REVIEW ARTICLE

A Review on Hemorrhagic septicemia: The outbreak, pathophysiological, diagnosis, treatment and antibiotic resistance

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ABSTRACT

Hemorrhagic septicemia (HS) is the most important disease of livestock caused by *Pasteurella multocida* serotype B: 2 (Asian countries) and serotype E:2 (African countries). The outbreak of *Pasteurella multocida* world widely gave serious economic impact in South and Southeast Asia, Africa and India. Respiratory system plays the main role in the route of transmission of the HS disease where the *Pasteurella multocida* enters the respiratory tract of infected animals through inhalation and passes into the bloodstream thus producing clinical signs including rising of body temperature, respiratory pain, inflammation, nasal discharge and lethargic. HS disease occurrence in peracute cases typically characterized as sudden onset which leading to rapid death of the infected animal. Diagnosis of HS disease was mainly based on the clinical sign and symptom, post mortem findings which polymerase chain reaction (PCR) frequently has been used for rapid, sensitive and specific detection of *Pasteurella multocida.* HS disease was usually treated with a wide range of antibiotics such as cephalosporins, florfenicol, tetracyclines, and fluoroquinolone. However, long term usage of the antibiotics resulting in multi-drug resistant against *Pasteurella multocida.* Thus, several studies on the development of a vaccine for HS disease was been done and still ongoing nowadays in preventing and control HS disease outbreak

Keywords: Pasteurella multocida; hemorrhagic septicemia; Diagnosis; Treatment; Antibiotic resistance

INTRODUCTION

Pasteurella multocida is a Gram-negative bacterium that has a pathogenic potential in domestic animals. The infection is well known over a century ago and termed as pasteurellosis. There range of infected animal hosts by *Pasteurella multocida* is very wide and it manifests differently. The bacteria have a broad range of hosts, but the uncharacteristic property is still not understood. *Pasteurella multocida* has an almost unlimited host range in mammals and birds[1]

Pasteurella multocida has five types of capsular serotypes which range from type A, B, D, E and F and each type of capsular produce different kind of diseases among animals. *Pasteurella multocida* type A is known for chloral in fowl and pneumonia in cattle and sheep and pig meanwhile capsular type D produces atrophic rhinitis in pig and snuffles in rabbits [2]. While Capsular type F mainly causes disease in poultry, especially turkeys, eventhough it has been reported at times in ruminats. In cattle, capsular serotypes B and E are associated with hemorrhagic septicemia in Asian (serotype B) and African (serotype B) countries. Under the Carter- Heddleston naming system B:2 and E:2 are the B and E serotypes, respectively, considered to cause typical hemorrhagic septicemia. *Pasteurella multocida* strains are generally classified using a combination of capsular and somatic typing. Serotypes are designated by the capsular type followed by the somatic type under the Carter-Heddleston naming system[3].

Pasteurella multocida can be found in the upper respiratory tract as normal flora or can act as a primary or secondary pathogen depending on the species of animal. Revole´e in 1877 explained that isolation of *Pasteurella multocida*is predominantly secondary to respiratory viral infection and environmental stressors. They are mostly isolated from the lungs of calves affected by enzootic pneumonia. This was further describes by Pasteur in 1880[4]

The aim of this review is to have a general and better understanding of hemorrhagic septicemia through current outbreaks of the disease, its pathophysiological, diagnosis, treatment and antibiotic resistance against hemorrhagic septicemia.

The outbreak of Hemorrhagic septicemia: Hemorrhagic septicemia (HS) is an acute, fatal septicaemic bacterial disease, affecting mainly India, Africa and the South and Southeast Asia. The mortality rate of HS is very high and in regard to livestock in South-East Asia, it is regarded as one of the most important diseases of livestock that can have economical implication. The common host for HS is usually Cattle and buffalo, even though goats, pigs and sheep are susceptible to HS[5,19].

The first report of HS in Malaysia was recorded in the year 1900[6]. Malaysia has a cattle and buffalo population of about 735000 and 186000 respectively. Outbreaks have had very serious economic effects with an estimated RM2.4 million loss annually[7]. A total of 48 outbreaks has been reported between the years 1994 and 2005. The outbreaks were reported almost every year excluding the year 2004. The highest numbers of outbreaks were seen between 1995 and 2000. During a Nipah virus outbreak in the year 2000, the HS outbreaks were at its highest [8]. All isolates from Malaysian outbreaks were found to be *Pasteurella multocida* serotype B: 2, whilst in the last 12

years states of Perlis, Selangor and Johor were free of any HS outbreaks; about 8 to 11 outbreaks were reported in the states of Pahang, Terengganu, Kelantan and Perak. In February 2006 in Pasir Mas, Kelantan HS disease was reported where 77 buffaloes were found dead.

