if possible, the number of paroxysms; to observe the severity of the cough and provide assistance when necessary; and to maximize nutrition, rest, and recovery without sequelae. Infants younger than 6 months very frequently require hospital admission. Patients of any age should be hospitalized if significant complications occur. Prematurely born infants and young children with underlying cardiac, pulmonary, muscular, or neurological disorders are at high risk for severe disease. The specific, limited goals of hospitalization are to assess progression of disease and likelihood of life-threatening events, prevent or treat complications, and educate the patient's parents in the natural history of the disease and in care that will be given at home.\(^2\)

Erythromycin estolate (40 to 50 mg/kg/d PO in 4 divided doses for 14 days; maximum 2 g/d) remains the treatment of choice for pertussis. It does not affect the course of the illness in the paroxysmal stage, but it does diminish infectivity. Erythromycin treatment during the catarrhal stage may ameliorate the clinical disease. It leads to eradication of the organism in 3 to 4 days.\(^2,11\)

Clarithromycin and azithromycin appear to be acceptable alternative therapies that have effects comparable to those of erythromycin. The dosage of clarithromycin used in one pediatric study was 15 mg/kg/d in 2 divided doses for 7 days.\(^30\) The patients in that study who received clarithromycin had fewer adverse events (45%) than those who received erythromycin (62%). In another pediatric study, the dosage of azithromycin was 10 mg/kg in a single dose on the first day and 5 mg/kg/d as a single dose on days 2 through 5.\(^31\)

Trimethoprim/sulfamethoxazole is also an alternative for patients who cannot tolerate erythromycin. The recommended dosage of trimethoprim for children is 8 mg/kg/d, and the recommended dosage of sulfamethoxazole is 40 mg/kg/d in 2 divided doses.\(^32\)

A 7- to 10-fold relative risk of infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants younger than 6 weeks who are treated with oral erythromycin. The highest risk appears to be in the first 2 weeks of life in full-term infants and with courses longer than 14 days.\(^2,32\) Because pertussis can be life-threatening in neonates and alternative therapies are not well studied, the American Academy of Pediatrics continues to recommend use of erythromycin for prophylaxis and treatment of disease caused by *B pertussis*.\(^32\) Physicians who prescribe erythromycin for newborns should inform the parents about potential risks and signs of IHPS.

Several other therapies, such as diphenhydramine, pertussis immunoglobulin, dexamethasone, and albuterol, have been used in an attempt to reduce the paroxysmal cough or decrease the duration of hospital stay. One review revealed no statistical benefit for any of these interventions. Diphenhydramine and albuterol did not change cough paroxysms, and pertussis immunoglobulin and dexamethasone did not decrease the length of hospital stay.\(^33\)

General supportive medical care is very important for hospitalized infants with pertussis. A quiet environment and gentle suctioning of respiratory secretions may help prevent paroxysmal coughing. Oxygen should be provided if hypoxemia is present. Adequate hydration and nutrition should be provided. When an intercurrent bacterial infection is suspected, an antibiotic selected in accordance with the clinician's best judgment may be administered until the causal pathogen has been determined.\(^2,4,11\)

Respiratory isolation should be instituted and continued until the patient has received a macrolide for 5 days or, in the absence of antibiotic therapy, until at least 3 weeks after the onset of paroxysms.\(^20\) Children with pertussis should not attend child-care facilities or school until they have received a macrolide for 5 days.

Contacts in whom immunization has been delayed should be immunized, as should children younger than 7 years whose last vaccination was given at least 6 months before the exposure.\(^11\) Antibacterial prophylaxis with erythromycin estolate (40 to 50 mg/kg/d PO in 4 divided doses for 14 days), clarithromycin, or azithromycin is recommended for close contacts of patients with pertussis.\(^4\)

**Immunization**
Universal immunization with pertussis vaccine for children younger than 7 years is recommended. Multiple diphtheria and tetanus toxoids combined with acellular pertussis (DTaP) vaccines are preferred over vaccines containing whole-cell pertussis (DTP vaccines) because they cause fewer adverse reactions (DTP is no longer used in the United States and Europe). All acellular pertussis vaccines contain inactivated PT and may contain 1 or more other bacterial components (FHA, pn, FM types 2 and 3). PT is detoxified either chemically or using molecular genetic techniques. In the United States, DTaP vaccine is recommended in a 5-dose schedule at 2, 4, 6, 15 to 18 months, and 4 to 6 years of age. The same vaccine dosage and schedule is recommended for preterm infants. Premature infants are able to mount a satisfactory immune response after the second dose of the vaccine, and the incidence of adverse effects is low.

