

Glanders

Farcy,
Malleus,
Droes

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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. Glanders also occurs occasionally in other mammals, including carnivores that eat meat from infected animals. Although cases in humans are uncommon, they can be life threatening and painful. Without antibiotic treatment, the case fatality rate may be as high as 95%.

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 tested against humans, and it was also used as a biological weapon against military horses in past wars.

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*.

Species Affected

The major hosts for *B. mallei* are horses, mules and donkeys. Most other domesticated mammals can be infected experimentally (pigs and cattle were reported to be resistant), and naturally occurring clinical cases have been reported in some species. Members of the cat family seem to be particularly susceptible, with cases documented in domesticated cats, tigers, lions, leopards and other felids. Deaths have also been reported in other carnivores that ate glanderous meat, including dogs, bears, wolves, jackals and hyenas, and clinical cases were described in dromedary camels. Hamsters and guinea pigs are susceptible to glanders after experimental inoculation, but mice do not become ill unless the dose of organisms is high, and laboratory rats are resistant to infection. Wild rodents (e.g., field mice and voles) can also be infected experimentally. Birds are highly resistant.

Zoonotic potential

B. mallei affects humans.

Geographic Distribution

Glanders is thought to be endemic in parts of the Middle East, Asia, Africa and Central and South America. This disease has sometimes reemerged in countries where it appeared to be absent or was limited to small foci of infection (e.g., India in 2006). It has been eradicated from Western Europe, Canada, the U.S., Australia, Japan and some other countries, and it was never endemic in New Zealand. The geographic distribution of *B. mallei* can be difficult to determine precisely, as cross-reactions with *B. pseudomallei* interfere with serological surveys.

Transmission

Glanders is mainly transmitted by contact with infected horses, mules and donkeys, most often via their respiratory secretions and exudates from skin lesions. Chronically or subclinically infected equids can shed *B. mallei* intermittently or constantly. This organism can enter the body by contamination of skin abrasions and mucous membranes, or inhalation in aerosols. Equids often become infected when they ingest *B. mallei* in contaminated food or water, and carnivores when they eat contaminated meat. There are reports of venereal transmission from stallions to mares, and vertical transmission from the dam.

B. mallei is readily spread on fomites including harnesses, grooming tools, and food and water troughs. Flies might act as mechanical vectors. Although this organism is inactivated by heat and sunlight, its survival is prolonged in wet or humid



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environments. It was reported to survive for up to 6 weeks in some infected stables, and one early report suggested that it might remain viable in room temperature water for up to 100 days. Under most conditions, however, it is not thought likely to survive in the environment for more than 2 weeks.

Humans can be infected by contact with sick animals, contaminated fomites, tissues or bacterial cultures. The organism is thought to enter the body through wounds and abrasions in the skin, and by ingestion or inhalation. Transmission through unbroken skin has been reported, but not proven (minor breaks in the skin could also explain these cases). Most laboratory-acquired infections have occurred during routine handling and processing 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.

Disinfection

B. mallei is susceptible to many common disinfectants including 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde, iodine, benzalkonium chloride, mercuric chloride in alcohol and potassium permanganate. It is less susceptible to phenolic disinfectants. This organism can be destroyed by heating to 55°C (131°F) for 10 minutes, or exposure to ultraviolet irradiation. In the environment, *B. mallei* is susceptible to drying and sunlight.

Infections in Animals

Incubation Period

The incubation period in equids is reported to range from a few days to many months, but many cases become apparent in 2-6 weeks. Infections can be latent for varying periods. Experimental infections can result in fever after a day or two, and other clinical signs after 3 days. Less is known about the incubation period in other species; however, some cats developed clinical signs 8-14 days after eating infected meat.

Clinical Signs

Horses, donkeys and mules

In equids, glanders is traditionally categorized into nasal, pulmonary and cutaneous forms, based on the most commonly affected sites.

