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A Review on the Potential Effects of Combination Treatments of Anti-microbial and Anti-inflammatory Drugs Towards Male Reproductive Physiology in Pneumonic Bucks

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ABSTRACT

Pneumonia is the inflammation of lung parenchyma due to various organisms resulting in numerous manifestations and sequelae. The environment in the tropical regions provides optimal conditions for infection to occur in small ruminants. Mannheimiosis caused by *Mannheimia haemolytica* is the most frequent isolated bacteria causing pneumonia in small ruminants. The bacteria may cause an acute infection which can lead to death without proper diagnosis and treatment. To date, there are still scarce study on the effect of anti-microbial and anti-inflammatory treatments on reproductive physiology that warrants investigation. Hence, this review paper aims to focus on the possible effect of a combined usage of anti-microbial and anti-inflammatory treatments toward male reproductive physiology.

Key words: Antibacterial, Anti-Inflammatory, Mannheimiosis, *Mannheimia Haemolytica*, Reproductive.

INTRODUCTION

Respiratory diseases are disorders involving the respiratory system as a result of pathological alterations which occur either at lower or upper respiratory tracts (Lacasta et al. 2008). Pneumonia is a condition related to the lower respiratory tract, primarily the lungs. The inflammatory response of the bronchioles and alveoli occurs when there is an infection, resulting in lung tissue consolidation (El-Deeb and Tharwat 2015). Incidence and clinical cases of pneumonia in small ruminants exist worldwide, especially in goats and sheep and this disease has a disastrous economic impact on the small ruminant livestock industries (Oremeyi et al. 2013). The occurrence of pneumonia in small ruminants ranges from 10 to 40%, while the mortality rate is more than 20% and young animals are particularly at high risk (Ramírez et al. 2017).

Among the common diseases leading to pneumonia includes Peste es Petits Ruminants, Parainfluenza (PI-3), Pasteurellosis, Ovine Progressive Pneumonia, Mycoplasmosis, Caprine Arthritis Encephalitis virus, Caseous Lymphadenitis, among other pneumonic diseases where lesions are mostly situated at the lung parenchyma in the alveoli and bronchioles (Pavia 2011; Kumar et al. 2013; Khan et al. 2018; Khaliq et al. 2020).

Disease involving bacteria is one of the most concerned. This is due to their various clinical manifestations, complexity, and the re-emergence of resistant bacterial strains towards anti-microbial drugs (Woldemeskel 2012). Bacterial diseases are economically important that has a major impact on small ruminant industries (Dohare et al. 2013). One study in Ethiopia revealed that 17.14% of sheep and 17.11% of the goats developed pneumonic lesions upon carcass inspection in abattoir, suggesting that this condition is one of the causes of organ condemnation (Mekibib et al. 2019). Among all respiratory pathogens, *Mannheimia* spp. and *Pasteurella* spp. are the most common causative agents contributing

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to the high prevalence of pneumonia cases in small ruminants (Chung et al. 2015). Both organisms are commensal in the upper respiratory tract and are spread to the susceptible animals through airborne, followed by the transmission to the lower respiratory tract (Nair and Niederman 2011).

In other countries, the common types of pneumonia reported are bronchopneumonia (Mishra et al. 2018) and followed by interstitial pneumonia (Emikpe et al. 2013; Mekibib et al. 2019). The infection is mostly from bacterial origin such as *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni,* and *Mycoplasma* spp. which often occurs when the animals are immunocompromised under multiple stress factors (N'jai et al. 2013; Mahmood et al. 2017).

Pneumonia

Cases of pneumonia caused by *Oestrus ovis*, a fly larva that shows the clinical sign of cavitary myiasis with seromucous nasal secretions, has also been reported. The reported case shows that the animal presented with severe respiratory such as loud, harsh breathing and emaciation highly indicate pneumonia (Gunalan et al. 2011). Pneumonic mannheimiosis and helminthiasis are found to be one of the primary causes of post-arrival mortalities (Salisi et al. 2012) who reported that transportation stress which includes handling, loading or unloading of the goats lead to the death of a goat from Australia to Malaysia. Furthermore, the hot and humid climate may exacerbate the occurrence of the disease. One study showed that animal transportation under the hot and humid weather with the influence of steroid treatment provide an ideal condition for the bacterial to flourish. It was found that *M. haemolytica* and *P. multocida* was isolated from the samples (Emikpe et al. 2013). Additionally, a retrospective study by Zakaria et al. (2019) revealed that more than 80% of pneumonic cases yielded single bacterial (32.6%) and mixed bacterial isolation (67.4%) of which several bacteria such as *Pasteurella* spp. (31.4%), *Escherichia coli* (23.3%), *Kleibsella pneumonia* (12.8%) and *Mannheimia* spp. (5.8%), respectively. Thus, this portrays that under stimulation of stress factor, opportunistic commensal bacteria in the upper respiratory tract of animal lead to pulmonary infections (Fitri et al. 2017; Barac et al. 2018).

