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Histophilosis in cattle: microbiology, epidemiology and pathology

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Abstract

Histophilosis is a group of diseases suffered by domestic and wild ruminants, produced by *Histophilus somni* (formerly *Haemophilus somnus*), a gram-negative bacterium considered an opportunistic pathogenic microorganism that lives in the mucous membranes of ruminants. It mainly affects the respiratory and reproductive tract, as well as the central nervous system; it is also associated with various generalized disorders such as myocarditis, polyarthritis, conjunctivitis, choroiditis, mastitis, epididymitis, otitis, and septicemia. The aim of this review is to provide updated information on this group of diseases affecting cattle, covering the characteristics of the etiological agent, its main virulence factors, epidemiological aspects, and the pathogenesis of the infection. Additionally, the distribution of the disease worldwide, its diagnosis, prevention, and control are included.

Keywords: Histophilosis; *Histophilus somni*; Cattle; Pneumonia; Infertility.

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Study contribution

An updated review of the literature related to histophilosis in cattle is presented so that veterinary doctors and researchers interested in the subject have information that allows them to update their knowledge in the prevention, control, diagnosis, and research of this disease. Microbiological, epidemiological, and pathological aspects are included.

Introduction

Currently, the different diseases caused by this microorganism have been grouped under the name of syndrome or disease complex caused by *Histophilus somni* (*H. somni*), or as histophilosis, because they appear in the form of clinical syndromes associated with the respiratory and reproductive tracts, in addition to occurring in septicemic and miscellaneous forms.

Angen et al.[1, 2] proposed the name *Histophilus somni* after identifying, from isolates obtained from different parts of the world, that *Haemophilus somnus*, *Histophilus ovis* and *Haemophilus agni* were the same microorganism by performing deoxyribonucleic acid (DNA) hybridization, 16S rRNA and rpoB gene sequencing, as well as polymerase chain reaction (PCR) studies.

Cases of histophilosis have been reported in cattle, sheep, goats, American bison, wild sheep[3] and yaks.[4]

Bacterial characteristics

H. somni, belonging to the family *Pasteurellaceae*, is a gram-negative, small, highly pleomorphic cocobacillus. It is a microorganism that presents difficulties for its growth since it requires enriched medium such as Columbia agar, nutrient agar, blood agar base, or brain heart infusion agar, supplemented with 10 % defibrinated sheep or bovine blood and a partial atmosphere of 5 to 10 % CO_2, incubation at 37°C for 24–48 h.[5] It has been observed that adding monophosphated thiamine to the culture media favors its development.[6] The colonies of *H. somni* reach a diameter of approximately 1–2 mm in 48 h, they are round and convex with a butter consistency and a slight yellowish-grey color, sometimes they usually present a weak hemolytic activity. The bacterium has no capsule, is immobile, does not have pili or flagella and does not produce spores.[5]

The isolates of *H. somni* are heterogeneous when considering their morphology, biochemical reactions, and antigenic expression.[7] The above is explained by sequencing and finding differences between the genomes of commensal and pathogenic strains, which leads to difficulties in identifying this microorganism by conventional methods.[8] The situation has been resolved with the establishment and use of molecular tools such as species-specific PCR,[2] the use of restriction enzymes[8] and, more recently, by nanotechnology, where fiber optic biosensors with hybrid DNA that recognized with high specificity and sensitivity to the DNA of *H. somni* in bacterial cultures and clinical samples were tested.[9]

Virulence factors

The virulence factors of *H. somni* are complex and are not yet fully identified, so studies continue in this regard. A very important advance is the complete sequencing of its genome, which facilitated the identification of chromosomal regions resembling islands of pathogenicity, which appear to be classic elements of horizontal transfer.[10]

One of the ways that the bacterium can protect itself against host defense mechanisms, in addition to promoting the colonization of several anatomical sites, is through the phase variation of the components of lipooligosaccharide (LOS), the most studied virulence factor. This variation is the result of a modification in the structure of the oligosaccharide due to translational changes. Studies suggest that the phase variation of this could alter the host's response to infection by *H. somni*.[11]

Another virulence factor is the sialylation of LOS, an important factor for evading the humoral immune response, which consists of the binding of sialic acid (N-acetyl neuraminic acid) to a galactose terminal, catalyzed by one or more sialitransferases. Sialylation can be used as camouflage; therefore, the bacterium escapes immunodetection because sialic acid is not immunogenic, as it is part of or a normal component of host tissues.[12]

Thrombosis is another important factor that occurs in cases of septicemia leading to the development of thrombotic meningoencephalitis (TME), where disseminated vascular coagulation is observed, suggesting that it is produced by local alterations of the endothelium, which contributes to the formation of thrombi in the brain.[13]

