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PURPOSE AND OBJECTIVES

Pertussis is a preventable disease that is more common in adults than many clinicians realize. Adults are a major reservoir of the disease in the US. Physicians in all specialties, especially those in primary care, have a crucial role to play in the prevention, diagnosis, and treatment of this disease. After reading this article, physicians should be able to understand the epidemiology and clinical presentation of pertussis in adults, to describe the CDC-adopted criteria for both clinical and laboratory confirmed case definitions for pertussis, to recognize the practical restrictions on the use of current laboratory tests for pertussis in adults, and to make informed decisions regarding use of booster immunization of adults with the newer acellular vaccine.

DISCLOSURE

In publishing this article in *Southern Medical Journal,* the Southern Medical Association recognizes educational needs of physicians in all specialties, especially those in primary care, for current information regarding infectious diseases. In this article, authors may have included discussions about drug interventions, whether Food and Drug Administration approved or unapproved. Therefore, it is incumbent on physicians reading this article to be aware of these factors in interpreting the contents and evaluating recommendations. Moreover, views of authors do not necessarily reflect the opinions of the Southern Medical Association. Every effort has been made to encourage the author to disclose any commercial relationships or personal benefit that may be associated with this article. If the author disclosed a relationship, it is indicated below. This disclosure in no way implies that the information presented is biased or of lesser quality.

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CURRENT CONCEPTS

Pertussis Infection in Adults

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ABSTRACT

Background. Pertussis is a potentially serious vaccine-preventable disease. Many clinicians are unaware that pertussis is common in adults, and that adults are a major reservoir of the disease in the United States.

Methods. A MEDLINE search was conducted of all English-language articles pertinent to pertussis infections in adults. Results of relevant articles were compiled into a narrative review.

Results. Studies have shown that sporadic cases of pertussis in adults are common in a variety of clinical settings. Patients typically present with a prolonged cough illness preceded by upper respiratory symptoms. Widespread outbreaks of pertussis occasionally occur in high schools, college campuses, and healthcare settings. The diagnosis and treatment of adults with pertussis are reviewed.

Conclusions. Pertussis infection, because of waning immunity, is common in adults. Routine booster immunization of adults with the newer acellular vaccine may lead to the elimination of the disease in both children and adults.

THE CLINICIAN TREATING an infant with paroxysmal cough, inspiratory whoops, cyanosis, and lymphocytosis will rarely miss the diagnosis of pertussis. However, pertussis is unlikely to be considered in the differential diagnosis when the parent of this infant has a prolonged cough. Pertussis infection in adults is frequently mild or subclinical, and many physicians are unaware that the disease occurs outside the pediatric population. Nevertheless, it is now evident that, because of waning immunity from childhood vaccination, pertussis infection is common in adults.

Physicians need to be familiar with pertussis in adults. Adults are the major reservoir of disease; susceptible infants may acquire pertussis not only from another child, but also from an infected adult. As many as 25% of coughing adult patients seen in primary care clinics have pertussis, though it may be unsuspected. The disease is also costly since patients may be evaluated many times, may have expensive diagnostic tests done, and often are prescribed multiple courses of antibiotics.

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HISTORICAL PERSPECTIVE

Pertussis has afflicted humans for several centuries. In 1578, an epidemic in Paris that clearly was pertussis was described.[1,2] The name of the illness was coined in 1670 by Sydenham when he described a condition called "infantum pertussis."[2] Pertussis was the largest single killer of children in the United States during the early part of this century. In fact, more annual deaths were reported from pertussis than from meningitis, scarlet fever, measles, diphtheria, and poliomyelitis combined.[3] The development of the pertussis vaccine led to a rapid reduction in the number of reported cases of pertussis, though the incidence began to decrease markedly in the United States well before the routine use of the vaccine in the 1950s. The highest reported incidence of pertussis in the United States was in 1934 when 260,000 cases were reported.[4]

