General Session IV

Real Life Bovine Pharmacology

Dr. W. G. Huber, *Presiding*

General Session IV will offer the practitioner practical information on the physiological response of various organ systems to disease processes. This information will then be related to potential responses by these systems to therapeutic agents. The group of speakers selected for General Session IV are considered authorities in their assigned areas. General Session IV is co-sponsored by AABP and American Academy of Veterinary Pharmacology and Therapeutics.

Real Life Bovine Pharmacology Physiology and Pharmacology of the Bovine Respiratory System: Pneumonia

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Introduction

While antibiotics are and will remain the mainstay of therapy for bovine pneumonia, there are many other factors besides simple bacterial growth that contribute to the pathogenesis of bacterial colonization, proliferation, and tissue damage. In particular, the body's responses to the factors which predispose to colonization, and its subsequent responses to the bacterium and its products, play a major role in the degree of damage and the eventual outcome. Pharmacological modification of these responses may alter the severity and outcome of the disease process, either positively or negatively. A review of the pathophysiology of bovine pneumonia will reveal areas where pharmacological intervention beyond antibiotics is indicated or contraindicated.

Pathophysiology of Bovine Pneumonic Pasteurellosis

Bovine pneumonia is usually the result of a complex interaction of management, environment, and infectious agents. The classical "shipping fever equation" of stress + primary viral infection + secondary bacterial invasion has been recognized for over 30 years, and is now generally accepted as an accurate description of the cause of most outbreaks of pneumonia.[28] The typical disease is a severe, fibrinous, anterior-ventral lobular bronchopneumonia. *Pasteurella haemolytica* is the most common bacterial component of the disease.[49] The pathogenesis of pneumonic pasteurellosis will therefore be used as a model of the pathophysiology of pneumonia in cattle.

Whether or not clinical disease results from the shipping fever equation depends on an interaction of the size of the infective dose, the virulence of the organism, and the integrity of the host defenses.[14] The veracity of this equation has been demonstrated by research, particularly regarding the interactions of P. haemolytica with the PI-3 and IBR viruses.[35 58] The exact mechanisms of these interactions have not been elucidated, but further research is shedding light in this area as well.[34] The necessity for a critical dose of bacteria, with or without a predisposing viral infection, has also been demonstrated.[3 27 59]

The respiratory defense mechanisms are normally quite efficient, as the lung is usually sterile distal to the first bronchial division.[42] These defenses must be breached for clinical *Pasteurella* pneumonia to result. The respiratory defense mechanisms can be divided into physical, cellular, and secretory components.[34] The physical components are operative mainly in the upper airways. The warming and humidifying functions of the nasal passages and turbinates are important for protection of the lower airways from chilling and dehydration.[7 17] Aerodynamic filtration is accomplished by inertial impaction, sedimentation, Brownian motion, and turbulence in the airways.[34] Filtration results in the removal of larger particles. However, particles of 0.5-3.0 um aerodynamic diameter commonly make their way to the bronchiolaralveolar junction. There is a sudden

increase in the total cross-sectional area of the respiratory tree at this point, resulting in a decrease in air velocity and therefore in sedimentation of these smaller particles.[17] Particles which are filtered out in the airways are trapped in the mucus lining of these airways, and are then moved toward the pharynx by the action of the ciliated epithelium, at a rate of 10-15 mm/minute. Particles can be cleared from deep in the lung in approximately 24 hours.[17] Normal composition, hydration, and viscosity of the mucus are critical to the function of this "mucociliary elevator". Sneezing, coughing, and bronchoconstriction in response to irritants are other physical mechanisms to help clear inhaled pathogens and irritants from the respiratory tree. Finally, though not a physical defense factor *per se,* the normal flora of the upper respiratory passages also serve as a defense mechanism by providing competition to pathogens for attachment sites, nutrients, etc.[17] Some of the normal flora may enhance while others may inhibit the growth of pathogens.[14]

The cellular defense mechanisms include the pharyngeal lymphoid tissues[17] and bronchial associated lymphoid tissue (BALT)[7] in the upper airways, and the various alveolar leukocytes. The alveolar macrophage is probably the most important defensive cell comprising about 87% of the leukocytes in the normal alveolus.[34] It has two major functions, phagocytosis of trapped particles and the elaboration of numerous mediators of inflammation. Lymphocytes comprise about 10% of alveolar leukocytes, and become important in the formation of helper and suppressor T-cells, cytotoxic cells, and antibody-producing B-cells. Neutrophils make up about 2% of the alveolar leukocytes, and eosinophils less than 1%.[34]

