Pertussis in Children

62

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62.1 Introduction

Pertussis, also known as "whooping cough," is an acute respiratory tract infection caused primarily by *Bordetella pertussis* and much less frequently by other *Bordetella* species. As a human disease, it can affect susceptible individuals in all age groups. Pertussis, a highly contagious and severe infectious disease, is endemic mainly in middle- and low-income countries and occurs most commonly in unprotected infants younger than 6 months of age and neonates. However, surveillance of pertussis is insufficient for precisely estimating the numbers of cases or deaths in many countries. Pertussis remains a significant health issue for children worldwide, although it has been among the vaccine-preventable diseases for a very long time.

62.2 Etiology

Currently, 10 species are known in the genus *Bordetella,* which belongs to the family of Alcaligenaceae. The classic species that cause pertussis are *B. pertussis, Bordetella bronchiseptica,* and *Bordetella parapertussis. B. bronchiseptica* generally causes disease in animals; it also leads to pertussis-like syndromes, mainly in

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C. Cingi et al. (eds.), *Pediatric ENT Infections*,
https://doi.org/10.1007/978-3-030-80691-0_62

immune-compromised individuals. *B. parapertussis* typically and much less frequently causes milder pertussis. *Bordetella holmesii* causes pertussis-like respiratory symptoms and invasive infections like bacteremia, endocarditis, and septic arthritis [1–6].

Bordetella species are small, thin, pleomorphic, strictly aerobic (except *Bordetella petrii*) gram-negative coccobacilli. They grow optimally at 35 °C to 37 °C. *B. pertussis* is a nonmotile, catalase- and oxidase-positive, nitrate reduction- and urease production-negative species; however, *B. parapertussis* is a nonmotile, catalase- and urease production-positive and oxidase- and nitrate reduction-negative species [1, 2, 4].

Although many *Bordetella* spp. have relatively simple requirements, sulfides, metal ions, peroxides, and fatty acids prevent the growth of *B. pertussis* in numerous laboratory media. *B. pertussis* is extremely sensitive and requires special media comprising starch, blood, or charcoal for isolation. *Bordetella* species are resistant to cephalexin, except *B. holmesii*. Therefore, cephalexin frequently is added to culture media for inhibition of growth of the other pathogens. Bordet-Gengou agar and Regan-Lowe agar are the selective culture mediums for isolation of *B. pertussis* [1, 2, 4, 5].

62.3 Epidemiology

In 2018, 151,074 pertussis cases were reported worldwide [7]. However, many pertussis cases are not diagnosed and, therefore, not reported. In line with a modeling study in 2014, approximately 24 million pertussis cases and 160,000 childhood deaths because of pertussis in children aged less than 5 years old were estimated to have occurred worldwide, mostly in low- and middle-income countries [8].

Before the introduction and nationwide use of a whole-cell pertussis vaccine in the United States (US) in the 1940s, pertussis was a major childhood illness. Pertussis was reported to frequently exceed 100,000 cases every year, with peaks of the disease occurring in 3- to 5-year cycles. Following the routine use of the pertussis vaccine, the number of cases declined by 99%. The 1010 patients reported in 1976 were the lowest number of cases in the USA. A gradual increase in the number of recorded cases occurred in the 1980s. In 2012, there were overall 48,277 cases, the highest number of pertussis patients in the USA since 1955. The number of reported cases decreased gradually within the following years and was reported to be 15,609 in 2018 [9].

The Pertussis Annual Epidemiological Report of the European Centre for Disease Prevention and Control (ECDC) for 2018 includes data from 30 European countries between 2014 and 2018 [10]. There were 35,627 cases of pertussis in 2018, the lowest number of annual cases over the 5 year study period reported by the 30 European countries. Germany, the Netherlands, Norway, Spain, and the United Kingdom reported 72% of the cases.

Pertussis is transmitted via respiratory droplets generated by coughing or sneezing. Pertussis is a highly contagious disease with an expected R_0 of 12 to 17, defined

as secondary cases produced by a primary patient in a completely vulnerable population [11, 12]. The transmission risk is related to repeated or prolonged exposure and closeness of contact with the index case. Attack rates among susceptible individuals are very high. However, studies found attack rates higher in household contacts than in school contacts; the family members usually infect children [1, 4, 13, 14]. The environmental conditions are not suitable for *B. pertussis* to survive for a long time. Fomites do not play a role in transmission. Pertussis can affect susceptible individuals in all age groups [6, 14, 15].

