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Bordetella pertussis

Bordetella is a genus of small (0.2 - 0.7 µmGram-negative, aerobic coccobacillus capsulate of the genus *Bordetella*, and the causative agent of pertussis or whooping cough. Unlike *B.bronchiseptica*, *B. pertussis* is nonmotile. Its virulence factorsinclude pertussistoxin, filamentoushæmagglutinin, pertactin,fimbria, and tracheal cytotoxin.

There does not appear to be a zoonotic reservoir for *B. pertussis*—humans are its only host.

The bacterium is spread by airborne droplets; its incubation period is seven to 14 days.

Pertussis

Pertussis (or whooping cough) is an infection of the respiratory system characterized by a "whooping" sound when the person breathes in. In the US, it killed between 10,000 and 20,000 people per year before a vaccine was available. Vaccination has transformed this; between 1985 and 1988, fewer than 100 children died from pertussis. Worldwide in 2000, according to the WHO, around 39 million people were infected annually and about 297,000 died. A graph is available showing the dramatic effect of introducing vaccination in England. *Bordetella pertussis* infects its host by colonizing lung epithelial cells. The bacterium contains a surface protein, filamentous haemagglutinin adhesin, which binds to the sulfatides found on cilia of epithelial cells. Once anchored, the bacterium produces tracheal cytotoxin, which stops the cilia from beating. This prevents the cilia from clearing debris from the lungs, so the body responds by sending the host into a coughing fit. These coughs expel some bacteria into the air, which are free to infect other hosts.

B. pertussis has the ability to inhibit the function of the host's immune system. The toxin, known as pertussis toxin (or PTx), inhibits G proteincoupling that regulates an adenylate cyclase-mediated conversion of ATP to cyclic AMP. The end result is phagocytes convert too much ATP to cyclic AMP, which can cause disturbances in cellular signaling mechanisms, and prevent phagocytes from correctly responding to an

infection. PTx, formerly known as lymphocytosis-promoting factor, causes a decrease in the entry of lymphocytes into lymph nodes, which can lead to a condition known as lymphocytosis, with a complete lymphocyte count over of 4000/μL in adults or over 8000/μL in children.

The infection occurs mostly in children under the age of one when they are unimmunized, or children with faded immunity, normally around the ages 11 through 18. The signs and symptoms are similar to a common cold: runny nose, sneezing, mild cough, and low-grade fever. The patient becomes most contagious during the catarrhal stage of infection, normally two weeks after the coughing begins. It may become airborne when the person coughs, sneezes, or laughs. Pertussis vaccine is part of the diphtheria, tetanus, and acellular pertussis (DTaP) immunization. The paroxysmal cough precedes a crowing inspiratory sound characteristic of pertussis. After a spell, the patient might make a “whooping” sound when breathing in, or may vomit. Adults have milder symptoms, such as prolonged coughing without the “whoop”. Infants less than six months also may not have the typical whoop. A coughing spell may last a minute or more, producing cyanosis,apnoea and seizures. However, when not in a coughing fit, the patient does not experience trouble breathing. This is because *B. pertussis* inhibits the immune response, so very little mucus is generated in the lungs. A prolonged cough may be irritating and sometimes a disabling cough may go undiagnosed in adults for many months.

Diagnosis

A nasopharyngeal or an oropharynx swab is sent to the bacteriology laboratory for Gram stain (Gram negative, coccobacilli, diplococci arrangement), growth on Bordet-Gengou agar or BCYE plate with added cephalosporin to select for the organism, which shows mercury-drop-like colonies.

Several diagnostic tests are available, especially ELISA kits. These are designed to detect FHA and/or PT antibodies of the following classes: IgG, IgA, IgM. Some kits use a combination of antigens which will lead to a higher sensitivity, but might also make the interpretation of the results harder since one cannot know which antibody has been detected. There is also a new rapid molecular test, real-time PCR, based on the so-called FilmArray technology . This test takes about one hour and detects about 15-17 viruses and bacteria, including B. pertussis.