Immunization should not be delayed beyond 8 weeks of age, and the regular immunization schedule based on chronological age should be followed. Preterm infants should receive full doses of vaccine rather than half doses. Immunization with half doses of vaccine results in poor immunological response without significant reduction in adverse effects. A single dose of an adolescent preparation of tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine is recommended at 11 to 12 years of age for those who have completed the DTaP series and have not received a tetanus-diphtheria (Td) booster dose. Adolescents 13 to 18 years of age who missed the 11- to 12-year-oldTd or Tdap booster dose or in whom it has been 5 years or more since the Td booster dose should receive a single dose of Tdap if they have completed the DTaP series. The most common reactions to DTaP vaccine include redness, edema, induration, and tenderness at the injection site; drowsiness; fretfulness; anorexia; vomiting; crying; and fever. These local and systemic manifestations occur within several hours of immunization and subside spontaneously without sequelae. The frequency of these reactions has been estimated to range from 1% to 4% after the fifth dose of DTaP.

Overall, systemic and local reactions, such as fever, are significantly less common with DTaP than with DTP. A temperature of up to 40.5°C (104.9°F) and persistent or inconsolable crying for 3 or more hours, all occurring within 48 hours after immunization, are considered precautions not contraindications for subsequent immunization against pertussis. The incidence of allergic reactions after immunization with DTaP is unknown. An immediate anaphylactic reaction occurring after immunization with DTaP is a contraindication to further immunizations with this vaccine.

The incidence of febrile seizures after immunization with DTaP has declined significantly (79%) compared with the incidence after immunization with DTP. Most of these seizures are brief, self-limited, and generalized. They usually occur in febrile children after the third or fourth dose of the vaccine series. These seizures have not been demonstrated to result in epilepsy or other neurological sequelae.

The incidence of hypotonic-hyporesponsive episodes after immunization with DTaP has declined significantly (60%) compared with incidence after immunization with DTP. Children who experience these episodes also have demonstrated no subsequent serious neurological damage or intellectual impairment. Seizures with or without fever or hypotonic-hyporesponsive episodes occurring within 48 hours of pertussis immunization are considered precautions but not contraindications for subsequent pertussis immunization. Encephalopathy (a severe, acute CNS disorder unexplained by another cause) may be manifested by major alterations of consciousness or by generalized or focal seizures that persist for more than a few hours without recovery within 24 hours. If this illness occurs within 7 days of pertussis immunization, further doses of pertussis vaccine are contraindicated. DTaP should be substituted for each of the recommended subsequent doses of diphtheria and tetanus toxoid. No causal relationship has been shown between pertussis vaccine and autism, infantile spasms, Reye syndrome, or sudden infant death syndrome (SIDS). Children with a family history of seizures or SIDS and children who are immunocompromised should receive pertussis vaccine on the regular schedule. Whether to immunize children with neurological disorders and when to immunize such children are difficult to determine. In general, children with corrected lesions or seizure disorders that are under control should be immunized according to schedule. The administration of vaccine to children whose neurological condition is evolving or changed should be postponed until their situation becomes clearer. A decision about whether to proceed with pertussis vaccination should be reached by the...
Of some concern is that local reactions after pertussis immunization increase from dose to dose, and whole-limb swelling at the site of injection may occur. Yet, these adverse effects are only temporary, without sequelae, and usually do not interfere with the child's well-being. Furthermore, they are considered to be less severe than those occurring after 5 consecutive doses of DTP. Providing timely and complete immunizations against pertussis for all infants, young children, adolescents, and possibly adults will help to better control pertussis in the future.

References: REFERENCES
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