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Pertussis in Adolescents

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ABSTRACT

Pertussis is a highly communicable respiratory infection caused by *Bordetella pertussis.* In spite of the widespread availability of effective vaccines and high levels of vaccination coverage, a significant resurgence in pertussis has been observed during the past 2 decades. The increase in reported cases is due in large part to infection in adolescents and adults, and waning immunity plays an important role. Pertussis in adolescents and adults often goes unrecognized because a persistent, uncharacteristic cough might be the only clinical presentation. Pneumonia is the most frequent complication. Culture and polymerase chain reaction are helpful in establishing the diagnosis if a specimen can be obtained early in the course of the illness. Serology is useful when the diagnosis is not suspected until a later stage. Treatment with a macrolide antibiotic is recommended for affected individuals, as well as for all household and other close contacts. Universal immunization is necessary for disease control. Immunization should begin in infancy and should continue with booster doses through adulthood. Two adolescent and adult formulations of acellular pertussis vaccine are licensed in North America and Europe. Both are combined with an adult formulation of diphtheria and tetanus toxoids. In the US, Adacel® (Sanofi Pasteur, Toronto, Ontario, Canada) is licensed for use in individuals aged 11 to 64 y while Boostrix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) is licensed for use in individuals aged 10 to 18 y. These vaccines are safe, immunogenic, and well tolerated. Routine vaccination of adolescents and adults is required for optimal control of pertussis.

Keywords: pertussis; adolescent; universal immunization

1103

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INTRODUCTION

Pertussis, or whooping cough, is a highly contagious respiratory infection that is caused by *Bordetella pertussis;* it is a frequent cause of chronic cough in children, adolescents, and adults.[1,2] Pertussis is one of the 10 most common causes of death in childhood. A total of 20 to 40 million cases of pertussis are reported annually in the world, 90% of which occur in developing countries; pertussis results in 200,000 to 400,000 deaths per year, most of which are reported in young infants.[3] In spite of the widespread availability of effective vaccines and high levels of vaccination coverage in developed countries, a significant resurgence in pertussis has been observed during the past 2 decades.[4] There has been a substantial increase in reported cases among adolescents and adults, who then become a potential source of pertussis for other susceptible individuals.[4] Pertussis in adolescents and adults often goes unrecognized because the presentation is atypical and the morbidity is not as severe as in infants. Lack of clinical awareness is such that the true number of cases might far exceed the number reported. Early diagnosis can lead to more effective treatment and control measures. Because vaccine-induced immunity wanes over time, concern has arisen that pertussis might not be controllable through current immunization programs. Universal immunization of adolescents with a booster dose of pertussis vaccine protects adolescents from pertussis and reduces the potential for transmission of the infection to susceptible individuals.

MICROBIOLOGY

B pertussis is a small, nonmotile, fastidious, Gram-negative, pleomorphic coccobacillus that is approximately 0.5 to 1 μm in length. This organism grows aerobically on starch-blood agar or on a completely synthetic medium that includes nicotinamide for growth, amino acids for energy, and charcoal or cyclodextrin resin for absorption of fatty acids and other noxious substances.[5] The organism grows best at 35°C to 36°C in highly humid ambient air.[6] *B pertussis* does not ferment carbohydrates.[7] Toxins that the bacterium produces include pertussis toxin (PT), adenylate cyclase toxin (ACT), tracheal cytotoxin (TCT), dermonecrotic toxin (DNT), and lipopolysaccharide (LPS) endotoxin; adhesions include pertactin (PRN) and filamentous hemagglutinin (FHA); and agglutinogens consist of fimbriae (FIM).[2] Of the *Bordetella* species, only *B pertussis* expresses PT, the major virulence protein.[2,5] *B pertussis* is exclusively a human pathogen.[8]

PATHOGENESIS

B pertussis has a strong affinity for the ciliated epithelium of the respiratory tract.[5,9] Attachment of this organism to ciliated epithelial cells is mediated by PT and LPS, surface adhesions such as PRN and FHA, and agglutinogens such as FIM.[2,5] *B pertussis* does not penetrate submucosal cells or invade the bloodstream. Colonization is followed by proliferation of the organism and production of a variety of toxins such as PT, ACT, TCT, and DNT, with resultant damage to the respiratory epithelium.[2,9] Infection is also facilitated by TCT, which is ciliostatic; PT and ACT, which impair host defenses by interfering with leukocyte function; and PT, which also induces lymphocytosis.[2]

