

Glanders

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Importance

Glanders is a serious zoonotic bacterial disease that primarily affects horses, mules and donkeys. Some animals die acutely within a few weeks. Others become chronically infected, and can spread the disease for years before succumbing. Although human disease is uncommon, it is life threatening and painful. Without antibiotic treatment, the case fatality rate can be as high as 95%. Occasionally, glanders also occurs in other mammalian species, particularly members of the cat family.

Glanders was a worldwide problem in equids for several centuries, but this disease was eradicated from most countries by the mid-1900s. Outbreaks are now uncommon and reported from limited geographic areas. In non-endemic regions, cases may be seen in people who work with the causative organism, *Burkholderia mallei*, in secure laboratories. An infection was reported in a U.S. researcher in 2000. Glanders is also considered to be a serious bioterrorist threat. *B. mallei* has been weaponized and was used as a biological weapon against military horses, or animals and humans, during the first and second world wars. If this organism is aerosolized during a biological attack or in a laboratory accident, the morbidity rate could be high.

Etiology

Glanders results from infection by *Burkholderia mallei*, a Gram negative rod in the family Burkholderiaceae. This organism was formerly known as *Pseudomonas mallei*. It is closely related to and appears to have evolved from the agent of melioidosis, *Burkholderia pseudomallei*.

Geographic Distribution

Glanders is thought to be endemic in parts of the Middle East, Asia, Africa and South America. Between 1998 and 2007, cases were reported from Brazil, Turkey, the former U.S.S.R., Eritrea, Ethiopia, Iran, Iraq, United Arab Emirates and Mongolia. This disease may also exist in Pakistan. The geographic distribution of *B. mallei* can be difficult to determine precisely, as cross-reactions with *B. pseudomallei* interfere with serological surveys.

In countries that have eradicated glanders, cases may occur in researchers who work with this agent. In 2000, this disease was reported in a U.S. researcher.

Transmission

Glanders is mainly transmitted by contact with skin exudates and respiratory secretions from infected equids. Latently infected as well as clinically ill animals can spread the disease. Horses, mules and donkeys often become infected when they ingest *B. mallei* in contaminated food or water. This organism can also be spread in aerosols, and by entry through skin abrasions and mucous membranes. Carnivores usually become infected when they eat contaminated meat. *B. mallei* is readily spread on fomites including harnesses, grooming tools, and food and water troughs. Although this organism is inactivated by heat and sunlight, its survival is prolonged in wet or humid environments. *B. mallei* remains viable in room temperature water for up to a month. Some sources suggest that it might be able to survive for more than a year in the environment, under some circumstances. Others state that it may survive for up to a few months in favorable environments, but it is likely to be inactivated within two weeks in unfavorable conditions.

Humans are infected by contact with sick animals, contaminated fomites, tissues or bacterial cultures. Transmission is often through small wounds and abrasions in the skin. Ingestion or inhalation can also occur. Transmission through unbroken skin has been reported, but not proven. Most laboratory-acquired infections have occurred during routine handling of cultures or samples, rather than after injuries or accidents. Rare cases of person-to-person transmission have been reported in family members who nursed sick individuals. Two cases were thought to have been sexually transmitted.

Aerosols may be the major route of infection in a bioterrorist attack.



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Disinfection

Burkholderia mallei is susceptible to many common disinfectants including benzalkonium chloride, 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde, iodine, mercuric chloride in alcohol and potassium permanganate. It is less susceptible to phenolic disinfectants. This organism can also be destroyed by heating to 55°C [131°F] for 10 minutes, or with ultraviolet irradiation.

Infections in Humans

Incubation Period

The incubation period is a few days to several weeks. It varies with the form of the disease: septicemia or localized disease usually becomes apparent after 1 to 5 days, while the pulmonary form typically develops after 10 to 14 days.

Clinical Signs

The symptoms of glanders vary with the route of exposure. Four forms of the disease - septicemia, pulmonary infection, acute localized infection and chronic infection - have been described in humans. One form of the disease can progress to another, and combinations of syndromes occur.

Localized infections are characterized by nodules, abscesses and ulcers in the mucous membranes, skin, lymphatic vessels and/or subcutaneous tissues at the site of inoculation. The nodules are white or gray and firm, with a caseous or calcified center. They are surrounded by areas of inflammation. When the mucous membranes are involved, a mucopurulent, sometimes blood-tinged discharge may be seen. These lesions are accompanied by fever, sweats, malaise and swelling of the regional lymph nodes. Abscesses often develop in the lymph nodes, and may drain. Mucosal or skin infections may disseminate after one to four weeks; symptoms of disseminated infections include a papular or pustular rash and abscesses in the internal organs. These abscesses are often found in the liver, spleen and lungs, but any tissue including the subcutaneous tissues and muscles can be affected. Disseminated infections often progress to septicemia.