The ability of *H. somni* to synthesize an exopolysaccharide (EPS), which it uses to form part of a complex matrix called biofilm, composed of bacterial cells, host cells, nucleic acids, nutrients, water, enzymes, and proteins, allows it to face and avoid host defense mechanisms and is essential for the binding of microcolonies by adhering strongly to surfaces where they are provided with a constant source of nutrients, in addition to being protected from the aggression of chemical substances such as antibiotics. Therefore, this biofilm is associated with the production of chronic and persistent diseases.[14–16]

The surface of *H. somni* is the first site of interaction with the host. This surface is composed of substances that are considered virulence factors, such as LOS, EPS, in addition to a fibrillar network of a protein nature and the outer membrane proteins within which the main outer membrane proteins are found. This variety of proteins that are involved in virulence and inducing protective immunity allow *H. somni* to evade the immune response, phagocytosis, and complement-mediated inactivation. It has been suggested that these could also act in combination with non-specific binding antibodies, thereby blocking the adhesion of specific antibodies to *H. somni*.[17] Protective antibodies directed against the 40 kDa outer membrane protein antigen have been reported, suggesting that this may be a virulence factor.[18] .

Pathogenesis

The ability of pathogenic bacteria to colonize, infect, and cause clinical manifestations of disease depends on the host cells' response to the bacteria. The variety of clinical syndromes caused by *H. somni* is indicative of the ability of this

opportunistic pathogen to interact with a wide variety of cellular tissues and evade local and systemic immune response. Probably, the ability of *H. somni* to survive inside phagocytic cells contributes in part to lasting infections, in addition to using leukocytes to transport themselves through the bloodstream to distant tissues to establish new foci of infection.[13]

The ability of *H. somni* to cause disease in the upper respiratory tract requires a tropism and adherence towards its epithelial cells, and from this site, it can reach the lower respiratory tract, where it participates together with *Pasteurella multocida* and *Mannheimia haemolytica* in bovine respiratory disease (BRD). If *H. somni* spreads through the bloodstream, it frequently results in thrombus formation.[13, 19]

The primary pathological process is vasculitis, accompanied or preceded by thrombosis and septic infarction. Once *H. somni* is located in one or more organs, it causes the separation of endothelial cells from small blood vessels and the consequent exposure of the basement membrane. This activates the coagulation mechanisms that lead to the formation of thrombi, as seen in the occurrence of TME. Histologically, the lesions consist of inflammation and infarction and are concentrated in the capillaries and venules. The immediate subsequent reaction involves the surrounding tissue, followed by thrombosis of larger vessels with ischemia and infarction. The inflammatory reaction is acute, and the cellular response is almost always neutrophilic. The clinical manifestation of infection by this bacterium appears to be due to the inflammatory response of the host, resulting in vasculitis and the death of endothelial cells.[13, 20, 21]

Epidemiology

It has been mentioned that the habitat of *H. somni* is the mucous membranes of ruminants, showing greater affinity in that of the reproductive tract, from where it is frequently isolated. It is concluded that the mode of dissemination is mainly by inhalation of aerosols produced by urine, ingestion of body fluids or venereally transmitted.[5, 21] This microorganism can remain viable in nasal mucus and blood for up to 70 days at 23.5 °C, in cervical mucus for 5 days, and in urine for no longer than 2 h.[20, 21]

Initially, histophilosis occurred in cattle in the form of TME in feedlots and was considered important; it is now known that it can also affect confined dairy cattle and grazing cattle.[5] Regarding the time of occurrence of TME, there is controversy because some studies report a higher prevalence in the winter months, while others report it in humid and temperate times, which is when more cases occur.[20] TME is related to the recent transport of cattle, as it has been observed that it occurs approximately 4 weeks after arrival in the feedlots.[21] The simultaneous occurrence of TME in newly transported calves and in animals that have remained in the farm indicates that other factors, in addition to transport, would be involved, so it is considered multifactorial.

In some regions of North America, cases related to respiratory syndrome have been reported to be more common in the spring, particularly in calves born in the prairies. Animals can be affected between 4 and 24 months of age, but most cases occur in animals aged 7 to 9 months.[3] The prevalence of *H. somni* as a disease producer is more frequent in intensive production units due to the stress conditions

to which livestock are subjected by handling and transport practices or to infections with primary agents such as viruses or mycoplasmas.[5, 20, 21]

Clinical cases have been reported in cattle produced by *H. somni* in different countries around the world, such as United States of America, Canada, South Africa, Switzerland, Germany, Denmark, New Zealand,[3] Turkey,[19] Italy,[22] Venezuela, Argentina, Uruguay,[23] the United Kingdom,[24] Brazil,[23, 25] Iran,[26] Australia,[27] Mexico[28, 29] and Russia,[30] among others.

