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Infection of Reproductive System of Buffaloes and Cattle with *Pasteurella Multocida*: A Review of Pathophysiological Alterations

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Abstract - Serotypes B: 2 and E: 2 of Haemorrhagic septicaemia found in Asia and Africa cause an economically important disease that affects cattle and buffaloes. The disease has a feature of short clinical course and high morbidity and mortality rates. However, animals surviving HS are usually characterized by decrease productivity. There is paucity of knowledge in the involvement of the reproductive system and its organizer hormones in animals afflicted with HS. Therefore, this review aimed to gather information and provide more details on reproductive pathophysiology and its modifications in buffaloes and cattle as a result of *P. multocida* B: 2 infections**.**

Keywords: Buffaloes, cattle, cytokines, haemorrhagic septicemia, *Pasteurella multocida*, reproductive hormones

Introduction

Pasteurella multocida a Gram-negative heterogeneous species of bacteria is a normal flora of the upper respiratory tract of various species of animals (De Alwis, 1992; Jesse et al., 2013d). *Pasteurella multocida* is composed of 5 capsular serogroups (A, B, D, E and F) and there is a connection between the capsular serogroup and disease predilection (Confer, 1993; Boyce and Adler, 2001). Haemorrhagic septicaemia (HS) an acute fatal disease mainly affecting buffaloes and cattle is caused by two specific serotypes E:2 and B:2 of *P. multocida* in Asia and Africa respectively (De Alwis, 1992; Zamri-Saad, Effendy, Israf, Azmi, 1999; De Alwis, 1999).The disease is of economic importance especially in Asia where majority of buffaloes are reared.The disease is less important in Africa where there are relatively fewer cattle than-buffaloes (De Alwis, 1999). The economic losses to HS not only or merely be inclined to the market value of the animal at the time of death, but also to the productive potential of the animal which include its capacity to reproduce and its draught power

have to be taken into account especially in animals that survived HS (De Alwis, 1992; De Alwis, 1999; Jesse, Adamu, Abdinasir, Zakaria, & Abdullah, 2013a). Although buffaloes and cattle are the most affected animals species, buffaloes are regarded as more susceptible to HS than cattle and they show more immense clinical signs of the disease (De Alwis, 1999; Shivachandra, Viswas, & Kumar, 2011; Jesse et al., 2013b). Predisposing factors played a vital role in the epidemiology of HS particularly in wet and humid weather conditions, and the animals that survive an outbreak of the disease become latent carriers (De Alwis, 1999; Boyce, Seemann, Adler, & Harper, 2012). Recent studies on buffaloes that survived HS, reported involvement of *P. multocida* B:2 in various parts of urinary and gastrointestinal tracts as new colonizing sites suggesting their ability to invade other sites rather than the respiratory tract(Abubakar and Zamri Saad, 2011; Jesse et al., 2013b; Annas, Zamri-Saad, Abubakar, Jesse, & Zunita, 2014a) .Other studies also confirmed the involvement of the nervous system in an outbreak of HS in which meningitis was the most obvious pathological changes observed (Lane, Kock, Hill, & Mohan, 1992; Marza et al., 2015). In HS experimental infection, acute encephalitis was the main finding in buffaloes (Abubakar and Zamri Saad, 2011) and mice (Khaleel et al., 2014). Furthermore, *P. multocida* has been reported as one of the potential uterine pathogens (Williams et al., 2005; Williams et al., 2007). Consequently, animals that survived HS might have direct effect on the reproductive system due to the infection ,or indirect effect due to the involvement of hypothalamus and pituitary gland which in turn will lead to the imbalance of the reproductive system regulatory hormones.Therefore, this review is aimed at highlighting the involvement of the reproductive system of buffaloes and cattle due to *Pasteurella multocida* type B:2 infection and draw attention on the implications of the pituitary gland regulating hormones in the pathophysiological changes of the disease.