There are a wide variety of secretory factors in both the upper and lower airways, including IgA (the main antibody class in the upper airways), IgG (the main class in the lung), interferon, lysozymes, lactoferrin,[17] alpha-1 antitrypsin, haptoglobulin, transferrin, complement components,[7] and a wide variety of monokines and lymphokines.[17 34] The relative importance of the various immunoglobulin classes, their functions, and the optimum means for their induction have been the subjects of considerable research, but are beyond the scope of this paper. Many of these secretory factors have the potential to harm the host as well as protect against pathogens.

It is obvious that the stresses and management procedures associated with weaning, shipping, and starting on feed provide ample opportunities for depression of host defenses, for viral infection, and for enhancement of the dose (and possibly even the virulence) of invading pasteurellae. Chilling, overheating, dampness, dehydration, starvation, overwhelming particulate loads (dust), noxious gases (ammonia from urine, exhaust gases, etc.), and acidosis all depress the mucociliary elevator and the function of alveolar macrophages.[17] In a recent study in a Colorado feedlot the incidence of pneumonia could be related to the concentration of 2.0-3.3 um diameter particles in the air and wide daily temperature fluctuations.[36] The mixing of populations and crowding of animals adds the possibility of exposure to large doses of previously unencountered viral and bacterial pathogens, further depressing the mucociliary mechanism and causing blockade of the alveolar macrophages. It has been proposed that alveolar macrophage blockade by viral infection is even more important than destruction of the mucociliary elevator mechanism.[34] The large numbers of viral particles released during initial replication, as well as the antigen-antibody complexes which occur after the antibody response, may block or overwhelm the alveolar macrophage function, leaving the lung susceptible to bacterial colonization. Antibiotic treatments associated with processing may alter the normal flora, allowing overgrowth of resistant pathogens. Endogenous corticosteroid release due to the stresses of fear, exhaustion, starvation, trauma, and social adjustments also depress the humoral and cellular defense mechanisms.

Pasteurella spp. can be found in the upper respiratory tract of up to 65% of normal animals.[29] *Pasteurella multocida* may predominate in normal cattle, but *P. haemolytica* predominates in those that have been shipped as well as in those with pneumonia.[21] Futhermore, in unstressed cattle, serotypes A1 and A2 of *P. haemolytica* are found in approximately equal numbers in the nasal flora. After transport, the more pathogenic A1 is highly predominant.[20] It has also been demonstrated that both IBR and PI-3 infections will induce renewed shedding of latent *P. haemolytica* nasal infections.[19] Environmental factors and viral infections therefore appear to alter the virulence and infective dose of *P. haemolytica* available in the upper respiratory tract.

Once the "shipping fever equation" is completed and the balance between dose, virulence, and host defenses is tipped, *P. haemolytica* reaches the critical bronchiolar-alveolar junction and multiplies. This area is critical because of the deposition of 0.5-3.0 um particles here, the poor mucus blanket and alveolar macrophage activity in this region, and the fact that it represents an anatomical "funnel" in the cross-sectional area of the respiratory tree. The pathological process appears to begin in this area.[17] A number of virulence factors then allow the organism to produce pulmonary injury. *Pasteurella* produces a neuraminidase which is mucolytic,[14] allowing more easy spread of the bacterium and less efficient trapping. It also has an antiphagocytic polysaccharide capsule. This capsule is most apparent in young log-phase cultures, and these cultures appear to be more invasive and more immunogenic than older, non-encapsulated cultures.[15 16] These facts plus the fact that A1 is the main serotype of importance in pneumonic lesions make this capsule an attractive candidate as a virulence factor, but this role is currently unproven.[2]

