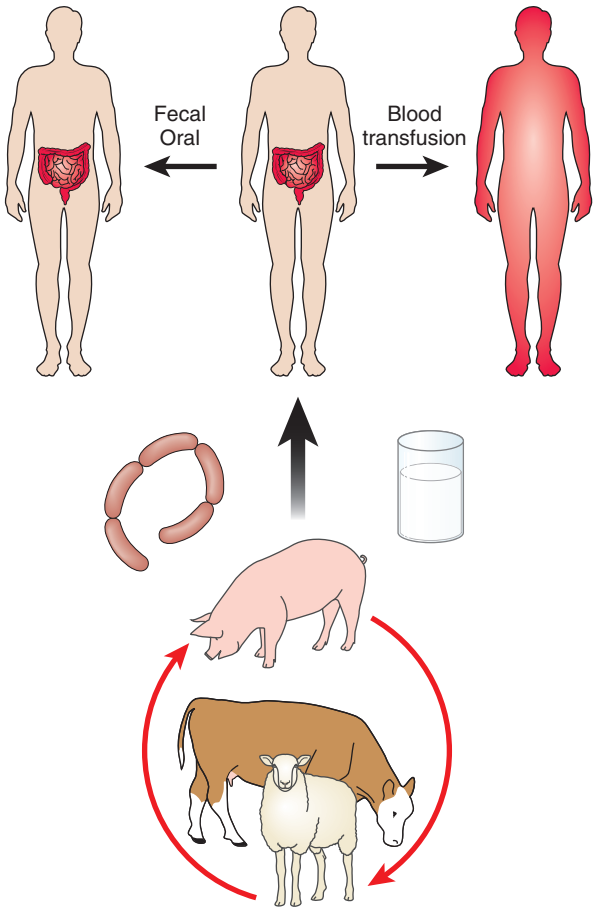

FIG. 229B.3 Transmission routes of Yersinia enterocolitica. Red circular arrows indicate zoonotic cycles. Wide black arrow indicates common routes of transmission to humans. Narrow black arrows indicate rare routes. *(Courtesy Paul Mead.)*

Systemic infections from *Y. enterocolitica* and *Y. pseudotuberculosis* are also observed, particularly in immunosuppressed patients, the elderly, and those with underlying conditions such as iron overload, alcoholism, cirrhosis, diabetes mellitus, cancer, and malnutrition.[23] The association between the treatment of iron overload with deferoxamine and *Yersinia* sepsis is well recognized in clinical practice. Deferoxamine enhances the growth of *Yersinia* and also inhibits neutrophil function.[24] Iron-loaded patients with β-thalassemia are at increased risk for severe yersiniosis, even when their body iron burden (as indicated by the serum ferritin level) is only moderately elevated and they are no longer receiving iron-chelating therapy with deferoxamine.[25]

A postinfection reactive polyarthritis can occur and has a predilection for patients with human leukocyte antigen (HLA)-B27, possibly due to molecular mimicry between HLA-B27 antigen and *Yersinia* antigens.[26] There is also some evidence for an association between *Y. pseudotuberculosis* infection and Kawasaki disease, possibly due to the YPM superantigen.[27–29]

CLINICAL MANIFESTATIONS

The incubation period after ingestion of the organism is 1 to 11 days, with diarrhea lasting for a few days to a few weeks (average of 2 weeks). Patients shed organisms in their feces and remain infectious during the symptomatic period. *Yersinia enterocolitica* presents as an invasive diarrhea characterized by fever, abdominal pain, mucus- and blood-containing stools, and the presence of fecal leukocytes.[30] Nausea and vomiting affects 15% to 40% of cases. Perforation of the ileum and rectal bleeding can occur in serious infections. Patients with mesenteric adenitis (Fig. 229B.4) or terminal ileitis have fever and right lower quadrant pain, which is more common in older children and adolescents

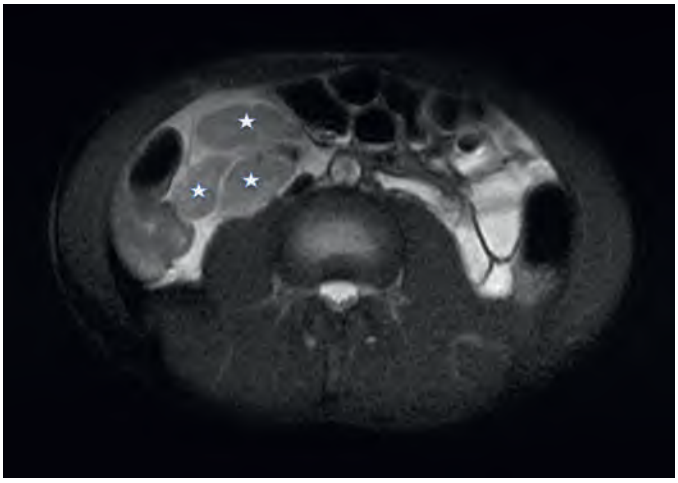

FIG. 229B.4 Abdominal MRI with *Yersinia* mesenteric adenitis. White stars indicate enlarged mesenteric lymph nodes. *(Courtesy Tara Palmore, MD.)*

and may be clinically indistinguishable from acute appendicitis (pseudoappendicitis).[31,32] When evaluating patients suspected of having acute appendicitis, computed tomographic scanning of the abdomen and pelvis may help avoid exploratory laparotomy by revealing a normal appendix and enlarged mesenteric lymph nodes.[33] Thickening and ulcerations of the terminal ileum and cecum can be seen on endoscopy, with raised round lesions on Payer patches, and can led to massive rectal bleeding.[34] Complications following gastrointestinal infections can include granulomatous enterocolitis[35] and granulomatous appendicitis.[36] Convalescent carriage of *Y. enterocolitica* in stool of untreated individuals may occasionally extend for weeks to months in a small percentage of those infected.

Yersinia pseudotuberculosis is more likely to cause abdominal pain and fever than diarrhea in all age groups. The most common manifestation in humans is mesenteric adenitis, which, like *Y. enterocolitica,* causes an acute appendicitis–like syndrome with fever and right lower quadrant abdominal pain. The infection is usually self-limited.

Acute pharyngitis can occur from *Y. enterocolitica,* with or without diarrhea, and fatalities have been reported.[37] The organism can also cause community-acquired pneumonia without accompanying diarrhea or other gastrointestinal symptoms.[38] Skin and soft tissue infections usually result from failure of the skin barrier on distal body parts, followed by spread of the infection to the regional lymph nodes from the ruptured skin.[39] Appropriate antibiotic therapy and surgical drainage are essential, because failures have occurred after common empirical antibiotics for cellulitis (e.g., vancomycin or cefazolin) were used.

Sepsis from *Y. enterocolitica* and *Y. pseudotuberculosis* is uncommon and presents as a severe illness with fever and leukocytosis. Patients are often elderly or have underlying medical conditions such as diabetes mellitus, liver disease, hemochromatosis, or iron overload. Human immunodeficiency virus infection has also been shown to be a risk factor for *Y. pseudotuberculosis* sepsis.[40,41] Septicemic patients may develop hepatic or splenic abscesses, peritonitis, septic arthritis, psoas abscesses, osteomyelitis, endocarditis, myocarditis, mycotic aneurysms, or meningitis. Rapid-onset septic shock is seen in transfusion-transmitted *Y. enterocolitica,* which is caused by a preformed endotoxin.[18] Serotype O:9 was implicated in a fatal case of posttransfusion sepsis from contaminated red blood cells following a vaginal delivery.[42]

Far East scarlet-like fever (FESLF) has been associated with certain strains of *Y. pseudotuberculosis* in eastern Russia, Korea, and Japan (Izumi fever). These strains produce the superantigenic toxin YPM (described earlier), which is integral to the pathogenesis of FESLF.[43] Six stages of FESLF have been identified[44]:

1. The incubation period, which is asymptomatic and lasts 7 to 10 days.
2. The initial onset, in which fever, rigors, headache, myalgias, arthralgias, weakness, loss of appetite, swelling of scleral vessels,

coryza, abdominal pain, and hyperemia of the face, neck, and conjunctiva occur.
3. The accrual stage, which occurs 3 days after symptom onset and is characterized by high fevers, abdominal symptoms, and a scarlet fever–like rash.
4. Remission, which usually occurs 6 days after disease onset and is characterized by a decrease in the severity of most symptoms, most notably fever, with persistence of rash and increased jaundice.
5. Recurrence with exacerbation, which typically occurs 8 days after disease onset and has an increase in symptom severity, with the exception of fever, with desquamation occurring and jaundice becoming maximal.
6. Convalescence, which usually occurs after 12 days with gradual resolution of all symptoms, including rash, desquamation, and jaundice.

POSTINFECTIOUS COMPLICATIONS

Reactive arthritis occurs after yersiniosis in approximately 10% to 20% of cases.[45,46] First described by Finnish physicians in 1969, it begins a few days to a month after the onset of diarrhea and can afflict both children and adults.[47] The typical clinical presentation is an inflammatory arthritis with a predilection for large weight-bearing joints.[48] Extraarticular inflammatory signs, including urethritis and conjunctivitis, are not uncommon. Symptoms usually resolve after 3 to 5 months, although it may take up to a year in some cases. Serologic testing of synovial fluid for *Y. enterocolitica* or *Y. pseudotuberculosis* can be helpful, although these tests may not discriminate recent infection from past exposure unless immunoglobulin M antibodies are inactivated by sample pretreatment.[49] Reactive arthritis and especially sacroiliitis is more likely to develop in people with the HLA-B27 antigen.[50] This may be a result of molecular mimicry, since YadA shares a linear tetrapeptide with HLA-B27.[51] However, not all strains associated with reactive arthritis have YadA, so it is likely that other factors also play a role.[52] For example, two major *Y. enterocolitica* antigens, Ye 19 kDa and Ye HSP60, induce synovial T-cell proliferation in patients with reactive arthritis.[53] In experimental models, tumor necrosis factor signaling alters the anti-inflammatory and proinflammatory cytokine balance and influences the development of severe chronic reactive arthritis after *Y. enterocolitica* infection.[54] Greater severity of gastrointestinal symptoms has been associated with the development of reactive arthritis.[55]

Erythema nodosum develops after yersiniosis in approximately 3% of cases.[56] Skin lesions typically appear on the legs about 2 weeks after the onset of abdominal symptoms and usually resolve spontaneously within a month (Fig. 229B.5). Women with erythema nodosum outnumber men by a ratio of 2:1 and there is no association with HLA-B27. The condition may result because of an increase in autoantibodies from polyclonal B-cell activation induced by *Yersinia*.[57]

Patients with thyroid disorders have a higher prevalence of antibodies to *Yersinia* than normal subjects or patients with other disorders.[58] *Yersinia enterocolitica* has high-affinity binding sites for thyroid-stimulating hormone and expresses antigens that cross react with thyroid-stimulating hormone receptor (TSHR). There is sequence homology between *Y. enterocolitica* outer membrane protein M and TSHR.[59] *Yersinia pseudotuberculosis* outer membrane protein FM has similarly been shown to cross react with TSHR.[60] Overall, a large number of studies have reported epidemiologic, serologic, and molecular evidence that *Yersinia* is involved in the pathogenesis of autoimmune thyroid disease and Graves disease, yet none has shown a direct correlation between infection and disorders of the thyroid. Indeed, most patients with yersiniosis do not develop thyroid disorders. One hypothesis is that the ability to produce anti-TSHR antibodies in response to *Yersinia* antigens homologous to the TSHR persists only in susceptible individuals, with *Yersinia* antigens acting as a trigger for disease development.[61]

PATHOGENESIS

Following ingestion of contaminated food or water, *Yersinia* bacteria travel to the distal part of the small bowel. There they attach to and invade the intestinal epithelium via microfold (M) cells. Adherence and invasion are facilitated at human body temperature by multiple virulence factors, including fimbriae, flagella, and the Inv and Ail proteins. Inv clusters and activates β_1 integrins on the apical surface of M cells, signaling actin cytoskeleton rearrangements that promote internalization by phagocytes.[62] The bacteria enter Peyer patches and macrophages, where they survive and multiply. Replication of *Y. enterocolitica* in Peyer patches may be facilitated by the immune regulator protein Gal-1, which has been shown to play a role in limiting bacterial clearance.[63] After an incubation period of 4 to 7 days, the phagocytized bacteria migrate to mesenteric lymph nodes, triggering an inflammatory response that leads to abdominal pain. Further spread can occur via the bloodstream to the liver and spleen. The dissemination of *Y. enterocolitica* but not *Y. pseudotuberculosis* requires C-C motif of chemokine receptor 7–dependent migration of dendritic cells and monocytes, which may be due to differences in surface adhesins/invasins, secreted factors between the pathogens, or both.[64] Once they reach the mesenteric lymph nodes, liver, and spleen, *Yersinia* form extracellular microabscesses surrounded by epithelioid granulation tissue. In severe cases, thrombosis of mesenteric blood vessels, intestinal necrosis, and hemorrhage may occur. The appendix often has a normal histologic appearance or demonstrates mild inflammation. Septicemia may lead to focal abscesses in distal organs, including the lungs and brain.

