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165 Pertussis and Other Bordetella Infections

of the organization’s water system, identification of high-risk areas (e.g., transplant units, oncology floors), identification of at-risk struc tures for Legionella growth, implementation and monitoring of con trol measures, methods for intervention if control measures fail, and procedures to assure documentation that policies are followed. All medical centers are required to have an awareness of water quality and to have systems in place to help prevent nosocomial Legionella pneu monia. Such policies leave water quality assessment, including testing for Legionella, up to the individual facility. In addition to hospitals, an increasing number of cities, including New York City, require similar water-management plans for cooling towers, with registration, testing, and mitigation options.

Even if detected in regional water systems, Legionella becomes a human pathogen only after replication in premise plumbing systems. In buildings, Legionella finds the ideal environment for logarithmic growth, which leads to exposures and subsequent disease. An impor tant first step in prevention within hospitals is a review of plumbing systems to identify areas of concern and a review of impact areas such as dental clinics, ICUs, rehabilitation units, and units that house high-risk patients. Specific water features, such as therapy pools, ice machines, and decorative fountains, need policies for cleaning and disinfection. Targeted approaches to management of cooling towers, such as high-efficiency drift eliminators and routine maintenance, are important considerations. In addition, areas that have undergone recent construction or renovation should be flagged, with prevention policies in place to address the associated risks. New construction or structural updates can lead to water stagnation, while modifications to plumbing can disrupt biofilms. Units with older premise plumbing are thought to be at higher risk, but even brand new facilities can become colonized during construction, with consequent outbreaks. PART 5 Infectious Diseases Testing for Legionella is an important step when presumptive or possible nosocomial pneumonia cases occur and can help address a facility’s potential risks. There are a number of methods for environ mental testing for Legionella, but environmental cultures are used in most hospitals because they quantify Legionella levels, allow species identification/serotyping, and can link environmental sources to nosocomial outbreaks. Testing usually focuses on locations where the index patient(s) may have had potential waterborne exposures (e.g., at showers and sinks). Other adjacent areas, along with those noted to be high-risk locations within the hospital, should be

considered for additional testing; positive results should widen the testing area. Pro active testing is increasingly being used to preclude nosocomial cases; however, if testing is planned, it should be coupled with a management plan that addresses how Legionella will be dealt with if it is found in the water system and where and how frequently testing should be done; we recommend biannual or quarterly testing of select sites within hospital systems. If a common-source outbreak is discovered, a number of approaches can be used to address Legionella. Regardless of source, immediate limitation of ongoing water exposures for patients in the affected room, unit, or floor is a crucial step in avoiding additional cases. Removing or replacing water features associated with exposures, such as decorative fountains and affected equipment or plumbing devices, may be needed. Immediate interventions such as heat shock (increasing water tempera tures for a limited period) and hyperchlorination may also be useful as short-term steps in addressing an outbreak. The addition of a disinfectant to the water system is one of the most common ways to address the presence of Legionella. Chemical disinfec tion with agents such as chlorine or monochloramine and copper and silver ionization are commonly used for secondary disinfection. Use of disinfectants requires routine maintenance and monitoring of chemical or ion levels to assure that they are sufficient for prevention. Lack of monitoring and system failures have led to breakthrough nosocomial Legionella cases. Another option is water filtration, which either can serve as a primary method for prevention or can be used in combina tion with secondary disinfection. Filters—either in-line with plumbing or at point-of-use sites—can be considered for either short- or longterm prevention during an outbreak. However, filters have a limited life span, can weaken water pressure, and are costly to maintain.

