8.6.15 Bordetella infection 1073

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However, the poten- tial persists for B. pertussis infection to cause fatal disease in young infants throughout the world. Aetiology Two of the seven Bordetella species that infect humans, B. pertussis and human-adapted B. parapertussis, are strictly human pathogens. They evolved independently from a common B. bronchiseptica an- cestor. The B. pertussis population is continuously evolving. As a re- sult, antigenic variation occurs between B. pertussis in circulation and the B. pertussis vaccine strains and composition. Use of both whole-cell and acellular vaccines is associated with clonal expansion of B. pertussis strains that could potentially lead to decreased vaccine efficacy. In immunocompromised hosts B. bronchiseptica causes respira- tory illnesses. B. holmesii and B. hinzii cause respiratory illnesses, bacteraemia, and endocarditis. B. trematum is occasionally isolated from ear and skin infections and B. petrii from patients with cystic fibrosis. Epidemiology The estimated number of pertussis deaths globally decreased from 390 000 deaths in 1999 to 160 700 in 2014. Underestimation and how this varies with age and surveillance in- tensity is central to understanding pertussis epidemiology. Pertussis occurs in all ages; however, incidence has always been highest in in- fants and children. It is estimated that each year 6% of adults ex- perience a B. pertussis infection. While most of these infections are asymptomatic, they remain a potential source for spread to those at risk of severe disease. The incidence of reported pertussis has increased over the past 30 years, and particularly so since the mid-2000s. Contributory factors to these increases include heightened awareness of the dis- ease as a cause of illness across the age range, increased availability of more sensitive diagnosis tests, the more rapid wane of immunity that occurs following immunization with acellular compared to whole- cell vaccines, and genetic changes in the bacterium. Mortality The propensity for pertussis to kill young infants is unique among vaccine preventable diseases, with the exception of tetanus. Estimates of pertussis mortality are complicated by the relationship between pertussis and malnutrition and by the very small proportion of deaths in young children globally for which the cause is medically certified. A prolonged period of weight loss frequently complicates pertussis in the developing world. In the developed world use of complimentary notification systems is required in order to prevent underestimation of the number of pertussis deaths. Pertussis deaths occur despite intensive care. Treatment of young infants with critical pertussis illness remains challenging. Morbidity Most pertussis incidence estimates are based on passive notifica- tion which identifies only a minority of cases. The proportion of cases notified decreases with increasing age and decreasing severity. Approximately 15–20% of acute persistent cough illnesses in school- age children, adolescents, and adults are caused by B. pertussis infection. The incidence rate, in adolescents and adults, of

 symptomatic cough illnesses caused by B. pertussis infection is 25 to 500 per 100 000. Prevention Neither disease nor immunization confer lifelong immunity. Pertussis vaccines protect against disease more than infection. Schedules consist of a three-dose infant series and subsequent booster doses. In infants, one dose of pertussis vaccine provides 50% protection and two doses provide 80% protection against severe dis- ease. Pertussis remains endemic in adolescents and adults. Without boosters it is also endemic in school-age children. Whole-cell and acellular pertussis vaccines are combined with other antigens. Acellular vaccines contain between one and five B. pertussis antigens. The most efficacious whole-cell and acellular vaccines induce protection against clinical disease in approximately 85% of recipients. In order to minimize the pertussis risk to infants the primary series must be completed without delay. However, without booster doses, timely completion of the primary series is insufficient to pre- vent disease in infants. Because the primary infant immunization series cannot protect the youngest

infants, a dose of pertussis vac- cine given during pregnancy is now a component of the immuniza- tion schedule in several countries. Immunity induced by whole-cell pertussis vaccines persists for approximately 5 years after completion of a primary series. Duration of protection is shorter following an acellular vaccine primary im- munization series. Protection following both disease and immuniza- tion is superior to either alone; hence those who have had pertussis should be immunized. Acellular vaccines are both safe and efficacious in adolescents and adults. In adolescents, protection against clinical pertussis wanes within two to four years of immunization. Currently immuniza- tion of pregnant women is the only adult immunization strategy for which there is evidence of prevention of pertussis in young infants. Acellular pertussis vaccine should be given during each pregnancy. Preferably it should be given early in the interval between 27 and 36 weeks gestation.

