Review On Glanders

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Summary: This paper is mainly aimed to review the glanders disease in equine and its zoonotic potential. Glanders is highly contagious, life threatening and OIE-listed disease of equids caused by the gram negative bacterium *Burkholderia mallei.* It is transmitted mainly through physical contact. Susceptibility varies from animal to animal, amongst the family of equidae, donkeys are most susceptible, mules less so and horses still less again. Whereas birds, cattle and swine are resistant to infection, small ruminants can become infected if maintained in close contact with affected horses. Glanders is a disease of the skin, lymphatics, and respiratory tract that characterized by ulcerating lesions of skin and mucous membrane. The pathogen causes nodules and ulcerations in skin, the upper respiratory tract and lungs. Based up on the clinical manifestation and site of infection glanders have nasal, pulmonary, cutaneous and asymptomatic forms. It can be diagnosed by using different serological techniques. Due to the absence of effective antibiotic treatment and vaccine the preventive and control measure of the disease becomes too tight and controversial. Control of glanders requires testing of suspect clinical cases, and elimination of positive reactors. *Burkholderia mallei* is considered as biological weapon. It causes huge economic loss and having zoonotic potential. Glanders is reported in central highland of Ethiopia. As glanders is economically very important disease in equine as well as human, therefore wisely designed preventive and control measure should be conducted.
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Introduction

World equine population is estimated 44 million donkeys, 11 million mules, and 59 million horses. From this huge world equine population, Ethiopia has more than 6 million donkeys, second largest donkey population next to China in the world, 1.9 million horse and 350000 mules (FAOSTAT, 2012). Glanders is an old disease, described as early as 400 BC by Hippocrates and 330 BC by Aristotle. It is a contagious, life-threatening, OIE-listed disease of equids caused by the gram negative bacterium *Burkholderia mallei.* Glanders *have* been given name, including cutaneous Does, Farcy, Pipes, Farcy Buds, *Bacillus mallei* and Malleus or equinia. However, glanders has generally been accepted as the term of choice. Previously it was classified variously as *Pseudomonas, Pfeiffer Ella, Loefflerella, Malleomyces or Actinobacillus)* of family Burkholderiaceae (Garrity *et al.,* 2005).

Primarily, glanders affects odd toe ungulates (mainly horse, mule and donkey). Solipedes are the natural reservoirs of *Burkholderia mallei*. Glanders present mostly in chronic form in horses and is acute in donkeys and mules. It is a disease of the skin, lymphatics, and respiratory tract. Glanders is characterized by ulcerating lesions of skin and mucous membrane. It is potentially zoonotic disease and considered as biological warfare of animal as well as humans. There is no effective antibiotic and vaccine available. Critical to effective prevention and control of glanders is prompt identification, euthanasia, affected premises shall be quarantined, movement controls strictly enforced, potentially contaminated areas must be disinfected, thoroughly and re-disinfected. The disease is highly contagious and has remarkable similarity to the causative agent of melioidosis, *Burkholderia pseudo mallei (*Lazar *et al*., 2009). Therefore, the objectives of this seminar paper are**:**

- To review the economic importance of glanders in equine and human.
- To indicate the prevention and control measure of the disease.
- To highlight the status of the disease in Ethiopia.

Litarture Review

Glanders is caused by gram negative bacterium *Burkholderia mallei*. The organism is non sporulating, rod shaped and facultative intracellular obligate mammalian pathogen. It does not have a readily visible capsule under the light microscope and do not

form spores. Outside the body, it is susceptible to heat, sunlight and common disinfectants (Nicoletti, 2007).

No report about its growth in soil or water is available although it can remain viable at room temperature. The presence of a capsule-like cover has been verified by electron microscopy. This capsule is composed of neutral carbohydrates and serves to protect the cell from unfavorable environmental factors. Unlike other organisms in the *Pseudomonas* group and its close relative *B. pseudo mallei, Burkholderia mallei* have no flagella and are therefore, non-motile (Sprague and Neubauer, 2004).