Bacterial detection

Infections of the reproductive organs of buffaloes and cattle can cause irritation, injuries of the endometrium, which result in uterine bacterial infections in addition to disruption of the ovarian function (Foldi et al., 2006; Azawi, Omran, & Hadad, 2008). Moreover, uterine bacterial infection suppresses luteinizing hormone secretion and leads to the disruption of ovulation and finally causes reduction in fertility and the efficiency of the reproductive system of the affected animals (Usmani, Ahmad, Shafiq, & Mirza, 2001; Azawi, Omran, & Hadad, 2007; Williams et al., 2007; Azawi et al., 2008: Pampori and Pandita, 2013). Uterine bacterial infection in buffaloes and cattle can be divided into three main categories; recognized uterine pathogens involved with uterine endometrial lesions e.g. *Arcanobacterium pyogenes, Prevotella melaninogenica and Escherichia coli*; possibility pathogens were exteriorized from the bovine uterine lumen in cases of endometritis but not usually associated with uterine lesions e.g. *Staphylococcus aureus,Enterococcus faecalis, Pasteurella multocida and Mannhiemia haemolytica*, and; opportunist contaminants transitorily isolated from the uterine lumen but not commonly involved in endometritis e.g. *Clostridium perfringens, Klebsiella pneumonia* and, coagulase negative *Staphylococcus* spp.(Williams et al., 2005' Williams et al., 2007; Razis, Ismail, Hambali, Ali, & Lila, 2006; Abdull Razis et al,.2008).However, the chance of specific bacterial species to induce uterine bacterial infection increased under stressful conditions which make the animal immunosuppressed and more susceptible to genital infections and finally result in reproductive failure (Shallali, Hussein, Salih, & Dafalla, 2001; Sheldon, Lewis, LeBlanc, & Gilbert, 2006:Sheldon et al., 2009; Ismail, Allaudin, & Lila, 2012). In natural infection and pathogenesis studies of *P. multocida*, the organs of respiratory and gastrointestinal tracts are frequently selected for bacterial isolation, while reproductive organs are infrequently selected (Graydon, Patten, & Hamid, 1992:Odugbo et al., 2005). Recent studies have shown the involvement of the urinary tract as a new location of *P. multocida* type B: 2in which the bacteria were successfully isolated in buffaloes and cattle that survived–experimental HS, suggesting the inability to translocate to other sites (Annas,

Zamri-Saad, Abubakar, Jesse, & Zunita, 2014a and Annas et al., 2014b). On the other hand, few studies recorded the infection of the reproductive system by *P. multocida*(Shallali et al., 2001; Williams et al., 2005; Williams et al., 2007; Abdullah et al., 2014a) and this may be due to the rapid multiplication of invaders at tropical temperatures and may induce the overgrowth of Pasteurella in material stored at room temperature (De Alwis, 1992 and De Alwis, 1999). However, recent studies by Jesse et al. 2013c and Jesse et al. 2014 recorded that the involvement of pituitary gland and reproductive organs in the disease pathogenesis after oral inoculation of *P. multocida* type B:2 in mice showed significant differences in histopathological lesions of the pituitary gland, testes and the ovaries, which in turn resulted in alterations in the levels of female and male reproductive hormones especially testosterone, progesterone and estrogen. These findings showed the importance of the reproductive system of buffaloes and cattle as most susceptible, in the disease course of HS, and whether the functions of the pituitary gland are significantly affected. These changes lead to the disturbance in the function of the reproductive organs and also the alterations in the reproductive hormone levels, and finally reduce the reproduction of affected animals. These complexities need further exploration.