Besides that, throughout the past four decades, HS is documented to be responsible for 45-55% of all bovine deaths in India. It is also reported about five million animals die annually in India from HS disease because the current vaccines have limitations in affording long term protection. While in Pakistan, likewise, 34.4% of all deaths in prone stock and 31.48% mortality have been reported in buffalo calves. Moreover, a study done by Farooq et al (2011)[9] reported that the overall morbidity, mortality and case fatality rates were 17.39, 14.66 and 84.30%, respectively, from 10 infected/outbreak villages in Pakistan with the total population of 4248 animals. It was obviously pointed out that HS is a vital hurdle in the economic uplift of the livestock sector with high incidence rates and alarming morbidity, mortality and case-fatality rates[10]. It is also stated that HS is a widespread disease in India[11], occurs more frequently in poor farming conditions. In the present instance, the animals were brought up under an extensive, free-range system. Such conditions are ideal surroundings for the spread of HS[10,12]

Fraz Munir Khan (2011) stated that an extensive outbreak of an HS occurred in the dromedary population of Greater Cholistan from mid of November 2010 to the mid of December 2010. Although *Pasteurella multocida* is not a common respiratory tract pathogen among dromedary yet HS is regarded as one of the five important camel diseases ad serious economic losses acquired by it[13].

In New Zealand an acute outbreak of septicemia in cattle usually resulting in high mortality, the main exotic differential diagnoses is HS and Anthrax. An outbreak of hemorrhagic septicemia in a naive population results in all ages of cattle and often with 100% mortality[3].

Pathophysiological of hemorrhagic septicemia: HS is caused by *P. multocida* serotype B: 2 (Asian countries) and serotype E:2 (African countries) in cattle and buffaloes[3]. A successful experiment showed the disease to be transmitted through intranasal and oral routes, producing a syndrome with clinical signs and lesions resembling a natural disease. It indicates that these may be the likely routes of infection of HS. However, a characteristic of HS disease is the rapid spread of infecting bacteria from the respiratory tract into the blood and lymph to cause fatal septicemia in less than 48 hours. The bacteria migrate through the epithelial layer into the pulmonary interstitial to pass into the bloodstream. The potential of *P. multocida* B:2 for attachment and invasion of mammalian cells may constitute a mechanism that enables the bacteria to invade the bloodstream[14].

Abubakar et al (2012) also stated that the role of the respiratory route in HS has been well established previously. However, the oral route may undertake a part in the epidemiology and pathology of HS. Inflammatory responses were observed along the gastrointestinal tract while *P. multocida* B:2 has been isolated from the small and large intestines of buffalo calves that died of HS. In addition, it was also described for the first time ultrastructural changes in the respiratory and tracts following oral exposure and compared with intratracheal route and/or respiratory route, which is believed to be the most common route of infection by *P. multocida* B:2[15].

Several components of the *P. multocida* B:2 serve as virulence factors, such as outer membrane proteins (OMP),capsule, lipopolysaccharides (LPS),putative hemolysin and fimbrial protein. The complex interaction of these virulence factors and the host immune system contribute to pathogenesis of HS. Even though the mechanism of pathogenesis of *P. multocida* infection in buffalo leading to HS is poorly understood, the disease is usually observed after reduction of animal immunity either due to immunosupression by intercurrent infection or stressful environmental condition. However, the characteristic of sudden onset leading to the rapid death of infected animals is similar to that seen in other clinical conditions known to involve endotoxic shock[16,17,18].

Essential fluctuations in weather, including the commencement of monsoon, malnutrition and apprehensiveness are the percentage of the inclining components which touch off the event of the illness in Pakistan. Clinical indications incorporate elevated body temperature, respiratory agony, nasal release, salivation, tongue bulge, absence of excitement to move, the advancement of sultry excruciating swelling and edema on throat, brisket or rarely forelegs[9].

Elshemey et al (2013) described that septicemia is the feature in all the HS illness conditions. The nurture period fluctuates from 3 to 5 days. In peracute cases, rapid demise with explicit clinical signs may be perceived. Most of the study done formerly indicated that the mechanism and pathogenesis of HS disease are obscure and still destitute. However, it still enables to understand that HS disease occurs through inhalation of *P. multocida* entering the respiratory tract system and passes into the bloodstream, which then spread to another system of infected animals[17].

Diagnosis: HS due to *P. multocida*is mainly diagnosed by the presenting clinical sign and symptom of the infected animal as well as post-mortem findinds of the deceased animal. In order to obtain a confirmatory diagnosis, the causative organism is required to be isoated and identified and with the help of several serooogical and biochemical tests *P. multocida*can be identifed in diagnostic laboratories[2].