The fact that pertussis is not solely a disease of children has been recognized for many years.[5,6] In past years, names such as "grandmother's whooping cough" and "nurse's cough" have been used to describe the disease in adults.[7] In 1921, Philips wrote that ". . . pertussis in adults is often unrecognized, and this is accountable in many cases for the spread of the disease" and "The prevalent idea among the laity, and sometimes among physicians and

TABLE 1. Frequency of Clinical Symptoms in Adult Patients Diagnosed With Pertussis[20,21,32,33]

Symptom	*Percent of Patients*
Paroxysmal cough	70-94
Whoops	8-38
Posttussive emesis	17-42
Awakened by cough	52-88
Sputum production	66-79
History of fever	26-38
Preceding upper respiratory symptoms	44-58
Pharyngitis	31
Sweating attacks	14

nurses, that adults seldom contract whooping cough is responsible for the lack of quarantine."[6]

The importance of waning immunity in adults became clear during a 1962 outbreak of pertussis in Grand Rapids, Michigan.[8] Individuals who were vaccinated more than 12 years before the outbreak had a much higher rate of infection than those with vaccination within 3 years of the outbreak. The waning immunity noted among adults in this study led authorities to believe that post-immune pertussis would become a relatively common occurrence.[9]

MICROBIOLOGY AND PATHOGENESIS

The presence of coccobacilli was noted in 1900 by Bordet in respiratory secretions he obtained from his daughter who was ill with pertussis. Six years later, Bordet and Gengou[10] were the first to culture the causative organism of pertussis, *Bordetella pertussis,* from a sample obtained from Bordet's son. Despite this isolation, there was debate in the scientific community that the pertussis syndrome was caused by a viral agent and not the recently documented organism.[11] Macdonald and Macdonald[12] settled the issue when they inoculated their own children with live *B pertussis* organisms. The children had clinical pertussis, thus confirming that *B pertussis* was the cause of the illness.

Bordetella pertussis is a small, gram-negative pleomorphic bacilli that is fastidious, survives for only a few hours in respiratory secretions, and requires special media for culture. Transmission of pertussis is by airborne spread of respiratory secretions. *Bordetella pertussis* has an affinity for ciliated epithelial respiratory tract cells where it causes local tissue damage. The bacteria are not invasive and do not penetrate submucosal cells or invade the bloodstream. The organism is generally pathogenic only in humans, though other primates can become infected and will have pertussis-like symptoms.

TABLE 2. Complications Reported in Adults With Pertussis

Respiratory tract
- Primary pneumonia
- Secondary bacterial pneumonia
- New onset reactive airway disease
- Hoarseness

Due to increased intra-abdominal/intra-thoracic pressure
- Urinary incontinence
- Lumbar strain
- Rib fracture
- Inguinal hernia
- Pneumothorax
- Pneumomediastinum
- Subconjunctival hemorrhage

Other
- Otitis media
- Encephalopathy
- Seizures
- Weight loss
- Cervical adenopathy
- Hearing loss
- Sleep disturbance
- Syncope

There does not appear to be an asymptomatic carrier state.

There are two species of *Bordetella* in addition to *B pertussis. Bordetella parapertussis* is a pathogen of humans and causes a pertussis-like illness that is typically milder than that caused by *B pertussis. Bordetella parapertussis* is frequently isolated concurrently with *B pertussis* during an epidemic, leading some to think that it is a degraded form of *B pertussis.*[13] *Bordetella bronchiseptica* causes respiratory disease in animals and is not typically a pathogen of humans.