The pulmonary form occurs after inhalation of *B. mallei*, or by hematogenous spread from other forms. It is characterized by pulmonary abscesses, pleural effusion and pneumonia. The onset is usually acute. The symptoms include fever, sweats, coughing and chest pain, progressing to dyspnea. Ulcers and nodules, accompanied by a mucopurulent discharge, can occur in the nose. Skin abscesses may also be seen; these abscesses can develop up to several months after the organisms were inhaled. Untreated pulmonary disease often develops into septicemia.

In the septicemic form, fever, chills, myalgia, headache and pleuritic chest pain develop acutely. Flushing, a pustular or papular rash, lymphadenopathy, cellulitis, cyanosis, jaundice, photophobia, diarrhea and granulomatous or necrotizing lesions may be seen. Tachycardia and mild hepatomegaly or splenomegaly have also been reported. Multi-organ failure is common, and death often occurs 24 to 48 hours after the onset of symptoms.

Chronic glanders is characterized by multiple abscesses, nodules and ulcers in a variety of tissues, with periodic recrudescence and milder symptoms than acute disease. A wide variety of organs can be affected including the skin, subcutaneous tissues, liver, spleen, gastrointestinal tract, respiratory tract and skeletal muscles. Weight loss and lymphadenopathy are often seen. This form of the disease can last up to 25 years.

Communicability

Person to person transmission has been reported, but appears to be rare. Some cases have been reported in family members who nursed sick individuals. Two other cases were thought to have been sexually transmitted.

Diagnostic Tests

Glanders can be diagnosed by culturing *B. mallei* from lesions. This organism may also be found in sputum, blood or urine, although blood cultures are often negative.

B. mallei can be stained with methylene blue, Wright or Gram stains, but the staining may be weak or irregular. Some authors report that this organism stains best with Giemsa. *B. mallei* is a nonmotile, Gram negative, straight or slightly curved rod; organisms from clinical samples and young cultures are rods, while bacteria from older cultures can be pleomorphic. Bipolar staining may be seen. *B. mallei* is not always found in smears from clinical samples; few bacteria may be present, and they may not stain well.

B. mallei can be isolated on ordinary culture media including blood agar and meat nutrient agar, but it grows slowly; a 48-hour incubation is recommended. On glycerol agar, a smooth, slightly cream-colored, moist, viscid confluent layer is seen after a few days; this layer eventually becomes thicker, tougher and darker brown. *B. mallei* also grows well on glycerol-potato agar, and a selective medium has been described. *B. mallei* is usually identified by biochemical tests, but this approach can take more than seven days. Automated bacterial identification systems do not always correctly identify this organism. In some commercial kits, cross-reactions can occur with nonvirulent bacteria. If necessary, *B. mallei* can also be isolated by inoculation into guinea pigs or hamsters.

Polymerase chain reaction (PCR) assays may be available in some laboratories. One recently published PCR assay can differentiate *B. mallei* from *B. pseudomallei*. Other genetic techniques used to

distinguish these two organisms include PCR–restriction fragment length polymorphism, pulse-field gel electrophoresis, 16S rRNA sequencing, variable number tandem repeat polymorphism and multilocus sequence typing (MLST). These specialized techniques may be available mainly in research laboratories.

Serology is sometimes helpful, but high background titers in normal serum complicate interpretation. In addition, serologic reactions to *B. mallei* cannot be differentiated from reactions to *B. pseudomallei*. Serologic tests include agglutination, indirect hemagglutination, enzyme-linked immunosorbent assays (ELISAs), immunofluorescence and complement fixation; these tests are not available in all countries. Positive reactions in agglutination tests develop after 7 to 10 days.

Radiography is helpful in the pulmonary form. The lesions may include bilateral bronchopneumonia, miliary nodules, segmental or lobar infiltrates, and cavitating lesions.

Treatment

Glanders is treated with antibiotics. Few studies have been published on the antibiotic susceptibility of *B. mallei*, but some treatment recommendations are available. This organism is usually resistant to some classes of antibiotics. Long-term treatment or multiple drugs may be necessary. Abscesses may need to be drained.

Prevention

Strict precautions should be taken when handling infected animals and contaminated fomites. Protective clothing including heavy gloves and face shields should be worn when working with infected animals. Protection from aerosols may also be appropriate. Biosafety level 3 practices are required for manipulating infected tissues and cultures. Postexposure prophylaxis with antibiotics may be used in some situations. No vaccine is available.

Although person-to-person transmission is rare, human glanders patients should be isolated. Infection control precautions should be taken, and disposable surgical masks, face shields, and gowns should be used as appropriate during nursing.

