BURKHOLDERIA MALLEI

B. mallei causes the equine disease glanders in Africa, Asia, and South America. The organism was eradicated from Europe and North America decades ago. The last case seen in the United States occurred in 2001 in a laboratory worker; before that, *B. mallei* had last been seen in this country in 1949. In contrast to the other organisms discussed in this chapter, *B. mallei* is not an environmental organism and does not persist outside its equine hosts. Consequently, *B. mallei* infection is an occupational risk for handlers of horses, equine butchers, and veterinarians in areas of the world where it still exists. The polysaccharide capsule is a critical virulence determinant; diabetics are thought to be especially susceptible to infection by this organism. The organism is transmitted from animals to humans by inoculation into the skin, where it causes local infection with nodules and lymphadenitis. Regional lymphadenopathy is common. Respiratory secretions from infected horses are extremely infectious. Inhalation results in clinical signs of typical pneumonia but may also cause an acute febrile illness with ulceration of the trachea. The organism may disseminate from the skin or lungs to cause septicemia with signs of sepsis. The septicemic form is frequently associated with shock and a high mortality rate. The infection may also enter a chronic phase and present as disseminated abscesses. *B. mallei* infection may present as early as 1–2 days after inhalation or (in cutaneous disease) may not become evident for months.

TREATMENT ***B. MALLEI* INFECTIONS**

The antibiotic susceptibility pattern of *B. mallei* is similar to that of *B. pseudomallei;* in addition, the organism is susceptible to the newer macrolides azithromycin and clarithromycin. *B. mallei* infection should be treated with the same drugs and for the same duration as melioidosis.

190 Salmonellosis

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Bacteria of the genus *Salmonella* are highly adapted for growth in both humans and animals and cause a wide spectrum of disease. The growth of serotypes *Salmonella typhi* and *Salmonella paratyphi* is restricted to human hosts, in whom these organisms cause enteric (typhoid) fever. The remaining serotypes (nontyphoidal *Salmonella*, or NTS) can colonize the gastrointestinal tracts of a broad range of animals, including mammals, reptiles, birds, and insects. More than 200 serotypes of *Salmonella* are pathogenic to humans, in whom they often cause gastroenteritis and can be associated with localized infections and/or bacteremia.

ETIOLOGY

This large genus of gram-negative bacilli within the family Enterobacteriaceae consists of two species: *Salmonella enterica*, which contains six subspecies, and *Salmonella bongori*. *S. enterica* subspecies I includes almost all the serotypes pathogenic for humans. Members of the seven *Salmonella* subspecies are classified into >2500 serotypes (serovars); for simplicity, *Salmonella* serotypes (most of which are named for the city where they were identified) are often used as the species designation. For example, the full taxonomic designation *S. enterica* subspecies *enterica* serotype Typhimurium can be shortened to *Salmonella* serotype Typhimurium or simply *S. typhimurium*. Serotyping is based on the somatic O antigen (lipopolysaccharide cell-wall components), the surface Vi antigen (restricted to *S. typhi* and *S. paratyphi* C), and the flagellar H antigen.

Salmonellae are gram-negative, non-spore-forming, facultatively anaerobic bacilli that measure 2–3 μm by 0.4–0.6 μm. The initial identification of salmonellae in the clinical microbiology laboratory is based on growth characteristics. Salmonellae, like other Enterobacteriaceae, produce acid on glucose fermentation, reduce nitrates, and do not produce cytochrome oxidase. In addition, all salmonellae except *Salmonella gallinarum-pullorum* are motile by means of peritrichous flagella, and all but *S. typhi* produce gas (H_2S) on sugar fermentation. Notably, only 1% of clinical isolates ferment lactose; a high level of suspicion must be maintained to detect these rare clinical lactose-fermenting isolates.

Although serotyping of all surface antigens can be used for formal identification, most laboratories perform a few simple agglutination reactions that define specific O-antigen serogroups, designated A, B, C_1, C_2, D, and E. Strains in these six serogroups cause ~99% of *Salmonella* infections in humans and other warm-blooded animals. Molecular typing methods, including pulsed-field gel electrophoresis, polymerase chain reaction fingerprinting, and genomic DNA microarray analysis, are used in epidemiologic investigations to differentiate *Salmonella* strains of a common serotype.

PATHOGENESIS

All *Salmonella* infections begin with ingestion of organisms, most commonly in contaminated food or water. The infectious dose ranges from 200 colony-forming units (CFU) to 10^6 CFU, and the ingested dose is an important determinant of incubation period and disease severity. Conditions that decrease either stomach acidity (an age of <1 year, antacid ingestion, or achlorhydric disease) or intestinal integrity (inflammatory bowel disease, prior gastrointestinal surgery, or alteration of the intestinal flora by antibiotic administration) increase susceptibility to *Salmonella* infection.

Once *S. typhi* and *S. paratyphi* reach the small intestine, they penetrate the mucus layer of the gut and traverse the intestinal layer through phagocytic microfold (M) cells that reside within Peyer's patches. Salmonellae can trigger the formation of membrane ruffles in normally nonphagocytic epithelial cells. These ruffles reach out and enclose adherent bacteria within large vesicles by *bacterial-mediated endocytosis*. This process is dependent on the direct delivery of *Salmonella* proteins into the cytoplasm of epithelial cells by the specialized bacterial type III secretion system. These bacterial proteins mediate alterations in the actin cytoskeleton that are required for *Salmonella* uptake.

After crossing the epithelial layer of the small intestine, *S. typhi* and *S. paratyphi*, which cause enteric (typhoid) fever, are phagocytosed by macrophages. These salmonellae survive the antimicrobial environment of the macrophage by sensing environmental signals that trigger alterations in regulatory systems of the phagocytosed bacteria. For example, PhoP/PhoQ (the best-characterized regulatory system) triggers the expression of outer-membrane proteins and mediates modifications in lipopolysaccharide so that the altered bacterial surface can resist microbicidal activities and potentially alter host cell signaling. In addition, salmonellae encode a second type III secretion system that directly delivers bacterial proteins across the phagosome membrane into the macrophage cytoplasm. This secretion system functions to remodel the *Salmonella*-containing vacuole, promoting bacterial survival and replication.

Once phagocytosed, typhoidal salmonellae disseminate throughout the body in macrophages via the lymphatics and colonize reticuloendothelial tissues (liver, spleen, lymph nodes, and bone marrow). Patients have relatively few or no signs and symptoms during this initial incubation stage. Signs and symptoms, including fever and abdominal pain, probably result from secretion of cytokines by macrophages and epithelial cells in response to bacterial products that are recognized by innate immune receptors when a critical number of organisms have replicated. Over time, the development of hepatosplenomegaly is likely to be related to the recruitment of mononuclear cells and the development of a specific acquired cell-mediated immune response to *S. typhi* colonization. The recruitment of additional mononuclear cells and lymphocytes to Peyer's patches during the several weeks after initial colonization/infection can result in marked enlargement and necrosis