In the nasal form, deep ulcers and nodules develop inside the nasal passages, resulting in a thick, mucopurulent, sticky, yellowish discharge. This discharge can be copious, may be unilateral or bilateral, and can become bloody. The ulcers may coalesce over wide areas, and nasal perforation is possible. Healed ulcers become star-shaped scars, which may be found concurrently with nodules and ulcers. The regional (mandibular) lymph nodes become enlarged bilaterally or unilaterally. They are usually indurated in acute illness, and may occasionally

suppurate and drain. Nasal infections can spread to involve the lower respiratory tract.

Pulmonary involvement occurs in most clinical cases, often in combination with other forms of glanders. Affected animals develop nodules and abscesses in the lungs, or bronchopneumonia in some cases. Some infections are inapparent; others are characterized by mild to severe respiratory signs (e.g., coughing, dyspnea), with fever or febrile episodes and progressive debilitation. If the upper respiratory tract was not involved initially, it may become infected via discharges from pulmonary abscesses.

In the cutaneous form (known as 'farcy') multiple nodules develop in the skin, along the course of lymphatic vessels. These nodules often rupture and ulcerate, discharging an oily, thick yellow exudate. Glanders ulcers heal very slowly, often continuing to discharge fluid, although dry ulcers may also be seen. The regional lymphatics and lymph nodes become chronically enlarged, and the lymphatics are filled with a purulent exudate. Some animals also have swelling of the joints, painful edema of the legs or glanderous orchitis (in intact males). While skin lesions may appear anywhere, they are reported to be most common on the inner thighs, limbs and abdomen. Animals with cutaneous glanders can remain in good condition for a time, but they eventually become debilitated and die.

Clinical cases are often a combination of forms, and may be acute (or subacute), chronic or latent, depending on the animal's resistance to disease. Donkeys and mules often develop acute glanders after exposure, although mules appear to be somewhat more resistant and the course of the illness may be slower. Acute glanders is characterized mainly by nasal and respiratory involvement, with clinical signs that commonly include a high fever, decreased appetite/ weight loss, depression, swelling of the nostrils, bouts of coughing and progressive dyspnea. An initial watery nasal discharge (often unilateral at first) can develop into the classic signs of the nasal form. There may also be a purulent ocular discharge. Neurological signs were reported in experimentally infected horses, possibly as the result of secondary bacterial (*Streptococcus zooepidemicus*) infection of the brain due to a compromised blood-brain barrier. Animals with the acute form of glanders usually die in a few days to a few weeks from septicemia and respiratory failure.

Horses usually develop chronic glanders. This form can also be seen in some mules. Chronic glanders develops insidiously and lasts for months to years, with periodic episodes of exacerbation, resulting in slowly progressive debilitation. Although the initial signs may be mild and easily overlooked (e.g., intermittent low fever and slightly labored breathing), progression of the lesions results in listlessness, generalized weakness and wasting, with an intermittent cough. Some animals become lame, with swelling of the joints in the hindquarters, or have hematuria, polyuria, diarrhea, epistaxis or orchitis. Signs of nasal glanders or skin involvement may be seen, and stressors can result in acute bronchopneumonia. Extension

of lesions to the brain has been reported in at least one case. Chronic glanders is eventually fatal in most animals, although a few may recover clinically while remaining carriers. Animals that recover from glanders can relapse.

In latent cases, lesions may occur sporadically in the lungs and other internal organs. The clinical signs are usually minimal, and most often consist only of intermittent low fever, nasal discharge and/or occasional labored breathing. Latent glanders is most common in resistant species, such as horses.

Other species

The clinical signs in naturally infected dromedary camels were similar to those in equids, and included fever, lethargy, emaciation, and nodules and ulcers in the nasal passages, with severe mucopurulent discharge. In cats that ate infected meat, nodules and ulcers were found in the nasal passages and on the conjunctivae, as well as deeper in the respiratory tract. Affected cats also had a purulent yellowish nasal discharge that sometimes became bloody. Additional clinical signs included swelling of the lymph nodes and dyspnea, and affected cats usually died in 1 to 2 weeks. Similar respiratory, nasal and nonspecific signs (e.g., anorexia, depression) have been reported in large felids during outbreaks at zoos. Some of these animals also vomited, had skin ulcers or developed swelling of the face and head.