Bordetella pertussis contains a variety of components that are responsible for the clinical effects of pertussis and for the inducement of protective immunity. Pertussis toxin (PT), formerly known as lymphocytosis promoting factor, is a secreted exotoxin and mediates many biologic effects including attachment to ciliated respiratory cells, promotion of lymphocytosis, and enhancement of immune responses. Antibody to pertussis toxin is protective in mice against the clinical effects of a challenge with live *B pertussis.* Filamentous hemagglutinin (FHA), a component of the cell wall of the organism, is also important in the adherence to the respiratory epithelium. Various other biologically active components of *B pertussis* also have a role in the clinical effects of the infection.[14]

EPIDEMIOLOGY OF PERTUSSIS IN ADULTS

The number of annual cases of pertussis has dropped significantly since the introduction of the whole cell vaccine in the 1940s, reaching a

TABLE 3. Differential Diagnosis of Patient With a Persistent Cough

Viral infections
Adenovirus species
Influenza A and B
Respiratory syncytial virus
Rhinovirus
Bacterial infections
Pertussis
Chlamydia pneumoniae
Mycoplasma pneumoniae
Streptococcus pneumoniae
Haemophilus influenzae
Tuberculosis
Noninfectious causes
Cough variant asthma
Foreign body
Postnasal drip
Gastrointestinal reflux
Malignancy

TABLE 4. Case Definition for Pertussis*

Clinical case definition
Cough illness lasting ≥2 weeks with one of the following: Paroxysms of coughing, inspiratory "whoop," or posttussive vomiting, without other apparent cause.
Laboratory criteria for diagnosis
Isolation of *Bordetella pertussis* from clinical specimen, or Positive polymerase chain reaction for *B pertussis*.
Case classification
Probable case: a case that meets the clinical case definition, is not laboratory confirmed, and is not epidemiologically linked to a laboratory-confirmed case.
Confirmed case: a case that is laboratory confirmed or one that meets the clinical case definition and is either laboratory confirmed or epidemiologically linked to a laboratory-confirmed case.
Comments
In outbreak settings, a case may be defined as a cough illness last ing ≥2 weeks without other symptoms. Direct fluorescent antibody testing should not be relied on for laboratory confirmation. Serologic testing is not standardized and is not used for national reporting purposes.

*Modified from criteria developed by the Centers for Disease Control and Prevention and the Council of State and Territorial Epidemiologists.[37] This case definition is not specific for adults.

nadir of only 1,010 reported cases in 1976.[4] However, the number of reported cases has been rising since then with an average of 4,619 reported cases per year during 1990 to 1995.[15] Pertussis outbreaks tend to occur in 3-year to 4-year cycles, with recent peaks in the reported number of cases occurring in 1986, 1990, 1993, and 1996. Interestingly, the number of reported cases has increased during each successive peak year over the past two decades. Only a small percentage of diagnosed cases of pertussis are actually reported to the Centers for Disease Control and Prevention (CDC).[16] Unlike many respiratory diseases, pertussis is common in both summer and winter months.

The number of reported cases of pertussis in individuals over age 15 has also risen dramatically during the past two decades. The proportion of cases of pertussis involving adolescents and adults rose from 15.1% between 1977 and 1979 to 26.9% between 1992 and 1993.[17] This rise in cases in adults appears to be due to a combination of increasing *B pertussis* in the community, waning immunity to childhood vaccination, and increased recognition of the disease in older individuals.

The actual extent of illness in adults is unknown since the disease is usually not diagnosed; however, studies from a variety of clinical settings have shown that infection is surprisingly common in patients with a prolonged cough. Robertson et al[18] diagnosed pertussis in 26% of Australian adults who were referred to a pulmonologist for a cough. A study of UCLA college students showed a similar prevalence of disease among students who had been coughing for a week or longer.[19] Wright et al[20] documented pertussis infection in 21% of adults coming to an emergency department with a complaint of a persistent cough; Nennig et al[21] found pertussis in 12% of Kaiser Permanente HMO patients who had a cough of 2 weeks or longer. Nennig et al[21] also were able to estimate that the annual incidence of pertussis among adults in their population was 176 cases per 100,000 person-years. Looking only at adolescents, Cromer et al[22] have documented an annual incidence of 6.1% of pertussis infection among healthy adolescents who were followed-up for 5 years.