EPIDEMIOLOGY

Pertussis is a worldwide problem that occurs at a significantly higher incidence in countries with low levels of vaccine coverage. In most populations, the disease is endemic and has a regular cyclic (epidemic) peak every 3 to 4 y.[10] Transmission occurs predominantly through aerosol droplets of respiratory secretions or through direct contact with respiratory secretions from the infected person.[11] This disease is most contagious during the catarrhal and early paroxysmal stages of illness.[8]

In the prevaccine era, pertussis was an infection that was primarily diagnosed in infants and young children and was the leading cause of infection-related childhood mortality in the United States. During the 1940s and prior to the introduction of pertussis vaccine, more than 200,000 cases of pertussis were reported annually to the Centers for Disease Control and Prevention (CDC).[12] Widespread use of pertussis vaccine is responsible for a greater than 99% decline in cases; a record low of 1010 cases was reported in 1976. Since that time, there has been a gradual increase in the number of reported cases in spite of high vaccination rates among children.[12] In 2003 and 2004, the numbers of pertussis cases reported to the CDC were 10,670 and 18,957, respectively.[13]

Although the numbers of reported cases have increased in all age groups, the greatest increase has occurred in adolescents.[12] The percentage of cases reported to the CDC among individuals 10 y of age or older has increased from 15.1% during the late 1970s to 26.9% during the early 1990s, and to 40% in the early 2000s.[14,15] In recent years, almost 50% of reported cases occurred in individuals older than 10 y of age; the greatest increase has been noted in individuals 10 to 19 y of age.[7] A similar trend has been noted in other countries.[16] In British Columbia, Canada, 14% and 27% of reported cases of pertussis in 2000 occurred among those 10 to 19 y of age and ≥20 y of age, respectively.[17] Waning immunity plays an important role in infection in these individuals.[18] It is estimated that infection-acquired immunity against pertussis wanes after 4 to 20 y, and that protective immunity after vaccination wanes after 4 to 12 y.[19] Other possible causes of the increased incidence include enhanced clinical awareness, better surveillance and reporting, improved sensitivity and availability of diagnostic tests, variable efficacy of earlier vaccines, and genetic variations in the *B pertussis* organism.[1,4,12,18,20]

CLINICAL MANIFESTATIONS

The incubation period ranges from 5 to 21 d but typically lasts 7 to 10 d.[11] Pertussis evolves through 3 distinct stages. The catarrhal stage lasts approximately 1 to 2 wk, the paroxysmal stage 4 to 6 wk, and the convalescent stage possibly as long as 2 mo.[8] The catarrhal stage is characterized by the insidious onset of rhinorrhea, sneezing, malaise, conjunctival irritation, and mild cough.[21,22] Fever is usually not present.[8,21] The paroxysmal stage is characterized by inexorable paroxysms of cough, which might be followed by an inspiratory gasp that causes the typical whoop. Posttussive vomiting is common and provides a major clue to diagnosis in adolescents and adults.[5] During the convalescent stage, a marked decrease is observed in the intensity of coughing and the frequency of paroxysms. Illness is more severe and prolonged in individuals who are partially immunized or not immunized at all. A persistent, uncharacteristic cough might be the only clinical feature of pertussis in

an adolescent or adult.[6,23] Studies of adolescents and adults who present with prolonged coughing show that 13% to 20% of episodes are the result of infection with *B pertussis*.[6,23] Increased awareness among physicians is important because unrecognized or untreated individuals might transmit the infection to other susceptible individuals, including infants. Pertussis in adolescents might present as a school outbreak.

COMPLICATIONS

The complication most often associated with pertussis is pneumonia, which occurs in approximately 2% of cases.[21] Other complications include sinusitis, otitis media, seizures, and encephalopathy. Subconjunctival hemorrhage, petechiae, and pneumothorax might result from increased intrathoracic pressure generated by severe coughing.[11] Children younger than 6 mo of age are likely to require hospitalization or admission to intensive care, to experience a higher rate of severe complications, and to have the highest mortality rate.[24]

DIFFERENTIAL DIAGNOSIS

Pertussis-like syndrome can be caused by adenovirus, *Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia trachomatis, B parapertussis,* and *B bronchiseptica*.[8,11,12]

LABORATORY EVALUATION

An elevated white blood cell count with marked lymphocytosis is characteristic of infection with *B pertussis*. Lymphocytes are normal small cells of T- and B-cell origin that contrast with the large, atypical lymphocytes seen in cases of viral infection. Lymphocytosis is not a characteristic of *B parapertussis* infection because this organism does not express PT.

