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Glanders in horses: A review of the literature

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ABSTRACT

Glanders is a common infectious disease of horses in certain parts of the world. The disease also affects other animal species and is of zoonotic importance. The causative agent is newly classified under the genus *Burkholderia* and the biochemical characteristics of the bacteria are listed. Clinical signs of the disease vary among horses but may be manifested by cutaneous nodules, bronchopneumonia and/or nasal ulceration. The diagnosis, differential diagnosis, treatment and control of glanders are discussed.

Key words: glanders, equine, horses, bacterial disease, *Burkholderia mallei*, zoonosis

Introduction

Glanders is primarily a disease of the skin, lymphatics, and respiratory tract of mature horses (RAF, 1984; JULINI, 1990). Aristotle made the first authentic description of the disease in horses in 330 B.C. under the name malignant or bad disease (HENNING, 1956). Many synonyms have been given to this disease, including cutaneous Droes, Farcy, Farcy Pipes, Farcy Buds, Malleus or Equinia. However, glanders has generally been accepted as the term of choice (JUBB et al., 1985). There are many clinical disorders associated with glanders which have been recognized with increased frequency in horses (RHEE et al., 1986; SINGH and YADAV, 1989). Only a few reports have appeared with regard to the occurrence of glanders in humans. These have been associated with persons handling glanderous animals, especially veterinarians (HOWE and MILLER, 1947; GANGULEE et al., 1966). Prophylaxis involves the elimination of all affected horses, routine mallein testing of all exposed animals, and disinfection of the premises (THEVES, 1993; YEHYA, 1994;

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NAGAL et al., 1995). The purpose of this review is to provide an update on the existing knowledge of glanders.

Etiology

Table 1. Major biochemical properties of *Burkholderia mallei*

Property	*B. mallei* (14 isolates)	% Positive
Fermentation		
Glucose	+	100
Fructose	+	100
Galactose	+	100
Mannose	+	100
Lactose	+	100
Sucrose	-	0
Maltose	+ or -	64
Mannitol	+	100
Arginine dihydrolase	+	100
Oxidase	+	100
Indole	-	100
Motility	-	0
Gelatin liquefaction	-	100
Voges-Proskauer	-	100

+ = Positive; - = Negative

After the verification of glanders as a clinical entity, scientists started investigating the specific etiology. Workers in Germany reported that equine glanders was caused by an organism, which they termed the glanders bacillus. FLUGGE (1967) called the organism *Bacillus mallei*. Other scientists proposed the name *Loefflerella mallei* and then *Pfeifferella mallei* (HENNING, 1956). MERCHANT and PACKER (1967) preferred the inclusion of the causative organism in the genus *Malleomyces*. At Cambridge, taxonomists placed the glanders organism in the genus *Pseudomonas* (WETMORE and GOCHENOUR, 1956; SMITH and CHERY, 1957; ROGUL et al., 1970). It was the only non-motile species in the genus *Pseudomonas* and required differentiation from *P. pseudomallei* (SMITH and CHERY, 1957; ROSE and FRIEDMAN, 1980). Taxonomists then classified glanders bacilli in the genus *Actinobacillus* (EVANS, 1966). The current name, *Burkholderia mallei,* was proposed in the early 1990's (YABUUCHI et al., 1992). The new name was based on the 16s rRNA sequences, DNA-DNA homology values, cellular lipid and fatty acid composition, and phenotypic characteristics (YABUUCHI et al., 1992). The organism is a non-motile, non-spore forming, Gram-negative, aerobic slender rod with rounded ends, 2-5 μm long

and 0.5 μm wide. Electron microscopy showed that *B. mallei* have a nucleus, particulate cytoplasm and triple-layered profile of the outer unit membrane component of the cell wall. The cell envelope consisted of a number of different structural layers (AL-ANI et al., 1992). When cultured on suitable media for 1 to 2 days, the organism produced small, round amorphous translucent colonies (WETMORE and GOCHENOUR, 1956; REDFEARN et al., 1966; POPOV et al., 1991). The characteristics of 14 equine isolates of *B. mallei* are shown in Table 1 (AL-ANI et al., 1998).

