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Most strains are inhibited by penicillin G in concentrations of 0.6 μg per ml or less.

Although many strains are still highly sensitive to ampicillin, there has been a recent increase in the frequency of strains resistant to this agent. This has become a sufficiently important problem so that it is now recommended that, after the necessary cultures have been carried out, the initial therapeutic agent of serious infections due to *H. influenzae* be chloramphenicol, as described below. If the organism proves to be resistant to ampicillin, treatment is completed with chloramphenicol. However, if the isolated strain is sensitive to ampicillin, administration of chloramphenicol is discontinued and ampicillin is substituted. For less serious forms of disease due to *H. influenzae* (otitis media, acute pharyngitis) resistant to ampicillin, a tetracycline compound may be effective initially; if the recovered strain proves to be sensitive to ampicillin, treatment is changed to this drug.

The dose of ampicillin in *H. influenzae* meningitis is 300 to 400 mg per kg per day, given in quantities of equal size and equally spaced. The management of otitis media or pharyngitis often requires no more than 100 to 150 mg per kg per day given by mouth. For adults with these infections, 2 to 4 g per day orally for 7 to 10 days usually suffices. Diarrhea is not infrequent in patients treated with ampicillin. Ampicillin therapy may fail in influenzal meningitis when complications, e.g., subdural empyema, supervene.

Although practically all strains of *H. influenzae* are sensitive to very small quantities of penicillin G, the therapeutic effects of this antibiotic are poor, and it must not be used as the sole agent for the treatment of meningitis due to this organism. The results with the tetracyclines are too variable to permit them to be recommended. An alternate regimen useful in influenzal meningitis is chloramphenicol (1 g intravenously every 6 h for adults; for children, 50 mg per kg per day in intravenous doses of equal size and equally spaced) plus sulfisoxazole or sulfadiazine (100 mg per kg per day). Regardless of the drug used, therapy should be continued for 2 weeks. Chloramphenicol or tetracycline is usually sufficient to treat upper respiratory tract infections, pneumonia, or otitis media in patients who are "sensitive" to penicillin.

## HEMOPHILUS PERTUSSIS

Whooping cough (pertussis) occurs in about 85 percent of all unimmunized children. It is characterized by an inflammation of the entire respiratory tract which produces paroxysmal cough and the typical inspiratory stridor, or "whoop."

**ETIOLOGY** The causative agent is *Hemophilus pertussis (Bordetella pertussis)*, a short or ovoid, gram-negative, nonmotile, nonsporulating, facultatively anaerobic bacillus. Bipolar staining is frequent, and encapsulation can be demonstrated by special stains.

The organism multiplies best on Bordet-Gengou medium. It contains two antigens. The heat-stable O antigen is common to all strains. Five varieties of a heat-labile specific agglutinogen K (1,2,3,4,5) are also present. All strains contain two or more of these antigens. This is of clinical importance because, in some areas of the world, the infecting strain has been found to have different K agglutinogens than those present in the vaccine being used to prevent the disease, resulting in failure of immunization.

Other infectious agents may rarely produce the syndrome of whooping cough. Among these are *B. parapertussis* and *B. bronchiseptica.* Several types of adenovirus (1,2,3,5,12) have been reported to produce a syndrome identical in all respects to that due to *B. pertussis.*

**EPIDEMIOLOGY** Pertussis is worldwide. Where the disease has not been present for several years, it tends to assume epidemic proportions when it reappears. In some areas, it is most common during the winter; in others it is seen with greatest frequency in the late summer and fall. The index of contagion is 80 to 100 percent; about 200,000 cases occur in the United States each year.

Approximately 40 percent of episodes of pertussis occur in the first 2 years of life; the same number is observed between the ages of two and five. At least 50 percent of all unvaccinated children have had whooping cough before they reach the age of five and 75 percent by the age of seventeen.

Pertussis is spread by droplets from the respiratory tract. Rarely, the organisms may be transmitted by fomites. Infectivity during the incubation period is questionable; the disease is most contagious during the catarrhal stage. Healthy carriers play no role in dissemination, but mild or missed cases are of great importance.

**PATHOLOGY** The initial lesion in whooping cough is hyperplasia of the peribronchial and tracheobronchial lymphoid tissue. The bronchi, trachea, larynx, and nasopharynx are soon involved in a necrotizing inflammatory reaction. The organisms are present in large numbers between the cilia of the trachea and following desquamation of the alveolar epithelium.

**CLINICAL MANIFESTATIONS** The incubation period of whooping cough averages 12 to 15 days but may be as long as 20 days. The first clinical manifestations (catarrhal stage) are slight nasal discharge, conjunctivitis, and mild cough without fever; these persist for 7 to 14 days.