Post-Mortem Lesions [Click to view images](#)

Nodules, granulomas and/or ulcers may be detected in various tissues of equids with glanders. Glanders nodules are firm, round and usually about 1 cm. in diameter, with a caseous or calcified center. They are typically surrounded by areas of inflammation. The upper respiratory tract is often affected, with ulcers, nodules and/or stellate scars in the nasal passages, larynx and other tissues. Internally, nodules are most likely to be found in the lungs, particularly beneath the pleura. The lungs may also contain diffuse miliary granulomatous nodules, and in acute or exacerbated cases, there may be evidence of severe bronchopneumonia. In addition, nodules and other lesions may be detected in other visceral organs, particularly the liver and spleen. Some animals have had bone lesions, and abscesses were found in the muscles of infected racehorses. Swollen lymphatics, with chains of nodules and ulcerated nodules, may be noted in the skin, while the lymph nodes may be enlarged, congested and/or fibrotic, and can contain abscesses. Orchitis may be seen in males.

Similar lesions have been reported in other species.

Diagnostic Tests

Glanders can be diagnosed by culturing *B. mallei* from lesions, lymph nodes, and nasal or other respiratory exudates. This organism is uncommonly detected in blood. Bacteriological diagnosis can be difficult when the animal is in the early stages of disease or subclinically infected.

Detailed guidelines for isolating *B. mallei*, which grows best on media enriched with glycerol, have been published by the World Organization for Animal Health (OIE) and other sources. While this organism can also grow on ordinary culture media (though not well on MacConkey agar), its slow growth and the potential for overgrowth by other bacteria may make isolation difficult. If necessary, it can also be recovered by inoculation into guinea pigs. Once isolated, *B. mallei* is usually identified with biochemical tests. The absence of motility is important in distinguishing it from other members of the *Pseudomonas* group, including *B. pseudomallei*. It can be misidentified by automated bacterial identification systems. Due to the risks of human infection, isolates suspected to be *B. mallei* are typically sent to a reference laboratory for identification. Genetic techniques available in specialized laboratories (e.g., PCR–restriction fragment length polymorphism, pulse-field gel electrophoresis, 16S rRNA sequencing) can distinguish *B. mallei* from its close relative *B. pseudomallei*. Several PCR tests have been described, but many have not yet been thoroughly evaluated with clinical samples. A few are reported to differentiate *B. mallei* from *B. pseudomallei*. Antigen detection assays (e.g., latex agglutination, immunofluorescence) have been investigated.

B. mallei can sometimes be observed in smears from fresh lesions, where it is usually present in large numbers, although the staining may be weak or irregular. It can be difficult to find in older lesions or tissue sections. This organism can be stained with methylene blue, Wright or Gram stains, but some authors report that it stains best with Giemsa. It is a Gram negative, straight or slightly curved rod; organisms from clinical samples and young cultures appear as rods, while bacteria from older cultures can be pleomorphic. In tissue sections, it may have a beaded appearance.

A hypersensitivity reaction called the mallein test was used in glanders eradication programs, and is still used to detect infected equids in some countries. In the 3 versions of the mallein test, a protein fraction of *B. mallei* is either injected into the eyelid (intra-dermo-palpebral test), administered in eyedrops, or injected subcutaneously at a site other than the eye. The intra-dermo-palpebral test is considered to be the most reliable and sensitive version. Reactors in this test develop marked eyelid swelling after 1 to 2 days. There may also be a purulent ocular discharge and an elevated body temperature. Conjunctivitis occurs after administration in eyedrops, and a firm, painful swelling with raised edges is seen within 24 hours after subcutaneous (non-ocular) injection. Mallein testing can cause transient false positives in subsequent serological tests, and such reactivity could become permanent if the animal is tested repeatedly. It can give inconclusive results in acute glanders, or in the late stages of chronic disease. Cross-reactivity has also been reported.