Pertussis is reported commonly in summer and fall as most cases are observed in August, September, and October, and the smallest number of cases occurs in January [16]. In a study conducted between 2008 and 2018 in Germany, *B. pertussis* infection was reported mostly in the months from June to September [17]. Pertussis cases peaked every summer in European countries between 2014 and 2018 [10]. Cyclical epidemics continue to occur every 3–5 years in the vaccine era too. A study from Italy reported the highest pertussis infection incidence in 2012–2013 and 2016–2017 [18].

Pertussis continues to be a crucial public health issue worldwide, particularly in low- and middle-income countries and where immunization coverage is insufficient. Herd immunity, the minimum percentage threshold to be immunized in a community for eliminating infection, is 92–94% for pertussis [12]. In 2019, approximately 85% of infants (116 million infants) worldwide had received three doses of diphtheria-tetanus-pertussis (DTP3) vaccine, and 125 member states of the World Health Organization (WHO) provided at least 90% coverage for the DTP3 vaccine [19].

Increased pertussis rates were seen in adolescents and adults in the last decade, with the illness still seriously affecting children aged <6 months. In 2018, 62% of reported pertussis cases in 30 European countries were seen in children over the age of 14 years [10]; 54% of patients in the USA were over 11 years in 2019 [20]. Adolescents and adults with undiagnosed pertussis are an essential reservoir for infection in infants and children. The actual incidence of pertussis based on the seroprevalence results was significantly higher than the clinically reported incidence in the Czech Republic [21]. Despite widespread vaccination programs, whooping cough continues to be one of the major health issues worldwide.

In addition to an increase in whooping cough cases in general, patients also have been appearing at older ages in many countries in recent years. Multiple factors have likely contributed to the change in the epidemiology of pertussis: increased vaccine failures resulting from genetic changes in circulating *B. pertussis* strains, increased pertussis disease awareness combined with the use of better diagnostic tests, such as polymerase chain reaction (PCR) testing, not achieving complete protection with previous infection or vaccination, the change of whole-cell pertussis vaccine to acellular pertussis vaccine, waning immunity, improved surveillance and reporting of pertussis, vaccine refusal, inadequate vaccination schedules, and decreases in vaccination coverage [1, 3, 5, 22, 23].

62.4 Pathogenesis

Pertussis is mainly a toxin-mediated disease. Pathogenesis of pertussis comprises five essential steps; exposure, attachment, escape from host defenses, local impairment, and systemic findings. Adhesins and toxins responsible for the clinical manifestations are virulence factors expressed by *B. pertussis*. The infection starts with the adhesion of *B. pertussis* to the human respiratory tract's ciliated epithelial cells. Adhesins are implicated in facilitating the attachment process. Once attached, various virulence factors allow evasion of host immune factors and destruction of the epithelial cells. Some toxins produced by *B. pertussis* and anoxia due to coughing paroxysms lead to systemic manifestations of illness without the direct effect of bacteria [1, 2, 4, 5, 16].

The main virulence factors of *B. pertussis* are pertussis toxin (PT), filamentous haemagglutinin, agglutinogens, fimbriae type 2 and type 3, adenylate cyclase toxin, tracheal cytotoxin, pertactin, dermonecrotic toxin, and lipooligosaccharide. The virulence determinants and their impacts are shown in Table 62.1 [1, 2, 4, 5, 16].