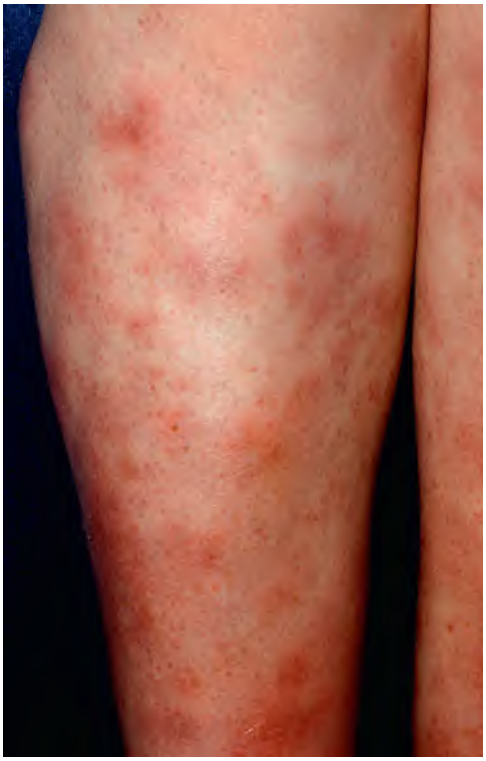

FIG. 229B.5 Erythema nodosum. *(Courtesy Dr. Gary M. White.)*

DIAGNOSIS

Fecal leukocytes are often present during acute illness, but the finding is nonspecific. *Yersinia* can be isolated from stool, blood, bile, wounds, throat, mesenteric lymph nodes, cerebrospinal fluid, and peritoneal fluid. *Yersinia,* particularly *Y. pseudotuberculosis,* can form pinpoint colonies on both blood agar and MacConkey agar in 24 hours.[65] *Yersinia enterocolitica* appears as small, lactose-negative colonies on MacConkey in 48 hours. Ornithine decarboxylase, sucrose, and sorbitol are all positive for *Y. enterocolitica* and negative for *Y. pseudotuberculosis.* Detection from stool can be problematic due to overgrowth of fecal flora, so cold enrichment followed by culture on CIN agar is a common protocol in clinical laboratories. A new type of chromogenic agar has been developed for *Y. enterocolitica* that is as sensitive as CIN but more specific and has a lower false-positive rate.[66] Recovery of organisms from otherwise sterile sites, such as blood and cerebrospinal fluid, is usually faster than recovery from stool samples.

A variety of serologic methods are available to aid in diagnosis. These include enzyme-linked immunosorbent assays, tube agglutination, and immunoblotting. *Yersinia enterocolitica* and *Y. pseudotuberculosis* cross react with one another and with other organisms, including *Brucella, Vibrio, Bordetella, Borrelia, Morganella, Salmonella,* and *E. coli.*[67–69] Agglutinin titers increase shortly after the onset of symptoms, peak in the second week, and generally disappear within 2 to 6 months, although elevated titers may persist longer in some cases. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectroscopy, which identifies bacteria according to specific protein profiles, has supplanted biochemical and phenotypic characterization in many laboratories, but this method has been challenged in differentiating *Y. pestis* and *Y. pseudotuberculosis.*[70,71] Whole-genome sequencing can identify *Yersinia* strains to the species level but is not yet widely available in the clinical microbiology laboratory setting.[72]

A number of polymerase chain reaction–based multiplex gastrointestinal pathogen identification panels are marketed for use with primary stool specimens. These assays offer substantially improved turnaround time on primary laboratory diagnosis compared with culture-based methods, although recovery of isolates from culture is still required for taxonomic classification and susceptibility testing.[65] False-positive results remain a concern, with one assay reported to have a sensitivity of only 48% for *Y. enterocolitica.*[73] Currently there are no commercially available multiplex polymerase chain reaction panels that include *Y. pseudotuberculosis* in the pathogen target list.

Patients with reactive arthritis after yersiniosis often have elevated inflammatory markers (e.g., erythrocyte sedimentation rate and C-reactive protein) and negative rheumatoid factor and antinuclear antibodies. Synovial fluid culture is sterile. There is no specific histopathologic characteristic that differentiates erythema nodosum from yersiniosis compared to other etiologies.[74]

TREATMENT

Care is primarily supportive, with hydration and proper nutrition being the mainstays of treatment. Antimotility medications should be avoided because they might increase the risk for bacteremia. Most isolates of *Y. enterocolitica* are susceptible to aminoglycosides, tetracyclines, trimethoprim-sulfamethoxazole (TMP-SMX), piperacillin, third-generation cephalosporins, and quinolones.[75] They are usually resistant to penicillin, ampicillin, and first-generation cephalosporins due to β-lactamase production. The role for antimicrobial therapy in uncomplicated acute diarrhea and mesenteric adenitis is unclear because these infections are usually self-limited. Antibiotics may be beneficial in cases of severe enterocolitis. They should be used in septicemia and in cases with extraintestinal manifestations, such as cellulitis, pneumonia, osteomyelitis, endocarditis, and meningitis. Also, select patient populations should receive antibiotic therapy, including the elderly, diabetics, cirrhotics, immunocompromised individuals, those receiving chemotherapy, and young children. Duration of therapy depends on the severity of illness, with 7 to 14 days being sufficient for many patients with enterocolitis,[76] 14 days for bacteremia,[77] and longer courses for complicated cases such as endocarditis and osteomyelitis. Deferoxamine therapy should be discontinued when an infection from *Yersinia* is suspected or confirmed.[78,79]

Yersinia pseudotuberculosis is usually sensitive in vitro to ampicillin, tetracycline, ciprofloxacin, cephalosporins, and aminoglycosides. Antibiotics are not necessary in most cases of mild disease and mesenteric adenitis. For moderate *Y. pseudotuberculosis* disease, TMP-SMX (TMP 8 mg/kg/day and SMX 40 mg/kg/day in two divided doses) can be used to treat children, and ciprofloxacin 500 mg twice daily can be used to treat adults. Patients with severe disease, including septicemia, should receive ceftriaxone (2 g daily in adults, 100 mg/kg in children, in 1 or 2 divided doses daily) plus gentamicin (5 mg/kg/day in 3 divided doses daily). The mortality rate in *Y. pseudotuberculosis* septicemia remains high despite appropriate antibiotic therapy and supportive care.[80,81]

Reactive arthritis is managed with nonsteroidal antiinflammatory drugs, intraarticular corticosteroid injections, and physical therapy. Systemic glucocorticoids can be used when the patient does not respond to nonsteroidal antiinflammatory drugs and intraarticular glucocorticoids or has a large number of involved joints. Antibiotics have not been shown to be beneficial and are not recommended.[82]

PREVENTION

Improving conditions and methods in slaughterhouses, such as avoiding head meat, is an important intervention that reduces *Y. enterocolitica*–contaminated processed pork.[83] The storage time of refrigerated but unfrozen foods should be limited. The consumption of unwashed raw vegetables, unpasteurized milk, and undercooked meats (especially pork and pork products, such as chitterlings), should be avoided especially by immunocompromised individuals. In health care settings, enteric precautions along with strict hand washing and control of environmental cross-contamination should be instituted. Blood bank personnel need to ask donors about any recent symptoms of gastroenteritis and tell them to notify the blood bank if symptoms occur after donation. Vaccine development for *Y. enterocolitica*[84] and *Y. pseudotuberculosis*[85] is underway, but currently none is approved for human or animal use.

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230 Bordetella pertussis

Valerie Waters and Scott A. Halperin

SHORT VIEW SUMMARY

Definition

- Pertussis, infection with *Bordetella pertussis,* is divided into three stages:
  - Catarrhal stage: rhinorrhea, nonpurulent conjunctivitis, occasional cough, low-grade fever
  - Paroxysmal stage: paroxysms or fits of coughing, inspiratory whoop
  - Convalescent stage: gradually diminishing cough lasting up to 8 weeks
- The clinical case definition includes cough for 14 days or longer and one or more of the following: paroxysmal cough, inspiratory whoop, or posttussive vomiting

Epidemiology

- With the introduction of whole-cell pertussis vaccine in 1940s, pertussis rates dropped dramatically.
- Peaks of disease continue to occur every 3 to 5 years.
- Most cases, hospitalizations, and deaths occur in unimmunized infants younger than 6 months.
- Outbreaks in children with high vaccine rates may be partly due to waning immunity from acellular pertussis vaccine.

Microbiology

- *Bordetella* organisms are small gram-negative coccobacilli; growth is fastidious.
- Filamentous hemagglutinin and fimbriae are two major adhesins.
- Pertussis toxin (PT) helps organisms evade host defenses and causes systemic manifestations; it also acts as an adhesin.

Diagnosis

- Diagnosis is traditionally made by means of culture from nasopharyngeal swabs or aspirates; specific swabs, transport media, and growth media should be used to enhance recovery.
- Newer polymerase chain reaction assays are more sensitive for detection of *B. pertussis* and are the procedure of choice.
- Antibodies to *B. pertussis* PT can be used for diagnosis.
- Direct fluorescent antibody testing is available but not recommended.

Therapy

- Erythromycin, 40 mg/kg/day in four divided doses, is recommended for children (maximum 2 g/day), or clarithromycin, 15 mg/kg/day in two divided doses (maximum 1 g/day) for 7 to 14 days. Azithromycin, 10 mg/kg/day for 4 days, is recommended for infants younger than 1 month. Five days of azithromycin is probably effective for treatment or prophylaxis in adults (500 mg first day, then 250 mg daily) and is better tolerated and has fewer serious drug interactions than erythromycin, 500 mg four times daily for 14 days.
- Supportive care is paramount in management of pertussis, especially in infants.

Prevention

- Immunization is the single most effective means of preventing pertussis.
- The pertussis immunization schedule in the United States and Canada for children and adolescents is as follows: DTaP (diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine, pediatric formulation) at 2, 4, 6, and 18 months, with booster at 4 to 6 years; and Tdap (tetanus toxoid, diphtheria toxoid, acellular pertussis vaccine, adult formulation [reduced doses of "d" and "ap" components]) for preadolescents and adolescents.
- In the United States and Canada, it is recommended that all adults age 19 years and older receive a single dose of Tdap. The exception is pregnant women who, in the United States, are recommended to receive Tdap for each pregnancy, ideally in the 27th to 36th weeks of pregnancy, to protect their newborns from pertussis.
- All health care workers with patient contact should be given a single dose of Tdap if they have not been vaccinated as an adult, irrespective of when they received the last dose of tetanus toxoid.
- Prophylaxis can be considered for close contacts exposed within 21 days of onset of cough in the index case. Adults and adolescents are given erythromycin 500 mg four times daily for 7 to 14 days, azithromycin 500 mg on the first day and 250 mg daily for 4 additional days, or clarithromycin 500 mg twice daily for 7 days.

HISTORY

The first epidemic of whooping cough was described in 1578 by de Baillou, who wrote the following: "The lung is so irritated that, in its attempt by every effort to cast forth the cause of the trouble, it can neither admit breath nor easily give it forth again. The sick person seems to swell up, and, as if about to strangle, holds his breath clinging in the midst of his jaws."[1] This vivid clinical description of whooping cough holds true to this day. In 1679, Sydenham[2] gave this respiratory illness the name "pertussis," meaning a violent cough of any type. The organism that causes whooping cough was discovered in 1900 by Bordet and Gengou.[3] They described a new gram-negative bacillus (subsequently named *Bordetella pertussis*, after Bordet) that they had found in the sputum of a 6-month-old infant with whooping cough. By 1906, they had developed a culture medium to support the growth of the organism and described in detail its morphologic features and virulence characteristics. In 1943, Joseph Lapin,[1] a pediatrician who worked in the whooping cough clinic at the Bronx Hospital in New York City, wrote an extensive monograph on the subject of pertussis.

DESCRIPTION OF PATHOGEN

B. pertussis is the pathogen that causes whooping cough or pertussis.[4] It is one of 10 known *Bordetella* species, namely, *B. pertussis, B. parapertussis, B. bronchiseptica,* ovine-adapted *B. parapertussis, B. avium, B. hinzii, B. holmesii, B. trematum, B. petrii,* and *B. ansorpii. B. pertussis* and *B. parapertussis* are the most common *Bordetella* species causing respiratory illnesses in humans. With improved molecular testing methods, polymerase chain reaction (PCR) assays can now distinguish between *B. pertussis* and *B. holmesii* and have detected *B. holmesii* in 0.1% to 20% of patients with pertussis-like symptoms.[5–7] *B. holmesii* can colonize the respiratory tract but also can cause a pertussis-like syndrome.[8] Unlike *B. pertussis, B. holmesii* can cause bacteremia or other nonpulmonary infections. Distinction between the two species can be through biochemical reactions, the distinctive brown pigment of *B. holmesii,* or use of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry.[9]

Although *B. pertussis* strictly affects humans and has no known animal reservoir,[10] many of the other *Bordetella* species are recognized

primarily for the diseases they cause in animals. *B. bronchiseptica* causes kennel cough in dogs and cats, and human infections occur primarily in immunocompromised patients, often after exposure to animals.[11–13] Ovine-adapted *B. parapertussis* causes respiratory tract infections in sheep.[14] *B. avium* is a pathogen of poultry[15] but has been isolated from the ear culture of a patient with chronic otitis media.[16] Similarly, *B. hinzii* also colonizes the respiratory tract of poultry and has been isolated from the sputum of cystic fibrosis patients.[17] It has been reported to cause bacteremia in immunocompromised[18,19] and in immunocompetent patients[20] and has been described as a cause of chronic cholangitis.[21] *B. trematum* has been isolated from patients with wounds or otitis media.[22,23] *B. petrii,* originally identified from an environmental source,[24] has been isolated from patients with chronic infections.[25–27] Finally, in 2005, a novel species of *Bordetella, Bordetella ansorpii,* was described after the isolation of a gram-negative bacillus from the purulent exudate of an epidermal cyst.[28] 16S ribosomal RNA (rRNA) gene sequencing has revealed that this bacterium belongs to the *Bordetella* genus but is distinct from other *Bordetella* species. This species was subsequently isolated from an immunocompromised patient in the United Kingdom.[29]

Bordetella species are small gram-negative coccobacilli.[30] Some species are motile and, except for *B. petrii,* are strictly aerobic. All species possess catalase activity and oxidize amino acids but do not ferment carbohydrates. *Bordetella* organisms grow optimally at 35°C to 37°C. *Bordetella* species are fastidious because their growth can be inhibited by components commonly found in laboratory media. In addition, their rate of growth is inversely related to their degree of fastidiousness. *B. pertussis* is the most fastidious and slowest growing of the *Bordetella* species. Its growth is inhibited by fatty acids, metal ions, sulfides, and peroxides. Isolation of *B. pertussis* requires a medium containing charcoal, blood, or starch. Traditionally, Bordet-Gengou (BG) medium has been used and consists of a potato-starch base. Charcoal medium (Regan-Lowe [RL] medium), supplemented with glycerol, peptones, and horse or sheep blood, can also be used and may provide better isolation of *B. pertussis* than the BG medium.