These studies show that sporadic cases of pertussis are common in a variety of clinical settings. However, widespread outbreaks of pertussis among adults are also relatively common in certain populations. Outbreaks in nursing homes and facilities for the developmentally disabled have involved both staff members and residents.[23-25] There have been several well-described outbreaks of pertussis infection in hospital employees, with resultant spread to hospital patients and family members of the employees.[26-28] High school and college campuses are other high-risk settings for outbreaks of pertussis. Close contact in classrooms and dormitories can lead to rapid spread of the organism with a high attack rate. An attack rate of about 25% was documented among high school students during a 1992 outbreak in a Massachusetts community.[29]

Another interesting finding is the frequency of pertussis among household contacts of infants who have been diagnosed with pertussis. Two recent studies have found laboratory confirmed attack rates ranging from 27% to

TABLE 5. Sensitivities, Specificities, and Predictive Values of Case Definitions for Pertussis Infections in Adults*

Case Definition	*Sensitivity*	*Specificity*	*Positive Predictive Value*	*Negative Predictive Value*
Cough (≥14 days)	1.00	.20	56	1.00
Cough (≥28 days)	.90	.60	.69	.86
Cough and whoop (≥14 days)	.80	.90	.89	.82
Cough and whoop (≥28 days)	.70	.90	.88	.75
Cough (≥14 days), whoop and/or vomiting	.90	.80	.82	.89
Cough (≥14 days), whoop and/or vomiting	.80	.90	.89	.82

*Modified from Davis et al.[48]

57% among adult household contacts of patients with pertussis.[30,31] Mild or asymptomatic illness was most common.

CLINICAL PRESENTATION

Adults with pertussis generally have mild illness and few typical pertussis symptoms; however, adults often have the three classic stages noted in infants. The first stage of the illness, the catarrhal phase, lasts for 1 to 2 weeks. This stage, which is clinically indistinguishable from a viral upper respiratory infection, is characterized by the presence of rhinorrhea, congestion, low-grade fever, and a mild cough.

The paroxysmal stage of the illness, lasting 2 to 4 weeks, follows the nonspecific catarrhal stage. Patients have a distressing cough, commonly described as paroxysmal. Only a small percentage of adults have the classic inspiratory whoops seen in pediatric illness.[20,32] Cyanosis is not seen in adults unless there is underlying pulmonary disease. Most patients have purulent or nonpurulent sputum production. Posttussive emesis, fever, and sore throat are sometimes present during this stage. Table 1 describes common signs and symptoms found in adults during the paroxysmal stage.

The convalescent phase consists of a prolonged cough that gradually fades away as the patient recovers. Paroxysms are less common during this stage. The total illness can last as long as 3 months, but the clinical spectrum of disease in adults is variable and most will have mild symptoms.

Table 2 lists complications reported in adults with pertussis. Serious complications in adults are not common, but minor complications are relatively frequent. A recent study of 79 adults with pertussis reported complications, mostly minor, in 23% of the patients.[33] Pneumonia occurs in adults in fewer than 5% of cases. Encephalitis has been reported in adults but is rare.[34] Rib fractures and back pain occasionally result from the forceful coughing episodes. Interestingly, sweating attacks were noted in 14% of adults in a recent study.[32] This finding has not been reported in children. Pertussis has also been reported to cause a prolonged cough illness in patients with the acquired immunodeficiency syndrome.[35]

DIFFERENTIAL DIAGNOSIS

The majority of patients with a prolonged cough probably have a viral illness, though few studies have been done to determine the prevalence of the various organisms. Adenovirus species have been known to cause outbreaks of illness in adults identical to that found with pertussis. Other viruses that should be considered in patients with a persistent cough include influenza A and B, rhinoviruses, and respiratory syncytial virus.

A number of bacterial pathogens also cause a prolonged cough. *Mycoplasma pneumoniae* is usually thought to play a major role in these patients. However, we found *M pneumoniae* in only 1 of 75 emergency department patients with a prolonged cough.[20] A low prevalence of *M pneumoniae* in patients with prolonged cough has been noted by others.[18,19] *Chlamydia pneumoniae* appears to play an important role in patients with a prolonged cough; we have documented that approximately 20% of adults with suspected pertussis actually had serologic evidence of *C pneumoniae* infection.[36]

A variety of noninfectious conditions can mimic the cough caused by pertussis. Cough variant asthma is probably the most important condition to consider in patients with a cough. Table 3 lists the conditions that should be considered in the patient with a persistent cough.