Table 62.1 Virulence factors of *Bordetella pertussis*[a]

Virulence factors	
Filamentous hemagglutinin (FHA)	Required for tracheal colonization Highly immunogenic
Fimbriae (FIM)	Serves as adhesin (facilitate attachment) Required for persistent tracheal colonization
Pertactin (PRN)	Adversely affects the innate immune response Promotes adherence of *B. pertussis* to the upper respiratory epithelium
Pertussis toxin (PT)	Potent adjuvant and primary component of pertussis vaccines Evasion from the immune system Responsible for the systemic manifestations (leukocytosis with lymphocytosis, hyperinsulinemia with resultant hypoglycemia, sensitization to histamine and serotonin, pertussis-associated encephalopathy)
Adenylate cyclase (CyaA)	Acts as an anti-inflammatory and antiphagocytic factor during infection Impairs phagocytosis Local tissue damage (induces apoptosis of the cell)
Dermonecrotic toxin (DNT)	Plays a role in local tissue damage Leads to the characteristic skin lesion when injected into test animals
Tracheal cytotoxin (TCT)	Local tissue damage to ciliated epithelial cells (kills the tracheal epithelial cells) Inhibits the regeneration of the respiratory tract epithelium.
Lipooligosaccharide (LPS)	Facilitates attachment Pyrogenic, mitogenic, and toxic

[a]Adopted from Refs. [1, 2, 4, 5, 16].

62.5 Clinical Manifestations

The median incubation period is 7–10 days (range: 5–21 days). Patients may disseminate microorganisms for weeks or months. *B. pertussis* can generally cause mild illness in adults and life-threatening disease in unimmunized infants [1, 4, 15]. The classic clinical presentation of pertussis is composed of catarrhal, paroxysmal, and convalescent phases. The duration of these phases depends on the patient's age and immunization status. Infection is highly contagious in the catarrhal stage and the early period of the paroxysmal stage.

The clinical spectrum of pertussis ranges from asymptomatic or mild disease to life-threatening illness. The severity varies depending on the patient's age, previous vaccination or natural infection, the transplacental transfer of maternal antibodies, use of appropriate antimicrobial therapy, respiratory coinfection, and other situations such as the level of exposure, host immunity, the genotype of the circulating strain, and virulence factors of the bacteria [1–3].

The initial catarrhal stage usually continues for 1–2 weeks and resembles a common cold but has a more extended incubation period. This stage is characterized by slight fever, mild cough, rhinorrhea, sneezing, and conjunctival erythema. Pertussis disease may not be suspected during this stage, and then the frequency and severity of cough gradually increase [1, 2, 4, 16, 24].

The paroxysmal stage is characterized by bouts of repeated coughing with 5–10 or more violently and exhausting coughs during one paroxysm, which generally leads to a clinical consideration of pertussis diagnosis. The character of the cough is dry, intermittent, and irritative. At the end of the paroxysms, strong inspiratory breathing occurs when there is no extra air in the lungs, so a distinctive high-pitched whooping voice emerges. During paroxysms, the patients usually appear to be very tired, dizzy, and apathetic. The attacks lead to cyanosis, the prominence of protruding eyes, lacrimation, outthrust of the tongue, salivation, and the appearance of petechiae on the face. The paroxysms are associated with the accumulation of thick and viscous mucus plugs in the airways and may end with these plugs' expulsion. At the end of the coughing paroxysm, post-tussive vomiting is common. The paroxysms are particularly more frequent and severe at night. Paroxysms of coughing may develop spontaneously or precipitated by external factors such as eating, drinking, yawning, sneezing, cold air, inhaled irritants, or physical exertion. The patients are entirely normal and may not appear ill between attacks if complications do not occur. The paroxysmal stage generally continues for 4–6 weeks but may last for up to 10 weeks in some patients [1, 2, 4, 5, 16, 24].

The convalescent phase, the respiratory tract recovery stage, is characterized by a decline in severity, duration, and coughing attack frequency. It generally continues from weeks to months and is often exacerbated by subsequent respiratory infections but does not occur due to recurrent disease or reactivation of *B. pertussis* [4, 22].

The illness of whooping cough in adolescents, adults, and children partially immunized by vaccination may represent a disease ranging from a mild to

intractable cough or one without symptoms. The pertussis diagnosis is usually not considered in adolescents and adults previously vaccinated who generally do not manifest classic pertussis presentation with paroxysms. However, pertussis should be considered in the presence of a cough lasting longer than 3 weeks in this age group [4].