Morbidity and Mortality

Glanders is a sporadic disease that usually occurs in people who work with clinical samples or have frequent, close contact with horses and their tissues. Risk groups include veterinarians, animal caretakers or other equestrian personnel, laboratory workers and abattoir workers. Human epidemics have not been seen. Transmission from horses to humans may be inefficient; even when morbidity rates in horses are 5-30%, zoonotic disease remains uncommon. However, some infections might be subclinical or mild; autopsy studies conducted in endemic areas found glanders-associated nodules in many people who had contact with horses. In laboratories, *B.*

mallei is highly infectious, particularly when it is aerosolized. With aerosolized bacteria, morbidity rates up to 46% have been reported.

The mortality rate for glanders is high, particularly when effective antibiotics are not given. In the septicemic form, the case fatality rate is 95% or higher in untreated cases and more than 50% when the infection is treated. The mortality rate in the pulmonary form is 90-95% if untreated, and 40% if treated. In chronic glanders, the case fatality rate can reach 50% even in treated cases. The mortality rate for localized disease is 20% when treated; untreated cases often progress to other forms. Intensive therapy with newer antibiotics may result in lower mortality rates than have been reported in the past.

Infections in Animals

Species Affected

The major hosts for *B. mallei* are horses, mules and donkeys, but other species of mammals can also be infected. Glanders has been reported in dogs, cats, goats, sheep and camels. Members of the cat family seem to be particularly susceptible to this disease. Outbreaks have been reported in captive large felids, and occasional cases are seen in domesticated cats. Cattle, pigs and birds are highly resistant to this disease.

Most domesticated animals other than cattle, pigs and rats can be infected experimentally. Wildlife species including bears, wolves, field mice, rabbits and voles have also been infected. Hamsters and guinea pigs are the most susceptible rodents. Mice are resistant to disease unless the dose of organisms is high.

Incubation Period

In animals, glanders may appear immediately or become latent. The incubation period varies from a few days to many months; two to six weeks is typical. Experimental infections can result in clinical signs after three days.

Clinical Signs

Horses, donkeys and mules

In equids, glanders is traditionally categorized into nasal, pulmonary and cutaneous forms. In the nasal form, deep ulcers and nodules occur inside the nasal passages, resulting in a thick, purulent, yellowish discharge. This discharge may be unilateral or bilateral, and can become bloody. Nasal perforation is possible. The regional (submaxillary) lymph nodes become enlarged and indurated, and may suppurate and drain. Healed ulcers become star-shaped scars. In the pulmonary form, nodules and abscesses develop in the lungs. Some infections are inapparent; others vary from mild dyspnea to severe respiratory disease. In more severe cases, the clinical signs include coughing, dyspnea, febrile episodes

and progressive debilitation. Diarrhea and polyuria may also be seen. Discharges from pulmonary abscesses can spread the infection to the upper respiratory tract. In the cutaneous form, the skin contains nodules that rupture and ulcerate, discharging an oily, purulent yellow exudate. The regional lymphatics and lymph nodes become chronically enlarged; the lymphatics are filled with a purulent exudate. In addition, there may be swelling of the joints and painful edema of the legs. Glanderous orchitis is a common symptom in males.

Clinical cases are usually a combination of these forms, and can occur as acute, chronic or latent disease. Acute disease is more likely to occur in donkeys, and chronic or latent disease is more common in horses. Sources disagree whether mules are more likely to develop acute or chronic disease.

Nasal and pulmonary signs are usually seen in the acute form. The symptoms include a high fever, decreased appetite, coughing, progressive dyspnea, nasal discharge, and ulcers and nodules on the nasal mucosa. Bloody crusting may be seen on the nostrils, and there may be a purulent ocular discharge. The submaxillary lymph nodes are usually swollen and painful. Neurological signs have been reported in experimentally infected horses, possibly as the result of secondary bacterial infections from a compromised blood-brain barrier. Animals with the acute form of glanders usually die in a few days to a few weeks.

The chronic form develops insidiously, and results in progressive debilitation. The symptoms may include coughing, malaise, dyspnea, an intermittent fever, enlargement of the lymph nodes, a chronic nasal discharge, and ulcers, nodules and stellate scars on the nasal mucosa. The skin and lymphatics may also be involved. The chronic form is slowly progressive and often fatal; however, affected animals may live for years before succumbing to the disease.

In the latent form, there may be few symptoms other than a nasal discharge and occasional labored breathing. Lesions may be found only in the lungs.

Cats

In cats, nodules and ulcers may be found in the nasal passages and on the conjunctivae, as well as deeper in the respiratory tract. Affected cats typically have a purulent yellowish nasal discharge that may become bloody. The lymph nodes are swollen, and dyspnea may be seen. Affected cats usually die in 1 to 2 weeks.