A variety of serologic tests have also been used to diagnose glanders and/or detect infected horses in

surveillance and import testing. Complement fixation and ELISAs are currently considered to be the most accurate and reliable assays in equids, although other tests may also meet this standard once they have been fully evaluated. Complement fixation has also been used to diagnose glanders in other animals, including camels and large zoo cats, and an ELISA test was positive in an infected camel. Immunoblotting appears promising in equids, and might be used in combination with other assays. A rose bengal plate agglutination test is sometimes employed in Russia. Cross-reactivity can be an issue in serological tests, and false negatives also occur, especially in chronically infected, debilitated, pregnant or old animals. Complement fixation is reported to detect chronically infected animals during episodes of exacerbation. Most serological tests cannot distinguish whether the animal has antibodies to *B. mallei* or *B. pseudomallei*.

Treatment

Some antibiotics may be effective against glanders, but treatment is often not allowed outside endemic areas. Treatment can be risky even in these regions, as infections can spread to humans and other animals, and treated animals may become asymptomatic carriers.

Designing effective treatments for glanders is complicated by differences in antibiotic susceptibility patterns between *B. mallei* isolates, and the inability of some drugs to penetrate into the host cells where this organism replicates. Treatment protocols that might be able to eliminate *B. mallei* have been published recently, but they have not yet been fully evaluated. Some require treatment for several months, using multiple drugs.

Control

Disease reporting

A quick response is vital for containing outbreaks in glanders-free regions. Veterinarians who encounter or suspect this disease should follow their national and/or local guidelines for disease reporting. In the U.S., state or federal veterinary authorities should be informed immediately.

Prevention

During outbreaks in non-endemic regions, animals that test positive are usually euthanized, and the premises are quarantined, cleaned and disinfected. Carcasses, contaminated bedding and food should be safely destroyed (e.g., burned or buried), and equipment and other fomites should be disinfected. Import testing (e.g., by serology) is used to help exclude infected animals from regions where glanders has been eliminated.

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 infected animals can eradicate the disease or reduce its incidence. Meat from

infected equids should not be fed to other animals (or used for human consumption). Vaccines are not available.

Morbidity and Mortality

Glanders can spread widely when large numbers of animals are in close contact. This disease is also reported to be more common in animals that are undernourished or otherwise in poor condition. A high percentage of infections may be subclinical or latent. Although acute glanders is usually fatal within a short period, animals with the chronic form can sometimes survive for years. Mortality rates are thought to be high, but estimates are difficult to make because infected animals are usually euthanized to prevent them from spreading the disease.

Cases of glanders are reported infrequently in animals other than equids. Among carnivores, felids appear to be particularly susceptible: more than one outbreak has been reported in captive large felids, and cases have been seen in domesticated cats.

Infections in Humans

Incubation Period

The incubation period for acute glanders is reported to be 1 to 14 days, with most cases of localized disease becoming apparent within 5 days. Chronic cases can take months to appear.

Clinical Signs

Forms of glanders that have been described in humans include septicemia, pulmonary infection, acute localized infection and chronic disease. One form can progress to another, and combinations of syndromes occur. Some patients have had a biphasic illness, separated by remissions lasting a few days to several weeks.

Localized infections are characterized by nodules, abscesses and/or ulcers in the mucous membranes skin and/or subcutaneous tissues at the site of inoculation. In skin, the initial lesion may appear as a blister that gradually develops into an ulcer. Involvement of the lymphatics in the area results in lymphangitis with numerous foci of suppuration. When the mucous membranes are involved, a mucopurulent, sometimes blood-tinged, discharge may be seen. The nose and the face may swell if the nasal passages are affected, and local tissue destruction can occur. Localized lesions may be accompanied by systemic signs of illness, including fever (which may be low grade and fluctuating), sweats, malaise, headache and swelling of the regional lymph nodes, sometimes with abscesses.

Mucosal or skin infections may disseminate to other organs. The lungs, spleen and liver are often affected, but any tissue including the muscles can be involved. The clinical signs can be nonspecific in disseminated cases (e.g., nausea, dizziness, night sweats, myalgia, severe headache, weight loss). A papular or pustular rash may also be seen. Disseminated infections often progress to septicemia.