The paroxysmal phase of pertussis follows and is characterized by paroxysms of coughing ending in a loud, crowing inspiratory noise (the whoop), the expulsion of varying quantities of thick, mucoid sputum from the respiratory tract, and vomiting. Episodes of cough may vary from 1 to 2 to 40 to 50 per day. Children under the age of six months frequently do not whoop. The mere presence of a whoop is in itself not diagnostic of pertussis. Rarely, the paroxysms of coughing are preceded by or replaced completely by sneezing.

Fever does not occur in the paroxysmal phase unless complications are present. Soreness over the trachea and main bronchi is common. Spasm, ulcer, or edema of the glottis sometimes occurs. In cases with severe vomiting and inability to retain food, serious inanition, wasting, and tetany may appear.

There is a bleeding tendency in pertussis. This is not associated with detectable defects in the clotting mechanisms; it has been suggested that it may be related to increased fragility of small blood vessels. Hemoptysis, epistaxis, purpura, and subconjunctival or intestinal hem-

orrhages occur but are usually of little clinical significance.

Findings on physical examination in pertussis are often entirely normal, but there may be injection of the blood vessels of the nose and pharynx. Although there are usually no abnormal findings in the lungs, fine, crackling, "sticky" rales are sometimes present. There are ulcers of the frenum of the tongue in about 20 percent of cases; these occur only in children in whom the lower central incisor teeth are present.

The paroxysmal stage of pertussis usually lasts from 1 to 6 weeks. When coughing persists beyond 6 weeks, it is usually due to the development of a so-called "habit whoop," not to continuation of the disease.

**LABORATORY FINDINGS** The total peripheral leukocyte count may be over 100,000 cells per $mm^3$, and mature lymphocytes may constitute 90 percent of the cells. This helps to distinguish the blood picture from that of acute lymphocytosis. The lymphocytosis appears to be induced by an intracellular product of the organism, most of the cells being released from lymphoid tissue including the thymus. Blood cultures are sterile. Nasopharyngeal cultures or "cough plates" on Bordet-Gengou agar are helpful in recovering the organism. X-ray study of the lungs in the uncomplicated case usually reveals only hilar lymphadenopathy and increase in the density of the bronchovascular markings.

**COMPLICATIONS** Bronchopneumonia occurs in from 1 to 10 percent of cases of pertussis; the organisms most frequently involved are group A *Strep. pyogenes, D. pneumoniae, Staph. aureus, H. influenzae,* and *B. pertussis.* Pneumonitis appearing during the course of chemotherapy is most often due to *Escherichia coli, Proteus* strains, *Klebsiella enterobacter,* or *Pseudomonas aeruginosa.* Another important complication is atelectasis; small areas of collapse are an almost constant finding, but major portions or a whole lung may be involved. Pneumothorax is rare.

The severe coughing of pertussis may lead to several complications. Hemorrhage may appear in the anterior chamber of the eye or in the retina. Detachment of the retina and blindness develop in rare cases. Prolapse of the rectum and inguinal or umbilical hernias have been noted.

Nervous system manifestations are not rare in pertussis. The commonest is convulsions; these often appear as fever develops rapidly during secondary bacterial infection. Other causes of seizures are encephalopathy (1 to 14 percent of cases), multiple petechial or gross hemorrhages of the brain, and cerebral hypoxia. The encephalopathy is characterized by an increase in the protein and cell content of the spinal fluid. Its etiology is unknown. Hyperreflexia, nuchal rigidity, cranial nerve palsies, areflexia, extensor plantar responses, flaccid hemiplegia, spasticity of the extremities, opisthotonus, difficulty in speaking, twitching, papilledema, nystagmus, blindness, strabismus, and dysphagia may occur. Some of the more important residua are mental retardation, recurrent convulsions, personality disorders, amnesia, aphasia, diffuse cerebral atrophy, chorea, and athetosis.

**DIAGNOSIS** The diagnosis of pertussis can frequently be made on clinical grounds alone. Knowledge of contact is helpful, but the appearance of paroxysms of typical coughing and whooping, after a short period of upper respiratory symptoms, is strongly suggestive of pertussis. It must be stressed, however, that in babies under the age of six months there is usually only paroxysmal coughing, without the characteristic whoop. An increased number of circulating lymphocytes is characteristic.

Isolation of *B. pertussis* from the respiratory tract establishes the diagnosis. Using "cough plates," nasopharyngeal swabs, and Bordet-Gengou medium, positive cultures can be obtained in 90 percent of patients in the catarrhal stage of the disease. The incidence of positive cultures is lower after paroxysmal coughing appears, and decreases with the duration of symptoms. The incidence of positive cultures in the catarrhal stage is about 90 percent. In the first week of the paroxysmal phase it is 75 percent; in the second week, 60 percent; in the third week, 45 percent; in the fourth week, 40 percent; in the fifth week, 10 percent.

Serologic studies are of little or no help in establishing the presence of pertussis.