PATHOGENESIS

B. pertussis infection and disease occur after four important steps: (1) attachment, (2) evasion of host defenses, (3) local damage, and (4) systemic manifestations.[4]

Filamentous hemagglutinin (FHA) and fimbriae (FIM) are two major adhesins and virulence determinants for *B. pertussis.* FHA is a 220-kDa surface-associated and secreted protein, and FIM is a filamentous cell surface structure. They are required for tracheal colonization, are highly immunogenic, and are components of certain acellular pertussis vaccines.[4] However, there is likely redundancy in the adhesion role of *B. pertussis* proteins, and it has been suggested that virulence factors such as pertactin (PRN) may mediate attachment in the absence of FHA.[31] Pertussis toxin (PT) also acts as an adhesin[32] and has specific recognition domains for human cilia.[33]

Evasion of host defenses occurs primarily through adenylate cyclase toxin (ACT) and PT.[34] ACT is a toxin secreted by *B. pertussis* that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which inhibits the migration and activation of phagocytes. It has also been shown to suppress T-lymphocyte activation and chemotaxis.[35] PT, one of the most important virulence factors of *B. pertussis,* also targets the innate immune system of the lung by inactivating or suppressing G protein–coupled signaling pathways. PT has two components, the A subunit and the B subunit. The B (binding) subunit binds to the cell surface to enable adenosine diphosphate (ADP)–ribosylation of G proteins by the A (active) subunit, thereby altering the cell.[34] Through this mechanism of action, PT delays the recruitment of neutrophils to the respiratory tract and targets airway macrophages to promote *B. pertussis* infection.[36] The virulence factors of *B. pertussis,* such as PT, are encoded by the *bvg* (or *vir*) gene. The *bvg* operon is composed of *bvgA* and *bvgS,* members of a two-component signal transduction system that controls the genetic state, or phase, of *B. pertussis.*[37] There are virulent and avirulent phases, and their expression is regulated by environmental factors.[38]

Original reports by Lapin described the local tissue damage caused by pertussis in the lung.[1] The initial pulmonary lesion is a lymphoid hyperplasia of peribronchial and tracheobronchial lymph nodes. Necrosis and desquamation of the bronchial epithelium follow, with diffuse infiltrations by macrophages (Fig. 230.1). Most of the damage to the ciliated epithelial cells is caused by tracheal cytotoxin (TCT). TCT is a disaccharide tetrapeptide derived from peptidoglycan, which triggers the production of an inducible nitric oxide (NO) synthase.[39] The synthase produces NO, which ultimately kills the tracheal epithelial cells. The induction of the NO synthase is likely caused by the cytokine interleukin-1 (IL-1), generated in response to TCT.[40] Dermonecrotic toxin (DNT), a 160-kDa heat-labile secreted toxin that activates intracellular Rho guanosine triphosphate (GTP)ases, may also have a role in local tissue damage.[41] DNT was first discovered by Bordet and Gengou and derives its name from the characteristic skin lesion produced when injected into test animals.

Unlike other bacterial diseases, there are few systemic manifestations of *B. pertussis* infection because it does not enter the circulation and disseminate. *B. pertussis* is relatively sensitive to killing by serum in vitro. However, in vivo, even serum-sensitive strains can efficiently infect mice.[42,43] *B. pertussis* has multiple mechanisms for avoiding antibody-mediated complement killing,[44] including the expression of BrkA, a surface-associated protein belonging to the autotransporter secretion system.[45] PT is the primary virulence determinant responsible for the systemic manifestations, of which the most prominent is leukocytosis with lymphocytosis.[34] Other systemic responses include sensitization to histamine and serotonin and sensitization of the beta-islet cells of the pancreas. This latter effect leads to hyperinsulinemia with resultant hypoglycemia, particularly in young infants.[1] Pertussis-associated encephalopathy is observed rarely[46]; some have suggested that it may be caused by the effect of PT on the central nervous system via monocyte chemoattractant protein-1 (MCP-1) overexpression.[47] Fatal pulmonary hypertension has also been associated with pertussis in infants.[48] Pathologic studies have demonstrated that, in addition to producing pulmonary vasoconstriction resulting from hypoxemia, pulmonary infection with *B. pertussis* triggers toxin-mediated leukocytosis, causing increased vascular resistance and subsequent refractory pulmonary hypertension.[49]

In addition to the direct effects of these virulence factors in the lung, some believe that they modulate, in a more global fashion, the immune system itself.[50] Studies investigating immunomodulation by *B. pertussis* have demonstrated skewing of the host immune response toward expansion of the Th17 subset of T lymphocytes, induced by the production of cytokine IL-23.[51] The Th17 immune response may be protective against some other gram-negative bacterial respiratory pathogens[52] but may also be associated with chronic autoimmune inflammation.[53] Some have suggested that the chronic cough seen with *B. pertussis* infection may be explained by this autoimmune phenomenon, akin to asthma,[50] although it has also been hypothesized to be a direct effect of mediators such as bradykinin released in response to tissue damage.[54]

EPIDEMIOLOGY

Despite vaccination, pertussis disease continues to be a problem in the developing and developed world (Fig. 230.2).[55] According to the World Health Organization (WHO), an estimated 24.1 million cases and 160,700 deaths occurred in 2014 in children younger than 5 years because of *B. pertussis.*[56] Case-fatality rates in developing countries may be as high as 3% in infants.[57] WHO recommended that a pertussis incidence of less than 1 case per 100,000 population be achieved in Europe by 2000. Data from countries represented in the Global Pertussis Initiative (GPI) have indicated that this incidence has not yet been achieved.[57]

Prevaccine Era

In the prevaccine era, pertussis was a major childhood illness and a leading cause of death. Pertussis disease has always been cyclic, with peaks occurring every 3 to 5 years.[58] From 1940 to 1948 in the United States, pertussis was responsible for more deaths in the first year of life than measles, scarlet fever, diphtheria, poliomyelitis, and meningitis combined.[4] Unlike the current age distribution of pertussis disease, however, pertussis affected children primarily 1 to 10 years of age. From 1918 to 1921 in Massachusetts, for example, more than 80% of pertussis

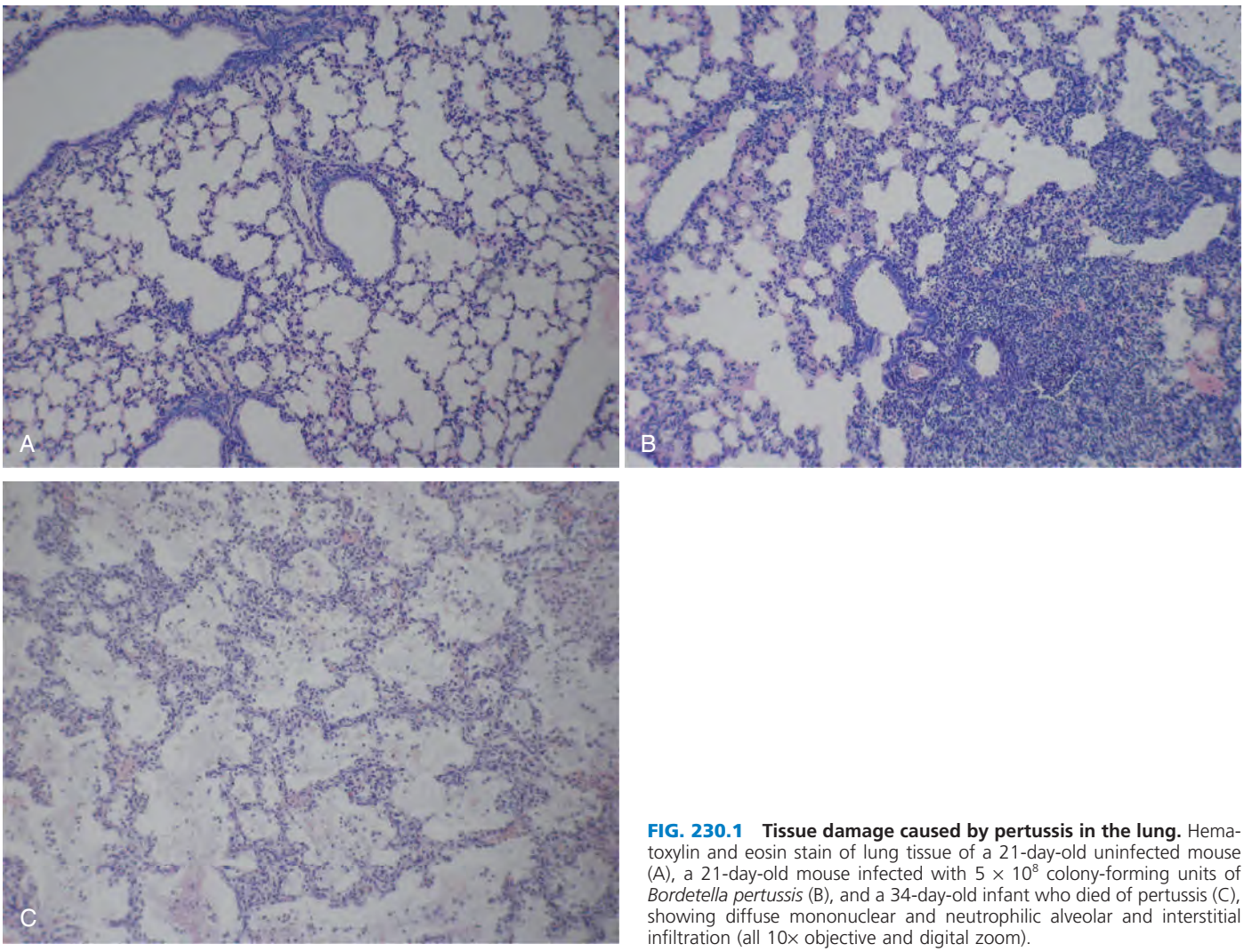

FIG. 230.1 Tissue damage caused by pertussis in the lung. Hematoxylin and eosin stain of lung tissue of a 21-day-old uninfected mouse (A), a 21-day-old mouse infected with 5×10^8 colony-forming units of *Bordetella pertussis* (B), and a 34-day-old infant who died of pertussis (C), showing diffuse mononuclear and neutrophilic alveolar and interstitial infiltration (all 10× objective and digital zoom).

cases occurred in children aged 1 to 9 years, whereas only 10% occurred in infants younger than 1 year.[59]

Vaccine Era

With the introduction of the whole-cell pertussis vaccine in the 1940s, pertussis rates dropped dramatically. They reached a nadir in the United States in the late 1970s to early 1980s, with a reported 0.5 to 1.0 cases per 100,000 population between 1976 and 1982.[59] There has been a gradual increase in pertussis rates over the last 20 years, with peaks of disease continuing to occur every 3 to 5 years.[60] The age distribution of pertussis disease has also changed, with the most cases occurring in unimmunized infants younger than 1 year. Data from the National Notifiable Diseases Surveillance System and the National (Nationwide) Inpatient Sample database in the United States have revealed that from 1993 to 2004, 86% of hospitalizations and all deaths caused by pertussis occurred in infants 3 months of age or younger.[61] Similarly, according to Canadian data from 1991 to 1997 from the Canadian Immunization Monitoring Program, ACTive (IMPACT) network, almost 80% of hospitalized patients with pertussis and all deaths secondary to pertussis occurred in children 6 months of age or younger.[62]

Current Issues Regarding Resurgence of Pertussis

In recent years, a resurgence in pertussis has been reported in many countries worldwide.[7,63–67] The reason for this resurgence is likely to be multifactorial.[64] One of the key factors is the finding that neither natural pertussis infection nor immunization produces lifelong immunity to pertussis.[68,69] Different pertussis vaccines have had varying rates of success over the years. In the 1990s, Canada experienced a resurgence of pertussis, primarily in young adolescents.[70] This was a result of the low effectiveness of the whole-cell pertussis vaccine used between 1985 and 1998 in that country. This resulted in a "marching cohort" effect, or an increase each year in the age of peak incidence by 1 year, which revealed the existence of a susceptible cohort (Fig. 230.3).[71] This was addressed with universal immunization programs to vaccinate adolescents with a more effective acellular pertussis vaccine.[70] However, despite a more effective acellular pertussis vaccine,[72] pertussis outbreaks continue to be reported in young adults and in young children who recently completed a full pertussis vaccine series.[65,73–78] In 2010, a large pertussis outbreak occurred in California, with the highest number of pertussis cases in more than 60 years.[78] Second to children younger than 6 months, the highest disease rates were observed in fully vaccinated preadolescents (7–10 years of age), as observed by others.[79] A case-control study of children 4 to 12 years of age who were PCR positive for pertussis, compared with PCR-negative and matched controls, demonstrated that PCR-positive children were more likely to have received the fifth DTaP (diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine) dose earlier than controls, with an odds of acquiring pertussis increasing by an average of 42% per year.[80] This suggests that immunity after acellular pertussis vaccination may begin to decline after 4 to 5 years, indicating that a booster dose may be appropriate. Epidemiologic studies have also shown that decreasing antibody levels to PT at a population level can precede large pertussis epidemics,[63] although long-term memory B cells in vaccinated children may persist despite waning antibody levels and may provide protection