It is also difficult to diagnose pertussis solely with clinical suspicion in children less than 1-year of age. In one study, pertussis was diagnosed with clinical suspicion only in 34.8% of the patients at admission [18]. Also, diagnosis with clinical suspicion was much lower in children under 3 months of age. Severe morbidity and mortality resulting from pertussis often occur in young infants, especially <3 months [3, 16, 18]. Infants usually present with nonspecific signs such as nonspecific coughs, apnea, and poor feeding. The initial findings are frequently apnea and cyanosis, and the characteristic cough attacks may not be seen, especially in the early period in newborn and young infants. Seizures in association with apnea, caused by hypoxia and severe pulmonary hypertension, are relatively common in this age group. Also, the length of hospitalization and intensive care unit admissions increase in these infants. Severe complications associated with respiratory, nutritional, and neurological problems can be fatal [3, 16, 18].

62.6 Complications

Complications frequently occur by severe coughing spells leading to hypoxia, pressure effects of severe paroxysms, secondary to feeding difficulties, and post-tussive vomiting, mostly during the paroxysmal stage. Pneumonia is the most frequent complication and the prevalent cause of pertussis-associated death, particularly in younger infants. Dehydration, sleeping difficulty, pulmonary hypertension, conjunctival bleeding, epistaxis, subdural hematoma, hernias, pneumothorax, pneumomediastinum, subcutaneous emphysema, rectal prolapse, urinary incontinence, syncope, apnea, neurologic complications such as seizures and encephalopathy, and otitis media are the other not infrequently encountered complications. Furthermore, *B. pertussis* infection is associated with sudden infant death syndrome [1, 2, 16, 22, 24].

62.7 Differential Diagnosis

A pertussis-like disease with a prolonged cough occurs during several respiratory tract infections caused by viruses, *Mycoplasma pneumoniae, Chlamydia trachomatis,* and *Chlamydia pneumoniae. Mycoplasma* infection is considered with the presence of symptoms such as malaise, fever, headache, rales in lung examination, and an occasional maculopapular rash. *C. trachomatis* causes *a* repetitive *staccato* cough, tachypnea, and rales in an afebrile, very young infant. Non-exudative pharyngitis and pulmonary rales are found in the *C. pneumoniae* illness. Respiratory syncytial virus (RSV) is distinguished by the presence of wheezing and seasonal

presentation. Adenoviral infection can be considered in patients with fever, sore throat, and conjunctivitis [1, 5, 6].

A total of 543 patients with respiratory symptoms were analyzed by reverse transcriptase (RT)-PCR in a study [25]. Rhinovirus, *B. pertussis*, RSV, adenovirus, parainfluenza viruses, metapneumovirus, bocavirus, coronavirus, influenza virus, and enteroviruses were determined in most patients. The remaining patients (21.4% of the total) had a negative PCR result for pertussis and viral infections. This study is important as it explained that pertussis could often be confused with viral respiratory infections [25]. However, pertussis is rare in infants hospitalized with acute bronchiolitis that is frequently caused by respiratory tract viruses [26]. The cough associated with gastroesophageal reflux or related to a foreign body in the airway can also be confused with pertussis [1, 6].

62.8 Diagnosis and Laboratory Findings

Early pertussis symptoms and signs are often nonspecific, especially in young infants, making the diagnosis difficult in catarrhal stages. Microbiological, molecular, and serology methods are helpful for the diagnosis in these situations.

The diagnosis of pertussis depends on the combination of clinical features and laboratory findings. Pertussis should be considered in any individual with a persistent cough. The features such as fever, malaise, myalgia, rash, sore throat, and hoarseness are not expected in patients with pertussis. And the systemic physical examination findings are usually normal if the complications do not occur [1, 6].

The Centers for Disease Control and Prevention (CDC) has a pertussis case definition for public health surveillance (Table 62.2) [27].

The growth of *B. pertussis* obtained from nasopharyngeal specimens on the appropriate media is the "gold standard" for the diagnosis of disease. However, this remains a nonsensitive method for several reasons: fastidious growth of bacteria, the requirement of specific swabs and media, and culture [1, 2, 15]. The appropriate specimen for culture can be obtained by swabbing the nasopharynx with polyester, dacron, or calcium alginate swabs, not cotton and rayon swabs, washing, or nasopharyngeal aspiration.