Pasteurella haemolytica contains endotoxin, which is released when the bacterium dies. Endotoxin has a wide range of adverse biological effects, including complement activation, coagulation, and chemotaxis, which result in

edema, fibrin accumulation, and thrombosis.[14] The role of endotoxin may be intimately associated with the host's neutrophil response. In one study, calves were exposed by aerosol to saline, *Staphylococcus epidermidis, P. haemolytica,* or endotoxin from *Salmonella typhimurium.* Bronchoalveolar lavage fluid was examined periodically for 4 hours. No significant changes occurred in the saline or *Staph* groups, but the *P. haemolytica* and endotoxin groups exhibited parallel changes, consisting of a gradual replacement of the alveolar macrophages by a 90% population of neutrophils. These researchers suggested that endotoxin may play an important role in the pathogenesis of pasteurellosis by recruiting neutrophils which are then killed by the leukotoxin of *P. haemolytica* (discussed subsequently). The dying neutrophils release large amounts of inflammatory mediators which result in tissue destruction.[56] In another experiment, calves were rendered neutropenic with hydroxyurea. These calves and normal calves were then challenged with *P. haemolytica.* The normal calves showed overt clinical signs of pneumonia and had severe hemorrhagic, necrotizing, exudative bronchopneumonia at necropsy, from which *P. haemolytica* could be isolated. The neutropenic calves remained clinically normal, had only minor lesions at necropsy, and were culturally negative for *P. haemolytica.* These researchers concluded that the signs of lung injury were neutrophil-mediated, via released or induced factors such as complement, arachidonic acid metabolites, oxygen radicals, and enzymes.[54]

Another major factor is the presence of a protein exotoxin of *P. haemolytica* which kills alveolar macrophages, monocytes, neutrophils, and lymphocytes. This leukotoxin appears to be specific for ruminants.[31] Since *P. haemolytica* is pathogenic primarily for ruminants, this factor would appear to be of major importance in the pathogenesis of the disease.[2] The leukotoxin is a soluble glycoprotein which is produced by log phase cultures; it is heat labile and oxygen and pH stable.[10] Iron appears to be necessary for its production.[23] Its effects are dose-dependent, ranging from depression of phagocyte functions to killing.[47] All twelve serotypes of *P. haemolytica* produce it, and antitoxin will neutralize its effects.[52] The fact that cattle dying of pneumonia had lower serum antitoxin levels than cattle dying from other causes suggests that the antitoxin may be protective.[53] Indeed, resistance to experimental challenge has been correlated with serum cytotoxin neutralizing titers.[22] Antibody without antitoxin activity appears to actually enhance the cytotoxicity of *P. haemolytica*, probably by increasing phagocytosis of opsonized cells, which then kill the phagocytes which have ingested them.[14]

The host defense mechanisms in pasteurellosis can also contribute to the pulmonary damage. The endotoxin/neutrophil interaction described above may be the source of this overexuberant inflammatory response. Complement components, Hageman factor activation (with the resulting coagulation cascade, bradykinin and kallikrein generation, and fibrinolysis), arachidonic acid metabolism (with prostaglandin, thromboxane, and leukotriene production), the phagocyte respiratory burst (with production of oxygen radicals), platelet activating factor release, and the release of numerous leukocyte enzymes and inflammatory mediators such as histamine can result in considerable tissue damage.[33] Some of the major end effects of these systems include thrombosis, disseminated intravascular coagulation (DIC), accumulation of masses of leukocytes, increased vascular permeability and edema, vasodilation, bronchoconstriction, and pain.

All of these activities result in the necrosis and sloughing of the thin Type I alveolar lining cells in the acute exudative phase of inflammation. The few organelles and high surface to volume ratio of these cells, which make them ideal for oxygen transport, also make them very susceptible to injury. If the damage is not too severe, the Type II cells proliferate. These cells normally produce surfactant, but retain the ability to proliferate and differentiate into Type I cells. Being more cuboidal and having more organelles, they are less susceptible to injury. These cells are very sensitive to oxygen at concentrations over 60%. Once they have relined the alveolus, they transform into flat Type I cells and repair is complete.[17]

The associated exudate progresses from a serous fluid with fibrin, to a purulent exudate with neutrophils, to alveolar macrophages in the clean-up stage. If the infection is particularly virulent, much more fibrin is produced, which is then converted to fibrous connective tissue. This is common in cattle, due to the virulence of pasteurella, the high fibrinogen content of bovine blood, the low plasminogen levels (plasmin is a fibrinolytic enzyme) and high levels of plasmin inhibitor in pulmonary tissue. In these cases, epithelialization does not occur and healing is by fibrosis. Interstitial inflammation with edema and cellular infiltrates is also prominent in ruminants. Residual scarring, atelectasis, bronchiectasis abscessation, necrosis with sequestion, and chronic bronchopneumonia are common sequelae. Fatalities are due to hypoxemia and toxemia.[17]