■ ■FURTHER READING Cassell K et al: Estimating the true burden of Legionnaires' disease. Am J Epidemiol 188:1686, 2019. Centers for Disease Control and Prevention: Developing a water management program to reduce Legionella growth and spread in buildings: A practical guide to implementing industry standards. June 24, 2021. Available at https://www.cdc.gov/legionella/wmp/tool kit/. Accessed October 10, 2023. Centers for Disease Control and Prevention: Legionnaires' dis ease surveillance summary report, United States 2018–2019. Available at https://www.cdc.gov/legionella/health-depts/surv-reporting/201819-surv-report-508.pdf. Accessed October 20, 2023. Kato H et al: Meta-analysis of fluoroquinolones versus macrolides for treatment of legionella pneumonia. J Infect Chemother 27:424, 2021. National Academies of Sciences, Engineering, and Medicine: Management of Legionella in Water Systems. Washington, DC, The National Academies Press, 2020. Pierre DM et al: Diagnostic testing for Legionnaires' disease. Ann Clin Microbiol Antimicrob 16:1, 2017. May S. ElSherif, Scott A. Halperin

Pertussis and Other

Bordetella Infections Pertussis is an acute infection of the respiratory tract caused by Bordetella pertussis. The word pertussis means "violent cough," which aptly describes the most consistent and prominent feature of the illness. The inspiratory sound made at the end of an episode of paroxysmal coughing gives rise to the common name for the illness, "whooping cough." However, this feature is variable: it is uncommon among infants ≤6 months of age and is frequently absent in older children and adults. The Chinese name for pertussis is "the 100-day cough," which describes the clinical course of the illness accurately. The identification of B. pertussis was first reported by Bordet and Gengou in 1906, and vaccines were produced over the following two decades. ■ ■MICROBIOLOGY Of the 10 identified species in the genus Bordetella, only four are of

major medical significance. B. pertussis infects only humans and is the most important Bordetella species causing human disease. B. paraper tussis causes an illness in humans that is similar to pertussis but is typi cally milder; co-infections with B. parapertussis and B. pertussis have been documented. With improved polymerase chain reaction (PCR) diagnostic methodology, up to 20% of patients with a pertussis-like syndrome have been found to be infected with B. holmesii, formerly thought to be an unusual cause of bacteremia. B. bronchiseptica is an important pathogen of domestic animals that causes kennel cough in dogs, atrophic rhinitis and pneumonia in pigs, and pneumonia in cats. Both respiratory infection and opportunistic infection due to B. bronchiseptica are reported occasionally in humans. B. petrii, B. hinzii, and B. ansorpii have been isolated from patients who are immunocompromised. Bordetella species are gram-negative pleomorphic aerobic bacilli that share common genotypic characteristics. B. pertussis and

B. parapertussis are the most similar of the species, but B. parapertussis does not express the gene coding for pertussis toxin. B. pertussis is a slow-growing fastidious organism that requires selective medium and forms small, glistening, bifurcated colonies. Suspicious colonies are presumptively identified as B. pertussis by direct fluorescent antibody testing or by agglutination with species-specific antiserum. B. pertussis

is further differentiated from other Bordetella species by biochemical and motility characteristics. B. pertussis produces a wide array of toxins and biologically active products that are important in its pathogenesis and in immunity. Most of these virulence factors are under the control of a single genetic locus that regulates their production, resulting in antigenic modula tion and phase variation. Although these processes occur both in vitro and in vivo, their importance in the pathobiology of the organism is unknown; they may play a role in intracellular persistence and personto-person spread. The organism’s most important virulence factor is pertussis toxin, which is composed of a B oligomer–binding subunit and an enzymatically active A protomer that ADP-ribosylates a gua nine nucleotide–binding regulatory protein (G protein) in target cells, producing a variety of biologic effects. Pertussis toxin has important mitogenic activity, affects the circulation of lymphocytes, and serves as an adhesin for bacterial binding to respiratory ciliated cells. Other important virulence factors and adhesins are filamentous hemaggluti nin, a component of the cell wall, and pertactin, an outer-membrane protein. Fimbriae, bacterial appendages that play a role in bacterial attachment, are the major antigens against which agglutinating anti bodies are directed. These agglutinating antibodies have historically been the primary means of serotyping B. pertussis strains. Other virulence factors include tracheal cytotoxin, a peptidoglycan fragment, which causes inflammatory respiratory epithelial damage; adenylate cyclase-hemolysin toxin, which impairs host phagocytic cell function; dermonecrotic toxin, which may contribute to respiratory mucosal damage; and lipooligosaccharide, which has properties similar to those of other gram-negative bacterial endotoxins. Since 2010, the emer gence of pertactin-negative strains worldwide has been attributed to immune pressure resulting from the use of pertactin-containing acel lular pertussis vaccines, reaching >80% dominance in some countries. ■ ■EPIDEMIOLOGY Pertussis is a highly communicable disease, with attack rates of 80–100% among unimmunized household contacts and 20% within households in well-immunized populations. The infection has a world wide distribution, with cyclical outbreaks every 3–5 years (a pattern that has persisted despite widespread immunization). Pertussis occurs in all months; however, in North America, its activity peaks in autumn and winter. In developing countries, pertussis remains an important cause of infant morbidity and mortality despite the reported worldwide decrease in inci dence following improved