The pulmonary form can occur acutely after inhaling *B. mallei*, but organisms may also reach the lungs by localized or hematogenous spread from other forms. Pulmonary abscesses, pleural effusion and pneumonia are characteristic. The symptoms include fever and other nonspecific signs (e.g., chills, sweats, headache, myalgia), coughing and chest pain, progressing to dyspnea. Lymphangitis, nasal involvement and gastrointestinal signs may also be seen, and skin abscesses can develop up to several months after organisms are inhaled. Untreated pulmonary disease often develops into septicemia.

In the septicemic form, fever, chills, myalgia, headache and pleuritic chest pain may develop acutely. Other symptoms may include flushing, a pustular or papular rash, lymphadenopathy, cellulitis, cyanosis, jaundice, photophobia, diarrhea and granulomatous or necrotizing lesions, tachycardia and mild hepatomegaly or splenomegaly. Multi-organ failure is common, and death can occur rapidly.

Chronic glanders is characterized by multiple abscesses, nodules and ulcers in various tissues, with periodic recrudescence and milder symptoms than in acute cases. Weight loss, lymphadenopathy and lymphangitis are common. This form of the disease has been reported to last up to 25 years.

Diagnostic Tests

Glanders can be diagnosed by culturing *B. mallei* from lesions, as in animals. This organism may also be found in sputum, blood or urine, although blood cultures are often negative. PCR assays or antigen detection tests could be useful, though they are not employed routinely. Serology can be employed in diagnosis, if tests are available; however, there can be unexplained high background titers in some normal sera, and seroconversion tends to occur late. Many serological tests cannot distinguish reactions to other species of *Burkholderia*, including *B. pseudomallei*. The mallein test is not used in humans.

Radiography is helpful in the pulmonary form, although it is not specific for glanders. The lesions can include bilateral bronchopneumonia, miliary nodules, segmental or lobar infiltrates, and cavitating lesions. Similar lesions may also be detected in other organs and tissues.

Treatment

Glanders is treated with antibiotics. The optimal treatment is still uncertain, but some treatment recommendations are available, and some cases have been treated successfully. Long-term treatment and/or multiple drugs may be necessary in some cases. Abscesses may need to be drained.

Prevention

Strict precautions, including appropriate personal protective equipment (PPE), should be taken when handling

infected animals and contaminated fomites. Biosafety level 3 practices are required for manipulating infected tissues and cultures. Postexposure prophylaxis with antibiotics might 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 PPE, including disposable surgical masks, face shields, and gowns, should be used as appropriate during nursing.

Morbidity and Mortality

Glanders is a sporadic, and currently rare, disease that usually occurs in people who work with clinical samples or have frequent, close contact with infected horses and their tissues. 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 is reported to be 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.

Mortality rates are reported to be high in untreated glanders, with a case fatality rate of 95% or greater in septicemia and 90-95% in the pulmonary form. With treatment, the case fatality rates for these forms are reported to be as high as 40-50%. The estimated mortality for localized disease is 20% when treated; untreated cases often progress to other forms. Chronic glanders is reported to be difficult to treat, with a case fatality rate as high as 50% in spite of treatment. It should be noted that these estimates were based on historical cases (and possibly extrapolated from melioidosis in some cases), and mortality could be lower with modern supportive care and effective antibiotics.

Internet Resources

Centers for Disease Control and Prevention (CDC)

<http://www.cdc.gov/glanders/>

eMedicine. Glanders and Melioidosis

<http://emedicine.medscape.com/article/830235-overview>

FAO. Manual on Meat Inspection for Developing Countries

<http://www.fao.org/docrep/003/t0756e/t0756e00.htm>

Public Health Agency of Canada. Pathogen Safety Data Sheets

<http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php>

The Merck Manual (Professional)

<http://www.merckmanuals.com/professional/index.html>

The Merck Veterinary Manual.

<http://www.merckmanuals.com/vet/index.html>

United States Animal Health Association. Foreign Animal Diseases
http://www.aphis.usda.gov/emergency_response/downloads/nahems/fad.pdf

World Organization for Animal Health (OIE)
<http://www.oie.int/>

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
<http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/>

OIE Terrestrial Animal Health Code
<http://www.oie.int/international-standard-setting/terrestrial-code/access-online/>

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