Because of the risk of nosocomial spread, healthcare workers should receive acellular pertussis vaccine booster doses. Pathogenesis/pathology Pathogenesis remains poorly understood and the pathophysiology of paroxysmal cough and other characteristic features of the illness remain unknown. B. pertussis is highly infectious, and each primary case produces approximately 15 secondary cases. Transmission is primarily by aerosolized droplets. There is an average of two weeks between suc- cessive cases. In immunized populations the household secondary attack rate remains greater than 80%, although many such infections are asymptomatic. Bordetella spp. have multiple virulence factors including fila- mentous haemagglutinin, fimbriae, pertactin, pertussis toxin, ad- enylate cyclase, tracheal cytotoxin, and lipopolysaccharide. While their individual effects have been characterized, how they act to- gether to cause pertussis disease is not known. Several are im- mune-modulatory. Pertussis is characterized by an inadequate immunological response. Impairment of the immune response by B. pertussis virulence factors is a potential mechanism that contrib- utes to disease severity. Clinical features Presentation varies with age, immunization, and previous infection. Mild illness which is difficult to distinguish from illnesses caused by other respiratory pathogens, is common. In infants, apnoea, cyanosis, and paroxysmal cough are key symp- toms. These can occur early in the illness before duration of cough allows for the pertussis clinical case definition to be met. Thus, per- tussis must be considered in infants presenting with an acute life- threatening event or apnoea. Pertussis in the nonimmunized child is a coughing illness increasing in severity over several weeks with distressing repeated forceful expirations followed by a gasping inhalation. Between par- oxysms symptoms can be minimal. The contrast between parental descriptions of the previous night’s events and the normal appear- ance the following morning can deceive the assessing clinician. Following pertussis, viral respiratory tract infections can cause coughing paroxysms to recur. In school-age children immunized in infancy, clinical symptoms which distinguish pertussis are whooping, vomiting, sputum pro- duction, and the absence of wheezing. Most B. pertussis infections in adults are asymptomatic or are atypical with few symptoms. Persistent cough is the cardinal fea- ture of clinical pertussis in adults. Pertussis should be considered in any adult with an acute cough that persists for two weeks or more. Cough is worse at night and often paroxysmal. Symptoms that, if present, increase the likelihood that a cough illness is caused by B. pertussis infection are the presence of whooping or post-tussive vomiting. Symptoms which decrease the likelihood that a cough illness is caused by B. pertussis infection are the presence of fever and/or the absence of paroxsymal cough. Differential diagnosis Not considering pertussis in someone with an acute persistent cough is a more important cause of a missed diagnosis than is an atypical presentation. In infants, coinfection with respiratory viruses occurs not infrequently, causing more severe disease and diagnostic confusion. A careful history of coughing illnesses in other household mem- bers is critical. Successive household members are

symptomatic over weeks to months rather than having almost concurrent re- spiratory illnesses. Infections with Mycoplasma pneumoniae, Chlamydia pneumo- niae, C. trachomatis, adenoviruses, and other respiratory viruses can cause illnesses which overlap clinically with pertussis. Particularly because it is also worse at night, cough from sinusitis can be con- fused with pertussis. Presentation of cough illness in adults is often delayed until symp- toms have persisted for several weeks. Other causes of chronic cough such as asthma, gastro-oesophageal reflux, tuberculosis, and malig- nancy need to be considered.