vaccine coverage (Fig. 165-1). Monitored as a 100% 80% 60% Coverage 40% 20% 0%

Coverage - Global, DTP-containing vaccine, 1st dose, WHO/UNICEF Estimates of National Immunization Coverage Coverage - Global, DTP-containing vaccine, 3rd dose, WHO/UNICEF Estimates of National Immunization Coverage Number of reported cases - Global, Pertussis FIGURE 165-1 Global annual reported cases of pertussis and rate of coverage with DTP3 (diphtheria toxoid, tetanus toxoid, and pertussis vaccine; one and three doses), 1980–2022. (Reproduced with permission from Diphtheria tetanus toxoid and pertussis (DTP) vaccination coverage (who.int). World Health Organization Immunization Data Portal; WHO 2023.)

surrogate to evaluate immunization programs, 2022 DTP3 (diphtheria, tetanus, and pertussis) coverage rates are still <50% in many developing nations while globally recovering to 84% from 2021’s 81%; the World Health Organization (WHO) estimates that 90% of the burden of pertussis is in developing regions. The overreporting of immunization coverage and underreporting of disease result in substantial underesti mation of the global burden of pertussis. WHO estimates are 40 million cases globally each year, with 400,000 deaths, mostly among infants

<3 months of age.

Before the institution of widespread immunization programs in the developed world, pertussis was one of the most common infectious causes of morbidity and death. In the United States before the 1940s, between 115,000 and 270,000 cases of pertussis were reported annu ally, with an average yearly rate of 150 cases per 100,000 population. With universal childhood immunization, the number of reported cases fell by >90%, and mortality rates decreased even more dramatically. Only 1010 cases of pertussis were reported in 1976 (Fig. 165-2). After that historic low, rates of pertussis increased slowly. In recent years, pertussis epidemics have been reported with increasing frequency in high-income countries, including Australia, the United Kingdom, and the United States. The United States experienced widespread pertus sis outbreaks in 2005, 2010, 2012, 2014, and 2015 at levels not seen in 40–50 years (48,000 reported cases in 2012). Although thought of as a disease of childhood, pertussis can affect people of all ages and is a known cause of prolonged coughing illness in adolescents and adults. In unimmunized populations, pertussis inci dence peaks during the preschool years, and well over half of children have the disease before reaching adulthood. In highly immunized popu lations such as those in North America, the peak incidence is among infants <1 year of age who have not completed the three-dose primary immunization series. An increase in pertussis incidence among adoles cents and adults began in the late 1990s and led to the introduction of an adolescent booster dose across North America by 2006. While the dis ease burden among adolescents decreased initially, children 7–10 years of age emerged as a high-risk group during a major outbreak in 2010. Most of the affected children were fully immunized. Subsequent outbreaks in 2012, 2014, and 2015 showed a shift in epidemiology, with pertussis incidence increasing among adolescents while still remaining elevated among 10-year-olds. The most highly affected cohorts were those who received acellular pertussis vaccines in infancy. Although adults contrib ute a smaller proportion of reported cases of pertussis than do children and adolescents, this difference may be related to a greater degree of underrecognition and underreporting. Several studies of prolonged CHAPTER 165 Pertussis and Other Bordetella Infections 2,500,000 2,000,000 Number of reported cases 1,500,000 1,000,000 500,000