Communicability

Horses, donkeys and mules can transmit glanders to other animals and humans; nasal discharges and exudates from lesions may contain large numbers of organisms.

Post Mortem Lesions

Ulcers, nodules and/or stellate scars may be found in the nasal passages, trachea, pharynx and larynx. Gray

nodules can also be found in other tissues, particularly the lung, liver, spleen and kidneys. Glanders nodules are firm, round and approximately 1 cm. in diameter, with a caseous or calcified center. They are usually surrounded by areas of inflammation. Catarrhal bronchopneumonia with enlarged bronchial lymph nodes may also be seen, particularly in acute disease. In recent experiments, horses with acute infections developed severe diffuse pulmonary edema with areas of hemorrhage, congestion or pneumonia. The lymph nodes may be enlarged, congested and/or fibrotic, and can contain abscesses. Swollen lymphatics, with chains of nodules and ulcerated nodules, may be noted in the skin. Orchitis can be seen in males.

In cats, nodules and ulcers have been reported in the nasal cavity, conjunctivae, larynx, trachea and bronchi.

Diagnostic Tests

Glanders can be diagnosed by culturing *B. mallei* from lesions or respiratory exudates.

This organism can sometimes be found in smears from fresh lesions, where it is usually present in large numbers. It can be difficult to find in older lesions or tissue sections. *B. mallei* can be stained with methylene blue, Wright or Gram stains, but the staining may be weak or irregular. Some authors report that this organism stains best with Giemsa. *B. mallei* is a nonmotile, Gram negative, straight or slightly curved rod; organisms from clinical samples and young cultures are rods, while bacteria from older cultures can be pleomorphic. Bipolar staining may be seen.

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A hypersensitivity reaction to *B. mallei*, called the mallein test, is also used to identify infected equids. In reactors, marked eyelid swelling occurs 1 to 2 days after

intrapalpebral injection of a protein fraction of *B. mallei*. Conjunctivitis occurs after administration in eyedrops, and a firm, painful swelling with raised edges is seen within 24 hours after subcutaneous (non-ocular) injection. Positive reactions by any of these three routes are accompanied by fever. The subcutaneous mallein test may interfere with future serologic testing, and the other two routes of administration are generally preferred. Mallein tests can give inconclusive results in acute glanders, or in the late stages of chronic disease.

A variety of serologic tests may be available, but the most accurate and reliable tests in equids are complement fixation and ELISA. A rose bengal plate agglutination test is sometimes used in Russia. Agglutination and precipitin tests are unreliable for horses with chronic glanders and animals in poor condition. Serological tests cannot distinguish reactions to *B. mallei* from reactions to *B. pseudomallei*.

Treatment

Some antibiotics may be effective against glanders, but treatment is given only in endemic areas. Treatment is risky even in these regions, as infections can spread to humans and other animals, and treated animals can become asymptomatic carriers.

Prevention

Animals that test positive for glanders are euthanized except in endemic areas. In an outbreak, the premises should be quarantined, thoroughly cleaned and disinfected. All contaminated bedding and food should be burned or buried, and equipment and other fomites should be disinfected. Carcasses should be burned or buried. Whenever possible, susceptible animals should be kept away from contaminated premises for several months.

In endemic areas, susceptible animals should be kept away from communal feeding and watering areas, since glanders is more common where animals congregate. Routine testing and euthanasia of positive animals can eradicate the disease. Vaccines are not available.

Morbidity and Mortality

Glanders can spread widely when large numbers of animals are in close contact. In Chinese experiments conducted during World War II, 30% of exposed horses became infected. Acute infections are usually fatal within a few days to two weeks. Animals with the chronic form can sometimes survive for years.

Internet Resources

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/ncidod/dbmd/diseaseinfo/glanders_g.htm
eMedicine. Glanders and Melioidosis
<http://www.emedicine.com/emerg/topic884.htm>

Food and Agriculture Organization of the United Nations (FAO). Manual for the Recognition of Exotic Diseases of Livestock
<http://www.spc.int/rahs/>
FAO. Manual on Meat Inspection for Developing Countries
<http://www.fao.org/docrep/003/t0756e/t0756e00.htm>
Public Health Agency of Canada. Material Safety Data Sheets
<http://www.phac-aspc.gc.ca/msds-ftss/index.html>
The Merck Veterinary Manual
<http://www.merckvetmanual.com/mvm/index.jsp>
United States Animal Health Association. Foreign Animal Diseases
http://www.vet.uga.edu/vpp/gray_book02/fad/index.php
World Organization for Animal Health (OIE)
<http://www.oie.int/>
OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/eng/normes/mmanual/a_summry.htm
OIE Terrestrial Animal Health Code.
http://www.oie.int/eng/normes/mcode/A_summry.htm

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*Link defunct as of 2007