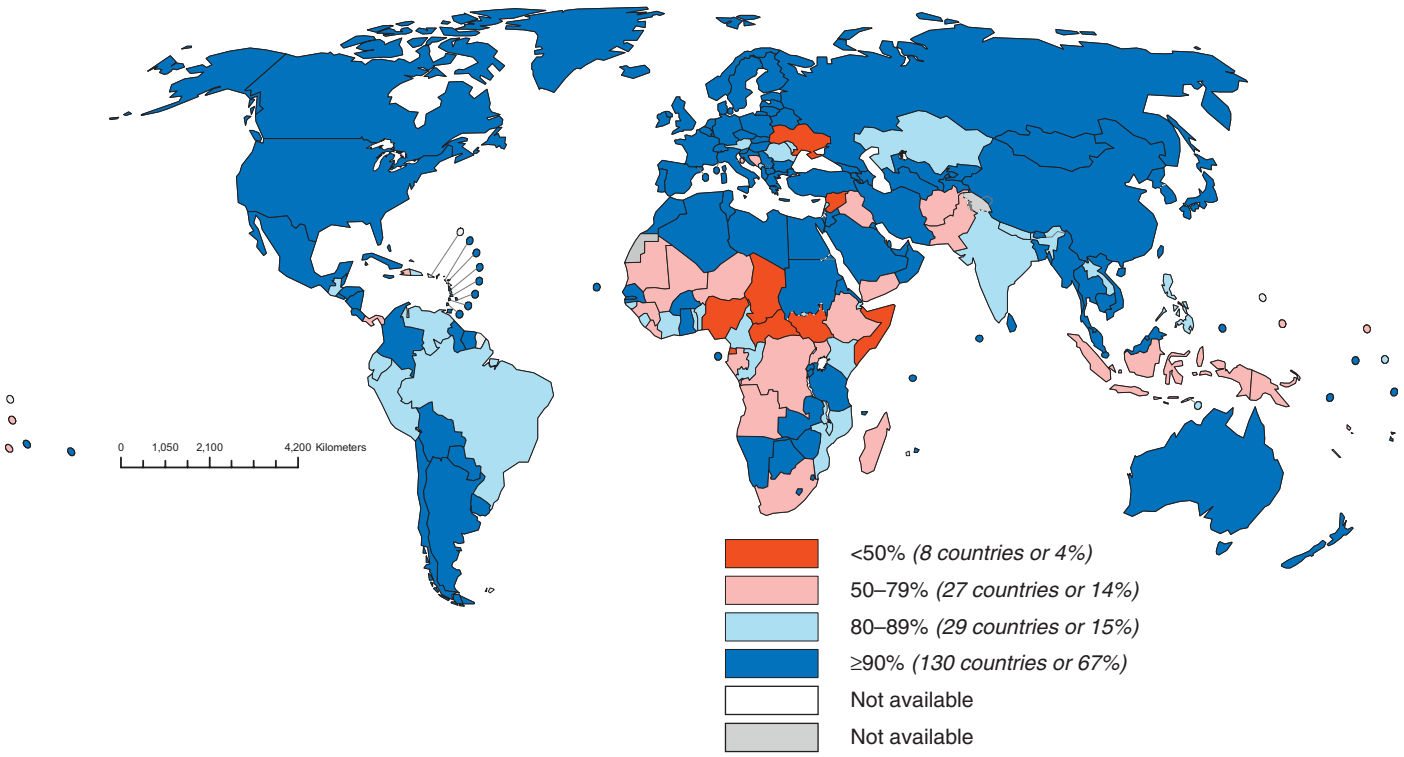

FIG. 230.2 Immunization coverage with diphtheria-tetanus-pertussis (DTP3) vaccine in infants in developing countries, 2016. *(From World Health Organization/United Nations Children's Fund coverage estimates 2016 revision, July 2017.)*

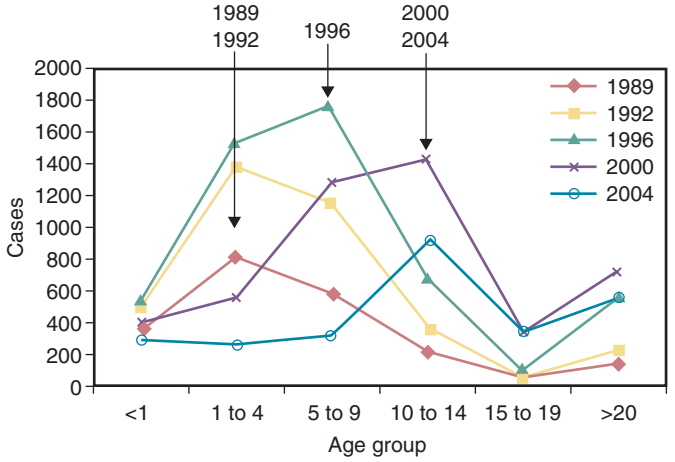

FIG. 230.3 Number of cases of pertussis reported in different age groups in Canada from 1989 to 2004. *Arrows* indicate the age group in which the incidence was highest in a given year, excluding infants younger than 1 year.

against pertussis disease.[81] Additional factors that may have contributed to the resurgence in reported pertussis include increased awareness and subsequent testing for pertussis with very sensitive molecular methods that can detect as little as one organism of *B. pertussis*, making it difficult to distinguish between colonization and disease (discussed further under "Carrier State").[82] Finally, it is possible that the bacterium itself has evolved and changed over time in response to vaccination practices; additional detail regarding strain variation among *B. pertussis* is included in the section "Molecular Diagnosis."

Carrier State

In the past, based on knowledge obtained from traditional culture methods, there was not considered to be a carrier state for *B. pertussis* in the nasopharynx. However, this may no longer be true, according to studies done with more sensitive PCR methods. In addition to circulating among adults, there may also be transient nasopharyngeal (NP) carriage of *B. pertussis* in immunized children. A case-control study[65] described a laboratory-confirmed (primarily by PCR assay) outbreak of pertussis occurring in preschool-aged children. This was not a classic pertussis, as evidenced by a lower number of cases meeting a clinical case definition, a very low hospitalization rate of unimmunized infants, and a low secondary attack rate in households. High vaccine rates may have moderated the outbreak, and, with respiratory coinfection in a significant proportion of cases, a positive PCR result may simply have reflected transient NP carriage of *B. pertussis* in the absence of evidence of seroconversion.

CLINICAL PRESENTATION

There is a spectrum of disease caused by *B. pertussis* infection, and its presentation will vary according to the patient's age, degree of immunity, use of antibiotics, and respiratory coinfection.[83]

Young Children

Joseph Lapin[1] wrote a detailed description of typical or classic pertussis in 1943 that remains true to this day. Pertussis is classically divided into three stages: the catarrhal or prodromal stage, the paroxysmal stage, and the convalescent stage. The catarrhal stage begins after a usual incubation period of 7 to 10 days, with a range of 5 to 21 days. In the catarrhal stage, children will present with signs and symptoms of a common upper respiratory tract infection, including rhinorrhea, nonpurulent conjunctivitis with excessive lacrimation, occasional cough, and low-grade fever. The catarrhal stage typically lasts 1 to 2 weeks and is followed by the paroxysmal stage. As its name suggests, the paroxysmal stage is characterized by paroxysms or fits of coughing. The child will typically have spasms of uncontrollable coughing, often 10 to 15 coughs in a row in a single expiration, the face may turn red or purple and, at the end of the paroxysm, he or she may have an inspiratory whoop. The whoop is caused by inspiring against a partially closed glottis. With the force of the coughing, the child may produce mucous plugs and often may have posttussive vomiting. Paroxysms occur more frequently at night. The paroxysmal stage lasts 1 to 6 weeks. During the end of

the first stage and beginning of the second stage, patients may exhibit signs of systemic disease such as leukocytosis with lymphocytosis, both risk factors for worse clinical outcome.[84–86] Hyperinsulinemia may also occur, although it is rarely associated with hypoglycemia.[87] Lastly, as symptoms begin to wane, the patient enters the convalescent stage. The length of the cough distinguishes pertussis from other respiratory tract illnesses. In classic pertussis, it usually lasts 1 to 6 weeks, although it can last longer; pertussis is known as the "cough of 100 days" from the Chinese. Most clinical case definitions require a cough of at least 14 days and at least one of the following symptoms: paroxysmal cough, inspiratory whoop, or posttussive vomiting.[83] The mean duration of cough in adults with pertussis is 36 to 48 days.[88] For up to 1 year after pertussis infection, it is not uncommon to have recurrences of the paroxysmal cough or inspiratory whoop with other respiratory illnesses.

Infants and Adults

Pertussis can present atypically in adults and infants. Infants are less likely to have the characteristic inspiratory whoop and a significant catarrhal stage and are more likely to present with gagging, gasping, cyanosis, or apnea and have a prolonged convalescent phase.[86,87,89] Infants often present with the nonspecific sign of poor feeding and can present with seizures. In adults, paroxysmal coughing is seen in most patients, and several studies have reported cough duration of longer than 21 days.[88] There is a wide range in the percentage of adult patients with pertussis who have whooping (8%–82%) and posttussive vomiting (17%–65%; mean, 50%). Unlike children, in adults, posttussive vomiting is strongly suggestive of pertussis.

COMPLICATIONS

Several complications are associated with pertussis. According to data from Canada and the United States, pneumonia is the most common complication of pertussis in hospitalized patients, especially among newborns younger than 1 month (10%–18%).[61,62] Pneumonia can be caused by *B. pertussis* infection itself (see Fig. 230.1) or coinfection with other respiratory pathogens. Respiratory syncytial virus (RSV) is the best described copathogen with *B. pertussis.* Rates of RSV coinfection in infants hospitalized with pertussis range from 5% to 33%.[61,89] Conversely, 8% to 16% of children with RSV infection may also be positive for *B. pertussis.*[90,91] The case-fatality rate of pertussis is highest in infants; approximately 1% of children younger than 6 months who are hospitalized with pertussis infection will die.[62] In a case-control study done by the IMPACT surveillance network, leukocytosis and pneumonia were independent predictors of death in infants hospitalized with pertussis.[84] Encephalopathy is a rare complication of pertussis.[46] It occurs more commonly in younger nonimmunized children (in 1.4% of infants younger than 2 months)[92] but can also occur in adults.[93] It typically manifests between the second and fourth weeks of cough.[94] Seizures are the most common clinical manifestation, although paresis and paraplegias, ataxia, aphasia, blindness, deafness, and decerebrate posturing have also been described. Pertussis-specific antigens may cross the blood-brain barrier and directly affect the central nervous system because high cerebrospinal fluid (CSF) antibody titers to PT and FHA have been reported in cases of pertussis encephalopathy.[46] Complications of pertussis such as pneumonia and urinary incontinence are surprisingly high in older patients and significantly more frequent in adults than adolescents, especially in those who smoke or who have asthma.[95] Other complications of pertussis caused by the forceful and persistent nature of the cough include subconjunctival hemorrhages, syncope, and rib fractures.

DIAGNOSIS

The first step in the diagnosis of pertussis is to have the appropriate index of suspicion for pertussis disease. For vaccine trials, WHO defines a case of pertussis as the presence of a paroxysmal cough for 21 days or longer and one or more of the following criteria: positive culture for *B. pertussis,* significant increases in immunoglobulin G (IgG) and IgA antibody against FHA, agglutinogen (AGG) 2 and 3 or PT, and proven contact with a culture-confirmed case.[83] This definition favors specificity of diagnosis rather than sensitivity. According to the Centers for Disease Control and Prevention (CDC),[96] a clinical case is defined as a patient with cough for 14 days or longer, in the absence of a more likely diagnosis, and at least one of the following: paroxysmal cough, whoop, or posttussive vomiting, or, in infants younger than 1 year, apnea. This is a more sensitive definition, but confirmation requires a positive laboratory finding by culture or PCR assay or a confirmed epidemiologic link.

Culture

Laboratory confirmation of pertussis has traditionally been made with culture methods.[30] Proper collection (including the timing of culture), transport, and storage of specimens are required to enhance the detection of *B. pertussis* by culture methods. Preferred patient specimens for the diagnosis of pertussis are NP aspirates and posterior NP swabs. These specimens contain the ciliated respiratory epithelial cells for which *B. pertussis* has an affinity. The advantage of NP aspirates over swabs is an increased culture positivity rate and added sample for any additional tests. If NP swabs are used, swab material should be calcium alginate, Dacron, or rayon because cotton will inhibit the growth of *B. pertussis.* Specific transport media should be used for NP specimens, including 1% acid-hydrolyzed casein or Amies medium with charcoal. Specimens may be inoculated into enrichment media such as RL transport medium, which contains half-strength charcoal agar and horse blood with cephalexin to suppress normal NP flora growth. For culture testing, specimens should then be inoculated onto BG or RL medium supplemented with glycerol, peptones, and sheep (or preferably horse) blood. Cephalexin is added to reduce the growth of normal flora but may inhibit the growth of some strains of *B. pertussis.* After incubation in ambient air at 35°C to 36°C, *B. pertussis* colonies may become visible after 3 to 4 days, although plates are typically held up to 7 days. *B. pertussis* colonies are round, domed, mercury silver in color, and shiny and produce hemolysis on BG agar. Polyclonal or monoclonal antibodies may be used to confirm identity, or *B. pertussis* can be identified with biochemical tests based on differential phenotypic characteristics.