In addition to pulmonary tissue changes, airway and cardiovascular changes also occur. Calves with pneumonia have increased total lung resistance and reduced compliance, due mainly to narrowing of large and small airways, inflammation of the lung parenchyma, and unequal ventilation of parallel segments. Pleural pressure differences and the work of breathing are increased. The tidal volume is decreased, probably due to inflammation-induced hypersensitivity of the Hering-Breuer reflex. The animal attempts to make up for the decreased volume by increasing the respiratory rate, but this results in mainly dead space ventilation.[44] Calves with mycoplasma pneumonia secrete a thicker, more acidic mucus, which is harder to remove[7] and results in airway plugging. Airway irritation results in coughing.

In the acute phase, pasteurellosis results in progressive hypoxemia, and pulmonary hypotension due to decreased pulmonary vascular resistance. The hypoxemia is probably

due to persistent or even increased perfusion of diseased (and therefore poorly ventilated) areas of lung, shunting of blood, and diffusion impairment. The pulmonary hypotension is likewise probably due to vasodilation, due in turn to vasodilator substances such as prostaglandin E_2 or prostacyclin released by the inflammatory process.[1]

Therapeutic Strategies to Alter the Pathophysiology of Pasteurellosis

The utility of ancillary therapies for pasteurellosis (i.e., treatments other than antibiotics) has received little attention. Many of the recommendations which follow are suggestions which may be beneficial, based on the pathophysiology of the disease. References are given in those few instances that have been investigated. Practitioners are cautioned that most of these ancillary drugs are not specifically approved for cattle.

1. *Restoration or alteration of the physical defense mechanisms.*

Although the measures discussed in this section are not all pharmacologic, they should be considered as important ancillary or nursing measures that can decrease the spread of the pathogen within the lungs of the affected animal, improve the response to therapy, hasten recovery by bolstering clearance mechanisms, and decrease the spread of disease in the group. Optimum temperature (55-70° F for calves) and humidity (70%) will help normal defense and clearance mechanisms and decrease stress-related corticosteroid release. Constancy is also important. Wide temperature extremes depress mucociliary function; high humidity results in increased aerosols and condensation on the hair, with attendant chilling; low humidity results in dust and dehydration of the mucus. Drafts also contribute to chilling. Procedures may range from controlled housing for calves or valuable individuals to at least providing adequate shelter for range or feedlot animals. In housing situations, adequate ventilation without drafts is important to decrease aerosols, noxious gases, infective doses, and chilling. A minimum of at least four changes of air per hour is recommended, more in hot weather. Optimally, filtration of the air in housing has been shown to reduce the microbial load in the air, with concomitant reductions in the amount of pneumonia in calves.[45] In the feedlot situation, measures to control dust are indicated. Crowding, whether in housing or pens, should be avoided, as a means of decreasing infective doses and stress. Sanitation will decrease noxious gases which depress mucociliary and alveolar macrophage function, and clean dry bedding will decrease chilling and presumably improve attitude and appetite. Nutrition should be adequate and palatable, as starvation has been shown to depress macrophage function. Febrile animals with septic processes have nutritional needs in excess of maintenance. Forestomach upsets should be avoided at all costs; in the feedlot, silage should be decreased and extra long-stem hay provided. The use of prophylactic antibiotics is certainly controversial, but one reason to avoid such use is the suppression of normal flora and the selection of resistant pathogens. In the Bruce County Project in Canada, the feeding of silage and the use of antibiotics in the water were two factors associated with a higher incidence of respiratory disease.[38]

Fluid therapy for dehydration is extremely important. Not only will rehydration improve clearance mechanisms, but volume expansion remains the foremost therapy for the toxemia and endotoxic shock associated with pasteurellosis. Balanced polyionic fluids are usually indicated. Therapy should be vigorous, but animals should be monitored carefully for signs of overhydration and pulmonary edema in the face of hypoalbuminemia and pulmonary inflammation.

