Acute Interstitial Pneumonia in Feedlot Cattle

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Introduction

General description of AIP

Acute interstitial pneumonia (AIP) is a descriptive term for a specific histopathological pattern, including hyaline membrane formation, and proliferation of type II alveolar epithelial cells.[6,18] Other lesions often identified are interlobular edema, hemorrhage and vascular congestion. The condition occurs secondary to alveolar wall damage resulting in transudation of relatively acellular, and fibrinogen-rich fluid into alveolar spaces and terminal airways.

Fibrin is compacted to form hyaline membranes and their presence may indicate an acute form of AIP. It is possible that these lesions may develop within a matter of hours. If an animal survives the acute episode, proliferation Type II alveolar epithelial cells occurs imparting a glandular appearance. This appearance may have lead to AIP once being described as pulmonary adenomatosis.[27] Acute interstitial pneumonia may result from exposure to a number of etiological agents that directly or indirectly damage the alveolar wall. As such, a diagnosis of AIP implies no specific etiology.

Probably the best characterized form of AIP is acute bovine pulmonary edema and emphysema (ABPE) or fog fever.[13,21,28,29] This condition occurs from movement of cattle from dry, dormant pastures to lush fields containing an abundant amount of the amino acid, tryptophan. Tryptophan is metabolized to 3-methylindole (3MI) as part of normal ruminal fermentation.[35] Three-MI is absorbed from the rumen,[14] transported to the lungs and metabolized to an electrophilic compound, 3-methyleneindolenine 3MEIN.[32] Three-MEIN binds to cellular macromolecules resulting in widespread cellular injury.[24] Hence, 3MI is nontoxic *per se* and must be activated to cause cellular injury. Enzymes responsible for activation, mixed function oxidases (MFO)[3,17] and prostaglandin H synthetase (PHS),[10] are found in high concentrations in Type I alveolar epithelial cells and Clara cells of ruminants.

Other exposures that have also resulted in AIP include 4-ipomeanol from moldy sweet potatoes,[7] ketones from the Perilla mint plant,[20] and potentially bovine respiratory syncytial virus (BRSV).

Clinical and postmortem appearance

Clinical manifestations of AIP are best described as acute respiratory distress syndrome (ARDS), and include a sudden onset of respiratory distress, sway back appearance, respiratory grunt, open shouldered stance, and sometimes aggression.[5]

At postmortem, AIP-affected lungs are large, heavy and fail to collapse.[18] The dorsocaudal regions of the lung are primarily affected unless the animal suffered a concurrent or a previous bout of bronchopneumonia. The lung surface may appear dark red to a combination of gray and red lobules, giving it a checkerboard appearance. On cut surface interlobular edema fluid is apparent. Sometimes interlobular emphysema and emphysematous bullae are present. Affected lobules are firm and independently movable.

Feedlot-associated AIP

Feedlot-associated AIP is an important source of economic and animal loss for some, but not all feedlots. Acute interstitial pneumonia is the primary cause of respiratory death loss behind fatal fibrinosuppurative bronchopneumonia (FFB).[18,33] The incidence proportion of AIP is reported to be between 0.03 to 0.15 percent,[16,18] and the case fatality rate is high even in the face of aggressive administration of available therapeutic regimens (personal observations). Although questioned by some, authors have indicated that AIP occurs more frequently during the summer and fall, and in animals that have been on-feed for 45 days or more,[18,30] whereas shipping fever primarily manifests early in the feeding period.[26] Thus, a substantial portion of losses due to AIP include feed consumed prior to death.

Although much speculation exists, no etiological agent has been identified as the definitive cause of feedlot-associated AIP. Feedlot AIP is also known as dust pneumonia, cow asthma, and allergic pneumonia. Some proposed etiologies of feedlot AIP include, but are not limited to, airborne dust, hypersensitivity to *M. feani*, 3MI, and BRSV.

In a review of respiratory disease, 144/149 fatal AIP cases had concurrent bacterial pneumonia.[16] Animals with AIP were more likely to have evidence of bronchopneumonia than animals that died from other causes. Yearlings that died from fatal AIP were more likely to

have been treated for other conditions compared to yearlings that did not develop clinically apparent AIP.