Molecular Diagnosis

Culture method is the most specific way to diagnose pertussis. The sensitivity of culture for *B. pertussis,* however, varies widely depending on specimen transport and collection methods, as described earlier, and patient factors such as previous immunization, interval since symptom onset, antibiotic use, and age.[83] Different studies have reported culture sensitivity rates for *B. pertussis* ranging from 15% to 80%.[97–99] Many clinical microbiology laboratories now use nucleic acid detection methods such as PCR assay as a more sensitive diagnostic test for pertussis. Different PCR assays target different chromosomal regions of *B. pertussis,* including the PT promoter region, a region upstream of the porin gene, the repetitive insertion sequence IS*481,* the ACT *(cyaA)* gene, and a region upstream of the flagellin gene.[30] PCR methods for *B. pertussis* include the standard PCR gel assay and the reportedly more sensitive real-time assay.[82] The main advantages of diagnosing pertussis with PCR are its aforementioned increased sensitivity and the rapidity of testing compared with culture methods. Appropriate PCR testing permits the differentiation between *B. pertussis* and *B. holmesii*, which can also cause a pertussis syndrome.[100,101] In addition, unlike culture, which is often positive only early in the course of the disease, the PCR result will remain positive even after 21 days of antibiotic treatment in more than half of pertussis cases.[102] However, one also needs to be cautious with the use of PCR testing for pertussis. Because the PCR detects genomic material, it will detect both live and dead bacteria. As with any PCR-based method, contamination is always a concern. Although *B. pertussis* is not an environmental organism, contamination at single collection sites, with positive cultures from environmental surfaces and staff, and even from aerosolized *B. pertussis* vaccine, has been described.[103–105] Contamination may also occur in the laboratory and may be responsible for pseudo-outbreaks of pertussis.[106] A commercially available PCR-based respiratory panel includes *B. pertussis* and *B. parapertussis* (BioFire, Salt Lake City, UT). PCR methodologies and results may vary significantly between laboratories. Depending on where the crossing threshold is set for real-time PCR positivity, the sensitivity and specificity may also vary widely. Studies suggest that PCR may be too sensitive a test to use alone as a screening

method for pertussis diagnosis in an outbreak setting[73] and, in the absence of clinical, serologic, or culture confirmation, positive results may simply reflect transient NP carriage.[65]

The advent of newer molecular methods has also furthered our understanding of the genetic variation among strains of *B. pertussis*. Several investigators have used genotyping methods involving DNA sequencing to look at polymorphisms in the genes encoding for the three major *B. pertussis* antigens: pertussis toxin (PT), PRN, and FIM.[107,108] Many large molecular epidemiologic studies throughout the world have found that *B. pertussis* strains have evolved over time, frequently into dominant clones in response to widespread vaccination pressures.[109,110] For example, studies in Australia and Europe have noted the emergence of *B. pertussis* strains carrying a new allele for the PT promoter *(ptxP3),* conferring increased PT production.[111–113] In the Netherlands, the emergence of *ptxP3* strains was temporally associated with increased incidence of hospitalizations and deaths and increased lethality caused by pertussis, suggesting that genetic adaptions in *B. pertussis* may permit the organism to evade vaccine-induced immunity.[114] In addition, PRN-deficient variants have been identified worldwide, ranging in prevalence from 2.6% in Finland to 27% in Japan. In the United States, there has been an increase in the prevalence of PRN-deficient strains; in the California outbreak in 2010, only 6% of isolates were PRN deficient, whereas in the Washington outbreak in 2012, 63% of isolates were PRN deficient.[115] This increase has not been observed in other countries such as Canada.[116] Although the likelihood of disease in vaccinated persons may be higher in PRN-deficient strains, these strains are not associated with worse clinical outcomes or decreased antibiotic susceptibility and are equally capable of being detected with nucleic acid amplification testing, raising the question as to their clinical significance.[117–120]

These genetic adaptations by the organisms may partially explain the recent resurgence in pertussis disease. Although it is not entirely clear what the natural evolution of *B. pertussis* is over longer periods of time and whether this evolution is directly influenced by vaccination programs worldwide, multiple reports now address these changes over sufficient periods of time to suggest that vaccine genes are evolving and that these changes are associated with vaccine pressure.[121,122] Hence, continued culturing of *B. pertussis* isolates from respiratory samples will be necessary to ensure the ongoing genetic characterization of the bacterium.

Serology

Pertussis can also be diagnosed with serologic methods.[123] The advantage of serology is that by the time the patient presents with typical symptoms of pertussis, the antibody response is usually present. In contrast, NP cultures are usually positive only early in the course of the disease. Most laboratories use an enzyme-linked immunosorbent assay (ELISA) to detect antibodies to *B. pertussis.* ELISAs have been developed with whole bacterial cells, PT, FHA, PRN, FIM, lipooligosaccharide, and ACT. Whole–bacterial cell ELISAs are limited by cross-reactivity with other *Bordetella* species and other bacteria. PT is the most common antigen used for *B. pertussis* serologic testing. PT is produced only by *B. pertussis*, making it a highly specific antigen, and it is an important protective antigen in the immune response to infection and immunization. Unfortunately, young infants may not produce an antibody response to PT. FHA has also been used as an ELISA antigen. However, the antibody response to FHA is not specific because all *Bordetella* species have FHA, and antibodies to *Haemophilus influenzae* and *Mycoplasma pneumoniae* have been shown to cross-react with FHA. In addition, the presence of FHA antibody has not been correlated with protection in human studies. PRN and FIM may also be used to detect a serologic response to *B. pertussis,* but antibodies to these antigens occur less consistently than those against PT. ELISAs using lipooligosaccharide and ACT have been described in only a few research laboratories. Although there are ELISAs to detect IgG, IgA, and IgM to *B. pertussis*, IgG assays are the most frequently used as a diagnostic test and are the best standardized and most widely available. IgG rises typically 2 to 3 weeks after infection or primary immunization and 1 week after booster immunization. Distinguishing between antibody responses secondary to infection and secondary to recent immunization may not be possible. Paired sera are the gold standard for serologic diagnosis, and a twofold increase is considered significant evidence of seroconversion.

The difficulty with *B. pertussis* serologic assessment, however, is that one rarely obtains acute- and convalescent-phase sera but rather obtains convalescent- and late convalescent-phase sera because pertussis is often recognized late in the course of the disease. In immunized individuals, the antibody response is rapid, and one may not see the antibody rise in convalescent serology. Single-serum antibody titers have thus been used to diagnose pertussis, and antibody cutoffs that correlate with acute infection based on population-derived antibody levels have been established.[124] Single-serum testing is particularly useful for adolescents and adults because cultures are often negative in this age group and pertussis immunizations are usually more remote. Modeling has suggested that these thresholds are still valid, even in the face of adolescent and adult vaccination with Tdap (tetanus toxoid, diphtheria toxoid, acellular pertussis vaccine, adult formulation).[125]

Direct Fluorescent Antibody

Finally, direct fluorescent antibody (DFA) testing can also be used to diagnose pertussis infection. Fluorochrome-conjugated monoclonal or polyclonal antibodies recognizing a lipooligosaccharide epitope directly detect *B. pertussis* in NP secretions.[30] However, although it is a rapid and inexpensive diagnostic test, it has poor sensitivity and specificity. The sensitivity of DFA compared with culture is reported to range from 30% to 71%.[99,126] In addition, the specificity of DFA is variable because of cross-reactivity with other organisms, such as *B. bronchiseptica, H. influenzae*, and diphtheroids.[30] DFA testing is not considered to provide laboratory confirmation of a case of pertussis for most national surveillance systems and has been replaced in large part in clinical laboratories by the other diagnostic tests described.

THERAPY

Antimicrobial Agents

There is controversy regarding the efficacy of antibiotic therapy in the different stages of pertussis disease. The difficulty is partly caused by the fact that most studies are powered for a primary outcome of NP microbial eradication rather than for a clinical outcome. The classic teaching is that antibiotics improve symptoms and ablate disease when given early in the course of the disease, during the catarrhal stage, but not when given in the paroxysmal stage (Table 230.1).[127] In an open randomized study by Bergquist and colleagues,[128] 17 patients with a positive culture for *B. pertussis* were treated with erythromycin for 10 days and compared with an untreated control group. Treatment eradicated

TABLE 230.1 Treatment for Pertussis

WHO	WHEN	WHAT
Infants <1 mo	Suspected or proven pertussis	Azithromycin 10 mg/kg/day as a single dose for 5 days
Children	Suspected or proven pertussis within 21 days of onset of symptoms	Azithromycin 10 mg/kg/day (max 500 mg) on day 1, then 5 mg/kg/day (max 250 mg/day) daily on next 4 days *or* Erythromycin 40 mg/kg/day in four divided doses (max 1–2 g/day) for 7–14 days *or* Clarithromycin 15 mg/kg/day in two divided doses (max 1 g/day) for 7 days
Adolescents and adults	Suspected or proven pertussis within 21 days of onset of symptoms	Erythromycin 2000 mg/day in four divided doses for 7–14 days *or* Clarithromycin 1000 mg/day in two divided doses for 7 days *or* Azithromycin 500 mg on day 1, then 250 mg daily on next 4 days

Modified from Kimberlin DW, Brady MT, Jackson MA, et al, eds. Red Book: 2018–2021 Report of the Committee on Infectious Diseases. *31st ed. Itasca, IL: American Academy of Pediatrics; 2018.*

the bacterium from the nasopharynx in all but 1 patient, and the treated group developed significantly fewer whoops than the control group. However, although patients were enrolled within the first 14 days of their illness, a significant proportion already complained of a whooping cough on their initial visit, suggesting that antibiotics may have an effect, albeit not a dramatic one, in the paroxysmal and the catarrhal stages of disease. The Erythromycin Study Group from Germany[129] has also reported improvement in the frequency and severity of coughing in patients in the early paroxysmal stage of pertussis when treated with erythromycin. However, a Cochrane review of 11 randomized or quasirandomized controlled trials of antibiotics for treatment of whooping cough concluded that although antibiotics are effective in eliminating *B. pertussis,* they do not alter the subsequent clinical course of the illness.[130]

Traditionally, oral erythromycin was the antibiotic of choice for treatment of pertussis.[131] Erythromycin estolate is considered superior to erythromycin ethylsuccinate or erythromycin stearate because of the higher drug concentrations achieved in the serum and respiratory secretions. The CDC recommends an erythromycin dose of 40 to 50 mg/kg/day in four divided doses for children to a maximum of 2 g/day for adolescents and adults for 14 days to treat pertussis.[127] Although the CDC recommends a 14-day treatment course, 7 days of a maximum of 1 g of erythromycin estolate treatment was found to be as effective for the eradication of *B. pertussis* and improved compliance in a randomized, controlled clinical trial in Canada.[132] The main problem with oral erythromycin treatment for pertussis is the frequency of gastrointestinal side effects. Up to 30% of patients may experience gastrointestinal symptoms such as nausea, vomiting, or diarrhea. Adults may have serious drug interactions between erythromycin and other drugs. In addition, there is an association between oral erythromycin and hypertrophic pyloric stenosis in infants younger than 1 month; azithromycin, 10 mg/kg daily for 5 days, should therefore be used in this age group.[133]

Several randomized controlled trials have assessed the role of newer macrolides in the treatment of pertussis.[134,135] A Cochrane review of these studies has determined that short-term antibiotics (azithromycin for 3–5 days or clarithromycin for 7 days) are as effective as long-term antibiotics (erythromycin for 10–14 days) in eradicating *B. pertussis* from the nasopharynx (relative risk [RR], 1.02; 95% confidence interval [CI], 0.98–1.05) but had fewer side effects (RR, 0.66; 95% CI, 0.52–0.83).[130] Despite the sparse clinical outcome data in adults, alternatives to erythromycin for treatment and prophylaxis appear to be azithromycin, 500 mg the first day, then 250 mg for 4 days, or clarithromycin, 500 mg twice daily for 7 days. Trimethoprim-sulfamethoxazole for 7 days may also be effective, although the efficacy data are not convincing.[136,137] Although fluoroquinolones have been shown to have in vitro activity against *B. pertussis,*[138] there is a lack of evidence of their clinical efficacy, and reports have described quinolone-resistant *B. pertussis* resulting from mutations in the DNA gyrase gene *(gyrA).*[139] *B. pertussis* strains are not tested routinely for antimicrobial susceptibility because there is no standardized method for antimicrobial susceptibility testing for *B. pertussis* and *B. pertussis* is often detected through molecular rather than culture methods.[131] Although erythromycin resistance, which predicts resistance to other macrolides, in *B. pertussis* strains has been identified and is likely caused by a mutation of the erythromycin-binding site in the 23S rRNA gene,[140,141] there is no evidence that erythromycin resistance in *B. pertussis* is increasing or spreading.[138] Continued surveillance through culture of *B. pertussis* isolates, however, is needed.

Supportive Care

In addition to antibiotic therapy, supportive care is paramount for the management of pertussis, especially in infants. Intubation and mechanical ventilation may be required in infants with apnea and cyanosis.[89] Physicians should also be aware of the potential for respiratory coinfection and treat patients appropriately. Adjunctive therapies such as corticosteroids, salbutamol, pertussis-specific immunoglobulin, and antihistamines have been used to manage the cough of pertussis symptomatically and are the subject of a Cochrane review.[142] Only six studies with a total of 196 participants reported data in sufficient detail to be included in the analysis. No statistically significant benefit was found for any of the interventions. Neither diphenhydramine nor salbutamol changed the frequency of coughing spells, and dexamethasone did not decrease the length of hospital stay. Pertussis immunoglobulin did not affect length of hospital stay and, although it was associated with a mean reduction in the number of whoops per 24 hours, the difference was not statistically significant. An efficacy study of pertussis immunoglobulin for the treatment of hospitalized infants with pertussis was terminated prematurely because of expiration of the immunoglobulin and unavailability of additional study product.[143]

PREVENTION

Immunization

Immunization is the single most effective means of preventing pertussis disease (Table 230.2) (see Chapter 316). The history of pertussis vaccination is long and began with attempts to develop a vaccine from the whole *B. pertussis* organism. The difficulty lay in striking the right balance between making a vaccine with enough bacteria that it was immunogenic versus making a vaccine that was too reactogenic because of additional impurities.[4] Before the 1940s, the efficacy of a vaccine could be assessed only in human trials until Kendrick and associates[144] developed the mouse potency test. In the mouse potency test, the efficacy of a vaccine was determined by immunizing a mouse intraperitoneally and then infecting it intracerebrally with live *B. pertussis.* Survival was measured at 14 days, and a potency unit was calculated according to WHO criteria. Using standardized potency vaccines, the British Medical Research Council performed multiple field trials during the 1940s and 1950s to test different vaccines and found a correlation between the results of the mouse potency test and degree of protection in children against pertussis disease.[145] Concurrently, the United States began routine immunization of children with whole-cell pertussis vaccines in the 1940s and observed a dramatic drop in the rates of pertussis. However, no formal prospective clinical efficacy trials were done to assess whole-cell pertussis vaccines, routinely given combined with diphtheria and tetanus toxoids (DTP vaccine). The best data available regarding their efficacy are from six vaccine trials done in four countries from 1990 to 1995, comparing acellular and whole-cell pertussis vaccines.[4] Except for the Connaught vaccine—thought to be less effective after attempts to make it less reactogenic—the percentage efficacy of DTP against typical pertussis ranges from 89% to 96%. WHO recommends immunization with DTP, and it continues to be used worldwide in many countries.[55] Updated WHO recommendations address the choice of vaccine and vaccination during pregnancy.[146] The problem with whole-cell pertussis vaccines is their reactogenicity. It is known that DTP vaccine causes significantly more local reactions (redness, swelling, and pain) and systemic reactions such as drowsiness, vomiting, and persistent crying than acellular pertussis vaccines and DT alone.[4] More serious adverse events such as convulsions and hypotonic and hyporesponsive episodes (HHE) are much rarer occurrences, especially after the introduction