Specimens are collected from the posterior nasopharynx containing the ciliated respiratory epithelial cells to which *B. pertussis* adheres. Specific media such as Regan-Lowe transport medium, Bordet-Gengou agar, and modified Stainer-Scholte broth are required for the growth of *B. pertussis*. The rate of *B. pertussis* isolation on selective media is the highest within the catarrhal and early paroxysmal stages [1, 2, 15].

Laboratory diagnosis of pertussis can be made by demonstrating a specific antibody titer rise between two blood samples obtained at least 2 weeks apart or an elevated single-serum antibody titer against *B. pertussis*. Pertussis toxin, a robust, specific *B. pertussis* protein as antigen, has an essential role in immune response, is also the most frequently used antigen for serologic diagnosis. But not all infected people, especially young infants, develop antibody responses to PT [3]. On the other

Table 62.2 The US CDC surveillance case definition for pertussis (2020) (Adopted from Ref. [27]

Clinical criteria	Laboratory criteria
In the absence of a more likely diagnosis, a cough illness lasting ≥2 weeks, with at least one of the following signs or symptoms: • Paroxysms of coughing, OR • Inspiratory whoop, OR • Post-tussive vomiting, OR • Apnea (with or without cyanosis)	Confirmatory laboratory evidence: • Isolation of *Bordetella pertussis* from a clinical specimen • Positive polymerase chain reaction (PCR) for *B. pertussis*
Epidemiologic linkage Contact with a laboratory-confirmed case of pertussis	
Case classification	
Probable: In the absence of a more likely diagnosis, an illness meeting the clinical criteria OR Illness with cough of any duration, with • At least one of the following signs or symptoms: – Paroxysms of coughing, OR – Inspiratory whoop, OR – Post-tussive vomiting, OR – Apnea (with or without cyanosis) AND Contact with a laboratory-confirmed case (epidemiologic linkage)	*Confirmed*: • Acute cough illness of any duration with Isolation of *pertussis* from a clinical specimen OR • PCR positive for *B. pertussis*

US United States, *CDC* Centers for Disease Control and Prevention.

hand, the first blood specimen is generally taken too late in the course of illness to demonstrate a specific antibody titer rise to establish an early diagnosis. Hence, monitoring a specific antibody titer rise is not helpful for the acute diagnosis of pertussis.

B. pertussis immunoglobulin (Ig) G test is the best-standardized and the most widely used diagnostic serologic test. IgG titer usually increases 2–3 weeks after the onset of infection or primary immunization. PT IgG level >90 or 100 IU/mL in a single serum sample suggests a recent illness and often is positive in the middle of the paroxysmal phase [5, 6, 15]. Distinguishing between antibody responses secondary to infection or recent immunization might not be possible, and thus, serological methods should not be performed if the pertussis vaccine was administered within the last year. Serology is unreliable in infants due to maternal antibodies and is insensitive in children ≤10 years old [2].

Nucleic acid amplification tests, including PCR assay, are the most commonly used diagnostic laboratory method for detecting *B. pertussis* because of their much higher sensitivity and rapid results. The PCR test requires collecting an appropriate nasopharyngeal specimen obtained by dacron or rayon or nylon-flocked swabs or by nasopharyngeal wash or aspirate. For PCR tests, calcium alginate and cotton swabs can be inhibitory and should not be used [2, 15, 28].

62.9 Treatment

Management of pertussis disease consists of antimicrobial therapy and supportive care. Antibiotic treatment aims to reduce the severity, duration, and frequency of symptoms and prevent infection transmission. On the other hand, antibiotics started late in the illness have a limited effect on the disease during the paroxysmal stage. However, antimicrobial treatment will eradicate the bacteria from the nasopharynx, and so communicability will decrease. Thus, antimicrobial therapy should be initiated immediately based on clinical suspicion without awaiting laboratory confirmation.

A 5-day course of azithromycin is the recommended first-line antibiotic regimen for treatment and postexposure prophylaxis. Other macrolides (erythromycin, clarithromycin), fluoroquinolones, and trimethoprim-sulfamethoxazole (TMP-SMX) are alternative preferred antibiotics. Erythromycin is not recommended in newborns (<1 month of age) because of the risk of infantile hypertrophic pyloric stenosis (Table 62.3) [2, 4–6, 15].