**PREVENTION** Active immunization is effective in preventing pertussis in the majority of individuals. This may be started at the age of three months; both antibody production and protection against invasion by *B. pertussis* result. If the procedure is carried out at this early age, a "booster" injection should be administered at the end of the first year of life, and again just before the child starts school. Vaccine should not be given in the presence of the active disease; not only is it useless, but it may provoke serious neurologic reactions. There is evidence that the administration of "quadruple" vaccine—poliomyelitis virus, tetanus and diptheria toxoids, and *H. pertussis*—leads to some degree of suppression of the response to the pertussis bacillus. For this reason, when poliomyelitis vaccine (formalinized) is used, it should be given separately from the "triple" vaccine.

In children who have been exposed to pertussis but have not been actively immunized, passive protection may be given by the injection of 20 to 30 ml of human hyperimmune pertussis antiserum or 2 ml of immune γ-globulin as soon as possible after exposure, and again 1 week later. Such prophylaxis is 75 to 85 percent effective. The use of hyperimmune serum should be avoided if possible because it has been associated with the subsequent development of infectious hepatitis.

**TREATMENT** Although most of the antimicrobial drugs have been employed in the treatment of pertussis, there is no good evidence that they are beneficial. Chlortetracycline, chloramphenicol, oxytetracycline, erythromycin, and other antibiotics have been used, but the results obtained in controlled studies are not convincing.

There are few controlled studies of serum therapy in whooping cough, but in many clinics it is the practice to administer human hyperimmune serum (20 ml every 48 h for three doses), or immune γ-globulin (2 ml every 48 h for three doses) to all children with pertussis under the age of two.

Most important in therapy of pertussis is repair of the water and salt loss which follows severe and frequent vom-

iting. If failure to retain food is combated by prompt refeeding, patients can be made to maintain or gain weight.

Early detection of complications is one of the most important factors in the reduction of mortality. The prompt recognition of secondary bacterial infections of the lungs or middle ear, and therapy with a properly selected antibiotic agent lead to cure in practically all cases. When gross atelectasis occurs, correction by tracheal catheter suction or bronchoscopy may be lifesaving. Little can be done to influence the course or outcome of such complications as cerebral hemorrhage or encephalopathy.

Proper management of whooping cough has made the outlook for complete recovery excellent.

## HEMOPHILUS APHROPHILUS

Human infections due to *H. aphrophilus,* although uncommon, are being reported with increasing frequency. This species differs from *H. influenzae* in some biochemical characteristics and requires the X but not the V factor for growth in an atmosphere containing 10 percent $CO_2$, but needs neither factor, in most instances, when incubated in moist air. The diseases produced by *H. aphrophilus* include endocarditis, brain abscess, bacteremia, acute and chronic sinusitis, otitis media, cervical abscess, pneumonia, meningitis, wound infection, and septic arthritis. Most strains of the organism appear to be fairly sensitive to penicillin G, cephalothin, gentamicin, chloramphenicol, and rifampin.

## HEMOPHILUS PARAINFLUENZAE

This member of the genus *Hemophilus* differs from *H. influenzae* by requiring the V but not the X factor for growth. The infections in which it has been involved are acute pharyngitis, upper respiratory tract syndromes, acute suppurative otitis media, pneumonia, subacute bacterial endocarditis, meningitis, and brain abscess. Disease produced by this organism responds to treatment with ampicillin, tetracyclines, or chloramphenicol.

## HEMOPHILUS VAGINALIS

This organism grows in the absence of both X and V factors. *Hemophilus vaginalis* is present in the vagina of about 30 percent of normal women; it is more common in individuals under forty years of age. Although it is a member of the indigenous vaginal microflora, evidence that it may produce a vaginitis has been presented; about 50 percent of normal volunteers developed acute vaginitis when *H. vaginalis* was introduced locally. The disease is characterized by a gray, malodorous discharge; failure to demonstrate trichomonads and culture of the fluid establish the etiologic diagnosis. The organism is often sensitive to ampicillin and the cephalosporins but may be resistant to the tetracyclines and penicillin G. Some strains may be inhibited by chloramphenicol.

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# *143* CHANCROID

*KING K. HOLMES*

**DEFINITION** Chancroid, or soft chancre, is an acute, sexually transmitted infection characterized by painful genital ulcerations usually associated with inflammatory, often suppurative, inguinal adenopathy. A presumptive diagnosis is supported by exclusion of syphilis, genital herpes, and other specific causes of genital ulceration, together with improvement following sulfonamide therapy. A specific diagnosis is proved only when *Hemophilus ducreyi* is isolated from the lesion or suppurative node.

**ETIOLOGY** The specific microbial etiology of chancroid has repeatedly been supported by isolation of Ducrey's bacterium, *H. ducreyi,* in mixed culture from chancroidal ulcers and in pure culture from buboes. However, anaerobic bacteria, particularly *Bacteroides fragilis, B. melaninogenicus,* and anaerobic gram-positive cocci, are often present in genital ulcers, and anaerobic spirochetes which