Reproductive hormones

Reproduction is a complex process that requires many factors to be achieved. The interaction of hypothalamus releasing hormones and pituitary tropic hormones are fundamental for the production of gonadal hormones; testosterone, progesterone and estrogen to maintain the cyclicity of animal's reproduction(Sheldon et al., 2008; Perera, 2011). Buffaloes and cattle are generally susceptible to uterine infections when progesterone level is high while they are resistant when the progesterone level is basal (Foldi et al., 2006; Sheldon et al.,2008; Azawi, 2013). Furthermore, any internal or external interruption of such precise process can lead to low fertility or sterility and ensue in failure of reproduction (Perera, 2011; Khuder et al., 2012). Buffaloes and cattle, however, can survive under unpleasant environmental conditions and poor forage. Thus, reproductive efficiency is often compromised by such conditions, resulting in many reproductive problems such as late sexual maturity, prolong postpartum anoestrus, poor oestrus expression, poor conception rates and long calving intervals(Azawi et al., 2008; Perera, 2011; Azawi, 2013).

Different bacterial species have been reported to affect the reproductive organs which finally resulted in major impact with colossal economic losses to buffalo and cattle breeders (Usmani et al., 2001; Jadon, Dhaliwal, & Jand, 2005; Foldi et al., 2006; Azawi et al., 2007; El-Wishy, 2007). Pampori and Pandita (2013) reported that the intravenous inoculation of lipopolysaccharides (LPS) of *E. coli* 055:B5 in cyclic female Murrah buffaloes affects estrogen and progesterone levels and also resulted in neutrophilia, suggesting that the buffaloes were under stress due to the LPS challenge. Furthermore, LPS of *E. coli* 055.B5 was found to suppress ovarian cell function and hormone production (Williams et al., 2008). However, little is known about the effect of *P. multocida* B: 2 or its LPS on the reproductive organs and gonadal hormones production. Williams et al. (2007) reported that *P. multocida* is one of the potential uterine pathogens isolated from cattle at day 7 of postpartum; infected uterus have perturbed ovarian follicular growth and function. In ovulating animals, the corpus luteum is small and produced less progesterone. A recent study conducted by Jesse et al. (2014) to assess the histopathological changes in the pituitary glands, reproductive organs and associated hormonal concentrations in mice inoculated orally with *P. multocida* typeB:2 and its LPS, reported significant differences in the levels of testosterone in males and progesterone and oestrogen in female mice inoculated orally with *P. multocida* type B:2. The tissue damages observed in testes and ovaries may contribute to the low hormone levels, which could perchance affect the cells producing the hormones or the hypo-pituitogonadal axis must have been interrupted. Similar findings were obtained

by Khuder et al., 2012, when evaluating sex hormone profiles and histopathological changes of reproductive organs of mouse inoculated with *Corynebacterium pseudotuberculosis* and its exotoxin phospholipase D (PLD) . According to the study, the PLD was responsible for damaging the tissues of testis and ovaries and resulted in low sex hormone concentration, especially the testosterone and to a lesser extent the progesterone.

The imbalance of sex hormones could affect the immune status of the animals (Ahmed, Nada, & Shalaby, 1993; Azawi et al., 2008). During the last two decades, sex hormones have become recognized as integral signaling modulators of the mammalian immune system (Pampori and Pandita, 2013). Bouman et al., (2005), reported that sex hormones have direct effect on the levels of immune mediators like tumor necrosis factor-alpha (TNF-α), xanthine oxidase or nitric oxide between the stages of the reproductive cycle. Another study by Cutolo and Wilder (2000) suggested through immunological proofthat female sex hormones play a role in the etiology and course of chronic inflammatory diseases. Sartin et al., (2003) have shown that progesterone and estrogen implants favorably modify the time path or disease severity of the numerous clinical manifestations related with coccidiosis and endotoxemia in calves.It is clear that the bacterial endotoxins and exotoxins have a direct effect on the reproductive organs and related hormones, which is obviously seen on the immune status of the affected animals. However, the exact mechanisms that enable these effects are poorly understood.