Penicillins, amino-penicillins (ampicillin, amoxicillin), cephalosporins, and tetracyclines are not recommended for treatment or chemoprophylaxis of pertussis because of ineffectiveness. Resistance to macrolides is rare in *B. pertussis* strains. The low rate of antibiotic-resistant *B. pertussis* strains may be explained partly by the infrequent isolation of *B. pertussis* isolated (related to the insensitive culture methods and greater reliance on PCR for diagnosing illness), thus inadequacy of data on antibiotic susceptibility tests. Resistance to macrolides was reported sporadically from China, Japan, Iran, and France since the first erythromycin-resistant *B. pertussis* case was detected in 1995. Resistance to erythromycin is dependent on a mutation in the 23S rRNA gene of *B. pertussis* [4, 30–34].

Supportive care, which includes the balance of fluid and nutrition and management of cough, is essential. Intravenous hydration, feeding by nasogastric tube, aspiration of secretions, and oxygen supplementation during attacks may be required. Exchange transfusion may be necessitated for hyperleukocytosis in severe cases of pertussis. Criteria for considering exchange blood transfusion in infants with pertussis less than 60 days of age have been proposed [35]. Symptomatic therapies with bronchodilators, corticosteroids, pertussis-specific immunoglobulin, antihistamines, and antitussive agents are not recommended for whooping cough. In a Cochrane review, diphenhydramine and salbutamol did not change the frequency of coughing episodes per 24 h [36]. The external factors that can trigger cough may be avoided [1–4, 6, 15].

62.10 Prognosis

The prognosis of pertussis is closely related to the age and vaccination status of the patient. The morbidity and mortality rates are highest in neonates and susceptible infants. Older children, adolescents, and adults have a better prognosis with a milder disease course or a prolonged cough. Antibiotics do not affect the disease's course

Table 62.3 Recommended antimicrobial treatment and postexposure prophylaxis for pertussis (Adopted from Refs. [2, 4–6, 15, 29])

Age group	When is treatment initiated	When is chemoprophylaxis initiated	Azithromycin	Erythromycin	Clarithromycin	TMP-SMX
<1 month	Suspected or proven pertussis anytime after the onset of symptoms	Exposed to a case of pertussis within 21 days of onset of cough in the index case	10 mg/kg/day in a single dose for 5 days	Not recommended Associated with infantile hypertrophic pyloric stenosis	Not recommended	Not recommended <2 months of age risk for kernicterus
1–5 months	Suspected or proven pertussis within 42 days of onset of symptoms	Exposed to a case of pertussis within 21 days of onset of cough in the index case	10 mg/kg/day in a single dose for 5 days	40–50 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	For infants age ≥ 2-month: TMP 8 mg/kg/day plus SMX 40 mg/kg/day in two divided doses for 14 days
6–12 months	Suspected or proven pertussis within 42 days of onset of symptoms	Exposed to case of pertussis within 21 days of onset of cough in index case	10 mg/kg in a single dose on day 1 (max. 500 mg), then 5 mg/kg/day (max. 250 mg) on days 2–5	40–50 mg/kg/day (max. 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (max. 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMX 40 mg/kg/day in two divided doses (max. TMP: 320 mg/day) for 14 days
Infants (aged ≥12 months) and children	Suspected or proven pertussis within 21 days of onset of symptoms	Exposed to case of pertussis within 21 days of onset of cough in index case	10 mg/kg in a single dose on day 1 (max. 500 mg), then 5 mg/kg/day (max. 250 mg) on days 2–5	40–50 mg/kg/day (max. 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (max. 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMX 40 mg/kg/day in 2 divided doses (max. TMP: 320 mg/day) for 14 days

[a]*Max* maximum, *TMP-SMX* trimethoprim-sulfamethoxazole.

since antibiotics are generally started in the advanced stages; however, the use of antibiotics limits contagiousness [1, 2].