A positive culture of secretions obtained from the nasopharynx and plated on a selective medium remains the gold standard for the diagnosis of pertussis. Nasopharyngeal secretions can be collected by swab or aspiration. A calcium alginate– or Dacron-tipped swab is preferred to a cotton- or rayon-tipped swab because the latter contain fatty acids that are toxic to *B pertussis*.[6] The tip of the swab must come into contact with ciliated epithelial cells in the posterior nasopharynx.[6] The advantage of nasopharyngeal aspiration is that a large-volume specimen can be obtained, but this technique is impractical in the outpatient setting. If the specimen cannot be inoculated immediately, the sample can be stored in 1% asamino acid liquid holding medium for up to 2 h.[5] Otherwise, the specimen should be stored in Stainer-Scholte broth with cyclodextrin or Regan-Lowe semisolid transport medium.[5] Stainer-Scholte medium with cyclodextrin resins or Regan-Lowe charcoal agar with 10% horse blood and 5 to 40 µg/mL cephalexin is now preferred to Bordet-Gengou agar as the culture medium of choice.[5] Although the positive predictive value of a culture is 100%, the sensitivity is lower if the specimen is taken later in the illness. False-negative cultures might result from improper collection of the specimen, delay in transportation of the specimen, improper inoculation technique, and recent or concurrent use of an antibiotic. The advantage of a culture is that it allows characterization of antigenic variation and antibiotic sensitivity testing, although antibiotic resistance is rare.[2,21]

Polymerase chain reaction (PCR) is more sensitive than bacterial culture because this technique can detect fewer than 10 organisms and the organisms do not have to be viable.[2,4,21] The specificity of PCR is close to 100%.[2] Similar to culture, the sensitivity of PCR decreases as the duration of symptoms increases.[2,22] Because calcium alginate–tipped swabs can inhibit PCR results, Dacron-tipped swabs should be used for collection of nasopharyngeal samples intended for both culture and PCR.[25]

Serologic testing, which is based on identification of a variety of antibodies to components of *B pertussis*, uses enzyme-linked immunosorbent assay in acute and convalescent samples.[21] Antigens most often targeted are PT, PRN, FHA, FIM, and LPS.[6,23] The antibody to PT is specific for *B pertussis*, and a 4-fold increase in antibody titer is considered diagnostic.[6] Alternatively, a single titer of immunoglobulin G (IgG)-PT of at least 100 U/mL has a specificity of 99% and a sensitivity of 76% for diagnosis of recent or active infection with *B pertussis*.[26]

Culture and PCR are recommended if specimens can be obtained early in the course of the illness. Serology is useful if the diagnosis is not suspected until a later stage, when *B pertussis* might not be detected in the nasopharynx.[2,21] This is especially true for adolescents and adults, in whom the presentation is atypical and the diagnosis is considered late in the infection. Serology is also useful for epidemiologic studies.

TREATMENT

Antimicrobial therapy is provided to eradicate *B pertussis* from the nasopharynx and to limit transmission of the organism to susceptible individuals. Once the infection has been established, antimicrobial therapy has no effect on the duration or severity of the clinical course.[8,27] Traditional treatment for pertussis consists of erythromycin 40 to 50 mg/kg/d orally, to a maximum of 2 g/d, in 4 divided doses for 14 d.[8,22] A meta-analysis of 12 trials that involved 1720 patients suggests that a shorter 7-d course of erythromycin is equally effective.[28] Azithromycin, 10 to 12 mg/kg/d, to a maximum of 1 g/d, in a single dose for 5 d, and clarithromycin, 15 to 20 mg/kg/d, to a maximum of 1 g/d, in 2 divided doses for 7 d, have been shown to be equally effective.[8,29] One large study showed that azithromycin, 10 mg/kg/d, given in a single dose on the first day, followed by 5 mg/kg/d on the second to the fifth day, was as effective as erythromycin estolate, 40 mg/kg/d for 10 d.[30] Both azithromycin and clarithromycin are superior to erythromycin, exhibiting better absorption, enhanced resistance to gastric acid, better tissue penetration, a longer half-life, and fewer adverse effects.[11,27] Trimethoprim-sulfamethoxazole is an alternative for those individuals who cannot tolerate a macrolide, or who are infected with a macrolide-resistant strain of *B pertussis*.[2,11]