DIAGNOSIS OF PERTUSSIS IN THE ADULT PATIENT

Clinical Criteria

Criteria for both clinical and laboratory confirmed case definitions for pertussis were recently adopted by the CDC in collaboration with the Council of State and Territorial Epidemiologists (Table 4).[37] A prolonged cough, if paroxysms, whoops, or posttussive emesis are present, should make a clinician strongly consider the diagnosis of pertussis. A prolonged cough alone is presumptively considered to be a case of pertussis during a known outbreak.

TABLE 6. Tests for the Diagnosis of Pertussis in Adults

Test	Advantages	Disadvantages
Bordetella pertussis culture	Readily available. No false positives. Criterion standard.	Rarely positive in adults with pertussis. Requires special media.
Direct fluorescent antibody testing	Readily available. Useful in outbreak settings.	Rarely positive in adults with pertussis. Cross reacts with other organisms.
Bordetella pertussis polymerase chain reaction	Easy to perform. Potential for fast results. More accurate than culture in adults.	Not available to most clinicians. Often negativelate in the illness.
Serologic testing	A single initial value may be diagnostic.	Not available to most clinicians. Not standardized. Results difficult to interpret. Need for convalescent titers delays diagnosis.

The presence of a prolonged cough is sensitive (present in those with the disease), but a cough alone is not particularly specific for pertussis. Table 5 describes sensitivities, specificities, and predictive values for a variety of clinical presentations for adults with pertussis.

Clinical criteria might suggest the diagnosis of pertussis in adults. However, an accurate diagnosis cannot be made based on clinical symptoms. A variety of laboratory tests are available to aid in the diagnosis of pertussis; unfortunately, most are of limited value in adults (Table 6).

Bordetella pertussis Culture

Culture for *B pertussis* is the mainstay of diagnosis in children and is considered the criterion standard. However, the culture is almost universally negative in adults with pertussis. In contrast to infants, pertussis is generally not suspected in adults until they have had a prolonged cough illness. Thus, there is little organism left in the nasopharynx when the culture is obtained and no organism is isolated.[20] The yield of culture may be increased in patients with shorter duration of symptoms (during the catarrhal stage). Patients who have been previously immunized (almost all adults in the United States) are also known to have a lower yield of positive cultures when infected.[38] Also, patients previously treated with antibiotics will have a lower rate of positive culture.[38] Thus, it is unlikely that a culture will identify the organism in adults, and we can question whether cultures should be routinely obtained. However, culture is one of the few diagnostic modalities available to the primary care clinician.

Direct Fluorescent Antibody Testing

The direct fluorescent antibody (DFA) is best used as a screening tool during an outbreak investigation.[37] The usefulness of the test is limited by the difficulty in preparing the slide for interpretation, inter-reader variability, and cross-reactivity with other organisms. Both false-positive and false-negative values occur. Studies of adults with pertussis have confirmed that the vast majority will have a negative DFA.[19,20] The DFA should not be relied on for confirmation of pertussis.

Bordetella pertussis Polymerase Chain Reaction

The polymerase chain reaction (PCR) for pertussis will likely become the standard of care for the rapid diagnosis of pertussis in both children and adults. The PCR has been found to be more sensitive than culture in adults; adults with pertussis were 10 times more likely to have a positive PCR (38.1%) than culture (3.6%) in one study.[33] The PCR is obviously better than culture in adults, but studies looking at the sensitivity and specificity in a large number of patients are lacking. The PCR is currently available only in research laboratories, though clinical reference laboratories will soon have the capability to do the test for community-based clinicians.