8.6.15 Bordetella infection 1075 Clinical investigations Laboratory diagnosis of pertussis has improved with the develop- ment of polymerase chain reaction (PCR) and serological assays. B. pertussis is a small Gram-negative coccobacillus. It is strictly aerobic and fastidious; special media such as charcoal blood agar are necessary. Culture lacks sensitivity. Careful collection and rapid transport of the nasopharyngeal sample to the laboratory is required. Immunization and antibiotic treatment reduce culture positivity. The organism is most abundant before the onset of par- oxysmal cough and is rarely recovered once cough has been present for three weeks. PCR is more sensitive than culture. Sensitivity decreases with illness duration and less so with antibiotic treatment. Real-time PCR assays enable laboratory confirmation within hours of specimen collection. Antibodies to pertussis toxin are specific to B. pertussis. Only measurement of IgG antibodies is recommended. In the absence of immunization in the previous two years a single antibody titre of 100 IU/ml has been shown to be sensitive and specific for recent B. pertussis infection. A sensitive and specific oral fluid assay that measures IgG to pertussis toxin has been developed. The preferred laboratory test varies with age and cough duration. PCR is particularly useful in infants. In older children, adolescents, and adults the sensitivity of culture and PCR is lower, and, particu- larly with later presentation, serology is more useful. Criteria for diagnosis The World Health Organization surveillance case definition is a case diagnosed as pertussis by a physician; or a person with cough for two weeks with at least one of: paroxysms of coughing, inspiratory whoop, or posttussive vomiting without other apparent cause. Laboratory confirmation is by isolation of B. pertussis; or detection of genomic sequences by PCR, or positive paired serology. Pertussis should be considered in anyone with paroxysmal cough of any dur- ation, or cough with inspiratory whoop, or cough ending in apnoea, vomiting, or gagging. Treatment (See Table 8.6.15.1.) Antibiotic treatment reduces infectivity. B. pertussis cannot be isolated from most patients after five days of an appropriate anti- biotic. If started within two weeks of symptom onset, antibiotic treatment may decrease symptom severity. Antibiotics are recommended if started within four weeks of illness onset. Erythromycin, azithromycin, and clarithromycin are effective against B. pertussis. Azithromycin is as efficacious, better tolerated, and requires a shorter treatment course than erythromycin. It should be used with caution in those with pro- longed QT syndrome and other proarrhythmic conditions. Trimethoprim-sulfamethoxazole is an alternative but data on its efficacy is limited. Azithromycin is the preferred macrolide for infants less than one month old with clarithromycin not recommended in this age group. Use of erythromycin or azithromycin in infants less than one month old is associated with an increased risk of infantile hyper- trophic pyloric stenosis, and monitoring for this condition should be continued for one month after treatment with azithromycin or erythromycin. Prophylaxis is most important when there is an infant at risk of exposure. Interruption of household transmission is only possible if treatment is started within three weeks of symptom onset in the primary case and before any symptomatic secondary cases. Table 8.6.15.1 Choice of antibiotic agents for the treatment or prevention of pertussis1,2 Age Antibiotic Recommended Alternative Azithromycin Erythromycin Clarithromycin

Trimethoprim- Sulfamethoxazole Younger than 1 month 10 mg/kg/day as a single dose daily for 5 daysa,b 40 mg/kg/day in four divided doses for 14 days Not recommended Contraindicated if age <2 months 1 to 5 months 10 mg/kg/day as a single dose daily for 5 daysa,b 40 mg/kg/day in four divided doses for 14 days 15 mg/kg per day in two divided doses for 7 days 2 mo or older: TMP, 8 mg/ kg/day; SMX, 40 mg/kg/ day in 2 doses for 14 days 6 months or older and children 10 mg/kg as a single dose on day 1 (maximum 500 mg), then 5 mg/kg/ day as a single dose on days 2 to 5 (maximum 250 mg/day)a 40 mg/kg/day in four divided doses for 7 to 14 days (maximum 1 to 2 g/ day) 15 mg/kg per day in two divided doses for 7 days (maximum 1 g/day) 2 mo or older: TMP, 8 mg/ kg/day; SMX, 40 mg/kg/ day in 2 doses for 14 days Adolescents and adults 500 mg as a single dose on day 1, then 250 mg as a single dose on days 2 to 5a 2 g/day in four divided doses for 7 to 14 days 1 g/day in two divided doses for 7 days M, TMP, 320 mg/day;
SMX 1600 mg/day in two divided doses for 14 days a TMP indicates trimethoprim; SMX, sulfamethoxazole. Azithromycin should be used with caution in people with prolonged QT interval and certain proarrhythmic conditions. b Preferred macrolide for this age because of risk of idiopathic hypertrophic pyloric stenosis associated with erythromycin.

1. American Academy of Pediatrics. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st edition. Elk Grove Village, IL. American Academy of Pediatrics; 2018, p. 625.
2. Tiwari T, Murphy TV, Moran J, National Immunization Program CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. Morbidity & Mortality Weekly Report 2005; Recommendations & Reports, 54(RR-14): 1–16.

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