Year

300,000 DTP 250,000 200,000 Number of cases 150,000 100,000 50,000

FIGURE 165-2 Reported cases of pertussis by year: United States, 1922–2021, marking the introduction of different vaccine types. (From the Centers for Disease Control and Prevention, Pertussis Surveillance Trend Reporting and Case Defintion | CDC. Available at https://www.cdc.gov/pertussis/surv-reporting.html. Accessed December 26, 2023.) coughing illness suggest that B. pertussis may be the etiologic agent in 12–30% of adults with cough that does not improve within 2 weeks. In one study of the efficacy of an acellular pertussis vaccine in adolescents and adults, the incidence of pertussis in the placebo group was 3.7–4.5 cases per 1000 person-years. Although this prospective cohort study yielded a lower estimate than the studies of cough illness, its results still translate to ~1 million cases of pertussis annually among adults in the United States. In addition, asymptomatic pertussis infection, estimated at 56% by a systemic review of tested household contacts, is common and appears to contribute to disease transmission. PART 5 Infectious Diseases Severe morbidity and high mortality rates, however, are restricted almost entirely to infants. In the United States between 2000 and 2017, infants <2 months old accounted for 84% of pertussis deaths with annual mean number of cases, hospitalizations, and deaths at 2957 (range 1803–4994), 1122 (range 544–1938), and 15 (range 3–35), respectively. Although school-age children are the source of infection for most households, adults are often the source for cases in high-risk infants and may serve as the reservoir of infection between epidemic years. ■ ■PATHOGENESIS Infection with B. pertussis is initiated by attachment of the organism to the ciliated epithelial cells of the nasopharynx. Attachment is mediated by surface adhesins (e.g., pertactin and filamentous hemagglutinin), which bind to the integrin family of cell-surface proteins, probably in conjunction with pertussis toxin. The role of fimbriae in adhesion and in maintenance of infection has not been fully delineated. Perhaps the result of redundancy of adhesins, no differences in virulence or clinical mani festations have been detected with the emergence of pertactin-negative strains. At the site of attachment, the organism multiplies, producing a variety of other toxins that cause local mucosal damage (tracheal cyto toxin, dermonecrotic toxin). Impairment of host defense by B. pertussis is mediated by pertussis toxin and adenylate cyclase-hemolysin toxin. There is local cellular invasion, with intracellular bacterial persistence; however, systemic dissemination does not occur. Systemic manifesta tions (lymphocytosis) result from the effects of the toxins. The pathogenesis of the clinical manifestations of pertussis is poorly understood. It is not known what causes the hallmark paroxysmal cough. A pivotal role for pertussis toxin has been proposed but has not been confirmed. It is thought that neurologic events in pertussis, such as seizures and encephalopathy, are due to hypoxia from cough ing paroxysms or apnea rather than to the effects of specific bacterial products. B. pertussis pneumonia, which occurs in up to 22% of infants with pertussis, is usually a diffuse bilateral primary infection. In older children and adults with pertussis, pneumonia is often due to second ary bacterial infection with streptococci or staphylococci. Deaths from