The organism can be aerobic and facultative anaerobic only in the presence of nitrate, growing optimally at 37°C. It grows well, but slowly, on ordinary culture media, including sheep blood agar. 72-hour incubation of cultures is recommended; glycerol enrichment is particularly useful. Various commercially available Burkholderia selective agars enable the growth of *B. mallei (*Glass *et al.,* 2009).

Even in fresh samples obtained under sterile conditions *B. mallei* is often overgrown by other bacteria or have evolved from the agent of melioidosis, *Burkholderia pseudomallie* which makes isolation extremely difficult (Wernery, 2009).

Epidemiology:

Geographic distribution

In earlier times, it was more widespread worldwide and now has been eradicated from most of the areas like Western Europe, Australia and Northern America (Van Zandt *et al*., 2013). It has regained the status as re-emerging disease (Khan *et al*., 2013). And it is still endemic in North Africa, Middle East, South America, and Asia (Dvorak and Spickler, 2008). Resurgence in high frequency and extensiveness of outbreaks of the disease in different area is reported (Malik *et al*., 2010). In recent years, glanders has been re-introduced into countries in which it was previously eradicated. The increase in trade is linked to a greater risk of spread of a wide range of equine infectious diseases (Timoney, 2007). As it is described in the figure below, glanders is worldwide disease and seen as outbreak in different countries of the world including Ethiopia.