Transmission

The mode of infection and transmission of equine glanders has been debated for several years but it is generally agreed that most transmission occurs by ingestion. According to HUTYRA and MAREK (1926), utensils and contaminated food and water could play a role in the transmission of the disease. The degree of survival of the glanders bacilli in tap water indicated that water sources might remain infectious to animals and man for several weeks after contamination (GANGULEE et al., 1966). *Burkholderia mallei* may be isolated from the manure and the skin of carrier animals. Risk factors for transmission include unsanitary and crowded stable conditions where infectious secretions may be directly passed from one animal to another, or indirectly by use of common grooming instruments (RADOSTITS et al., 1994). Experimental intratracheal deposition of *B. mallei* produces clinical glanders (LOPEZ et al., 2003). The common house fly (*Musca domestica*) may play an important role in the spread of glanders when feeding on the oozing lesions of a horse with glanders (HENNING, 1956).

Glanders of horses may occur when crowding and unsanitary conditions prevail (AL-ANI et al., 1987; JERABEK, 1994; NAGAL et al., 1995). All breeds and sexes of horses are susceptible to the disease, but animals over two years of age are more susceptible to cutaneous farcy (JUBB et al., 1985; RADOSTITS et al., 1994). Although the disease may develop during any season, its incidence is highest among horses exposed to severe cold weather. Horses receiving inadequate nutrition and kept under poor environmental conditions are the most susceptible (Al-ANI et al., 1987).

Occurrence

In Iraq, the disease has been reported in the Baghdad province (AL-ANI et al., 1987; AL-ANI et al., 1998). The disease still exists in the Middle East (YEHYA, 1994), in India and Pakistan (VAID et al., 1981; RAY, 1984; UPPAL and YADAV, 1987; KRISHNA et al., 1992; NAGAL et al., 1995), in Vietnam and Korea (HEO et al., 1987; PARK et al., 1988; SUGIYAMA, 1993), parts of Africa (HENNING, 1956), Italy (GALATI et al., 1973), and China, Russia and Mongolia (ZHANG and LU, 1983). The disease, widespread in United Kingdom in

the nineteenth century, was finally eradicated in 1928. The disease was eliminated from horses in the United States during the 1940s (WISER et al., 1986).

Animal susceptibility

Glanders is a highly communicable disease of horses, mules and donkeys (MAHADEVAN et al., 1987; THEVES, 1993). Horses tend to be chronically affected, whereas donkeys and mules develop the acute form. Apparently recovered animals remain carriers. Dogs and cats may be infected. Wild animals may develop the disease, especially members of the cat family, including lions that have been fed on infected horse meat (HART, 1916; GALATI et al., 1973; ALIBASOGLU et al., 1986). Infections have also been reported in sheep and goats (HU et al., 1958). Guinea pigs and hamsters are reported to be highly susceptible, and die within twenty-four hours following the inoculation of a massive dose, and within 3 weeks after a small one (HENNING, 1956).

Glanders in man

Glanders is zoonotic. It is rare in humans and no epidemics have been reported. Human cases of glanders have occurred in veterinarians and animal caretakers, and in occupational settings such as laboratories. The disease is usually acquired through direct skin or mucous membrane contact with infected animal tissues (BALLARINI, 1985). The disease in man occurred in Russia during World War I. Chronic glanders in man has been described by a British veterinarian who contracted the disease in India (GANGULEE et al., 1966). Although glanders had been eradicated from horses in the United States in the 1940s, one recent human case of glanders was reported in a laboratory worker in 2000 (SRINIVASAN et al., 2001). This was the first human case reported in the United States since 1945 (CDC, 2000). During World War II, six unrelated cases of laboratory-acquired infection with *B. mallei* occurred at Camp Detrick, Frederick, Maryland (CDC, 2000). Some of these cases were attributed to inhalation of infectious aerosols generated by spillage of liquid culture media containing the bacterium, although some cases occurred due to cutaneous injuries (VESLEY and HARTMAN, 1988; SUGIYAMA, 1993; WHEELIS, 1998; McGOVERN et al., 1999).