60,000 50,000 40,000 30,000 20,000 10,000

Tdap DTaP

pertussis among young infants are frequently associated with very high levels of leukocytosis and pulmonary hypertension. ■ ■IMMUNITY Both humoral and cell-mediated immunity are thought to be impor tant in pertussis. Although immunity after natural infection was thought to be lifelong, seroepidemiologic evidence demonstrates that it is not and that subsequent episodes of clinical pertussis are prevented by intermittent subclinical infection. Pertussis agglutinins were corre lated with protection in early studies of whole-cell pertussis vaccines. Antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae are all protective in animal models. Serologic correlates of protection conferred by acellular pertussis vaccines have not been established, although antibody to pertactin, fimbriae, and (to a lesser degree) pertussis toxin correlated best with protection in two efficacy trials. The duration of immunity after whole-cell pertussis vaccina tion is short-lived, with little protection remaining after 10–12 years. Waning of immunity is even more rapid in adolescents and children who have received all their immunizations with acellular vaccines— i.e., within 2–4 years after the fifth or sixth dose. The type of immune response elicited may affect duration of protection; natural infection and whole-cell pertussis vaccine elicit a Th1/Th17-predominant response, whereas acellular pertussis vaccines stimulate a Th2-biased response. Controlled Human Infection Models of pertussis are under development to facilitate better understanding of immunity after infec tion and after vaccination. ■ ■CLINICAL MANIFESTATIONS Pertussis is a prolonged coughing illness with clinical manifestations that vary by age (Table 165-1). Although not uncommon among ado lescents and adults, classic pertussis is most often seen in preschool and TABLE 165-1 Clinical Features of Pertussis, by Age Group and Diagnostic Status PERCENTAGE OF PATIENTS ADOLESCENTS AND ADULTS INFANTS AND CHILDREN FEATURE Cough Paroxysmal 70–99 89–93 Worse at night 61–87

Whoop 8–82 69–92 Post-tussive vomiting 17–65 48–60 Source: Reproduced with permission from PE Kilgore et al: Pertussis: Microbiology, disease, treatment, and prevention. Clin Microbiol Rev 29:449, 2016.

school-age children. After an incubation period averaging 7–10 days, an illness develops that is indistinguishable from the common cold and is characterized by coryza, lacrimation, mild cough, low-grade fever, and malaise. After 1–2 weeks, this catarrhal phase evolves into the par oxysmal phase: the cough becomes more frequent and spasmodic with repetitive bursts of 5–10 coughs, often within a single expiration. Posttussive vomiting is frequent, with a mucous plug occasionally expelled at the end of an episode. The episode may be terminated by an audible whoop, which occurs upon rapid inspiration against a closed glottis at the end of a paroxysm. During a spasm, there may be impressive neck-vein distension, bulging eyes, tongue protrusion, and cyanosis. Paroxysms may be precipitated by noise, eating, or physical contact. Between attacks, the patient’s appearance is normal, but increasing fatigue is evident. The frequency of paroxysmal episodes varies widely, from several per hour to 5–10 per day. Episodes are often worse at night and interfere with sleep. Most complications occur during the parox ysmal stage. Fever is uncommon and suggests bacterial superinfection. After 2–4 weeks, the coughing episodes become less frequent and less severe—changes heralding the onset of the convalescent phase. This phase can last 1–3 months and is characterized by gradual resolution of coughing episodes. For 6–12 months, intercurrent viral infections may be associated with a recrudescence of paroxysmal cough. Not all individuals who develop pertussis have classic disease. The clinical manifestations in adolescents and adults are more often atypical. The cough is severe, prolonged, and often paroxysmal. Though uncom mon, a whoop and vomiting with cough are more specific signs of