Cytokines

Cytokines, a bioactive protein, is produced by various cells of the immune system and plays a role in different inflammatory disease states and maintains homeostasis (Praveena, Periasamy, Kumar, & Singh, 2010; Stenken and Poschenrieder, 2015). Cytokines are released by macrophages but also by other cells or tissues in response to different external or internal stimuli like Kupffer cells, keratinocytes, and mucosal epithelium (Yoshioka et al., 1998; Murata, Shimada, & Yoshioka, 2004). Cytokines can be divided into two major groups with respect to APPs induction, namely IL-1 type cytokines; these include, interleukin-1-beta (IL-1-β) and tumor necrosis factor-alpha (TNF-α). Interleukin-6 (IL-6) type cytokines, include IL-6 (Nakagawa-Tosa et al., 1995; Yoshioka et al., 1998; Petersen, Nielsen, & Heegaard, 2004; Ceciliani, Ceron, Eckersall, & Sauerwein, 2012; Abdullah et al., 2013). Praveena et al. (2010), found a surge in pro-inflammatory cytokines (IL-1β, and TNF-α) in response to inoculation of *P. multocida* serotype A1 in mice. These results were consistent with the findings of a recent study by Ali et al.,(2014), where significant alteration in IL-1-β and IL-6 are found in mice inoculated through the oral route with graded doses of *P. multocida* type B:2 and its LPS. On the other hand, IL-6 was found to have direct influence on female sex hormones suggesting a potential role for this cytokine in the autocrine and/or paracrine regulation of ovarian function (Gorospe, Hughes Jr, & Spangelo, 1992).However, little is known about the relationship between proinflammatory cytokines involvement in the physiology of the reproductive hormones in buffaloes due to *P. multocida* B: 2 infections. Further research is needed to uncover the gray areas for better understanding of the reproductive pathophysiology of buffaloes affected with HS diseases.

Histopathology

In animals affected by HS, many factors affect the type and severity of the histopathological lesions such as strain type, type of inoculum, dose and route of inoculation, animals species and the immune status of the animal (Horadagoda et al., 2001; Abubakar and Zamri Saad, 2011; Jesse et al., 2013d; Abdullah et al., 2014a).Accordingly, different types of histopathological changes have been recorded mainly including inflammatory cell infiltration, degeneration and necrosis, and haemorrhage, while the presence of oedema and Kupffer cells were found in the lungs and liver, respectively (Abubakar

and Zamri Saad, 2011; Jesse et al., 2013a; Jesse et al., 2013b; Jesse et al., 2013d; Annas et al., 2014b; Chung et al.,2015b).Furthermore, lungs, heart liver, kidneys are usually selected as the most suitable organs to study pathological changes due to HS (Graydon et al., 1992; Odugbo, Turaki, Itodo, Okwori, & Yakubu, 2005). On the other hand, reproductive organs such as the uterus and ovaries are seldom selected for routine pathological examination in such studies (Abubakar et al., 2013; Abdullah et al., 2014a). To date, there is paucity of information concerning the cellular changes in the reproductive organs of buffalo due to *P. multocida* B: 2 infection. To the very best of our knowledge, Jesse et al. (2014) reported the effect of *P. multocida B:2* and its LPS on the male and female reproductive organs and related hormones in mice. The most evident cellular changes found in this study were degeneration and necrosis, oedema and haemorrhage, in the testes, ovaries and the pituitary glands, suggesting that *P. multocida* B: 2 has affinity towards the hormone producing cells in pituitary glands and also the cells in the ovaries and testes which may affect the infiltration of inflammatory cells into the respective organs. The most important question is related to the pathogenicity of *P. multocida* to induce irreversible gross changes in the reproductive organs which might have a direct proportional effect on the reproductive ability of the animals that survived HS disease, especially the carrier ones.

Conclusion

Haemorrhagic septicaemia is a distinct bacterial disease entity which is well established and has economic importance especially in Asia. The pathophysiology of the disease regarding the reproductive system and related regulatory hormones in buffaloes and cattle still needs further research for better understanding of such important disease.

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