Four clinical manifestations of *B. mallei* infection in man have been described (ROBINS, 1906; BERNSTEIN and CARLING, 1909; MILLER et al., 1948; GANGULEE et al., 1966). The pneumonic form may develop when bacteria is aerosolized and enters the respiratory tract via inhalation or haematogenous spread. The incubation period is 1 to 14 days. Pneumonia, pulmonary abscesses, and pleural effusions may occur (UPPAL and YADAV, 1987; WILKINSON, 1993). Generally, there is fever, mucopurulent nasal discharge and a generalized pustular skin eruption. Death invariably occurs in 7 to 10 days. The

disease attacks chiefly those who come into close contact with horses, such as ostlers, groomers and coachmen (HOWE and MILLER, 1947; RAF, 1984; RAY, 1984). The localized form occurs when bacteria enter the skin through a laceration or abrasion, and a local infection with ulceration and/or nodular formation develops. Incubation period is 1-5 days. Swollen lymph nodes may develop. The septicemic form is usually fatal within 7 to 10 days. The septicaemia that develops affects multiple systems, including the skin, liver and spleen (HOWE and MILLER, 1947). The chronic form occurs when multiple abscesses develop in the liver, spleen, skin, or muscles. This form also is known as "farcy".

Pathogenesis

Miller and his group studied the virulence of *B. mallei*. Their work revealed that strains of very low virulence of *B. mallei* produced subacute or chronic infection in hamsters, moderately virulent strains produced acute fulminating infections in hamsters and ferrets, and subacute or chronic infection in guinea-pigs, while virulent strains caused the acute fulminating form of the disease in hamsters and guinea-pigs (MILLER et al., 1948). The development of small animal models has allowed an assessment of the role of a number of putative virulence determinants in the pathogenesis of glanders in horses (LOPEZ et al., 2003). Experimental studies by HU (1958) and his colleagues showed that the intravenous or intratesticular inoculation of *B. mallei* produced acute toxaemia and rapid death in sheep and goats. The subcutaneous injection was also lethal to sheep and goats but the infection was less acute. These authors concluded that the virulence of the strain is responsible for the type of disease produced, and might explain the occurrence of all the gradations of glanders in horses (HU et al., 1958). Ingestion is the main route of infection (RADOSTITS et al., 1994). This could be explained by the presence of glanderous lesions in internal organs as well as causing orchitis (ZUBAIDY and AL-ANI, 1978; MOHAMMAD et al., 1989). The lungs and upper respiratory passages appear to be the predilection sites (ZUBAIDY and AL-ANI, 1978). Emboli in pulmonary and nasal vessels might be evidence that the organisms are carried to the blood when acquired by ingestion, inhalation or through cutaneous wounds entering the lymphatic system and general circulation and localize in the lungs from which they spread to the nasal passages (ZUBAIDY and AL-ANI, 1978).

Clinical signs and pathological changes

The incubation period is 2 to 3 days following intratesticular injection of *B. mallei*. Contact infections usually require 2 weeks, but exceptionally virulent strains might require only 7 to 10 days (AL-ANI et al., 1998). The highly variable incubation period under field conditions (a few days to several weeks or months) led to an arbitrary classification of the

disease into two forms: clinical and subclinical or latent glanders (HUTYRA and MAREK, 1926).

In the author's (Al-Ani) experience, equine glanders can be classified into four forms: cutaneous, pulmonary, nasal, and asymptomatic carrier (AL-ANI et al., 1987). Cutaneous glanders may result from skin injury or may be due to a secondary manifestation of the respiratory form. It consists of nodules, pustules and ulcers that occur over any part of the body but are most frequently observed on the legs (MOHAMMAD et al., 1989; AL-ANI et al., 1992). These nodules usually appear in chains along the course of the lymphatic vessels. Initially, the lesions appear as nodules, which tend to break down and form crater-like ulcers discharging thick yellowish viscid and sticky purulent material heavily laden with the glanders organism. This is usually referred to as farcy pipes. Like other bacterial infections, glanders induces a neutrophilic leukocytosis in the infected horse (AL-KAFAWI et al., 1977). Also, *B. mallei* infection causes severe anaemia probably because of depressed erythropoietic activity of the bone marrow (AL-KAFAWI et al., 1977). The pulmonary form of equine glanders is the most common clinical manifestation of the disease. It is characterized by the formation of round, greyish, firm, encapsulated nodules embedded throughout the lung tissue (ZUBAIDY and AL-ANI, 1978). Cough and high fever reflect the fulminating bronchopneumonia that characterizes the acute form. At necropsy, most of the pulmonary lesions are discrete firm miliary granulomatous nodules which have a caseonecrotic centre with degenerate neutrophils (ZUBAIDY and AL-ANI, 1978). The nasal form of glanders appears in the form of nodules or ulcers in the upper air passages. The ulcers are commonly seen on the lower parts of the turbinate and on the cartilaginous nasal septum (JUBB et al., 1985). A bloody mucopurulent nasal discharge appears when those nodules rupture. The asymptomatic carrier form of glanders develops after a period of illness of some months. The affected equine makes an apparent recovery but persists as an occult case. Mallein test is positive but no obvious skin lesions can be seen (AL-ANI et al., 1987).