The cough mechanism probably should not be altered in most pneumonic cattle. Coughing is usually not a prominent feature in pasteurellosis; what coughing occurs is usually productive, and is therefore beneficial. The cough is often soft, and may be suppressed by the animal due to painful pleuritis. Finally, cows cough with an open glottis[41] and the cough is therefore not likely to produce emphysema. Cough suppression is therefore not indicated, and is probably contraindicated. In those rare cases where the cough is frequent, harsh, nonproductive, and therefore potentially debilitating, codeine at 0.2 to 2 grams per cow orally has been recommended.[5] The author has no experience with this drug in cattle.

Expectorants may be beneficial in alleviating the thick mucous plugs in the airways. In view of the limited efficacy of the open-glottis cough in the cow, and the inability to achieve postural drainage in larger animals, expectorants should be used with caution so that increased pooling in the ventral areas does not result. There are three classes of expectorants: sedative, stimulant, and anodyne expectorants. The sedative expectorants are further subdivided into the saline, demulcent, and nauseant drugs. The only ones commonly used in food animals are the iodine (saline) expectorants. Ethylenediaminedihydriodide (EDDI) at 500 mg/head/day will produce an obvious expectorant effect in about 5 days.[9]

Mucolytic agents have similar indications and cautions for their use. The agents most commonly used in small animals and humans include acetylcysteine (Mucomyst) and various enzymes such as pancreatic dornase (a DNA depolymerizer) and streptokinase-streptodornase. These are usually applied endoscopically, followed by suction of the dissolved material, or via nebulization. These substances can be very irritating, and acetylcysteine can react with rubber and a variety of antibiotics. They are therefore not commonly used[39] and due to the difficulty of application, would be even less applicable to the large animal situation. The use of steam, vaporizers, and nebulizers would fall under a similar category of expectorants/mucolytics. Steam and most vaporizers probably affect only the extreme upper airways, but their benefit there can be considerable. Steam will hydrate the mucus, thin it, and increase production of

thin mucus by causing mucosal hyperemia. Depending on how the vapor is delivered, care must be taken to avoid overheating the animal or wetting the haircoat. Nebulizers which produce particles less than 3um diameter will deliver moisture deeper into the tract. The addition of antibiotics and so forth is controversial,[39] but appears to be a current topic of interest in the Russian literature. One Russian investigator has recommended the use of aerosols of iodine triethyleneglycol with or without turpentine; 3% H_2O_2; 5% chloramine B; 1.5-2.0% sodium hypochlorite; or immune serum as a preventative measure. Bronchodilators such as aminophylline, epinephrine, ephedrine, and atropine, and antibiotics such as sulfathiazole, nitrofurazone, neoarsphenamine, and others were recommended for treatment. Sodium bicarbonate, ammonium chloride, trypsin, deoxyribonuclease, and ribonunclease were proposed as mucolytics.[32]

The final physical factor to be considered is bronchoconstriction. Removal of the inciting agents and control of inflammation (as with corticosteroids or non-steroidal anti-inflammatory drugs) will do much to relieve bronchospasm. In severe cases, beta-2 agonists or xanthines can be used to achieve bronchodialation. Beta-2 agonists include drugs such as metaproterenol, terbutaline, and clenbuterol. Clenbuterol currently is widely used in Europe and Canada for chronic obstructive pulmonary disease in horses, and has been found to reduce dyspnea and coughing and to hasten recovery in calves with bronchopneumonia. When given at 0.8 ug/kg body weight IV, the drug resulted in significiant increases in compliance, tidal volume, and tidal volume per unit change in pleural pressure, and significant decreases in the change in pleural pressure and work of respiration.[44] This drug is not currently available in the U.S. Aminophylline, a xanthine, is available though not specifically approved. Recommended doseage for an adult cow is 3-5 gm PO QID or 1 gm IM QID, and 0.5-1.0 gm PO QID for calves. The oral route is of questionable benefit in adults, the intramuscular route is painful, and in any case, QID administration is unlikely in cattle.[37]

Alpha agonists such as phenylephrine and phenylpropanolamine are useful as decongestants due to their vasoconstrictive properties. They should not be used systemically because they are bronchoconstrictors, but the author has used these drugs to good effect as nasal sprays in calves with severe nasal congestion and edema. Overuse can lead to rebound phenomena and mucosal necrosis. Atropine is a bronchodilator and decreases respiratory secretions. However, it should generally be avoided because it also thickens the secretions[39] and decreases mucociliary activity.