P.multocida strains are differentiated using phenotypic methods. However these methods have major limitation and hinder their usefulness as phenotypic methods lack discriminatory power to distinguish and the fact that they do not reflect the population structure. Although it has been established that different serotypes are associated with different hosts and clinical presentations[19].

The drawback of conventional methods used in isolation and identification of *P. multocida* is that they are extensive and time-consuming. However, in recent years bacterial identification using genotypic methods have proven advantageous over the pheynotypical and conventional methods and overcoming the limitations rendered by those methods.

With the progression and improvement of various molecular detection assays, organisms can now be directly detected from clinical samples or even from a small amount of cultured bacterial cells. Amongst the nucleic acid-based assays polymerase chain reaction (PCR) has been espscially useful in bacterial identification with high level of specificity, sensitivity strain, species, genus, or type. Thus, it showed that PCR assay can be applied for rapid, sensitive and specific detection of *P. multocida*[20,21].

The application of the advanced diagnostic techniques such as electron microscope investigation, microbial and biochemical or DNA analysis of the *Pasteurella multocida* enable early detection of HS disease and has helped a great deal in the elucidation of the virulence factors of the organism and their encounter in pathogenesis, as well as help in finding new-targeted generations of antibiotics for efficient treatment of HS disease[22].

Nevertheless, quick and inexpensive diagnosis of HS disease is still needed instead of relying on current diagnostic methods that are quite costly and time-consuming due to sudden onset of HS disease in peracute cases which led to the rapid death of infected animals.

Treatment and antibiotic resistance against hemorrhagic septicemia: Various types of antibiotics have been used for the treatment of HS disease. Penicillin, amoxicillin, erythromycin, trimethoprim/sulfamethoxazole, cephalothin, tetracycline, ceftiofur, cefquinome, streptomycin, gentamicin, spectinomycin, florfenicol, sulfonamides, tilmicosin, enrofloxacin and norfloxacin were antibiotic agents that have proven their clinical efficacy on *Pasteurella multocida*[22].

Ferreira et al (2012) also stated that infections caused by *Pasteurella multocida* were usually treated with a wide range of antibiotics. Based on the antimicrobial susceptibility study carried on *P. multocida*isolates from HS, the most effective drugs found to be cephalosporins, florfenicol, tetracyclines, and fluoroquinolones. Similar result was reported from several studies besed in France, North America, and Japan. It has also been reported that the *P. multocida isolates present* high resistnace towards sulfonamides and cotrimoxazole[23].

Besides that, sixteen field isolates of *Pasteurella multocida* were tested against fifteen different antibiotics using antibiogram assay in the previous study done by Naz et al (2012). It was found that 87.5% isolates susceptible to ciprofloxacin, ofloxacin, enrofloxacin and gentamicin followed by 81.25% isolates to norfloxacin and amikacin and 75% isolates were susceptible to kanamycin. 56.25% isolates were susceptible to tetracycline and 50% isolates were susceptible to chloramphenicol, doxycycline and vancomycin respectively. 25 isolates were susceptible to erythromycin whereby sulfadiazine showed the least susceptible (12.5%). In the study, it is also found that 50% of the isolates were resistant to erythromycin and sulfadiazine[24].

Similarly, an antibiotic susceptibility test was done using amoxicillin, augmentin, cotrimoxazole, aztreonam, ofloxacin, norfloxacin, cephalexin, gentamycin and ceftiofur. In the study, it was found that *Pasteurella multocida* was resistant to augmentin and cotrimoxazole and more susceptible to amoxicillin and aztreonam and sensitive to gentamycin and ceftiofur[22].

Throughout time, antibiotics were used for treatment of hemorrhagic septicemia. However, the lengthened and haphazard use of antibiotics has resulted in resistant organism and even multidrug-resistant (MDR) forms of *Pasteurella multocida*. According to studies conducted previously, *Pasteurella multocida* was mostly resistant to sulfonamides and cotrimoxazole.

CONCLUSION

It can be concluded that HS disease endemically occurring in South and Southeast Asia, Africa and India caused by *Pasteurella multocida* serotype B (Asian countries) and E (African countries) respectively. The pathogenesis of HS disease most likely transmits through inhalation entering the respiratory tract of infected animals with several environmental factors enhancement towards it. HS is diagnosed using PCR method and eventually treated with a wide range of antibiotics. However, prolonged usage of antibiotics is ineffective, due to multidrug resistance. Therefore, attempts in vaccince development for HS disease were carried out simultaneously now and then.

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