Diagnosis

Glanders may be diagnosed based on clinical signs, the mallein test, serological tests and bacterial isolation (ALLEN, 1929; UPPAL and YADAV, 1987; THEVES, 1993; PRITCHARD, 1995). The following diagnostic tests can be performed:

1. Isolation and identification of the causative agent.

Culture of *B. mallei* from an unopened cutaneous nodule, lymph node or pulmonary lesion is of diagnostic value (AL-ANI et al., 1998). Cultured swabs of the purulent contents on glycerin agar reveal small, round, amorphous, translucent colonies (MILLER et al.,

1948; QUINN et al., 1994; OIE, 1996). Its Gram stain morphology, biochemical activities and male guinea-pigs inoculation (MILLER et al., 1948; AL-ANI et al., 1998) can identify *B. mallei*. Many different media have been developed to support the growth of *B. mallei* (ROGUL et al., 1970). Brain heart infusion agars supplemented with 3% glycerin have been used to propagate the organism in large quantities. The Straus reaction is performed by the intra-peritoneal injection of male guinea pigs with suspected materials to help in diagnosis. Swelling and periorchitis occur 3 to 7 days post-inoculation.

2. Cell- mediated immunity tests.

An *in vivo* test of cell-mediated immunity includes the commonly used intradermopalpebral mallein test (ROSE and FRIEDMAN, 1980; VERMA et al., 1994; OIE, 1996). The test is performed by injecting 0.1 mL of mallein into the skin close to the edge of the lower eyelid. A positive reaction usually develops within 48 to 72 hours and is characterized by marked oedema of the lid with blepharospasm and severe purulent conjunctivitis. The mallein test has a positive predictive value of 92% in acute and chronic cases and a negative predictive value of 96% in advanced cases (WILSON and MILES, 1975). Others have reported limitations in sensitivity, especially in clinically advanced cases, (JANA et al., 1982) and false-positives associated with *Streptococcus equi* infections (AL-ANI, 1987). The mallein test may cause uninfected horses to produce antibodies against *B. mallei* causing a positive complement fixation test (CFT) (HAGEBOCK et al., 1993). An *in vitro* test of cell-mediated immunity is the lymphocyte stimulation test. A combination of lymphocyte blastogenesis, CFT and culture for the diagnosis of glanders yields high sensitivity and specificity rates.

3. Serological tests.

Serological tests have the greatest application in epidemiological investigations. The presence of more than one isolate in an area might complicate the serologic interpretation, although variable data indicate that common antigens are shared by different isolates (MISRA and ARORA, 1990).

a. Agar-gel immunodiffusion (AGID) test.

The AGID test has been used successfully as a screening test for the diagnosis of glanders (SEN et al., 1968; AL-ANI, 1989). The main disadvantage of this test is that large amounts of antibodies (a titer $\geq$ 1:128) are necessary to produce visible precipitin lines. The AGID test is rapid, inexpensive and accurate in clinical cases of glanders and results are available within 48 hours.

b. Counterimmunoelectrophoresis (CIE) test.

Counterimmunoelectrophoresis is based on the principle of immunodiffusion modified by the electrophoretic driving of the antigen and antibody towards each other.

The test is currently used to detect antibodies in the sera of infected horses (JANA et al., 1982). This test is rapid, simple, economic and suitable for the screening of a large number of sera.

c. Fluorescent antibody (IFA) test.