Collins *et al* demonstrated an association with BRSV infection.[6] In their study, 11 of 15 cattle with AIP, compared to 5 of 18 cattle with other respiratory tract disease, were positive for BRSV (P=0.01). The odds of an AIP infected animal being positive for BRSV was 3.6 compared to other respiratory tract disease. However, we believe that BRSV is probably not the predominant cause of feedlot AIP because BRSV typically causes an outbreak of disease in newly arrived cattle and BRSV-affected cattle have a pronounced fever, whereas AIP occurs in the latter stages of finishing, clinically affected animals are afebrile, and BRSV is rarely identified in AIP-affected lung tissue in other studies (Personal observations; T. A. McAllister, personal communication 1999).

Miles *et al* observed that animal with AIP generally have elevated ruminal pH.[23] In a follow-up field study, animals suffering AIP, either clinically or at postmortem, had detectable ammonia concentration in the rumen gas cap, whereas other animals generally did not (P<0.05; Gould and Hoffman, unpublished). These findings may indicate that AIP may be associated with an alteration in ruminal nitrogen metabolism. Another intriguing observations involved heifers that died from AIP often have evidence of a recent ovulation, even though they were administered melengestrol acetate (MGA; Miles and Hoffman, personal communication 1999).

More recently, Canadian and Colorado researchers have found that animals suffering AIP had increased concentrations of 3MEIN,[11,22] the proposed toxic metabolite of 3MI.[19,32]

Current Research

Association of AIP with 3MEIN

It seems plausible to hypothesize that feedlot AIP is associated with increased 3MI because fog fever, which has an identical histological pattern to feedlot AIP, occurs secondary to excessive ruminal 3MI generation. However, elevated blood or ruminal 3MI were not identified in feedlot cattle suffering AIP (T. A. McAllister, personal communication 1999). Further, feedlot rations are fairly consistent with regard to tryptophan content, and AIP generally affects animals that are adapted to a feedlot ration late in the feeding period.

On the other hand, there is some evidence for altered ruminal nitrogen metabolism, and this might involve a temporary surge in 3MI production. If 3MI is associated with feedlot AIP, a temporary peak in 3MI would occur prior to AIP. Once clinical signs of AIP develop, feed intake would cease. The plasma half life of 3MI is less than 30 minutes, so identification of altered 3MI concentrations in animals that have developed AIP is very unlikely.[3] For these reasons, 3MI was not implicated in feedlot AIP for many years.

Recent advances in biochemical toxicology have enabled the identification of the metabolites of 3MI. These are bound to cellular macromolecules and relatively stable over time. An assay for the proposed toxic metabolite of 3MI, 3MEIN, was developed and research evaluating 3MEIN and AIP was possible.[19]

The first such study was performed using cattle in Southern Alberts feedlots suffering ARDS (T.A. McAllister, personal communication 1999). In their study, they did not identify an alteration in lung 3MEIN concentrations, but did demonstrate elevated blood 3MEIN concentrations in animals suffering AIP compared to blood samples take from animals with other causes of respiratory distress. These researchers have ongoing research of AIP and 3MEIN.

Another observation was that heifers were predominantly affected with AIP, and that these heifers were fed MGA. In a controlled experiment, sheep were fed a high concentrate ration, and half of them were additionally fed MGA at 0.15 mg per head.[25] All sheep were challenged with 3MI. Those receiving MGA developed respiratory disease sooner and more severely than controls. It is unclear what, if any, role MGA has on feedlot AIP.

In research performed on cattle from feedlots in the Great Plains of the U.S., animals dying from AIP had significantly higher lung cytosol 3MEIN concentrations than animals that died from other disorders (unpublished data). Additionally, animals with ARDS, that were later confirmed to be suffering AIP, had higher blood 3MEIN concentrations compared to clinically healthy pen-mates.

The results from Canada and the U.S. indicate that feedlot AIP is associated with increased 3MEIN concentrations in blood samples. Because nontoxic 3MI is primarily activated to 3MEIN in pulmonary tissue, we believe that increased blood 3MEIN occurs secondary to increased pulmonary activation of 3MI, and subsequent release of 3MEIN adducts to blood. It is likely, however, that increased pulmonary production of 3MEIN is not the sole cause of feedlot AIP. Rather, 3MEIN is possibly one of several factors that contribute to the development of feedlot AIP and result in the epidemiological and toxicological characteristics observed.