Mannheimia, a bacterium was named after Walter Mannheim, a German biologist who contributed to the knowledge of the *Pasteurellaceae* family's taxonomy (Bahr et al. 2021). *Pasteurella haemolytica* is classified into two biotypes: Arabinose (A) and Trehalose (T) based on sugar fermentation patterns determined by rapid plate agglutination test. There are 12 biogroups (extended phenotyping including sugar and glucoside fermentation patterns), and 17 serotypes related to biotype A (A1, A2, A5, A6, A7, A8, A9, A12, A13, A14, A16 and A17) categorized as *M. haemolytica* while the A11 serotype is later known as *Mannheimia glucosida* based on DNA-DNA hybridization and 16s RNA sequencing (Klima et al. 2017). *M. haemolytica* is a gram-negative, encapsulated and small (1–2µm x 0.3–0.6µm) aerobic coccobacillus bacterium, grows on blood agar and MacConkey agar (Tabatabaei and Abdollahi 2018). Most species of *Mannheimia* are opportunistic pathogens found in the respiratory tracts of ruminants and are able to infect them when their body defenses are compromised by various stress factors (Singh et al. 2020). In the early stage, animals may show signs of anorexia, pyrexia and rapid shallow breathing with mucopurulent discharges. Later, animals may exhibit a severe cough, dyspnea and an exhalation grunt (Hodgson et al. 2013).

Jesse et al. (2019) stated that goats infected with *M. haemolytica* A2 infection exhibited different severity of crackling lung sound upon auscultation according to the severity of the pneumonic infection. Additionally, acute infection of *M. haemolytica* was more severe in goats than cattle of which the infection may expected to cause mortality in animal within 24 hours or may cleared off after a few days, should the animal survived (Hanzlicek et al. 2010). Pneumonia due to *M. haemolytica* is characterized by acute cranioventral fibrinous to fibrinopurulent pleuropneumonia where extensive infiltration of neutrophils and exudation of fibrin into the pleura, alveoli, bronchi and bronchioles were observed (Taunde et al. 2019; Rawat et al. 2019).

Virulence factors of *M. haemolytica* play a vital role in the pathogenesis of mannheimiosis, which includes the capsular structure, fimbriae, endotoxin lipopolysaccharide (LPS) and exotoxic leukotoxin (LktA) which is known for bacterial adhesion, colonisation and proliferation during infection (Marru et al. 2013). Lipopolysaccharide of *M. haemolytica* is composed of a lipid A known as endotoxin, and an O antigen which is made of core oligosaccharide and polysaccharide chain (Jeyaseelan et al. 2002). The LPS may cause hormonal disorders of which LPS-induced endometrial reactions lead to acute or chronic inflammation that affects reproductive function by inhibiting the production of gonadotropin-releasing hormone (GnRH) from hypothalamus, secretion of luteinizing hormone (LH) in the pituitary gland and the reduce sensitivity of the pituitary to GnRH in small ruminants, causing infertility (Sheldon et al. 2009). As previously mentioned, both *Pasteurella* spp. and *Mannheimia* spp are genetically related to each other and both can cause pneumonic pasteurellosis in ruminants. Thus, it can be concluded that both of these virulence factors cause negative impact on the reproductive performance in both female and male animals (Jesse et al. 2020).

Lack of proper management practices such as overcrowding and poor housing conditions lead to increased susceptibility to infectious organisms causing pneumonia (Kumar et al. 2014). This leads to economic losses to the farmers due to low production value. Climatic changes also contribute to the development of a disease (Lacasta et al. 2008). The environment in the tropic regions is in optimal conditions for the infection to occur in small ruminants (Chakraborty et al. 2014).