Life-threatening and severe complications such as apnea, secondary bacterial pneumonia, seizures, pulmonary hypertension, and encephalopathy can occur mostly in unvaccinated or incompletely immunized infants younger than 6 months. The mortality rate is highest in neonates and infants younger than 2 months. During admission to the hospital, high levels of mean heart rate, coinfection of RSV, leukocytosis, and lymphocytosis are poor prognostic criteria. The presence of acute respiratory failure, leukocytosis, and pulmonary hypertension, which define malignant pertussis, is almost always fatal [1, 37–39].

In patients with severe pertussis, neurodevelopmental problems can also be seen in long-term follow-up. In a study including pertussis cases requiring the intensive care unit, the patients' cognitive developments were evaluated by the Mullen Scales of Early Learning (considers gross motor, visual reception, and receptive and expressive language) at the end of the first year [40]. In 37% of the patients, abnormal scores were detected in at least one domain; language development was the most frequently affected area.

62.11 Prevention and Control

In addition to standard precautions in hospitalized patients, droplet precautions are recommended 5 days after effective therapy is initiated [15].

Postexposure chemoprophylaxis is frequently recommended for asymptomatic close contacts, high-risk individuals, and close contacts who may contact high-risk individuals. Also, active immunization of incompletely vaccinated exposed persons of all ages should be provided. The high-risk individuals include infants-age <1 year, pregnant women in the third trimester, individuals with various immune-deficiency disorders, or certain underlying medical conditions. Preferred chemoprophylactic antibiotics, dosages, and chemoprophylaxis duration are similar to treatment regimens (Table 62.3) [2, 4–6, 15, 29].

Immunization is the single most effective method of protection against pertussis infections. Whole-cell vaccines, the first pertussis vaccines, have been used worldwide since the 1940s. Purified acellular-component pertussis vaccines were initially introduced in 1997. The acellular pertussis vaccines contain three or more *B. pertussis* antigens: inactivated PT, filamentous hemagglutinin, fimbrial proteins, and pertactin. In the subsequent years, they were replaced with whole-cell vaccines in many countries. Whole-cell and acellular pertussis vaccines have a difference regarding the duration of immunity they induce. The whole-cell pertussis vaccines protect for 5–14 years, and acellular vaccines protect for 4–7 years. This difference is mainly based on their distinct way of producing immunity. The whole-cell pertussis vaccines induce the T helper (Th)-1 and Th-17 cellular immune responses, whereas the acellular pertussis vaccines induce a predominantly Th-2 cellular immune response [1, 4, 6, 15].

Five doses of diphtheria and tetanus toxoid and acellular pertussis (DTaP) vaccines are recommended in children age <7 years. The first four doses should be administered before the age of 2, and the fifth dose is recommended before kindergarten and after the age of 4. The first dose can be administered at 6 weeks at the earliest. There should be 4 weeks between each dose of the first three doses, and there should be at least a 6-month interval for the subsequent doses [6, 15].

DTaP vaccines are licensed to use in children under 7 years of age. Tdap vaccines include "the adolescent or adult type of acellular pertussis vaccine (ap)" composed of diminished amounts of pertussis antigens and should not be administered instead of DTaP. If the Tdap vaccine is administered mistakenly for the initial 3 doses of pertussis vaccination instead of DTaP in a child less than 7 years of age, it is not accepted as a valid vaccination. Thus, the DTaP vaccine should be administered for revaccination at an appropriate time. However, more than six doses of vaccines that contain diphtheria and tetanus vaccines should not be administered before the age of 7 years. If this does occur, adverse reactions, including mostly local reactions, can be observed [6, 15].

Immunization is generally performed at 2, 4, 6, 15–18 months, and 4–6 years of age for protection against pertussis in many countries. However, neither vaccination nor previous infection protects children lifelong against pertussis or reinfection. Thus, vaccination is recommended in children who have had the disease as well. DTaP vaccine is protective for 2 years following four doses of the vaccine, and then immunity decreases over the years. Hence, a Tdap booster dose is recommended at 11–12 years old [15, 41].