The organism is oxidase positive, but urease, nitrate reductase, and citrate negative. It is also nonmotile.

Pertussis — commonlycalled **whoopingcough** (/ˈhuːpɪŋ kɒf/ or /ˈhwuːpɪŋ kɒf/) — is a highly contagious bacterial disease caused by *Bordetella pertussis*. In some countries, this disease is called the 100 days' cough or cough of 100 days

Symptoms are initially mild, and then develop into severe coughing fits, which produce the namesake high-pitched "whoop" sound in infected babies and children when they inhale air after coughing. The coughing stage lasts approximately six weeks before subsiding.

Prevention by vaccination is of primary importance given the seriousness of the disease in children. Although treatment is of little direct benefit to the person infected, antibiotics are recommended because they shorten the duration of infectiousness. It is currently estimated that the disease annually affects 48.5 million people worldwide, resulting in nearly 295,000 deaths.

Signs and symptoms

The classic symptoms of pertussis are a paroxysmal cough, inspiratory whoop, and fainting and/or vomiting after coughing. The cough from pertussis has been documented to cause subconjunctival hemorrhages, rib fractures, urinary incontinence, hernias, post-cough fainting, and vertebral artery dissection. Violent coughing can cause the pleura to rupture, leading to a pneumothorax. If there is vomiting after a coughing spell or an inspiratory whooping sound on coughing, the likelihood almost doubles that the illness is pertussis. On the other hand, the absence of a paroxysmal cough or posttussive emesis makes it almost half as likely.

The incubation period is typically seven to ten days with a range of four to 21 days and rarely may be as long as 42 days, after which there are usually mild respiratory symptoms, mild coughing, sneezing, or runny nose. This is known as the catarrhal stage. After one to two weeks, the coughing classically develops into uncontrollable fits, each with five to ten forceful coughs, followed by a high-pitched "whoop" sound in younger children, or a gasping sound in older children, as the patient struggles to breathe in afterwards (paroxysmal stage).

Fits can occur on their own or can be triggered by yawning, stretching, laughing, eating or yelling; they usually occur in groups, with multiple episodes every hour around the clock. This stage usually lasts two to eight weeks, or sometimes longer. A gradual transition then occurs to the convalescent stage, which usually lasts one to two weeks. This stage is marked by a decrease in paroxysms of coughing, both in frequency and severity, and a cessation of vomiting. A tendency to produce the "whooping" sound after coughing may remain for a considerable period after the disease itself has cleared up.

Regulation of virulence factor expression

The expression of many *Bordetella* adhesins and toxins is controlled by the two-component regulatory system BvgAS. Much of what is known about this regulatory system is based on work with *B. bronchiseptica*, but BvgAS is present in *B. pertussis*, *B. parapertussis* and *B. bronchiseptica*and is responsible for phase variation or phenotypic modulation.

BvgS is a plasma membrane-bound sensor kinase which responds to stimulation by phosphorylating a cytoplasmic helix-turn-helix-containing protein, BvgA. When phosphorylated, BvgA has increased affinity for specific binding sites in Bvg-activated promoter sequences and is able to promote transcription in *in vitro* assays.

Most of the toxins and adhesins under BvgAS control are expressed under Bvg^+ conditions (high BvgA-P_i concentration). But there are also genes expressed solely in the Bvg^- state, most notably the flagellin gene *flaA*. The regulation of Bvg repressed genes is mediated by the product of a 624-bp open reading frame downstream of *bvgA*, the so-called Bvg-activated repressor protein, BvgR. BvgR binds to a consensus sequence present within the coding sequences of at least some Bvg-repressed genes. Binding of this protein to the consensus sequence represents gene expression by reducing transcription.

It is not known what the physiological signals for BvgS are, but *in vitro* BvgAS can be inactivated by millimolar concentrations of magnesium sulfate or nicotinic acid, or by reduction of the incubation temperature to ≤ 26°C.