PROPHYLAXIS OF CONTACTS

A course of a prophylactic antibiotic is recommended for all household and close contacts exposed within the previous 21 d, regardless of age, immunization status, and symptoms.[21,31] This recommendation includes individuals in child care facilities. Recommended antimicrobial agents and dosing regimens are the same as those for the treatment of pertussis.[11] Erythromycin should be avoided in infants 1 mo of age or younger because of the increased risk for infantile hypertrophic pyloric stenosis

after erythromycin is given to infants in this age group.[32] Close contacts younger than 7 y of age who have received fewer than 4 doses of a pertussis-containing vaccine should be given additional doses to complete the recommended series.[5] Close contacts younger than 7 y of age who received a third dose 6 mo or longer before exposure, or a fourth dose 3 y or longer before exposure, should also be given a booster dose.[5]

PREVENTION

Universal immunization of children, adolescents, and adults with pertussis vaccine is necessary for optimal disease control.[7,12] Immunization should begin during infancy and should continue with booster doses through adulthood. In the United States, acellular pertussis vaccines (aP) combined with diphtheria and tetanus (DTaP) are routinely provided to children at 2, 4, and 6 mo of age; booster doses are administered at 15 to 18 mo and 4 to 6 y of age.[10] In Canada, the DTaP vaccine is administered as a pentavalent combination that consists of DTaP-inactivated poliovirus/*Haemophilus influenzae* type b vaccine at 2, 4, 6, and 18 mo of age, along with a quadrivalent booster of DTaP-inactivated poliovirus at 4 to 6 y of age.[33] Any unimmunized or partially immunized child should receive a "catch-up" vaccination.[10]

Whole cell pertussis (wP) vaccine consists of inactivated *B pertussis* organisms. Most wP vaccines are available in combination with diphtheria and tetanus toxoids (DTwP). Common adverse events include fever, chills, hyperirritability, headache, generalized body ache, nausea, pain, erythema, and swelling at the injection site.[34] Rare adverse events include inconsolable crying, anaphylaxis, and hypotonic-hyporesponsive episodes.[35] wP vaccine is no longer available on the North American or European market.

All aP vaccines contain inactivated PT and, depending on the manufacturer, other *B pertussis* antigens such as FHA, PRN, FIM2, and FIM3.[35,36] aP vaccines that contain 3 or more pertussis antigens are more effective than those with 1 or 2 pertussis antigens.[36,37] aP vaccines are safer and less reactogenic and are associated with fewer adverse events compared with wP vaccines because endotoxin has been removed from these vaccines.[5,36,37] No incremental increase in adverse events has been reported with the addition of aP antigens to diphtheria and tetanus toxoids.[29] Furthermore, it has been shown that antibodies induced by adolescent and adult pertussis vaccine formulations in the form of aP vaccine combined with an adult formulation of diphtheria and tetanus toxoids (Tdap), when administered to adolescents and adults, are higher than those elicited in infants at 7 mo of age after administration of 3 doses of DTaP.[38]

Two adolescent and adult formulations of Tdap are licensed in North America and Europe. Adacel® (Sanofi Pasteur, Toronto, Ontario, Canada) is licensed for use in individuals aged 11 to 64 y. Boostrix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) is licensed for use in individuals aged 10 to 18 y. These vaccines are safe and highly immunogenic. The National Advisory Committee on Immunization recommends that a single booster dose of Tdap should be administered to adolescents and adults instead of the current Td to protect against pertussis.[34] The American Academy of Pediatrics and the Advisory Committee on Immunization Practices (ACIP) of the CDC recommend the routine use of Tdap instead of Td for booster immunization in adolescents between 11 and 18 y of age.[39,40] The preferred age for

Tdap immunization is 11 to 12 y. Adolescents 11 to 18 y of age who have received Td but not Tdap are encouraged to receive a single dose of Tdap.[39,40] The ACIP further recommends replacement of Td boosters with Tdap for individuals 19 to 54 y who have not yet received Tdap, who have frequent exposure to infants, or who wish to decrease the risk of pertussis.[18] Such strategies enhance herd immunity among adolescents and adults. An interval of at least 5 y between Td and Tdap is suggested to reduce the risk of local and systemic reactions after Tdap vaccination.[39,40] An interval shorter than 5 y may be used, however.[39,40]

Lifetime protection against pertussis should be the ultimate goal. Universal immunization is necessary for disease control. Immunization should begin during infancy and should continue with booster doses through adulthood. Current pertussis immunization programs do not provide lifelong protection. Because adolescents and adults are a frequent source of infection, eradication of pertussis is possible only through elimination of these reservoirs. Physician advocacy and increased public funding are necessary to achieve this goal.

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