Local reactions such as redness, swelling, and pain and systemic reactions such as fever (≥38.6 °C [100.1 °F]), fussiness, drowsiness, anorexia, and vomiting are not uncommon after pertussis vaccination. More severe adverse events such as seizures, hypotonic-hyporesponsive episodes, fever 40.5 °C (104.8 °F) or higher, or prolonged crying (≥3 hours) are rare. Local reactions (i.e., limb swelling) increase slightly in frequency and severity after administration of the fourth and fifth doses of vaccines. These conditions are not contraindications for the next dose(s). Most local and systemic reactions are significantly less common with acellular pertussis vaccines than with whole-cell pertussis vaccines. A severe allergic reaction (e.g., anaphylaxis) or encephalopathy within 7 days after administration of a previous pertussis vaccine is a contraindication for the next dose(s) [1, 6, 15].

Severe pertussis and related deaths occur mostly in the first months of life. In this period, infants have not been vaccinated, or only the first dose vaccine has been administered. This situation makes the infants at this age the most vulnerable and unprotected population. Experts consider two strategies to protect this population [42]. In the cocoon strategy, vaccination is recommended for all caregivers or close contacts of this age group. Transmission to infants usually occurs through close contacts who are caregivers, especially mothers and fathers [43]. Prevention of transmission tried by the cocoon strategy provides indirect protection. This strategy is recommended in some countries, including the USA, Belgium, France, and Germany. However, there is limited data about the effectiveness of the cocoon

strategy [42]. A study reported from Australia showed that the risk of pertussis was reduced by 51% in those younger than 4 months whose mother and father are vaccinated [44].

Computer modeling methods have been used to assess the effectiveness of the cocoon strategy. It has been reported that the cocoon strategy is not effective in regions where the incidence is low. And a large number of individuals need to be vaccinated to obtain favorable results regarding the disease of pertussis [42]. A study reported that the number of required parental immunizations to prevent hospitalization, intensive care unit admission, and death of one case from pertussis was 10,000, 100,000, and one million, respectively [45]. Therefore, the cocoon strategy was not found to be cost-effective. In addition, a minimum of 2 weeks is required for maximal antibody development in vaccinated individuals. If vaccination is administered immediately after delivery, it should be kept in mind that the newborn will still be at risk for the first 2 weeks [42].

The second strategy aims to increase the protective antibodies transmitted to the fetus by the maternal vaccination during pregnancy. Thus, the passive transfer of maternal antibodies results in sufficient protective antibody levels against severe pertussis infection in the neonatal period and first months of life. During pregnancy, the maternal pertussis vaccination program is recommended in many countries, including the USA (the preferred strategy), the United Kingdom, New Zealand, Australia, and Israel [42, 46, 47].

Eberhardt et al. showed that maternal Tdap immunization administered in the early second-trimester significantly increased neonatal antibodies [48]. In the United Kingdom, initially in 2012, maternal vaccination as a single dose of Tdap was recommended to all women for each pregnancy at 28–38 gestational weeks. Subsequently, in 2016 maternal vaccination was recommended between 20 and 32 gestational weeks, the earliest at 16 weeks. In this way, more pregnant women are vaccinated, and more premature newborns are protected [46].

A case-control study was conducted by Dabrera et al. in the United Kingdom to estimate vaccination effectiveness during pregnancy. The adjusted efficacy of vaccination in infants <8 weeks of age was 93% [49]. Maternal immunization during pregnancy is preferred over the cocoon strategy. If it is not possible, a complete cocoon strategy is performed. If this is not possible, both parents' vaccination should be administered, especially mothers' [42].

A systematic review showed that vaccination during pregnancy did not adversely affect the course of the pregnancy, the developmental features of the fetus, and neonatal outcomes. Self-limiting mild local and systemic reactions were reported, and vaccination was well tolerated during pregnancy [50].

There is no risk in vaccination of nursing mothers or pregnant women planning to breastfeed. Some studies report increased pertussis antibodies in the breast milk of women vaccinated during pregnancy, at delivery, or in the early postpartum period. Pertussis antibodies can be detected even at 8 weeks postpartum in the breast milk of women vaccinated during pregnancy and may help reduce the risk of developing illness in younger infants [46, 51–53].

62.12 Conclusion

Even though the pertussis vaccine coverage is high in infants worldwide, the current immunization programs and the acellular vaccines used in most countries are insufficient to control the illness. Therefore, the development of new-generation pertussis vaccines should be targeted, or the currently available vaccines with various immunization programs should be enhanced [4].

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