Current researches on pneumonia in small ruminants concentrate on the prevalence of pneumonia as a pathological investigation of the condition caused by various agents (Mekibib et al. 2019). Research in establishing diagnostic tools to diagnose the severity of pneumonia in small ruminants is also important for early diagnosis which helps with the clinical management of the disease (Jesse et al. 2019). Among other growing research areas in small ruminants is using biomarkers as early disease detection. These include the evaluation of cytokines and acute phase proteins from various diseases in small ruminants that involves the investigation of interleukin-1ß, interleukin-6 (El-Deeb and Tharwat 2015), haptoglobin, and serum amyloid A over the years (Kiafar et al. 2022).

Nonetheless, most of the research in this area is largely focused on the large ruminant compared to small ruminant. Although the research field in small ruminants has becoming increasing popular these days, knowledge related to the therapeutic effects of antimicrobial and anti-inflammatory treatments in pneumonic goats towards the reproductive physiology is somehow limited. Therefore, this paper aims to review the therapeutic effects of antibiotic and anti-inflammatory treatments towards male reproductive physiology in pneumonic bucks, which may help in effective treatments administration for animal's welfare.

Negative Effects of Bacterial Infection on Male Reproductive System

M. haemolytica and *P. multocida* were shown to have deleterious effects on the reproductive organs and hormones (Abbas et al. 2019). It is believed that the bacteria and their toxin cause a considerable reduction in testosterone hormone concentration and decrease sperm quality and scrotal circumferences in bucks (Khuder 2012). Endotoxin may negatively affect the affected animal's male reproductive system (Jesse et al. 2019). Endotoxins are highly poisonous substances and impact sheep and goats' reproductive and visceral organs with rigorous degenerative alterations in testicles (Abbas et al. 2019). *Pasteurella* could reach epididymis due to bacteremia or ascending infection (García et al. 2009). Poulsen et al. (2006) hypothesized that the *Pasteurella* cluster, such as *Mannheimia, Pasteurella* and *Bibersteinia* isolated in their study, could be causes for the pathological lesions observed in the reproductive system of the rams. Bacterial infections in small ruminants can impair the animal's overall health and reproductive viability (Jesse et al. 2019).

A study by Danek (2003) showed that the administration of endotoxin of *E. coli* negatively influences the quality of stallion semen. Several spermatozoa morphological abnormalities were seen in rams (Wallgren et al. 1989) and boars (Wallgren et al. 1993) when exposed to *Salmonella typhimurium* endotoxin. Endotoxin directly cause impairment of the tail and abnormal acrosomes characterized by knobbed shaped, loose head and midpiece including the internal and external acrosomal membranes in small ruminants (Diemer et al. 2003).

García Álvarez et al. (2009) revealed that the reduction of semen quality in the affected animals as a result of stress and pyrexia caused by bacterial infection, when it spread hematogenously, including to the reproductive organs resulting in severe lesions in the testicles such as testicular atrophy, epididymitis, spermatic granulomas, and adhesions between the vaginal tunic and the scrotum of rams. Besides, a study by Marza et al. (2015) concluded that inoculating mice with *P. multocida* type B:2 and its lipopolysaccharides can affect the pituitary gland, disrupting organ functions and also cause suppression of reproductive hormone levels in animals. Similarly, Umer et al. (2020) described the findings in bucks infected with *Corynebacterium pseudotuberculosis* showed irregular shrinkage of lumen, oedema, degeneration and necrosis of spermatogonia cells within seminiferous tubules as well as sloughing, degeneration and germinal epithelium necrosis. A recent study conducted by Azhar et al. (2021) on bucks challenged with *M. haemolytica* serotype A2 and its lipopolysaccharide (LPS) endotoxin indicated that infection of *M. haemolytica* A2 and its LPS potentially disrupt normal pathophysiological responses which would alter the reproductive functions of bucks. This, in turn, leads to reproductive inefficiency in infected animals. From the literature above, it can be concluded that virulence factors released from Gram-negative bacteria can increase the level of pro-inflammatory cytokines, which then alter the concentration of reproductive hormones and induce gross pathological changes that may impair their reproductive functions. However, there are lack of studies carried out to observe the effect of the therapeutic regime on pneumonia in bucks and to observe the effect on the male reproductive physiology.