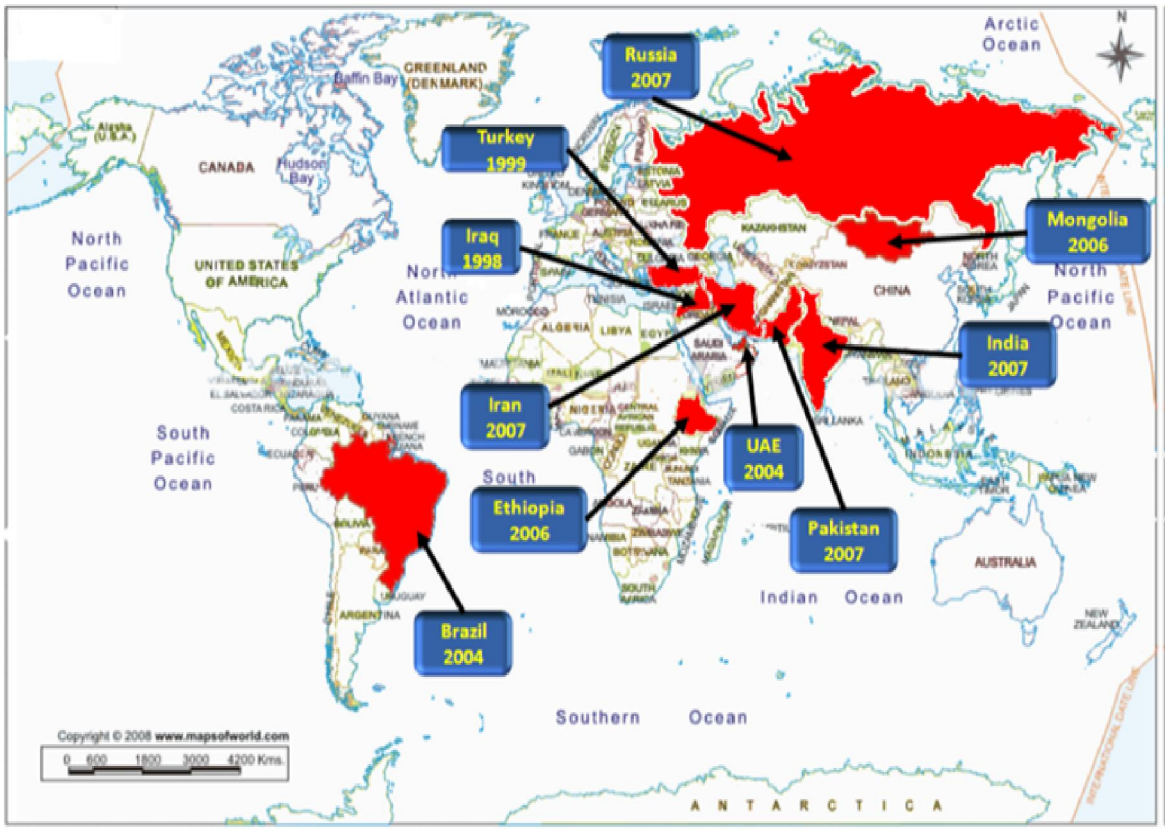

Figure 1: Map of outbreaks of equine glanders during last decade. Source: (Saqib *et al*., 2003).

Transmission

Glanders can be transmitted by direct or indirect means. Most commonly, it is spread through directphysical contact with horses affected with nasal, cutaneous or pulmonary forms of the disease. The co mmon 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. (Fernandez and White, 2010).

Indirectly, glanders can be transmitted through the ingestion of food or drinking water contaminated with discharges from the respiratory tract or ulcerated skin lesions of affected horses. It can also be contracted through horses sharing feed troughs or containers, water bowls or buckets and items of harness contaminated with infective material. The risk of spread of the disease is enhanced under conditions of stress or overcrowding. A high number of *B. mallei* bacteria are present in nasal secretions and skin exudates of glanderous equids that can contaminate fomites and spread the disease from animal to animal, animal to person and person to person (Gregory and Wagg, 2007).

Animal susceptibility

Glanders is a highly communicable disease of horses, mules and donkeys. All breeds and sexes of horses are susceptible to the disease, but animals over two years of age are more susceptible to cutaneous farcy. Amongst the family Equidae, donkeys are most susceptible, mules less so and horses still less again, especially cases of chronic infection in endemic areas. Whereas birds, cattle and swine are resistant to infection, small ruminants can become infected if maintained in close contact with affected horses. This disease is also reported in human. 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. Apparently recovered animals remain carriers. Infections have also been reported in sheep and goats also rarely in camelidae, canidae and felidae (Wernery *et al*., 2011).

Pathogenesis

Following the entry the pathogen through ingestion, mucous membranes and the integuments of the host, bacteria penetrate the mucosa and travel via lymph vessels and finally reach lymphatic sentinels. *Burkholdreria mallei* proliferate in these lymph nodes and takes its way to the bloodstream and spread to the visceral organs haematogenously. Thus, lymphatic and blood circulatory systems play a vital role in the formation of musculoskeletal lesions (Pitt and Dance, 2005). But its chronicity is facilitated by the presence of a cytoplasmic membrane, Three layered cell wall and a capsule which are helpful to escape from host immune response and impermeable against some antibiotics. *Buekholderia mallei* produce necrotizing endotoxin that causes lymphangitis, lymphadenitis, and tissue reaction of smooth muscle and sloughing of mucous membranes in addition to this lymphadenopathy and cording of lymphatics is common (Vegad and Katiyar, 2001).

Clinical finding

Glanders can be classified into four forms: cutaneous, pulmonary, nasal, and asymptomatic). Individual horses may be affected with more than one form of the disease. The incubation period can range from a few days up to six months, based on various agent, host and environmental factors. Cutaneous glanders sometimes called as “farcy” may result from skin injury or may be due to a secondary manifestation of the respiratory form (Wittig *et al* 2006). As shown in the figure below, ulcer and nodular manifestations of cutaneous glanders are frequently observed on the mouth and leg region.

Figure 2: Cutaneous lesions of glanders: around mouth and on fetlock region of glanderous horse.
Source: (Wernery *et al*., 2005).

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. A yellowish-green nasal discharge appears when those nodules rupture and forming stellate or star shaped scars after recovery. 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. 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 that might develop central calcification (Al-Ani, 2007).