The identification of a specific point mutation in the BvgS gene which locks *B. bronchiseptica* in an intermediate Bvg phase revealed a class of

BvgAS-regulated genes that are exclusively transcribed under intermediate concentrations of BvgA-P_i. This intermediate (Bvg_i) phenotype can be reproduced in wild-type *B. bronchiseptica* by growth of the bacteria in a medium containing intermediate concentrations of the BvgAS modulator, nicotinic acid. In these conditions, some, but not all of the virulence factors associated with the Bvg^+ phase are expressed, suggesting this two-component regulatory system can give rise to a continuum of phenotypic states in response to the environment

Diagnosis

Methods used in laboratory diagnosis include culturing of nasopharyngeal swabs on Bordet-Gengou medium, polymerase chain reaction (PCR) , direct immunofluorescence (DFA), and serological methods. The bacteria can be recovered from the patient only during the first three weeks of illness, rendering culturing and DFA useless after this period, although PCR may have some limited usefulness for an additional three weeks.

For most adults and adolescents, who often do not seek medical care until several weeks into their illness, serology may be used to determine whether antibody against pertussis toxin or another component of *B. pertussis* is present at high levels in the blood of the patient. By this stage they have been contagious for some weeks and may have spread the infection to many people. Because of this, adults, who are not in great danger from pertussis, are increasingly being encouraged to be vaccinated.

A similar, milder disease is caused by *B. parapertussis*.

Prevention

The primary method of prevention for pertussis is vaccination. There is insufficient evidence to determine the effectiveness of antibiotics in those who have been exposed but are without symptoms. Prophylactic antibiotics, however, are still frequently used in those who have been exposed and are at high risk of severe disease (such as infants).

Vaccine

Pertussis vaccines are effective routinely recommended by the World Health Organization and the Center for Disease Control and Prevention, and saved over half a million lives in 2002. The multi-component acellular pertussis vaccine, for example, is between 71-85% effective with greater effectiveness for more severe disease. Despite widespread use of the vaccine however, pertussis has persisted in vaccinated populations and is today one of the most prevalent vaccine-preventable diseases in Western countries. Recent resurgences in pertussis infections are attributed to a combination of waning immunity and new mutations in the bacteria that existing vaccines are unable to effectively control. Immunization against pertussis does not confer lifelong immunity, a 2011 study by the CDC indicated that the duration of protection may only last three to six years. This covers childhood, which is the time of greatest exposure and greatest risk of death from pertussis. For children, the immunizations are commonly given in combination with immunizations against tetanus, diphtheria,polio and haemophilus influenzae type B at ages two, four, six, and 15–18 months. A single later booster is given at four to six years of age. (US schedule). In the UK, pertussis vaccinations are given at 2, 3 and 4 months, with a pre-school booster at 3 years 4 months.

Dr. Paul Offit, chief of the Director of the Vaccine Education Center at the Children's Hospital of Philadelphia, comments that the last pertussis vaccination people receive may be their booster at age 11 or 12 years old. However, he states that it is important for adults to have immunity as well to prevent transmission of the disease to infants. While adults rarely die if they contract pertussis after the effects of their childhood vaccinations have worn off, they may transmit the disease to people at much higher risk of injury or death. To reduce morbidity and spread of the disease, Canada, France, the U.S. and Germany have approved pertussis vaccine booster shots. In 2012, a federal advisory panel recommended that all U.S. adults receive vaccination. Later that year, health officials in the UK recommended the vaccination of pregnant women (between 28 – 38 weeks of pregnancy) in order to protect their unborn children. Designed to protect babies from birth until their first standard vaccination at eight weeks of age, this vaccine was introduced in response to the ongoing outbreak of pertussis in the UK, the worst in over a decade.