The IFA technique has been developed for diagnosis of glanders (MA et al., 1986). Of 53 naturally affected mules, 47 were positive to IFA, in close agreement with that of ELISA (MA et al., 1986). It was concluded that IFA is quick and simple for the diagnosis of glanders. Also, IFA distinguishes between the antigens of *B. mallei* and the antigens of other bacteria, which are easily confused by the CFT.

d. Indirect haemagglutination (IHA) test.

Passive HA test can be routinely used for herd diagnosis and survey purposes (AL-ANI et al., 1998). Titers ≥ 1:80 are regarded as positive. In India, an HA titer of 1:640 is considered positive (GANGULEE et al., 1966).

e. Complement Fixation Test (CFT).

The CFT has been used as a reliable test for the diagnosis of glanders (SEN et al., 1968; VERMA, 1990; AL-ANI et al., 1992). A titer of 1:32 may be regarded as positive. POPPE (1919) tested 2665 by CFT. His results showed that 26 horses gave false-positive results and 59 horses gave false-negative results. There is general agreement that the CFT is superior to other serological methods in diagnosis of glanders (SEN et al., 1968; AL-ANI et al., 1993). However, according to WILSON and MILES (1975), CFT may give a positive cross-reaction in horses suffering from strangles, equine influenza or petechial fever, and in emaciated horses not suffering from glanders.

f. Enzyme linked immunosorbent assay (ELSA).

The ELISA has been developed recently (NIEDERWOHRMEIER and BOHM, 1990; VERMA et al., 1990; AL-ANI et al., 1993). In a comparative study conducted in Iraq, 125 horses' sera were tested by ELISA, CFT, AGID and HA and compared with culture results. Results showed that ELISA correctly identified 100% of confirmed clinical cases of horses with glanders, whereas the latter tests gave only 90.9% positive reaction (AL-ANI et al., 1993). Thus, ELISA test could be routinely adopted as a highly sensitive diagnostic test for glanders.

g. DNA-sequencing and Polymerase Chain Reaction (PCR) using primers to amplify part of the bacterial genome have been developed to differentiate between glanders, melioidosis and other related organisms (YABUUCHI et al., 1992; GEE et al., 2003; GODOY et al., 2003). The use of 16S rRNA gene sequencing to rapidly identify *B. mallei*, *B. pseudomallei*, and differentiate them from closely related organisms by a molecular method, has been used (GEE et al., 2003).

h. Bacteriophage specific for *B. mallei* has been developed (WOODS et al., 2002). Bacteriophage phiE125 has been found to form plaques on *B. mallei* but not on any other bacterial species tested, including *B. thailandensis* and *B. pseudomallei*.

Differential diagnosis

Glanders might be clinically confused with epizootic lymphangitis, ulcerative lymphangitis, strangles and sporotrichosis. The differential diagnosis between these diseases should be conducted because of the strict control measures required by legislation, and is as follows:

1. Epizootic lymphangitis is a chronic granulomatous and suppurative fungal infection chiefly affecting horses (AL-ANI and AL-DELAIMI, 1988). The causative organism is the fungus, *Histoplasma farciminosum*. The disease involves the cutaneous lymphatics, may be asymptomatic or mild and may result in an apparent recovery persisting as an occult infection. Diagnosis can be readily made by the identification of *H. farciminosum* by direct smears and/or culture.

2. Sporotrichosis is a chronic subcutaneous lymphatic mycosis. It occurs only sporadically in affected groups of animals and this helps to differentiate it from glanders. Positive identification of sporotrichosis could be made on the presence of a gram-positive fungus, *Sporotrichum schenki*, which forms single-walled spores.

3. Ulcerative lymphangitis is a bacterial disease of horses and cattle caused by *Corynebacterium pseudotuberculosis*. The disease is characterized by the formation of nodules in the subcutaneous tissues, particularly around the fetlock joint. Diagnosis is confirmed by isolation of the causative organism (ADDO, 1983).

4. Strangles is an acute bacterial disease of horses caused by *Streptococcus equi*. Inflammation of the upper respiratory tract and abscessation of the adjacent lymph nodes characterize the disease. The disease responds well to penicillin therapy.