Clinical manifestations

Central nervous system (CNS) condition

TME mainly affects calves from 6 to 10 months of age that arrived in the feedlot two or three weeks before and does not usually behave as a contagious disease because, when there is an outbreak, individual cases occur sporadically in pens.[21] The clinical signs are depression, fever, blindness, convulsions, lameness with stiff gait, ataxia, paresis, otitis, coma, and sudden death.[20] The classic lesion is a multifocal hemorrhage with necrosis in the brain that can range from moderate to severe. Reddish-brown infarcts of 1—30 mm in diameter are observed in the brain.[20, 21] Initially, the CNS condition was considered the main problem caused by *H. somni*, however, a constant decrease in this disease was detected in subsequent reports; instead, other pathologies associated with the respiratory and reproductive tracts were present and increased, in addition to occurring in septicemic form and other miscellaneous forms.[3]

Bovine respiratory disease

Respiratory tract infections in cattle are multi-etiological, involving at the same time *H. somni*, *M. haemolytica*, and *P. multocida*, in addition to viral agents. *H. somni* has gained importance because it is considered to be the route of entry to produce septicemia. In the upper respiratory tract, it can cause tracheitis and laryngitis; in the lower respiratory tract, it can cause suppurative bronchopneumonia, and fibrinous pleuritis, as well as significantly participating in the classic syndrome known as shipping fever. Signs of bovine respiratory disease (BRD) are fever, tachypnea, cough, runny nose, tearing, depression, loss of appetite, depression, and death. A predisposition for cattle to become ill with pulmonary histophilosis are infections with some viruses, such as infectious bovine rhinotracheitis, bovine respiratory syncytial virus, parainfluenza type 3, bovine viral diarrhea, and bovine coronavirus.[3, 31, 32]

The lesions in lung tissue that can be observed are not necessarily characteristic of histophilosis, since the appearance of BRD involves the parallel participation of *M. haemolytica* and *P. multocida*, so a fibrinosupurative bronchopneumonia can be observed with bilateral lobular lesions in the cranioventral lobes.[21] Areas of gray-red consolidation are observed, and there may be the presence of exudate in the air passages.[3] The occurrence of severe fibrinous pleuritis between 30 and 90 days after the arrival of the cattle to the feedlots is the most common manifestation of histophilosis in western Canada.[33]

The economic impact of histophilosis and subclinical BRD has not been evaluated, but some authors consider it to be the most frequent and costly disease affecting the livestock industry in the United States of America.[34, 35]

Reproductive tract disease

Regarding the reproductive tract, this is considered the ecological niche or reservoir of *H. somni*, which has been isolated from clinically healthy bulls and steers from the foreskin by 71 %; from the semen, bladder, testicles, and accessory sexual glands by 19 %; and from the ampulla by 10 %.[36] Calves of infected cows are born weak and die in a short time or do not develop properly.[37] It has also been observed that 2-month-old calves can develop suppurative epididymitis.[38] Cows have been reported to have cases of vaginitis, cervicitis, endometritis, infertility, and abortion,[5, 22, 28] so genital infection is considered to result in infertility, increased open days, and repetition of services for achieving gestation.[39]

Septicemic and miscellaneous form

When *H. somni* penetrates the circulatory system, it is distributed in several areas and organs of the body and can thus be found simultaneously in more than one place. This microorganism has been found in the brain, heart, skeletal muscle, joints, larynx, liver, and kidneys. Another manifestation of the septicemic form that is frequently observed is myocarditis, which causes acute heart failure and sudden death. Within the so-called miscellaneous forms, cases of otitis, mastitis, conjunctivitis, and polyarthritis have been reported.[3, 5, 40]

Diagnosis

Due to the different clinical presentations of histophilosis, it is difficult to make the diagnosis by clinical examination, so it is necessary to use the laboratory. Depending on the clinical manifestation, the samples can be from lung, heart, brain, cerebrospinal fluid, or any tissue with macroscopic lesions.[3] Initially, the main objective in the diagnosis was to isolate *H. somni* from affected tissues to subsequently confirm its identification by conventional means or using endpoint PCR, a process that on average takes approximately 2 weeks.[2, 5] At present, the livestock industry requires a rapid and accurate differential diagnosis, so techniques have been developed that allow it to be carried out from clinical samples such as semen or lung tissue, and even tests that include the simultaneous detection of pathogens from both the respiratory and digestive tracts are being evaluated.[41–43]