TABLE 230.2 Vaccination for Pertussis

WHO	WHEN	WHAT
Children	2, 4, 6, and 15–18 mo Booster at 4–6 yr	DTaP or DTaP combination vaccines
Adolescents	11–18 yr, 11–12 yr preferred	Tdap
Adults	Single adult dose	Tdap
Health care workers	Single adult dose	Tdap
Pregnant women	Every pregnancy; 27–36 wk of gestation preferred	Tdap

[a]Based on US schedules.
DTaP, Diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine, pediatric formulation; *Tdap,* tetanus toxoid, diphtheria toxoid, acellular pertussis vaccine, adult formulation (reduced doses of "d" and "ap" components).
Modified from Kimberlin DW, Brady MT, Jackson MA, et al, eds. Red Book: 2018–2021 Report of the Committee on Infectious Diseases. *31st ed. Itasca, IL: American Academy of Pediatrics; 2018; and Liang JL, Tiwari T, Moro P, et al. Prevention of tetanus, diphtheria, and pertussis with vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep. *2018;67(RR-2):1–44.*

of acellular vaccines.[147] There has also been much discussion surrounding the role of pertussis vaccine in causing neurologic injury and death.[148] From the 1940s to the 1970s, there were multiple case reports and series reporting possible vaccine complications ranging from encephalopathy and coma to death.[149,150] The ensuing controversy about pertussis vaccination affected much of Europe, Japan, the United States, the Soviet Union, and Australia. A large case-control study, the National Childhood Encephalopathy Study (NCES), investigated the relationship between DTP immunization and neurologic injury and found the risk to be very low (1 in 111,000). In 1991, the US Institute of Medicine reviewed all the literature and concluded that there was no evidence to support an association between pertussis immunization and permanent neurologic damage.[151] In addition, according to IMPACT data from 1993 to 2002 in Canada, there was no evidence of encephalopathy after more than 6.5 million doses of pertussis vaccine.[152] There was also initial concern regarding the possible association between pertussis vaccination and sudden infant death syndrome (SIDS).[153,154] However, several large controlled studies failed to find a cause-and-effect relationship between pertussis immunization and SIDS.[153,154] It is likely that any possible association between pertussis immunization and infantile seizures or SIDS is a result of the fact that these conditions occur coincidentally with the time at which the two- or three-dose primary series of DTP is administered.

Acellular Pertussis Vaccines

In response to concerns regarding reactogenicity, pertussis vaccines composed of acellular components of *B. pertussis* were developed. Sato and coworkers[155] from Japan were the first to design an acellular pertussis vaccine containing two purified hemagglutinins (HAs): FHA and leukocytosis-promoting factor HA. By removing endotoxin (lipopolysaccharide [LPS]) from the preparation, they were able to produce a vaccine that was as effective as the whole-cell vaccine and caused fewer side effects. The vaccine was used for mass immunization in Japan beginning in 1981 during an epidemic of pertussis. Although efficacy data for this first acellular pertussis vaccine were limited, its use spurred the development of further prototypes. Several different versions of acellular pertussis vaccines have since been developed and include one-, two-, three-, four-, and five-component vaccines (composed of a combination of PT, FIM types 2 and 3, PRN, and/or FHA). All are less reactogenic than their whole-cell counterparts because they do not contain LPS.[4] Their efficacies vary depending on the type of study done and the case definition used but range from 59% to 93% for pertussis cases defined according to the WHO criteria.[156] Vaccines containing PT, FHA, PRN, and FIM are likely more effective against mild disease than vaccines containing PT, FHA, and/or PRN alone, suggesting that FIM may have a role in protection against infection and/or milder disease.[157] The recently developed baboon model of clinical pertussis provides some insight into the differing immune responses to whole-cell versus acellular pertussis vaccines.[158] Baboons who clear wild-type pertussis infection mount very strong Th17 and Th1 responses and a very low Th2 response. In contrast, baboons vaccinated with acellular pertussis vaccine remain heavily colonized in the airway, can transmit pertussis, and have a strong Th2 response with low Th17 and Th1 responses. Baboons vaccinated with whole-cell pertussis vaccine fall in between these two presentations, being able to eventually clear infection with low Th17 and Th1 responses and no Th2 response.[159,160] These data may help to explain the pertussis resurgence seen in the era of acellular pertussis vaccination.

Vaccination Schedules

Most North American immunization schedules recommend pertussis vaccination (DTaP, pediatric formulation) at 2, 4, 6, and 18 months of age, with a booster at 4 to 6 years of age. Although there are many different pertussis immunization schedules throughout the world, most will have two or three doses in the first year of life, another dose in the second year of life, and a preschool booster. Childhood immunization with pertussis-containing combination vaccines has been demonstrated to be safe, immunogenic, and effective for the control of pertussis.[161] However, pertussis outbreaks continue to occur in the adult[75,162] and adolescent population.[77,163] Because adolescents and adults continue to be a source of pertussis transmission,[164,165] immunization of this group was investigated in the Adult Pertussis Trial (APERT).[166] In this study, 2781 healthy subjects were randomized to receive either a tricomponent acellular vaccine or a hepatitis A vaccine. Vaccine protection against pertussis disease was 92% during the study follow-up period (median duration, 22 months). Several prospective, randomized, controlled trials have assessed the reactogenicity and immunogenicity of Tdap in several thousand adolescents and adults.[167–169] The Tdap vaccine elicited robust immune responses and had a similar safety profile to the Td vaccine. Follow-up data from several of these studies demonstrated that antibody titers to pertussis exceeded preimmunization levels 1, 3, and 5 years later.[170] Further studies have shown that Tdap boosters (Adacel [Sanofi Pasteur, Toronto, Canada] or Boostrix [GlaxoSmithKline, Research Triangle Park, NC]; lower case letters "d" and "ap" indicate reduced dose compared with DTaP) can be given safely at any interval after prior tetanus, diphtheria, or pertussis vaccinations in adolescents.[171–173] Both cellular and humoral immune responses occur after acellular pertussis immunization of adults and adolescents, but the cell-mediated immune response may be of greater magnitude and longer duration and thus more reflective of long-term protection.[174] Both the National Advisory Committee on Immunization (NACI) and the Advisory Committee on Immunization Practices (ACIP) of the CDC have recommended routine Tdap vaccination for adolescents and to replace Td with Tdap boosters in adults.[175–177] Tdap has also been shown to be safe and immunogenic in older individuals[178] and is now also recommended for adults older than 65 years.[179] Experience in Canada[70,180,181] and in the United States[182,183] has demonstrated that an adolescent pertussis vaccine program can be implemented on a national scale, is safe, and can result in a further decrease in the incidence of pertussis. To date, however, Tdap programs for adults have been more difficult to implement.[184]

Vaccination of Health Care Workers

Health care workers are another potential source of pertussis transmission, particularly to patients. Multiple nosocomial pertussis outbreaks have been described,[185–187] with significant patient health consequences and costs incurred by the health care system.[188–190] Costs included direct medical center costs for treatment and prophylaxis, costs for personnel time, and indirect medical center costs for time lost from work. It is more cost-effective to vaccinate health care workers than to manage a nosocomial exposure of pertussis.[191] ACIP recommends that health care workers who work in hospitals or ambulatory care settings and have direct patient contact should receive a single dose of Tdap if they have not been vaccinated previously as an adult, regardless of when they received their last dose of Td.[177] Given its cost-effectiveness, health care institutions should provide universal Tdap immunization to their health care workers.

Protection of Infants

Infants are most vulnerable to severe pertussis disease, so specific strategies have been examined to protect neonates from pertussis transmission.[192] A cocoon strategy of vaccinating household members has been suggested to provide partial protection to unimmunized infants because parents are known to be important sources of infection in these cases.[177] One study showed a 70% decrease in the number of pertussis cases in infants 0 to 3 months of age in households in which a cocoon strategy had been implemented.[193] Another study demonstrated an ability to vaccinate more than 90% of postpartum women with Tdap.[194] However, there are practical and logistical difficulties in implementing vaccination programs to reach all potential infant contacts, including fathers and other family members.

Vaccination During Pregnancy

In light of the increased incidence of pertussis and known serious complications that can occur with neonatal pertussis disease, ACIP recommended the use of Tdap during pregnancy[195] after reviewing the safety data from registries and small studies.[172,196] Subsequent reviews of reports to the Vaccine Adverse Event Reporting System (VAERS) did not identify any concerning patterns in maternal, infant, or fetal outcomes after Tdap vaccination of pregnant women.[197] In October 2012, ACIP updated its recommendations, advising that Tdap also be

given during each subsequent pregnancy. Although pertussis antibodies cross the placenta, maternal antibody levels are low and decay rapidly.[198] Administering a pertussis booster dose during pregnancy may increase neonatal antibody titers but may not help with the infant's cellular immune response to infection. However, a case-control study in England and Wales estimated that vaccination during pregnancy was 93% effective in preventing pertussis during the first 2 months of life.[199] A subsequent randomized, double-blind, placebo-controlled clinical trial of Tdap immunization of pregnant women at 30 to 32 weeks' gestation demonstrated higher concentrations of maternal pertussis antibodies at delivery and higher antibodies in their infants at birth and at age 2 months compared with those whose mothers received placebo.[200] In addition, antibody responses in infants born to women who received Tdap during pregnancy were not different after the fourth dose of DTaP. There is a concern, however, that maternal immunization may interfere with an infant's ability to respond to active immunization. A large Canadian, randomized, controlled, multicenter trial in which 273 pregnant women received either Tdap or Td in the third trimester revealed that infants whose mothers had received Tdap had lower antibody levels to PT, FHA, PRN, and FIM antigens at 7 months of age (after pertussis vaccination at 2, 4, and 6 months) compared with infants whose mothers had received only Td.[201] Furthermore, antibody levels to PT, FHA, and FIM were lower in these infants when measured 1 month after the 12-month pertussis booster. Reassuringly, a retrospective cohort study of almost 150,000 newborns from 2010 to 2015 in California showed that maternal Tdap vaccination was 91.4% effective at preventing neonatal pertussis during the first 2 months of life and 69% effective at preventing pertussis during the first year of life, providing additional protection to infant DTaP immunization. As a result of ACIP recommendations, Tdap vaccination coverage during pregnancy in the United States has increased from <1% before 2009 to 54% in 2015. Attempts to further refine the optimal timing (gestational week) for vaccination continue. A prospective trial of vaccination in the third trimester showed improved cord blood antibody levels in mothers vaccinated in the early period (28–36 + 6 weeks) compared with the late period (32–38 + 6 weeks).[202] A trial initially designed to demonstrate the noninferiority of second-trimester vaccination instead showed superiority by rates of both seropositivity and concentration of infant antibody.[203] Second-trimester maternal Tdap vaccination also leads to higher birth anti-PT titers in preterm neonates compared with third-trimester maternal vaccination, providing possible improved protection for a particularly vulnerable patient population.[201] The durability of vaccination during pregnancy with Tdap suggests that antibodies wane significantly 9 to 15 months after delivery.[204]

Neonatal Vaccination

Finally, neonatal pertussis vaccination has also been studied as a method of preventing pertussis. Vaccination of newborn infants with whole-cell pertussis vaccine resulted in "immune tolerance" or reduced antibody responses to *B. pertussis* antigens compared with infants who received their first pertussis vaccine at 2 months of age.[205,206] However, early neonatal immunization with acellular pertussis vaccine was safe, was well tolerated, and accelerated the acquisition of pertussis antibodies in infants without inducing immune tolerance.[207,208] The difficulty with the current inactivated pertussis vaccines, however, is that they require interferon-γ (IFN-γ) production as part of a Th1 response to effectively induce vaccine-mediated protective immunity, and neonatal T cells produce lower levels of IFN-γ.[209,210]

Investigators have therefore developed a live-attenuated *B. pertussis* vaccine to be delivered intranasally in an attempt to replicate the long-lasting and vigorous immunity seen with natural infection in neonates. Such a live-attenuated vaccine was shown to induce significantly better protection against pertussis disease in infant mice than an injectable acellular vaccine[211] and to produce long-term cellular and humoral immune responses in mice.[212] A phase I double-blind, placebo-controlled, dose-escalating study of a nasal live-attenuated *B. pertussis* vaccine (BPZE1) was conducted in 48 healthy adult male volunteers and demonstrated that the vaccine was safe and induced colonization, particularly in the higher-dose group.[213] In addition, colonization was associated with significant increases in serum antibodies against PT, PHA, PRN, and FIM and in memory B-cell responses to PT, FHA, and PRN.[214] However, certain participants were not colonized. These individuals were noted to have significantly higher prevaccination antibody levels to FHA, PRN, and FIM, possibly due to prior infection with *B. pertussis*. This suggests that previous exposure to the organism may induce immunity, preventing BPZE1 uptake.[215] Phase Ib clinical trials of intranasal immunization with high-dose BPZE1 in healthy volunteers are ongoing (NCT02453048).