pertussis in adults with prolonged cough. Other suggestive features are a cough at night, sweating episodes between paroxysms of coughing, and exposure to other individuals with a prolonged coughing illness. ■ ■COMPLICATIONS Complications are frequently associated with pertussis and are more common among infants than among older children or adults. Sub conjunctival hemorrhages, abdominal and inguinal hernias, pneumo thoraces, and facial and truncal petechiae can result from increased intrathoracic pressure generated by severe fits of coughing. Weight loss can follow decreased caloric intake. Urinary incontinence, rib fracture, carotid artery aneurysm, and cough syncope have also been reported in adolescents and adults with pertussis. In a series of >1100 children <2 years of age who were hospitalized with pertussis, 27.1% had apnea, 9.4% had pneumonia, 2.6% had seizures, and 0.4% had encephalopa thy; 10 children (0.9%) died. Pneumonia is reported in <5% of ado lescents and adults and increases in frequency after 50 years of age. In contrast to the primary B. pertussis pneumonia that develops in infants, pneumonia in older children, adolescents, and adults with pertussis is usually caused by a secondary infection with encapsulated organisms such as Streptococcus pneumoniae or Haemophilus influenzae. ■ ■DIAGNOSIS If the classic symptoms of pertussis are present, clinical diagnosis is not difficult. However, particularly in older children and adults, it is difficult to differentiate infections caused by B. pertussis and B. par apertussis from other respiratory tract infections on clinical grounds. Therefore, laboratory confirmation should be attempted in all cases. Lymphocytosis (absolute lymphocyte count >108–109/L) is common among young children, in whom it is unusual with other infections, but not among adolescents and adults. Culture of nasopharyngeal secre tions remains the gold standard of diagnosis because of its 100% speci ficity, although DNA detection by PCR has replaced culture in most laboratories because of substantially increased sensitivity and quicker results. Multitarget real-time PCR methodology includes primers that differentiate between B. pertussis, B. parapertussis, and B. holmesii. The best specimen is collected by nasopharyngeal aspiration, in which a fine flexible plastic catheter attached to a 10-mL syringe is passed into the nasopharynx and withdrawn while gentle suction is applied. Since B. pertussis is highly sensitive to drying, secretions for culture should be inoculated without delay onto appropriate medium (Bordet-Gengou or Regan-Lowe), or the catheter should be flushed with a phosphatebuffered saline solution for culture and/or PCR. An alternative to the

aspirate is a Dacron or rayon nasopharyngeal swab; again, inoculation of culture plates should be immediate or an appropriate transport medium (e.g., Regan-Lowe charcoal medium) should be used. Results of PCR can be available within hours; cultures become positive by day 5 of incubation.

Nasopharyngeal cultures in untreated pertussis remain positive for a mean of 3 weeks after the onset of illness; these cultures become negative within 5 days of the institution of appropriate antimicrobial therapy. The duration of a positive PCR in untreated pertussis or after therapy is not known but exceeds that of positive cultures. Since much of the period during which the organism can be recovered from the nasopharynx falls into the catarrhal phase, when the etiology of the infection is not suspected, there is only a small window of opportunity for culture- or PCR-proven diagnosis. Cultures and PCR from infants and young children are more frequently positive than those from older children and adults; this difference may reflect earlier presentation of the former age group for medical care. As a result of the difficulties with laboratory diagnosis of pertussis in adolescents, adults, and patients who have been symptomatic for

4 weeks, increasing attention is being given to serologic diagnosis. Enzyme immunoassays detecting IgA and IgG antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae have been developed and assessed for reproducibility. Two- or fourfold increases in antibody titer are suggestive of pertussis, although cross-reactivity of some antigens (such as filamentous hemagglutinin and pertactin) among Bordetella species makes it difficult to depend diagnostically on seroconversion involving a single type of antibody. Criteria for serologic diagnosis based on comparison of results for a single serum specimen with established population values are gaining acceptance, and serologic measurement of antibody to pertussis toxin is becoming more widely standardized and available for diagnostic purposes, par ticularly in outbreak settings and for surveillance. CHAPTER 165 ■ ■DIFFERENTIAL DIAGNOSIS A child presenting with paroxysmal cough, post-tussive vomiting, and whoop is likely to have an infection caused by B. pertussis or B. paraper tussis; lymphocytosis increases the likelihood of a B. pertussis etiology. Viruses such as respiratory syncytial virus, rhinovirus, and adenovirus have been isolated from patients with clinical pertussis but probably represent co-infection, particularly in children <1 year of age. Pertussis and Other Bordetella Infections In adolescents and adults, who often do not have paroxysmal cough or whoop, the differential diagnosis of a prolonged coughing illness is more extensive. Pertussis should be suspected when any patient has a cough that does not improve within 14 days, a paroxysmal cough of any duration, a cough followed by vomiting (adolescents and adults), or any respiratory symptoms after contact with a laboratory-confirmed case of pertussis. Other etiologies to consider include infections caused by Mycoplasma pneumoniae, Chlamydia pneumoniae, adenovirus, influenza virus, and other respiratory viruses. Use of angiotensinconverting enzyme (ACE) inhibitors, reactive airway disease, and gas troesophageal reflux disease are well-described noninfectious causes of prolonged cough in adults. TREATMENT Pertussis ANTIBIOTICS The purpose of antibiotic therapy for pertussis is to eradicate the infecting bacteria from the nasopharynx; therapy does not sub stantially alter the clinical course unless given early in the catarrhal phase. Macrolide antibiotics are the drugs of choice for treatment of pertussis (Table 165-2); macrolide-resistant B. pertussis strains have been reported but are rare. Trimethoprim-sulfamethoxazole is rec ommended as an alternative for individuals allergic to macrolides. SUPPORTIVE CARE Young infants have the highest rates of complication and death from pertussis; therefore, most infants (and older children with