Therapeutic Regime of Anti-Microbial and Anti-Inflammatory Use in Ruminant and Pneumonic Bucks

Respiratory diseases in ruminants can be managed based on the etiology of the disease. Ideally, the effectiveness of the antibiotics of choice over the course of disease should be accompanied by prompt diagnosis as well as the prudent use of the drugs including correct dosage, route of administration and duration (Lorenz et al. 2011). Apart from antibiotics, anti-inflammatory drugs can be used to reduce the inflammation. For example, flunixin meglumine which is a non-steroidal anti-inflammatory drugs (NSAIDs) that prevents the formation of cyclooxygenase derived eicosanoid inflammatory mediators by inhibiting cyclooxygenase enzymes in the arachidonic acid cascade (Brentnall et al. 2013). Flunixin meglumine commonly used in treating acute mastitis, endotoxemia, calf pneumonia and diseases related to musculoskeletal conditions because it also had analgesic and antipyretic effects (Rantala et al. 2002; Beretta et al. 2005).

As both antibiotics and anti-inflammatory are useful to treat bacterial infection in respiratory system, combination of both class of drugs are recommended for the treatment of respiratory diseases caused by bacterial origin. Rahal et al. (2008) recommended the usage of any broad-spectrum antibiotics or oxytetracycline combined with any anti-inflammatories such as dexamethasone, flunixin meglumine, or dimethyl sulfoxide as a therapeutic plan for respiratory system disease, in which antibiotic able to stop the further infection and anti-inflammatories help animals able to swallow and breathe.

Antibacterial and anti-inflammatory are used most frequently in multiple drug prescriptions. It is documented that concurrently administered of both types of drugs may alter pharmacokinetics of one another (Patel et al. 2018). Standalone use of antibiotics is not effective to alleviate the inflammatory changes. In respiratory infections, inflammatory mediators are released due to pathogen interaction with the host cells which in response secrete pro-inflammatory cytokines such as TNF-α (Li et al. 2016; Singh et al. 2020). The use of anti-inflammatory drugs may reduce the tissue damage caused by over secretion of the chemical mediators release by the damage cells, thus aids in recovery, alongside minimizing the infection. Another study reported the combination of oxytetracycline and meloxicam which helps to resolve pneumonia in claves (Bednarek et al. 2003).

Additionally, combination of both antibiotics and anti-inflammatory as well as fluid therapy was proved as effective treatment for pneumonic pasteurellosis in small ruminants. Abdullah et al. (2014) reported the use of Norodine 24 (Trimethoprim 2.5g and sulfadiazine 12.5g) (1mL/16kg) combine with flunixin meglumine (2.2 mg/kg, intravenously) and addition fluid therapy (0.9% (v/v) sodium chloride to correct the dehydration status had successfully resolved the pneumonia in infected goat. All treatment was administered intravenously over the course of three days. In another case study by Chung et al. (2015), two Boer-crossed kids were diagnosed with pasteurellosis and were successfully treated with flunixin meglumine (2.2mg/kg) and penicillin-streptomycin (1mL/16kg) by injection via intramuscularly. This showed that combination therapy is imperative to reduce the severity of infection and inflammation, which helps to speed up the recovery process of the infected animals, without the use of antibiotic as a standalone treatment (Hirao et al. 2011; Yatoo et al. 2018).

Combination therapy was deemed to be effective in treating mannheimiosis in small ruminants and studies over the years have been only targeting on the respiratory system. However, the treatment effects on the reproductive physiology of the infected animals remains unclear. Therefore**,** we elucidated that a combination of antibiotic and anti-inflammatory certainly have a positive impact on reproductive physiology in animals infected with mannheimiosis.

Efficacy of Flunixin Meglumine and Oxytetracycline Used in Reproductive Physiology

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful medications for the modulation of prostaglandin production since they inhibit COX pathway (Bednarek et al. 2003). According to Königsson et al. (2003) findings, flunixin meglumine delivered at dosage 2.2 mg/kg has effectively inhibited Prostaglandin E_2 (PGE2) production regardless of the mode of administration, indicating that it is likely to be an appropriate dose for clinical usage in goats. Furthermore, Atef et al. (2019) in his study concluded that NSAIDs apparently have an antagonistic effect on tissue proteins binding affinity, resulting in higher concentrations of free antibiotics in the blood, consequently enhancing their metabolism and elimination.