Serologic Testing

The majority of research studies have relied on serologic testing for antibodies to pertussis antigens. Serology is difficult to interpret and is generally available only in research laboratories, though some state health departments will do the tests.[29] Most investigators use a fourfold rise in antibodies to PT or FHA as part of the diagnostic criteria in the interpretation of serology. However, most adults with pertussis come for treatment late in the disease, and the "acute" specimen is actually obtained during the mid-illness. Thus, a fourfold rise in titers is uncommon; the "acute" specimen frequently has a higher value than the "convalescent" specimen. Thus, most recent investigators have also included in the diagnostic criteria the use of a single value above a defined reference value.[18-21,33] One advantage of using a single value is the possibility of rapid confirmation of the etiology of the cough by analysis of a sample at the beginning of the illness without having to wait for a convalescent titer. Unfortunately, at present, there is no universally accepted reference value for PT or FHA that will distinguish acute from past infection

or immunization. The CDC does not recognize serologic testing as a criterion for the diagnosis of pertussis.[37]

TREATMENT OF ADULTS WITH PERTUSSIS

Treatment of adults with pertussis is controversial, and few treatment studies have been done. Treatment is considered mainly to improve the symptoms and to shorten the duration of the illness. However, it has never been shown that treatment with an antibiotic improves the symptoms or alters the course of the illness in adults. Most patients come for treatment late in the course of the illness; it is possible that individuals with only a few days of symptoms would benefit from early treatment. Another reason to consider treatment would be to decrease infectivity; however, there is little organism present in the nasopharynx by the time most adults come for medical attention. Treatment of patients early in the course of the illness, during the catarrhal stage, would likely decrease infectivity.

If treated, erythromycin is the antibiotic of choice. A recent study has shown that a 7-day course is as efficacious as the traditional 14-day course.[39] The other available macrolide antibiotics, azithromycin and clarithromycin, are acceptable alternatives if erythromycin cannot be tolerated.[40] Trimethoprim-sulfamethoxazole is an option to the macrolide antibiotics but may be less effective.[41] Quinolones, including ciprofloxacin and levofloxacin, have in vitro activity, but there is little clinical experience with these agents.[42] Penicillin, amoxicillin, and cephalosporins are not adequate therapy for pertussis.[43] A strain of *B pertussis* resistant to erythromycin was recently detected in Arizona.[44] Widespread erythromycin resistance does not appear to be present, and the implications are unclear at this time.

Prophylactic antibiotics are formally recommended for close contacts and household members of patients with pertussis regardless of age or vaccination status.[29] In particular, prophylaxis of unvaccinated infants, who are at the greatest risk for serious disease, should be considered. Widespread chemoprophylaxis following sporadic cases generally is not recommended; however, it has been shown to be effective in outbreak situations.[24,28,29]

Patients should be considered infectious for 5 days after initiation of antibiotic therapy, or until 3 weeks after the onset of the paroxysmal cough if not treated.[45] Exposure of health care workers is particularly problematic. Health care workers who have upper respiratory symptoms or cough after exposure to a patient with pertussis should be removed from direct patient contact. Treatment with antibiotics should be initiated, and no direct patient contact should be made for a minimum of 7 days.

VACCINATION OF ADULTS

Routine vaccination of infants and children has markedly decreased the incidence of pertussis in that population. Unfortunately, immunity from childhood vaccination is short-lived, and infection in adolescents and adults is common. Many authorities believe that routine vaccination of adolescents and adults should be considered to decrease their burden of disease and control transmission to susceptible infants.[19-21,23,33] In addition, routine vaccination may help decrease the considerable financial burden of this illness.[46]

The whole cell vaccine, which has been used in children for decades, is rarely given to adults since it is poorly tolerated. However, the newer acellular vaccines have been shown to be well tolerated, safe, and immunogenic in adults.[47] Large scale trials of the vaccine are currently being conducted to determine their efficacy in preventing disease in adults. Routine booster immunizations of adults would appear to be warranted if these studies confirm the safety, tolerability, and efficacy found in earlier reports. The routine use of the acellular pertussis vaccine in adults may eventually lead to increased control of pertussis, both in children and in adults.

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