2. *Restoration or magnification of the cellular and secretory defense mechanisms.*

There are very few currently available immunomodulators with proven immunity-enhancing effects. Perhaps the best known example is levamisole. Levamisole promotes the synthesis of cGMP in lymphocytes, resulting in lymphocyte proliferation, increased lymphokine production, increased macrophage phagocytosis, and enhanced chemotactic responsiveness of neutrophils. Levamisole increased the response of mice to *Brucella* vaccines, and prevented leucopenia associated with BVD infection in calves.[40] It increased the response to Strain 19 vaccine when given after vaccination in calves.[12] In general, levamisole seems to have more consistent effects on cellular immune functions, and more equivocal effects on humoral functions, particularly the primary humoral response. The recommended immunomodulatory dose is less than the anthelmintic dose, i.e. 2-3 mg/kg body weight given intermittently. Beneficial effects are most likely when given to an animal with suboptimal immune function, and even then the results are not consistent. Prolonged use can result in granulocytopenia.[40]

Ascorbic acid (Vitamin C) is a controversial immunomodulator. It occurs in high concentrations in neutrophils, where it may serve to inactivate oxygen radicals or to promote oxidative killing of bacteria. Glucocorticoids, which depress neutrophil function, decrease the ascorbic acid content of neutrophils. Ascorbic acid has been shown to overcome the steroid-induced reduction in neutrophil oxidative metabolism as well as reversing some of the neutrophil defects in the Chediak-Higashi syndrome in people. Ascorbic acid at 20 mg/kg body SC enhanced neutrophil oxidative metabolism and antibody-dependent cell-mediated cytotoxicity in cattle and reversed some of the neutrophil depressing effects of dexamethasone.[48] Vitamin C is routinely used in treating pneumonia in feedlots in the northern Colorado area, with apparently beneficial results. In view of the apparent neutrophil-mediated lung damage in pasteurellosis, controlled studies are needed on the use of ascorbic acid in this disease. Vitamin E may be regarded as an immune modulator since it has been shown to improve the immune response in chickens and sheep.[43 51] Selenium deficiency depresses neutrophil function in mice, goats, and cattle, and selenium supplementation will restore normal function.[4] Both ascorbic acid and Vitamin E may also act as antioxidants and may therefore be of additional value in modifying the inflammatory response.

In colostrum-deprived calves, plasma transfusions may be of benefit in restoring humoral antibody titres. Future possibilities in the modulation of cellular and humoral defense mechanisms include the mass production of lymphokines such as interferon and interleukin-2 by recombinant DNA technology; the production of synthetic immunomodulators such as isoprinosine and other synthetic nucleotides; the use of antiviral drugs; and refined use of bacterial products as immune stimulants.[60 40]

3. *Measures to combat the bacterial virulence factors.*

At present there are no specific pharmacological agents to circumvent the antiphagocytic capsule or the leukotoxin. Certain management decisions before the onset of disease may modify the response to these factors however. Killed bacterins appear to be not only ineffective in preventing pasteurellosis, but may even increase the severity of the disease.[21 57] This phenomenon may be related to induction of

anticapsular antibody without antileukotoxin antibody and the resulting increased phagocytosis of opsonized bacteria without the benefit of antitoxin.[14] Although results have been variable, various modified live bacterins appear to be more effective.[13 30 46] One possible explanation is that these bacterins not only induce anticapsular antibody, but also release leukotoxin, promoting antitoxin production. Subunit vaccines may eventually give us some degree of control over this disease. Since the leukotoxin appears to require iron for formation, iron supplementation should be avoided. Several host defense mechanisms are thought to involve the sequestration of iron from the pathogen, and supplementation would be counterproductive.