It is important to note that to respond to current diagnostic demands, new methodologies emerge and are evaluated every day. As an example of these, where nanotechnology is used, they tested fiber optic biosensors with hybridized DNA that recognizes with high specificity and sensitivity the DNA of *H. somni*, present in bacterial cultures and clinical samples.[9] Another example is the evaluation of two quantitative PCRs (qPCR) to detect and quantify bacterial and viral pathogens involved in the occurrence of BRD, resulting in rapid, specific, and sensitive assays for the detection of *H. somni*, *M. haemolytica*, *P. multocida*, and *Mycoplasma bovis*.[42]

The amplification of polymerase recombinase is a method similar to PCR, which detects the genetic material of the microorganisms participating in BRD, with the advantage that being isothermal does not require the use of sophisticated laboratory equipment. The technique is performed at a temperature of 37 to 42 °C, and the results are obtained within 3 to 10 minutes.[43]

Another molecular tool is isothermal amplification with loop or hoop formation, which can qualitatively or quantitatively identify the DNA of infectious agents; this technique was tested for the detection of *H. somni*, *M. haemolytica*, and *P. multocida* in nasal exudate samples from cattle, giving 99 % sensitivity and 89 % specificity.[44] This same modified technique, as a colorimetric assay, was tested and performed in a feedlot where nasal exudates from steers were studied, giving results that are between 60 and100 % consistent with PCR assays performed in the laboratory with the same samples. At this point, the authors, PascualGarrigos et al., propose in the future to carry out more tests on the farm to quantify the pathogens in the clinical samples and to be able to differentiate healthy from sick animals.[45]

Prevention and control

There are predisposing factors in the different clinical presentations of histophilosis, so a comprehensive prevention program must be established to avoid the stress conditions that make cattle more susceptible to this disease. Therefore, it is important to review and, where appropriate, correct aspects such as facilities, handling programs, nutrition and health. A common handling practice in feedlots is to perform metaphylaxis upon arrival of animals as a measure of prevention of an outbreak of BRD. For example, in the United States of America, 92.6 % of feedlots were found to use mass antibiotic treatment to prevent BRD in calves.[34]

The impact of the above is the appearance of antimicrobial resistance, as demonstrated by a study carried out over three years with isolates of *H. somni*, *M. haemolytica* and *P. multocida*, where a tendency towards resistance was observed, being greater in *M. haemolytica*; when comparing the isolates of *H. somni*, it was observed that those from treated animals showed greater resistance.[46] Other studies on the subject show similar results; for example, in Canada, isolates of *H. somni*, *M. haemolytica*, and *P. multocida* obtained from cattle in feedlots with conventional handling and cattle from pens where they are raised without antibiotics were evaluated and compared, finding a greater presence of macrolide resistance genes in isolates obtained from conventionally raised animals.[47] In Russia, when studying 18 isolates of *H. somni*, they found resistance to streptomycin in 50 %: neomycin, in 40 %, and sulfonamides in 33 %.[48]

Within health programs, vaccination is another way to prevent histophilosis, using biologicals formulated with the bacteria that participate in BRD, finding variable results of protection, so Capik et al.[49] performed a systematic review of what has been published on the subject and concluded that further research in biologicals is needed in the future to prevent BRD.

Conclusion

This review provides an overview of the complexity of histophilosis, its multiple clinical presentations, as well as the different factors and etiological agents that, together with *H. somni*, participate in producing this condition. This complexity can have a negative impact on several aspects, such as the presumptive clinical misdiagnosis made on farms, and, therefore, when diagnostic support is required

by the laboratory, specific analyses for this disease are not requested. Although it is true that practices are carried out to prevent and control diseases such as bovine respiratory disease or reproductive tract diseases in which *H. somni* actively participates, in each of the farms there is no exact knowledge of the participation of this microorganism.

What has been observed in Mexico over several years is that in most diagnostic laboratories there is no information on the subject nor established protocols to isolate and identify *H. somni*, and, for example, in the case of BRD, the diagnosis focuses mainly on determining the participation of *M. haemolytica* and *P. multocida*. Therefore, it is considered necessary that this type of information be disseminated in order to determine the future significance of this disease and its possible effect on the production of the cattle industry.

Data availability

All relevant data are included in the document.

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Conflicts of interest

The authors declare that there is no conflict of interest related to this manuscript.

Author contributions

Conceptualization: F Aguilar.
Writing-original draft: F Aguilar.
Writing-review and editing: JF Trigo, F Suárez.

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