5. Melioidosis (Whitmore's disease) is caused by *Burkholderia pseudomallei*. Glanders and melioidosis are related diseases. They have similar pathophysiologic consequences, although the epidemiology differs. *Burkholderia pseudomallei* thrive in tropical climates, and the disease is endemic in Southeast Asia, the Philippines, Indonesia, and other tropical areas. It is most widespread in Thailand, where in one hospital it was responsible for 19% of community-acquired sepsis and 40% of deaths from community-acquired septicaemia (THUMMAKUL et al., 1999). Both humans and other susceptible animals may contract the disease (DANCE, 2000). The organism is distributed widely in soil and water in the tropics. It is spread to humans through direct contact with a contaminated source or by inhalation of aerosols or dust (THUMMAKUL et al., 1999).

Treatment and control

As a rule, veterinary authorities forbid the treatment of any equine species which proves to be infected with glanders (WOLTER, 1984). All infected animals are killed according to laws and legislation. Optimal antibiotic therapy of the disease has not yet been determined. Systemic treatment of glanderous horses with antibiotics, including penicillin and streptomycin, is usually ineffective in controlling the disease. Although there is some contradictory evidence for ampicillin, gentamicin, and tetracycline, evidence has accumulated that enrofloxacin (Baytril®), erythromycin, ampicillin, sulfonamides, gentamicin and tetracycline might be effective against *B. mallei*. This evidence has emerged from *in vitro* antibiotic sensitivity testing and from treatment studies in experimentally infected guinea pigs (BATMANOV et al., 1996; AL-ANI et al., 1998). In mice and monkeys doxycycline and ciprofloxacin have been effective therapies (RUSSELL et al., 2000; KHOMIAKOV et al., 1998). Recently, excellent results have been reported in treating experimentally infected guinea pigs with a single daily 5 mg/kg body mass intramuscular dose of enrofloxacin (Baytril®). This regimen may also be beneficial in equine glanders (AL-ANI et al., 1998).

A few antibiotics have been used to treat humans. According to HOWE and MILLER (1947) sulfonamides are quite effective in the treatment of man and laboratory animals. Sulfadiazine (25 mg/kg intravenously, four times a day) was efficacious in some cases (HOWE and MILLER, 1947). For localized infection, a 60- to 150-day course of oral amoxicillin and clavulanate may be used. For severe and/or septicemic disease, the initial 2-week parenteral therapy is followed by oral therapy for 6 months by ceftazidime, combined with trimethoprim and sulfamethoxazole.

FATHI et al. (1953) reported that the combination of a formalized vaccine and sulfadiazine is effective in the treatment of horses affected with glanders. Administration of one dose of an autogenous vaccine, plus a trimethoprim-sulfonamide combination in a daily dose of 20 mg/kg BW for one month, has significantly altered the course of the disease in horses with clinical lesions. Horses with advanced lesions usually failed to respond to treatment. In areas in which glanders is endemic, routine mallein testing at intervals of 3 weeks should be conducted until all reactors have been removed (RADOSTITS et al., 1994). It is currently recommended that mallein testing and control methods should be instituted simultaneously (BLANCOU, 1994a; 1994b). Culling or isolation of all infected horse, rearing foals in isolation, and thorough cleaning and disinfecting of the environment may help in controlling the disease. All positive cases should be terminated.

Commercial vaccine against glanders is not available. However, the use of a locally produced autogenous vaccine may be of importance. In endemic areas, some authors recommend routine vaccination of all foals at 6 months of age. Vaccinations are then repeated 3 weeks later and then at 6 months intervals thereafter (AL-ANI, 1989). A killed

B. mallei vaccine has shown good protective results (MOHLER and EICHORN, 1914; ZHANG and LU, 1983).

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SAŽETAK

Sakagija je česta zarazna bolest konja u određenim dijelovima svijeta. Bolest napada i neke druge životinjske vrste, a važna je kao zoonoza. Uzročnik je u najnovije doba svrstan u rod *Burkholderia*. Navode se njegove biokemijske značajke. Klinički znakovi bolesti u konja variraju, a očituju se tvorbom čvorova po koži, bronhopneumonijom i/ili ulceracijama po nosnoj sluznici. Opisana je dijagnostika, diferencijalna dijagnostika, liječenje i kontrola bolesti.

Ključne riječi: sakagija, konj, bakterijska bolest, *Burkholderia mallei*, zoonoza