Pathology

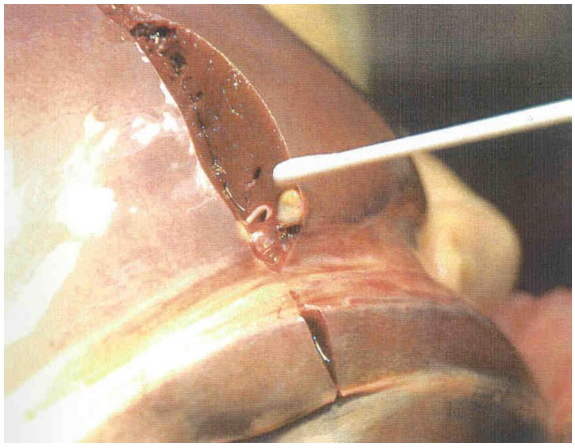

Figure 3: Nodules were found in the glanderous equid`s spleen and liver after post-mortem. Source: (Wernery *et al*., 2005)

Variable post-mortem lesions of glanders were observed in equids including granulomas and ulcers in a variety of tissues, nodules and fulminating ulcers were found on mucous membranes of nasal passages (nasal form of glanders), larynx, and upper lip. In pulmonary glanders lungs show nodular foci underneath the pleura while diffuse military granulomatous nodules with a case necrotic center. Edema of lungs lobes and sever bronchopneumonia is observed in acute glanders. Cervical, mandibular and mediastinal regions show lymphadenitis that will lead to ulceration with sebaceous contents. And also liver and spleen show lymphadenitis (Lopez *et al*., 2003).

Diagnosis

Glanders can be diagnosed based on clinical sign, history, the mallein test, serological tests, culture and bacterial isolation. A suspected case of glanders is screened serologically by CFT or competitive ELISA (Thepthai, 2005). In addition to this the Rose Bengal plate agglutination test (RBT) has been described for the diagnosis of glanders in horses and other susceptible animals; and has been validated in Russia. In a study of Pakistan, the RBT showed a sensitivity of 90% and a specificity of 100% (Naureen *et al.,* 2007).

ELISA test could be routinely adopted as a highly sensitive diagnostic test for glanders, 100% confirmatory test except for their cross-reactivity with *Burkolderia pseudo* mallei that can occur false positives in areas where melioidosis is endemic. The mallein test is best diagnostic approach of glanders which is hypersensitivity test against *B. mallei* that not generally recommended because of animal welfare concerns, however it can be useful in remote endemic areas where sample transport or proper cooling of samples is not possible. Mallein is water soluble protein component of the organism, is injected into the dermis of the lower eyelid or administered in eye drops. The protein elicits an allergic reaction in infected animals within 12-72 hours; the test is usually read at 48 hours. Alternatively nucleic acid of the pathogen can be detected by the polymerase chain reaction (Ulrich *et al.,* 2006).

Differential diagnosis

There are a significant number of other infectious diseases, bacterial, fungal and viral that, based on their clinical features, need to be considered in the context of a differential diagnosis for glanders, These are Epizootic lymphangitis, Melioidosis, Ulcerative lymphangitis and strangles (Fernandez and White, 2010).

Treatment

Animal treatment of glanders with broad spectrum antibiotics, such as penicillin and other alternative drugs including streptomycin, doxycycline and gentamycin are usually ineffective due to development of resistance of the pathogen. But sulfonamides are quite effective in the treatment of man and laboratory animals. Commercial effective antibiotic against glanders is not available and still now there is no availability of vaccine in the world (Whitlock *et al*. 2007).

Prevention and control

The critical and effective prevention and control measures of glanders are prompt identification, euthanasia, affected animals shall be quarantined, and movement controls strictly enforced, potentially contaminated areas must be disinfected, thoroughly cleaned and re-disinfected. All feeding or bedding place should be kept hygienic and appropriate disposal of all positive cases of the disease (Wittig *et al.,* 2006*).* No vaccine is available for prevention of glanders for animals as well as humans (Burtnick *et al*., 2012).