4. *Measures to combat harmful reactions to the bacterium.*

Pharmacologic agents are available to combat the endotoxin of *P. haemolytica*, or more properly, the body's reaction to it. Corticosteroids have been recommended in severe cases[8] and have been commonly used in practice. Their utility in helping to reverse endotoxic shock is generally accepted. It is also commonly argued that limited doseage may not affect immunity, and that the beneficial effects in decreasing inflammation, edema, and bronchospasm and improving attitude and appetite may hasten recovery. However, in a field trial in a Colorado feedlot, the use of dexamethasone at 20 mg/day was associated with a poorer response to initial therapy, a higher relapse rate, higher death losses, and prolonged course to death when compared to controls receiving the same treatment without dexamethasone.[11] The nonsteroidal anti-inflammatory drugs (NSAID) are also potent inhibitors of the biological effects of endotoxin, but without the immunosuppressive properties. In addition, they are also potent analgesics and antipyretics. Ibuprofen prevented the *P. haemolytica* endotoxin-induced increases in plasma prostanoids and serotonin and fever in sheep.[18] Flunixin meglumine is the drug of choice for endotoxemia in the horse. Kinetic studies in the cow indicate that a loading dose of 2.2 mg/kg followed by maintenance doses of 1.1 mg/kg every 8 hours should provide levels similar to those required for analgesia and prostaglandin inhibition in the horse.[26] Studies have indicated that considerably lower doses are needed for prostaglandin inhibition than for analgesia in the horse.[50] Aspirin is available for use in cattle; the recommended doseage is 100 mg/kg orally twice daily.[24] Phenylbutazone can be given at 6 mg/kg for loading, followed by 3 mg/kg daily for maintenance, IV or PO. These inhibit the enzyme cyclooxygenase, thereby decreasing prostaglandin and leukotriene production.

DMSO is another compound with possible anti-inflammatory properties. One of its main beneficial effects is thought to be its ability to scavenge oxygen radicals. It is therefore attractive as a possible means to prevent neutrophil-mediated tissue damage in pasteurellosis. DMSO may also have analgesic effects, reduce platelet aggregation and coagulation, and improve tissue perfusion. Although DMSO has been used for pneumonia in the field, such use has not been critically evaluated. The dose is not well established. Doses of 1 gm/kg delivered as a 10% or less solution in 5% dextrose are used for cerebral edema.[6] Heparin therapy, in an effort to decrease activation of the coagulation cascade and subsequent fibrinolytic activity, has been advocated for diseases involving endotoxemia and DIC. In the dog, heparin has been advocated for use in pulmonary thromboembolism[55] and for DIC.[25] The dose varies widely, and the activated clotting time is used to monitor the response. A 1.3-2.5 fold increase in the ACT is the target. Such use has not been investigated in the cow. Extrapolating from the horse, doses of 20-40 IU/Kg TID-QID should be safe, but may have questionable efficacy. Heparin therapy has largely been supplanted by aggressive fluid therapy and the use of non-steroidal anti-inflammatory drugs such as flunixin. Antihistamines likewise are of questionable efficacy when compared to the potential benefits of the NSAIDs.

5. *Amelioration of the interstitial reaction and hemodynamic events.*

If severe interstitial edema results, the animal may benefit from a diuretic such as furosemide. Severe diffusion impairment can be at least partially overcome by oxygen therapy. Oxygen has the potential to dry the airways and injure the Type II cells. It should therefore be humidified, and should be used in concentrations of 50% or less. The addition of 5% CO_2 will stimulate deeper respiration and the production of thinner mucus. Oxygen may be difficult to administer to a cow, and the restraint required may be more detrimental than the benefits gained. Some cattle may tolerate a small nasal catheter. The use of antiinflammatory drugs as discussed above may also help reduce the interstitial inflammation and thereby improve compliance and gas exchange. Furthermore, since the acute hemodynamic events of vasodilation and pulmonary hypotension are possibly related to arachidonic acid metabolism,[1] the NSAID's may also be of benefit in this area as well.

Summary

In addition to appropriate antibiotic therapy, ancillary therapies may be of benefit in the management of the pathophysiology of bovine pneumonia, particularly in the valuable individual. Good nursing care (shelter, temperature and humidity regulation, ventilation, dust control, sanitation, and nutrition) is important in all situations. Fluid therapy and the use of NSAID's are practical measures that are likely to be of considerable benefit. More exotic measures or those of more questionable benefit may include expectorants, aerosol therapy, bronchodialators, decongestants, immune modulators (such as levamisole, ascorbic acid, or Vitamin E), DMSO, heparin, and oxygen therapy.

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