TABLE 165-2 Antimicrobial Therapy for Pertussis PRIMARY AGENTS ALTERNATE AGENT PATIENT AGE GROUP AZITHROMYCIN (AZ) ERYTHROMYCIN (ER) CLARITHROMYCIN <1 month AZ is the recommended agent for this age group, at 10 mg/kg per day in a single dose for 5 days ER is not preferred, only use if AZ unavailable; 40–50 mg/kg per day in 4 divided doses for 14 days 1-5 months 10 mg/kg per day in a single dose for 5 days 40–50 mg/kg per day in 4 divided doses for 14 days Infants (≥6 months) and children 10 mg/kg on day 1, 5 mg/kg mg per day (maximum 500 mg)

on days 2–5 40–50 mg/kg per day (maximum

2 g/d) in 4 divided doses for

14 days Adults 500 mg on day 1, 250 mg/d on days 2–5 2 g/d in 4 divided doses for

14 days Comments Abdominal discomfort, prescribed with caution to cardiac patients Frequent gastrointestinal side effects, hypersensitivity reactions aTrimethoprim-sulfamethoxazole (TMP-SMZ) replaces macrolides only in the event of a macrolide-resistant strain of Bordetella pertussis or when patients older than 2 months are allergic to or cannot tolerate macrolides. Source: T Tiwari et al: Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. MMWR Recomm Rep

54(RR-14):1, 2005. severe disease) should be hospitalized. A quiet environment may decrease the stimulation that can trigger paroxysmal episodes. Use of β-adrenergic agonists and/or glucocorticoids has been advocated by some authorities but has not been proven to be effective. Cough suppressants are not effective and play no role in the management of pertussis. INFECTION CONTROL MEASURES Hospitalized patients with pertussis should be placed in respiratory isolation, with the use of precautions appropriate for pathogens spread by large respiratory droplets. Isolation should continue for 5 days after initiation of macrolide therapy or, in untreated patients, for 3 weeks (i.e., until nasopharyngeal cultures are consistently negative). PART 5 Infectious Diseases ■ ■PREVENTION Chemoprophylaxis Because the risk of transmission of B. pertussis within households is high, chemoprophylaxis is widely recommended for household contacts of pertussis cases regardless of their immuniza tion status and should be initiated within 21 days of cough onset in the index case. The effectiveness of chemoprophylaxis is supported by sev eral epidemiologic studies of institutional and community outbreaks. In the only randomized, placebo-controlled study, erythromycin esto late (50 mg/kg per day; maximum dose, 1 g/d) was effective in reducing the incidence of bacteriologically confirmed pertussis by 67%; how ever, there was no decrease in the incidence of clinical disease. Despite these results, authorities continue to recommend chemoprophylaxis, particularly in households with members at high risk of severe disease (children <1 year of age, pregnant women). Data on the use of the newer macrolides for chemoprophylaxis are not available, but these drugs are commonly used because of their increased tolerability and their effectiveness. Immunization (See also Chap. 129) The mainstay of pertussis prevention is active immunization. Pertussis vaccine became widely used in North America after 1940; the reported number of pertussis cases subsequently fell by >90%. Whole-cell pertussis vaccines are pre pared through the heating, chemical inactivation, and purification of whole B. pertussis organisms. Despite their efficacy (average estimate, 85%; range for different products, 30–100%), whole-cell pertussis vaccines are associated with adverse events—both common (fever; injection-site pain, erythema, and swelling; irritability) and uncom mon (febrile seizures, hypotonic-hyporesponsive episodes). Alleged associations of whole-cell pertussis vaccine with encephalopathy,