Flunixin meglumine has a very beneficial effect on the semen characteristics altered by endotoxin caused by bacteria infection. A study by Danek (2004), found that the effects of flunixin meglumine on stallions challenged with endotoxin had improved the reproductive viability of the animal in terms of spermatozoa motility, concentration and morphological defects, respectively. This is probably due to drug ability to significantly reduced endotoxin-induced polymorphonuclears (PMNs) infiltration into the testicular interstitium and morphological alterations in Leydig cells (Danek 2004). The drug works by reduces prostaglandins concentration in the epididymis which is essential for sperm production and viability (Dacheux et al. 2016). Flunixin meglumine activity in the epididymis enables the formation of a conducive environment for sperm viability, which may improve seminal quality after drug application (Neto et al. 2017). Another study by Neto et al. (2017) stated that the post-treatment with flunixin meglumine indicated a significant improvement of seminal characteristics related to sperm motility and quantitative numbers of semen and normal sperm and minor and major defects in bucks and rams.

Another study by Aké-López et al. (2005) which targeting female reproductive hormone revealed that flunixin meglumine has been vastly used due to its modulation activity in the production of prostaglandin F2 alpha (PGF2α), which has been useful to extend the luteal phase in the estrous cycle of sheep and to assist reproductive methods, such as embryo transfer in and to improve conceive rates. Additionally, the study concluded that ram and buck treated with flunixin meglumine showed no significant alterations on scrotal circumference at the different times in either species, which demonstrates the lack of influence of the drug on this parameter during experimentation periods. However, major defects observed were significantly reduced in both species after flunixin meglumine applications. This concluded that this drug may have an effect in the final spermatogenesis phases. Despite of literature reviews mentioned above, there is still a limited information on the effect of flunixin meglumine in pneumonia treatment for small ruminants and observed changes in the male reproductive physiology. Hence, the studies on the effect of this drug after mannhaemiosis treatment (whether using combination or standalone treatment) on male reproductive physiology are warranted.

Tetracyclines are broad-spectrum bacteriostatic antibiotics group and effectively work against various Gram-positive and Gram-negative bacteria such as anaerobes, rickettsiae, chlamydiae, mycoplasmas and against some protozoa by inhibiting protein synthesis via binding to 30S ribosomal subunit of the bacteria (Kumar et al. 2012). Oxytetracycline is the second tetracycline group of antibiotics that is frequently used for gastrointestinal and respiratory system diseases (Aktas and Yarsan 2017). Presently, oxytetracycline is widely used for the treatment of bacterial infection in animals including aquaculture fish species, because of its broad spectrum of activity, low toxicity and capacity for diffusion into most body fluids and tissues (Sharma et al. 2016). In a study by Owagboriaye et al. (2018), tetracycline caused a significant decrease in testosterone levels in rats, as it capable of penetrating blood-testis barrier resulting in an alteration in the microenvironment of seminiferous tubules, thus reduce in sperm motility. Yücel et al. (2021) also found that used of oxytetracycline in Saanen bucks negatively reduced sperm concentration and serum testosterone levels. Despite frequently use as a growth promoter, oxytetracycline was reported to have detrimental effects on animal's hematological, biochemical and immunological parameters on long term administration (Kumar et al. 2012). To date, it is still not known the effects of tetracyclines (use alone or combination with anti-inflammatory drugs) for mannhaemiosis treatment on male reproductive physiology in small ruminants that warrants further investigation.

Co-administration of flunixin meglumine and the broad-spectrum antibiotic oxytetracycline was more effective in treating respiratory diseases (Doherty et al. 2001). Pharmacokinetic and pharmacodynamic interactions between antimicrobial drugs and anti-inflammatory have been studied in cattle and goats (Mestorino et al. 2007; Dutta et al. 2007; Sidhu et al. 2010). When diclofenac is administered along with streptomycin in treating tuberculosis, it was proven to be more effective as it has synergistic effect (Dutta et al. 2007). Additionally, oxytetracycline has been demonstrated to exhibit anti-inflammatory activity regardless of its antibacterial action, which may provide an additive or synergistic anti-inflammatory effects when combined with anti-inflammatory drugs (Ci et al. 2011).

Conclusion

Respiratory infections, particularly pneumonia, are major contributors to the economic losses in small ruminant industries. This review highlights Gram-negative bacteria and their virulence factors can that exert adverse effects on the male reproductive physiology, which may reduce their reproductive performance. Even though several diagnostic tools and therapy regimens have been developed to combat the problem, the issue remains due to the disease's intricacy. Further research is needed to investigate the combination treatment of anti-microbial and anti-inflammatory toward male reproductive pathophysiology in bucks infected with *M. haemolytica*, thus, it can help in developing successful treatment strategies without jeopardize the reproductive physiology and better control programs to fight against microbial infections can be achieved.

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Authors Contribution

All authors contributed equally and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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