The pertussis booster for adults is combined with a tetanus vaccine and diphtheria vaccine booster; this combination is abbreviated "Tdap" (Tetanus, diphtheria, acellular pertussis). It is similar to the childhood vaccine called "DTaP" (Diphtheria, Tetanus, acellular Pertussis), with the main difference that the adult version contains smaller amounts of the diphtheria and pertussis components — this is indicated in the name by the use of lower-case "d" and "p" for the adult vaccine. The lower-case "a" in each vaccine indicates that the pertussis component is acellular, or cell-free, which improves safety by dramatically reducing the incidence of side effects. Adults should request the Tdap instead of just a tetanus vaccination in order to receive the multi-vaccine. The pertussis component of the original DPT vaccine accounted for most of the minor local and systemic side effects in many vaccinated infants (such as mild fever or soreness at the injection site). The newer acellular vaccine, known as DTaP, has greatly reduced the incidence of adverse effects compared to the earlier "whole-cell" pertussis vaccine, however the efficacy of the acellular vaccine declines faster that the whole-cell vaccine.

Infection with pertussis induces incomplete natural immunity that wanes over time. Natural immunity lasts longer than vaccine-induced immunity, with one study reporting maximum effectiveness as long as 20 years in the former and 12 in the latter.

Management

People with pertussis are infectious from the beginning of the catarrhal stage (runny nose, sneezing, low-grade fever, symptoms of the common cold) through the third week after the onset of paroxysms (multiple, rapid coughs) or until 5 days after the start of effective antimicrobial treatment.

A reasonable guideline is to treat people age >1 year within 3 weeks of cough onset and infants age <1 year and pregnant women (especially near-term) within 6 weeks of cough onset. If the patient is diagnosed late, antibiotics will not alter the course of the illness and, even without antibiotics, the patient should no longer be spreading pertussis

Antibiotics decrease the duration of infectiousness and thus prevent spread.

The antibiotic erythromycin or azithromycin is a front-line treatment Newer macrolides are frequently recommended due to lower rates of side

effects . Trimethoprim-sulfamethoxazole (TMP-SMZ) may be used in those with allergies to first-line agents or in infants who have a risk of pyloric stenosis from macrolides. Effective treatments of the cough associated with this condition have not been developed.

Erythromycin, clarithromycin, and azithromycin are preferred for the treatment of pertussis in persons ≥1 month of age.

Prognosis

Common complications of the disease include pneumonia, encephalopathy , earache, or seizures.

Most healthy older children and adults will have a full recovery from pertussis, however those with comorbid conditions can have a higher risk of morbidity and mortality.

Infection in newborns is particularly severe. Pertussis is fatal in an estimated 1.6% of hospitalized infants who are under one year of age. Infants under one are also more likely to develop complications e.g., pneumonia (20%), encephalopathy(0.3%), seizures (1%), failure to thrive, and death (1%) -perhaps due to the ability of the bacterium to suppress immune response against it. Pertussis can cause severe paroxysm-induced cerebral hypoxia and 50% of infants admitted to hospital will suffer apneas. Reported fatalities from pertussis in infants have increased substantially over the past 20 years.

Epidemiology

Worldwide, whooping cough affects 48.5 million people yearly. As of 2010 it caused about 81,000 deaths, down from 167,000 in 1990. This is despite generally high coverage with the DTP and DTaP vaccines. Pertussis is one of the leading causes of vaccine-preventable deaths world-wide. 90% of all cases occur in developing countries.

Before vaccines, an average of 178,171 cases were reported in the U.S., with peaks reported every two to five years; more than 93% of reported cases occurred in children under 10 years of age. The actual incidence was likely much higher. After vaccinations were introduced in the 1940s, incidence fell dramatically to less than 1,000 by 1976. Incidence rates have increased since 1980. In 2012, rates in the United States reached a high of 41,880 people; this is the highest it has been since 1955 when numbers reached 62,786.

Pertussis is the only vaccine-preventable disease that is associated with increasing deaths in the U.S. The number of deaths increased from four in 1996 to 17 in 2001, almost all of which were infants under one year. In Canada, the number of pertussis infections has varied between 2,000 and 10,000 reported cases each year over the last ten years.

Australia reports an average of 10,000 cases a year, but the number of cases has increased in recent years. In the U.S. pertussis in adults has increased significantly since about 2004