TRIMETHOPRIM (TMP)- SULFAMETHOXAZOLE (SMZ)a Not recommended in this age group Contraindicated in infants <2 months 15 mg/kg per day in 2 divided doses for 7 days Only for infants ≥2 months (otherwise contraindicated); TMP 8 mg/kg per day, SMZ 40 mg/kg per day in 2 divided doses for 14 days 15 mg/kg per day (maximum 1 g/d) in 2 divided doses for 7 days TMP 8 mg/kg per day, SMZ 40 mg/kg per day in 2 divided doses for 14 days 1 g/d in 2 divided doses for 7

days TMP 320 mg/d, SMZ 1600 mg/d in 2 divided doses for 14 days Epigastric distress and cramps For patients allergic to macrolides, data on effectiveness are limited sudden infant death syndrome, and autism, although not substantiated, spawned an active anti-immunization lobby. The development of acel lular pertussis vaccines, which are effective and less reactogenic, has greatly alleviated concerns about the inclusion of pertussis vaccine in the combined infant immunization series. Although a wide variety of acellular pertussis vaccines were devel oped, only a few are still marketed widely; all contain pertussis toxoid and filamentous hemagglutinin. One acellular pertussis vaccine also contains pertactin, and another contains pertactin and two types of fimbriae. Adult formulations of acellular pertussis vaccines have been shown to be safe, immunogenic, and efficacious in clinical trials in adolescents and adults and are now recommended for routine immu nization of these groups in several countries. Although whole-cell vaccines are still used extensively in devel oping regions of the world, acellular pertussis vaccines are used exclusively for childhood immunization in much of the developed world. In light of evidence of early waning of immunity among chil dren who received acellular pertussis vaccine in infancy, the WHO Strategic Advisory Group of Experts (SAGE) recommends that countries using whole-cell pertussis vaccine for the primary infant immunization series continue to do so. In countries using acellular pertussis vaccines in infancy, additional booster immunizations in older children, adolescents, and adults are recommended to prevent pertussis in high-risk infants. Pertussis immunization is also recom mended during pregnancy to increase passive transfer of maternal antibodies to the fetus. Studies in high-income countries demonstrate that immunization of women during pregnancy is 90–93% effective at preventing pertussis in infants <2 months of age and is safe. In North America, acellular pertussis vaccines for children are given as a threedose primary series at 2, 4, and 6 months of age, with a reinforcing dose at 15–18 months of age and a booster dose at 4–6 years of age. Adolescents (11–18 years of age) and all unvaccinated adults should receive a dose of the adult-formulation diphtheria–tetanus–acel lular pertussis vaccine. Immunization is specifically recommended for health care providers, individuals in close contact with infants, and women at 27–36 weeks of every pregnancy, preferably in the earlier weeks of this range. Pertussis vaccine coverage among U.S. adolescents was 89.9% in 2022; among pregnant women, it was 55.4% during October 2022 to January 2023; and it was low among adults, at 30.1% in 2019. Further improvements in adult vaccine coverage may permit better control of pertussis across the age spectrum, with collateral protection of infants too young to be immunized. However, more effective vaccines with longer-lasting protection will ultimately be needed to control this disease.

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