Chemoprophylaxis

In addition to immunization, chemoprophylaxis may be used to prevent the transmission of *B. pertussis*. In the United States, erythromycin prophylaxis is recommended for all household contacts and other close contacts, including those in child care.[127] In Canada, chemoprophylaxis is recommended only for infants or pregnant women (third trimester) and household contacts (Table 230.3).[216] However, erythromycin prophylaxis of pertussis contacts is not practiced uniformly throughout the world. In fact, in a Cochrane review of two randomized, controlled trials of antibiotic treatment of contacts,[217,218] the authors concluded that chemoprophylaxis of contacts older than 6 months does not significantly improve clinical symptoms or the number of cases developing culture-positive *B. pertussis*.[130] It is important to note, however, that these randomized trials did not specifically investigate the use of erythromycin in high-risk populations, such as children younger than 6 months, who might benefit the most from any added protection. Although there are reports of successful chemoprophylaxis against pertussis, these are often the results of uncontrolled or poorly controlled studies.[219,220] It is likely, in many cases, that transmission occurs before pertussis is diagnosed in the index case, thus limiting the usefulness of chemoprophylaxis. If chemoprophylaxis is to be of any benefit, it needs to be given early in the course of the disease in the index case and before the occurrence of the first secondary case.[221] Chemoprophylaxis

TABLE 230.3 Postexposure Prophylaxis for Pertussis for Close Contacts

WHO	WHEN	WHAT
Infants	Exposed to case of pertussis	Azithromycin 10 mg/kg/day as a single dose for 5 days
Children	Exposed to case of pertussis within 21 days of onset of cough in index case	Erythromycin 40 mg/kg/day in four divided doses (max 1–2 g/day) for 7–14 days *or* Clarithromycin 15 mg/kg/day in two divided doses (max 1 g/day) for 7 days *or* Azithromycin 10 mg/kg (max 500 mg) on day 1, then 5 mg/kg/day (max 250 mg) daily next 4 days *plus* Age-appropriate pertussis vaccination
Pregnant women (third trimester)	Exposed to case of pertussis	Erythromycin 2000 mg/day in four divided doses for 7–14 days *or* Clarithromycin 1000 mg/day in two divided doses for 7 days *or* Azithromycin 500 mg, then 250 mg daily next 4 days *plus* Tdap vaccination (if not already given in this pregnancy)
Other adolescents/adults	Exposed to case of pertussis within 21 days of onset of cough in index case	Erythromycin, clarithromycin, and azithromycin dosages as for pregnant women; plus Tdap vaccination

Tdap, Tetanus toxoid, diphtheria toxoid, acellular pertussis vaccine, adult formulation (reduced doses of "d" and "ap" components).
Modified from Kimberlin DW, Brady MT, Jackson MA, et al, eds. Red Book: 2018–2021 Report of the Committee on Infectious Diseases. *31st ed. Itasca, IL: American Academy of Pediatrics; 2018.*

is generally not recommended if 21 days have elapsed since the onset of cough in the index patient.[127]

Pertussis in Schools and Daycare Centers

Children and staff with pertussis should be excluded from attendance until 5 days after initiation of macrolide treatment. Those untreated should be excluded for 21 days after onset of illness. Exposed children, particularly incompletely immunized children, should be observed for 21 days after the last contact.

FUTURE DIRECTIONS

Although much has been learned about pertussis since the time of Lapin, there remain several unanswered questions. How much pertussis disease is there in adults? Do adults require multiple doses of pertussis vaccine, and will this result in less cough illness? Is there an NP carrier state for *B. pertussis*? Is maternal immunization a safe and effective way of preventing neonatal pertussis? Future research is needed in these and other areas to further our understanding of pertussis.

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The complete reference list is available online at Expert Consult.

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231 Rat-Bite Fever: *Streptobacillus moniliformis* and *Spirillum minus*

Vijayashree Mekala and Ronald G. Washburn

SHORT VIEW SUMMARY

Definition
- Rat-bite fever is an acute febrile illness characterized by rash and relapsing fever. It is caused by *Streptobacillus moniliformis* and *Spirillum minus.*

Epidemiology
- The infection is transmitted by bites or scratches from rodents or carnivores that prey on rodents or by ingestion of contaminated milk or water. Rat-bite fever is not generally reportable, and the incidence is probably higher than the literature reflects.

Microbiology
- In the United States and Europe, rat-bite fever is caused by *S. moniliformis,* a fastidious gram-negative bacillus. In Asia, the causative organism is *S. minus,* a spirochete that has never been grown in culture.

Diagnosis
- *S. moniliformis* is diagnosed by clinical presentation plus culture in enriched media or polymerase chain reaction. *S. minus* is diagnosed by clinical presentation plus direct visualization or xenodiagnosis.

Therapy
- Penicillin is the treatment of choice for both types of rat-bite fever.

Prevention
- Preventive measures include eradication of rats, avoidance of nonpasteurized milk and water, and use of gloves by laboratory workers when handling rats.

Rat-bite fever is a rare systemic febrile illness typically transmitted by the bite of a rat or other small rodent. The infection has a worldwide distribution and can be caused by either *Streptobacillus moniliformis* or *Spirillum minus,* bacteria commonly found in the oropharyngeal flora of rodents. Streptobacillary disease accounts for the vast majority of cases of rat-bite fever in the United States,[1] whereas *S. minus* infections occur mainly in Asia. Table 231.1 compares the two different forms of rat-bite fever.

Illness after rat bites has been known in India for more than 2000 years,[2] and the characteristic syndrome of rat-bite fever was recorded in the United States as early as 1839.[3] Early in the 20th century, the causative gram-negative bacillus, initially named *Streptothrix muris ratti,* was recovered from clinical material.[4,5] In 1925, a blood culture isolate from a laboratory worker with fever, rash, and arthritis was called *S. moniliformis*, based on its morphologic resemblance to a beaded necklace.[6] In 1926, a similar organism, *Haverhillia multiformis,* was grown from the blood of patients during an epidemic illness resembling rat-bite fever in Haverhill, Massachusetts.[7] Both *H. multiformis* and *S. muris ratti* were subsequently shown to be identical to *S. moniliformis,* the causative agent of streptobacillary rat-bite fever.[2]

STREPTOBACILLUS MONILIFORMIS

Bacteriology

S. moniliformis is a pleomorphic, nonmotile, nonsporulating, nonencapsulated gram-negative bacillus in the family Leptotrichiaceae,[8] measuring 0.3 to 0.7 µm wide by 1 to 5 µm long.[9] Filaments and beadlike chains up to 150 µm long may contain 1- to 3-µm-wide fusiform swellings (Fig. 231.1).[10] The organism is microaerophilic and capnophilic, requiring a partial pressure of carbon dioxide between 8% and 10% for primary isolation at 37°C. Trypticase soy agar or broth must be supplemented with 10% to 20% rabbit, sheep, or horse serum; defibrinated blood; or ascites to support optimal growth. A shell vial cell culture technique that used human endothelial cells rescued viable *S. moniliformis* after conventional culture methods failed.[11] Sodium polyanethol sulfonate, a substance sometimes added to aerobic blood culture bottles as an anticoagulant or to trypticase soy or thioglycollate broth to inhibit the antibacterial activity of human blood, impedes the growth of *S. moniliformis* in concentrations of at least 0.0125%.[12,13] Thus if rat bite fever is suspected, the laboratory should be informed and serum-supplemented broth or agar medium without sodium polyanethol sulfonate should be used.

On blood agar plates, nonhemolytic cotton-like colonies, 1 to 2.5 mm in diameter, appear after approximately 3 days of incubation. In broth media, characteristic flocculent "puffballs" are seen at the bottom of the broth after 2 to 10 days (Fig. 231.2). Penicillin-resistant L-phase variants may form spontaneously or in the presence of penicillin both in vivo and in vitro.[14] Low muramic acid content in cell envelopes may contribute to the propensity of *S. moniliformis* to produce L forms,[15] which impart a turbid appearance to broth media and a "fried egg" colony morphology on solid agar.[9] Sugar fermentation is variable but often includes galactose, glucose, maltose, and salicin. Fatty acid analysis by gas-liquid chromatography is useful for the rapid identification of *S. moniliformis* isolates.[9,16–20] In addition, sodium dodecyl sulfate–polyacrylamide gel electrophoresis patterns of cellular proteins may be useful for epidemiologic studies of the epidemic (Haverhill fever) form of the infection.[21] Guanine plus cytosine content is 24 to 26 mol%, and the complete genome sequence has been reported.[8,9]

Epidemiology

In the United States, where 50% to 100% of rats are colonized with *S. moniliformis,* persons who are at risk for percutaneous inoculation with *S. moniliformis* include animal laboratory personnel and individuals (especially children) inhabiting crowded urban dwellings or rural areas infested with wild rats.[1,22,23–27,28] Although rat bite fever is not reportable, based on an estimated 20,000 rat bites annually and a 10% bite infection rate, an incidence of more than 1000 cases per year is estimated.[9] The infection is typically transmitted by the bite or scratch of rats, mice, guinea pigs, squirrels, or carnivores that prey on those rodents, including cats, dogs, pigs, ferrets, weasels, and snakes.[22,29,30,31] One reported case followed the bite of a gerbil,[32] another the scratches of a rooster.[33] The infection may also be acquired by handling rats, without any apparent breach of intact skin[23,34,35] or with a portal of entry, such as varicella lesions.[36] Wild rats as well as laboratory and pet rats harbor *S. moniliformis* in their nasopharyngeal microbiota,[23,37–40] and they may develop otitis media.[41] In contrast, healthy laboratory mice are generally not colonized with *S. moniliformis* but are susceptible to epizootic infections characterized by polyarthritis, septicemia, pneumonia, otitis media, and high rates of abortion.[2,38,42–44] *S. moniliformis* has also been reported to cause pleuritis in a koala,[45] cervical abscesses and pneumonia in guinea pigs,[46] arthritis in turkeys and a monkey, and endocarditis in a macaque.[47]

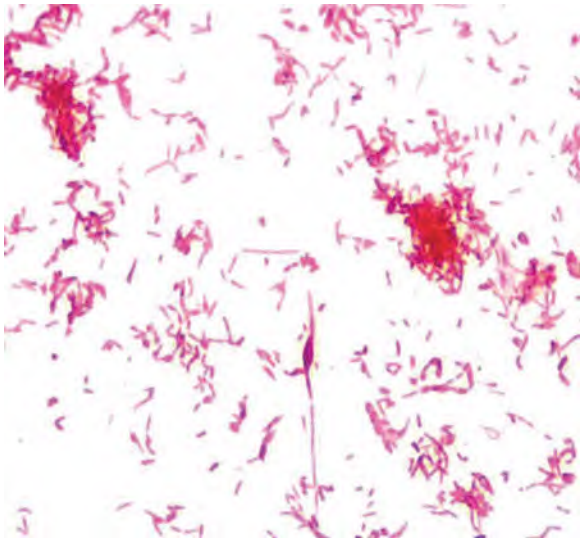

FIG. 231.1 Pleomorphic gram-negative bacilli—*Streptobacillus moniliformis.* *(From Albedwawi S, LeBlanc C, Shaw A, et al. A teenager with fever, rash and arthritis.* CMAJ. *2006;175:354.)*

TABLE 231.1 Comparison of Two Different Types of Rat-Bite Fever

PARAMETER	ORGANISM	
	Streptobacillus moniliformis	***Spirillum minus***
Organism	Gram-negative bacillus	Gram-negative coiled rod
Geographic distribution	North America, Europe	Asia
Mode of transmission	Rat bite, ingestion	Rat bite
Clinical syndrome:		
Ulceration of initial bite wound	No	Yes
Arthritis	Yes	No
Regional lymphadenopathy	No	Yes
Rash	Yes	Yes
Relapsing fever	Yes	Yes
Diagnosis	Culture, polymerase chain reaction	Direct visualization, xenodiagnosis
Therapy	Penicillin G	Penicillin G

Pathophysiology

The clinical disease is probably the consequence of failed local cutaneous defenses and bacterial dissemination. The few available published pathology reports described interstitial pneumonia, lymph node hyperplasia, erythrophagocytosis, vasculitis,[48,49] and intravascular thrombi.[50,51]

Oral ingestion of organisms has caused several epidemics of Haverhill fever (erythema arthriticum epidemicum), an illness clinically resembling rat-bite fever. Potential sources of such outbreaks include foods such as turkey, or milk or water contaminated with rat excrement.[6,7,12,23,52–54] Presumably, once ingested, *S. moniliformis* organisms gain access to the peripheral circulation by penetrating the gastrointestinal mucosa.

Clinical Manifestations

After the rat bite, a brief incubation period (1–22 days, usually <10 days), is followed by abrupt onset of fever, chills, headache, vomiting, and severe migratory arthralgias and myalgias that mark the beginning of clinical disease. By that time, the wound itself has usually already healed. The diagnosis is often initially obscured by the fact that patients are unaware of bites occurring during sleep. In contrast to *S. minus* infection, regional lymphadenopathy is minimal or absent. The peripheral white blood cell count may be as high as 30,000/mm^3 with a leftward shift, and approximately 25% of patients have false-positive nontreponemal syphilis serologies.[30,48] Within 2 to 4 days after the onset of fever, a nonpruritic maculopapular, morbilliform, petechial,[55] vesicular[53] or pustular[48,56] rash erupts over the palms, soles, and extremities (Fig. 231.3). Skin lesions may become purpuric[50,57,58] or confluent and may eventually desquamate.[22] Approximately 50% of patients develop asymmetrical polyarthritis or true septic arthritis[59–61] concurrently with the rash or within a few days thereafter.[24,62,63,64–67] The knees are most commonly involved, followed by the ankles, elbows, wrists, shoulders, and hips.[52,65,66] Typically, fever subsides after 3 to 5 days, even without specific antibiotic therapy, and the remaining symptoms gradually resolve within 2 weeks. However, fever may occasionally relapse in an irregular pattern for weeks or months,[14] producing a clinical picture of fever of undetermined origin. Alternatively, arthritis may persist for as long as 2 years.[9] Haverhill fever differs clinically from percutaneously acquired rat-bite fever chiefly in the high incidence of pharyngitis and heightened severity of vomiting.[12,22]

Reported complications of *S. moniliformis* infection include endocarditis,[23,52,64,68–75] myocarditis,[23,37] pericarditis,[2,68] sepsis,[76,77] cutaneous leukocytoclastic vasculitis,[78] systemic vasculitis,[79] meningitis,[71] pneumonia,[23,71] hepatitis,[35] septic arthritis,[24,80–83] diskitis,[84] amnionitis,[85] and anemia.[2,37] Abscesses have been observed in almost all organs, including brain,[86] liver, spleen, kidney, epidural space[87,88] and vertebrae,[31,89,90] skin,[10,91] muscle,[33] and the female genital tract.[19] In infants and young children, diarrhea and weight loss may be prominent.[23,27,71] The mortality of untreated cases ranges as high as 13%,[71] and endocarditis in the

FIG. 231.2 "Puffballs" in broth culture—*Streptobacillus moniliformis.* *(From Albedwawi S, LeBlanc C, Shaw A, et al. A teenager with fever, rash and arthritis.* CMAJ. *2006;175:354.)*

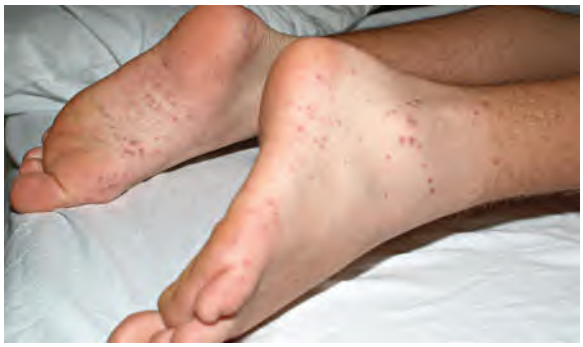

FIG. 231.3 Petechial rash of rat-bite fever. *(From Albedwawi S, LeBlanc C, Shaw A, et al. A teenager with fever, rash and arthritis.* CMAJ. *2006;175:354.)*

preantibiotic era was often lethal. Most of those intravascular infections involved prosthetic materials,[74,92] or native valves that were previously damaged by rheumatic valvulitis or calcification,[52] but one case involved a previously normal mitral valve.[74]

Diagnosis

In a febrile patient with rash and recent rat exposure, the diagnosis can usually be narrowed down to rat-bite fever or leptospirosis. However, the physician caring for a laboratory worker may step into the trap of attributing a seemingly benign febrile illness to viral infection. Furthermore, without a positive exposure history, the diagnosis may be even more elusive because diagnoses such as meningococcemia, enteric fever, drug reaction, and viral exanthem enter into consideration. When the rash involves the palms and soles, rat-bite fever may mimic Rocky Mountain spotted fever[93] or secondary syphilis. The presence of oligoarticular or migratory polyarthritis heightens concerns about disseminated gonococcal infection, Lyme disease, brucellosis, septic arthritis, infective endocarditis, rheumatoid arthritis, and acute rheumatic fever.