Zoonotic Importance Of Glanders

Glanders is rarely zoonotic, but serious disease in humans and no epidemics have been reported. Human cases of glanders have occurred in veterinarians and animal care takers, and in occupational settings such as laboratories. The disease is usually acquired through direct skin or mucous membrane contact with infected animal tissue that lead to a localized cutaneous infection. Inhalation of aerosol or dust containing *B. mallei* can lead to septicemic, pulmonary, or chronic infections of the muscle, liver, and spleen. *Burkholderia mallei* have been classified as a category bioterrorism agent on the basis of its potential for dissemination, its ability to cause human morbidity and death. Although glanders had been eradicated from horses in the United States in the1940s, 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).

Burkholderia mallei are highly infectious for human when it is aerosolized (Neubauer *et al.,* 1997). The pathogen cause major destructive effect on human health because of its ability to cause opportunistic infections in diabetic and perhaps otherwise immunocompromised persons (Estes *et al*., 2010).

Glanders In Ethiopia

Apart from the fragmented report of (OIE, 2013a) and anecdotal information based up on clinical sign, the epidemiology of glanders has not been previously investigated in Ethiopia. But recently number of each equine species are examined and % serologically positive for glanders test in central highland of Ethiopia is reported. Donkeys (n=657), mules (n=48), horse (n=277) and total (n=982) with their sero-positive percentage 0.2 %, 0%, 12.3%, and 3.8 % respectively. In addition to this different species of equids are examined from different agro-ecological zones such as highland (n=621), midland (n=210), lowland (n=151) having with sero-positive percentage 4.5 %,1.4 % and 2.4 % respectively. This was the first report of serological evidence of the disease in all agro ecological zone showing its wide distribution among equine population in central highland of Ethiopia. Donkey are reported to be the most susceptible, that often developing the acute form of the disease. The main reasons for this are donkeys prone more to cross contamination in public places such as market, flour mill, trade route across the country with poor hygienic, stress full condition and traditional ceremonies (OIE, 2013a).

Moreover, the highly prevalent harness inflicted wound and fly population play significant role in the transmission of the disease in the country. Glanders is highly reported in highland than other lowland of Ethiopia. From1998 to 2007, glanders is reported not only from Ethiopia but also from neighbor courtiers Eritrea and Sudan (OIE, 2008).

Economic Importance Of Glanders

Glanders is the most economically important disease of equine due to high degree of infectivity, in capacitation of infected animals and high economic losses, Cause high mortality and morbidity in untreated cases. In the septicemic form, the case Fatality rate recorded up to 95% in 3 weeks or higher in untreated cases and more than 50% if treated. Mortality rate in the pulmonary form is 90–95% if untreated, and 40% if treated. In its chronic form, the case fatality rate is 50% even in treated cases. Not only animals are affected but also it is life threatening disease in humans and other mammalian. Greatly the disease has zoonotic and political implication. It is OIE listed devastating equine disease (Anon, 2010). B. mallei is the first infectious agents to be used for biological warfare purposes (Lehavi *et al.,* 2002).

Conclusion And Recommendations

Glanders is the most economically important disease of equine and occasionally other mammalian including man. It is a disease of the skin, lymphatics, and respiratory tract. Glanders is characterized by ulcerating lesions of skin and mucous membrane having four forms: cutaneous, pulmonary, nasal, and asymptomatic). Individual animal may be affected with more than one form of the disease. The causative bacterium *(B. mallei)* has the potential to be used as biological weapon in terrorism. The disease is highly contagious, fatal in nature and that has no still effective antibiotic and vaccine. For this notifiable disease, regulatory measures call for culling or disposal of diseased animals is recommended. Since it is highly contagious and zoonotic disease it causes huge loss of economy resulting from high mortality and culling of important breed during control program. As per the review of glanders and conclusion reached accordingly, the following recommendations are forwarded:

- Effective antibiotics and vaccine should be produced.
- Early isolation or culling of postive animals should be applied.

- Educating of the owner about zoonotic effect of the disease and its prevention mechanism.
- Studies on the epidemiology of the disease, prevention and control programs should be conducted in Ethiopia.

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