Direct visualization of pleomorphic bacillary organisms in Giemsa-, acridine orange–, or Gram-stained smears of blood, joint fluid,[50] and pus may provide an early clue to the diagnosis. However, laboratory diagnosis ultimately rests on culturing *S. moniliformis* using enriched media.[94] An enzyme-linked immunosorbent assay has been developed for detection of specific antibodies against *S. moniliformis.*[95] More recently, polymerase chain reaction (PCR) techniques that amplify bacterial 16S ribosomal RNA have been used to detect *S. moniliformis* infection in rodents[40,96,97] and humans.[a] Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry has also been used for positive identification of the organism from blood cultures.[80,101,102]

Therapy and Prevention

Both agents of rat-bite fever, *S. moniliformis* and *S. minus,* are susceptible to penicillin. In the past, procaine penicillin G was given intramuscularly (IM) as 600,000 units every 12 hours for 10 to 14 days.[2,22,62] Currently, intravenous (IV) penicillin G or ceftriaxone appear more appropriate. The Jarisch-Herxheimer reaction may complicate initial therapy of *S. minus* infections. Oral tetracycline, 500 mg every 6 hours, is preferred for penicillin-allergic patients.[2,16] Streptomycin (7.5 mg/kg) can be given IM every 12 hours, although potential ototoxicity makes this less desirable. Limited experience indicates that ceftriaxone,[50,56,67,79,88] erythromycin,[103] chloramphenicol,[12,93] or clindamycin[23,37] might also be effective.

Most patients respond promptly to therapy. For individuals who appear well after 5 to 7 days of parenteral therapy, the course can be completed with an additional week of oral penicillin V or ampicillin, 500 mg every 6 hours. Patients with mild disease can probably be successfully treated by the oral route for the entire course.

Endocarditis is so rare that optimal therapy is uncertain. It is probable that 4 weeks of IV penicillin, with or without streptomycin or gentamicin,[72,75] are adequate. A total daily dose of 20 million units has been advocated for patients whose isolates are resistant to 0.1 μg/mL.[69]

After a rodent bite, the wound should be thoroughly cleaned, and tetanus prophylaxis should be administered if warranted by the patient's immunization history. A prophylactic 3-day course of oral penicillin (2 g/day) would seem reasonable, although efficacy is unknown, and the patient should be advised to report any subsequent symptoms. Measures to limit the incidence of rat-bite fever include eradication of rats in urban areas, avoidance of nonpasteurized milk and potentially contaminated water, and the use of gloves by laboratory workers when handling rodents.

SPIRILLUM MINUS

S. minus causes a significant portion of rat-bite fever cases in Asia but rarely produces infection in the United States.[1,25] A case occurred in a traveler returning from Vietnam to Italy.[104] In Japan, the infection is called *sodoku (so,* rat; *doku,* poison).

The causative organism was discovered by Carter during the 19th century.[105] In the early years of the 20th century, specimens from patients with *sodoku* were shown to contain spirochetes capable of infecting guinea pigs. Those bacteria were initially called *Spirocheta morsus muris* or *Sporozoa muris.*[2] The organism was renamed *Spirillum minus* in 1924.[106]

Bacteriology

S. minus is a short, thick, gram-negative, tightly coiled spiral rod measuring 0.2 to 0.5 μm by 3 to 5 μm.[22,107] The organism has two to six regular helical turns. Terminal polytrichous flagella confer darting motility, which can be demonstrated with darkfield examination. The flagella can be stained with silver impregnation methods (e.g., Fontana-Tribondeau staining). Despite reports to the contrary, *S. minus* has not been cultured on artificial media, and its name derives from its appearance alone. No attempt at sequence analysis of the organism in body fluids has been reported.

Epidemiology, Pathogenesis, and Pathology

The epidemiology of *S. minus* infections is similar to that of streptobacillary rat-bite fever, with the exception that oral ingestion has not been shown to cause spirillary disease. The major route of transmission is through rat bites. Approximately 25% of tested rats were positive for *S. minus* in conjunctival and nasopharyngeal secretions, pulmonary lesions, and blood.[23] Human-to-human transmission has not been documented. The reasons for the marked geographic differences are not known.

Relapses of spirillary rat-bite fever have been postulated to be caused by seeding of blood and distant foci during periodic reactivation of the primary bite lesion. The available recorded autopsies show granulomatous inflammation at the original site of inoculation, with epithelial necrosis and mononuclear infiltration of the dermis. Regional lymph nodes are hyperplastic. Deep tissue specimens from distant areas of skin rash contain dilated blood vessels and round cell infiltrates. Liver, spleen, renal tubules, myocardium, and meninges may be hemorrhagic, with areas of necrosis in liver and kidney.

Clinical Manifestations

The initial bite wound heals promptly but then becomes painful, swollen, and purple approximately 1 to 4 weeks later, and is associated with regional lymphangitis and lymphadenitis. This local inflammatory lesion ushers in a systemic illness characterized by fever, chills, headache, and malaise. In contrast to streptobacillary rat-bite fever, arthritis and myalgias are rare in *S. minus* infection. Next, the bite wound progresses to chancre-like ulceration and induration with eschar formation. During the first week of fever, a blotchy violaceous or reddish-brown macular rash erupts over the extremities, face, scalp, and trunk, and then it fades during subsequent afebrile intervals. On occasion, the rash may be urticarial.[22] Leukocytosis with peripheral white blood cell counts in the range of 10,000 to 20,000/mm^3 may be observed, and up to 50% of patients have false-positive syphilis serologies.

Without specific antibiotic therapy, fevers lasting 3 to 4 days recur at regular intervals between afebrile periods of 3 to 9 days. Spontaneous cure usually occurs within 1 to 2 months, but in selected instances, fevers have relapsed for years.[22]

The most serious complication of untreated spirillary rat-bite fever is endocarditis. Most of these rare intravascular infections have been observed in patients with preexisting valvular disease, but one reported case occurred on a normal aortic valve.[107] The spectrum of reported complications also includes myocarditis, pleural effusions, hepatitis, splenomegaly, meningitis, epididymitis, conjunctivitis, and anemia.[22,27] Overall mortality of untreated *S. minus* infections in the preantibiotic era was 6% to 10%.

Diagnosis and Therapy

Diagnosis depends on the history of rat bite, typical clinical features, and demonstration of the organisms on examination of blood, exudate, or lymph node tissue by using Giemsa stain, Wright stain, or darkfield microscopy. Organisms have been recovered from mice or guinea pigs 1 to 3 weeks after intraperitoneal inoculation,[22,108] but the animals must be prescreened to rule out the presence of preexisting spirochete infections. No specific serologic test or PCR assay is available for *S. minus* infection. Therapy is the same as for *S. moniliformis* infection.

[a]References 11, 30, 35, 53, 57, 61, 79, 81, 83, 88, 90, 92, 98–100.

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The complete reference list is available online at Expert Consult.

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232 Legionnaires' Disease and Pontiac Fever

Paul H. Edelstein and Craig R. Roy

SHORT VIEW SUMMARY

Definition
- Legionnaires' disease is a noncontagious type of bacterial pneumonia caused by *Legionella* spp. bacteria, most commonly *Legionella pneumophila.*
- Pontiac fever is a several-day-long, nonpneumonic, febrile, influenza-like illness associated with exposure to *Legionella* spp. that resolves spontaneously.
- Legionellosis includes legionnaires' disease, Pontiac fever, and extrapulmonary *Legionella* spp. infection not associated with pneumonia.

Epidemiology
- Legionnaires' disease is acquired by inhaling a water aerosol containing *Legionella* spp. bacteria, and possibly by microaspirating *Legionella* spp.–containing water.
- About 20 to 80 cases annually per million population occur in most developed countries, with the elderly, males, cigarette smokers, and immunosuppressed patients most at risk.
- About 1% to 5% of patients hospitalized for community-acquired pneumonia have legionnaires' disease.
- Pontiac fever is associated with inhalation of *Legionella* spp.–containing water but not necessarily caused by the bacterium. It occurs in sporadic and epidemic form at apparently low incidence but may be more common than is reported.

Microbiology
- Constituted of more than 60 known species, the *Legionella* bacteria are ubiquitous in the aqueous environment and probably moist soils.
- Optimal bacterial growth requires specialized media that contain cysteine and iron.
- The bacteria are facultative intracellular parasites of free-living amebae and human monocytes and macrophages that use hostlike proteins to masquerade as host and to avail themselves of intracellular resources.

Diagnosis
- Clinical and roentgenographic differentiation of legionnaires' disease from common causes of pneumonia is not generally possible.
- Specific and specialized laboratory testing can be helpful for disease diagnosis but is not highly sensitive in all settings. Urine antigen testing, the most commonly used test, is about 70% and 30% sensitive in community-acquired and nosocomial disease, respectively.

Therapy
- Macrolides, tetracyclines, and quinolone antimicrobials can all be used to successfully treat the disease, with azithromycin and levofloxacin being the most active. Tetracyclines may not be active for *L. longbeachae*–caused disease.
- For cure, 3 to 14 days' therapy is required, depending on disease severity, host factors, and type of therapy used.

Prevention
- No vaccine is available.
- Proper environmental design and maintenance reduce disease risk.

HISTORY

Legionnaires' disease (LD) is an acute pneumonic illness caused by gram-negative bacilli of the genus *Legionella*, the most common of which is *Legionella pneumophila (Lp).* Pontiac fever (PF) is a febrile, nonpneumonic, systemic illness closely associated with, if not caused by, *Legionella* spp. *Legionellosis* is the term that encompasses all diseases caused by, or presumed to be caused by, the *Legionella* bacteria, including LD, focal nonpulmonary infections, and PF.

LD was first recognized when it caused an epidemic of pneumonia at a Pennsylvania State American Legion convention in Philadelphia in 1976; 221 people were affected, and 34 died. Despite intensive laboratory investigation, the cause of the outbreak went undetected for many months. Epidemiologic investigation concluded that the disease was most likely airborne, and focused primarily at one convention hotel, which closed because of adverse publicity.[1,2] About 6 months later, Joseph McDade and Charles Shepard, investigators at the Centers for Disease Control and Prevention, discovered the etiologic agent, a fastidious gram-negative bacillus.[3] Because of the historical association with the American Legion convention, this disease is now called "legionnaires' disease," and the etiologic agents belong to the family *Legionellaceae,* with *Lp* being the agent responsible for the 1976 Philadelphia epidemic. Several past unsolved outbreaks of pneumonia in the 1950s to the early 1970s had been LD.[4–6] An unsolved epidemic of a nonpneumonic febrile illness in Pontiac, Michigan, was found to be associated with *Lp* exposure; this illness was termed "Pontiac fever".[7,8] Prior epidemics of PF occurred as early as 1949.[9] Bacterial isolates from the 1940s through the 1960s, previously thought to be rickettsial agents, were found to be *Legionella* bacteria.[10–15] Both the organism and the disease had been studied decades before, but major advances in technology were required to properly determine its cause.

Even with identification of *Lp* in 1977 as the cause of LD, how best to diagnose the disease and ways to abort epidemics of LD remained uncertain for several years. Epidemics of the disease, especially nosocomial ones, commonly lasted for years.[16–22] It was discovered that *Lp* and other *Legionella* spp. were naturally occurring aquatic bacteria that grew in warm water, in cooling towers, water heaters, and potable water plumbing. These discoveries led to the end of several multiyear outbreaks of the disease.[23] It is now unusual for LD outbreaks to last more than a week or two.

LD occurs in both sporadic and epidemic forms, sometimes involving many hundreds of victims.[24–27] The disease, while a relatively rare (1%–5%) cause of community-acquired pneumonia that is often easily treated and relatively mild, can cause severe, and fatal, disease.

THE ETIOLOGIC AGENT

The *Legionella* spp. are small gram-negative bacilli with fastidious growth requirements. Amino acids are the main energy source for extracellular growth, with glycerol or glucose used during intracellular growth.[28] Obligate aerobes, the bacteria grow at temperatures ranging from 20°C to 42°C. *Coxiella burnetii,* an obligate intracellular parasite and the etiologic agent of Q fever, is the closest relative of the *Legionellaceae.* L-Cysteine is required for the growth of all but one of the clinically important *Legionella* spp., and this amino acid is needed for the initial growth of all described *Legionella* spp. from environmental or clinical sources. Soluble iron is required for optimal growth, and for initial isolation of the bacterium from both clinical and environmental sources.