Microbial contributions to AIP

Data from human literature indicates that a similar disease may occur secondary to cytokine release. The primary cytokines of interest are interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α). Concentrations of these cytokines were greater in bronchoalveolar lavage fluid of at-risk patients who developed ARDS compared to those that did not.[31] In ARDS cases, those who died had greater concentrations at the onset of disease than those patients who survived.[15]

In experimentally induced *Pasteurella* infections in cattle, both IL-1β and TNF-α were present in lavage fluid.[36] Exposure to endotoxin, leukotoxin, and viral infection can also result in IL-1β and TNF-α release by macrophages.[8,9,37] Thus, there are many possible mechanisms that may result in release of these pro-inflammatory cytokines. It has been proposed that AIP may result from an overwhelming and unregulated release of IL-1β and TNF-α in response to a specific triggering event.[34]

Researchers from the University of Georgia have proposed to investigate the role of infectious agents and feedlot AIP (A.R. Woolums, personal communication 2000). Their working hypothesis is that BRSV infection occurring at the time of subclinical bacterial infection of the lung or liver leads to feedlot ARDS, through a mechanism involving elevated concentrations of inflammatory mediators induced by these bacterial infections. These mediators are proposed to prime the lung for a massive pulmonary inflammatory response triggered by BRSV infection, leading synergistically to feedlot ARDS.

We believe that the above areas of research evaluating 3MEIN and infectious agents in feedlot AIP are complementary. In an 2X2 factorial experimental, researchers investigated the effects of 3MI and BRSV on calves.[2] Treatments used were control, BRSV, 3MI, and a combination of BRSV and 3MI. Those calves that received both 3MI and BRSV developed the most severe clinical signs and pulmonary changes. This research demonstrated a synergistic relationship between 3MI and a common feedlot pathogen. Potentially, elevated pulmonary production of 3MEIN may act synergistically with important feedlot pathogens and enhance the risk of feedlot AIP.

Epidemiology of AIP

In an investigation of AIP in a single feedlot, heifers were associated with a greater risk of mortality due to AIP compared to steers (unpublished data). Cattle that had been on-feed for greater that 60 days were at greater risk compared to animals that had been on-feed for 60 days or less. The greatest incidence of AIP was during summer months compared to winter. If there was at least one digestive death in a pen, then on average the incidence of AIP increased.

Implications

Acute interstitial pneumonia of feedlot cattle may result from an interaction of several factors, such as ambient temperature, airborne dust, concomitant microbial infection, antioxidant depletion through consumption of rancid fat or other compounds, endotoxin exposure, and increased 3MEIN production in pulmonary tissues. Recent research has increased our knowledge of the epidemiology and association with 3MEIN concentrations.

Two aspects seems certain, i.e., there appears to be no magical cure for animals affected with AIP, and the case fatality rate is high. However, based on recent and preliminary results, it is possible to speculate on management factors that may affect the occurrence of AIP. It must be stressed that these have not been evaluated at the time of manuscript preparation and more research is required.

It is not clear if the observed increase in blood and lung 3MEIN concentrations were the result of increased rumen 3MI production, increased conversion of 3MI to 3MEIN in the lung, or a combination of both. Monensin is known to reduce rumen 3MI production.[12] However, AIP still affects cattle consuming monensin. A second approach it to inhibit either PHS or MFO. Experimentally, inhibition has resulted in some protection from 3MI induced lung injury.[1,4] It may be possible to economically inhibit PHS with non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin. If this is so, aspirin could potentially be added to the ration of at-risk pens of cattle, i.e., long-fed heifers during the hottest months of the year. A team of researchers from the Integrated Livestock Management Program, Colorado State University, will be evaluating the effect of aspirin and vitamin E on blood and lung 3MEIN concentrations. This research will commence during the latter half of 2000.

It is unclear what, if any, role that MGA contributes to feedlot-AIP. Postmortem observations have shown that AIP-affected heifers often have evidence of a recent ovulation, thus indicating that the AIP-affected heifer did not receive sufficient MGA to arrest ovarian activity. This may happen via inadequate ration mixing, extremely high ambient temperatures that result in substantially lowered feed consumption for an individual, or both. It may be that animals that have recently ovulated are at increased risk for AIP development. It seems prudent to recommend that every attempt is made to ensure that heifers on MGA receive an adequate dose to prevent ovulation. This may require close attention to ration formulation, addition of ration components, and ration mixing times. Such an approach will also ensure cattle receive appropriate concentrations of monensin, potentially decreasing ruminal 3MI generation.

It appears that AIP affects cattle in some feed yards, but not others. In feed yards where AIP occurs frequently, the occurrence may be determined by the number of long-fed heifers on-feed during the hottest months of the year. If it is feasible, reducing the proportion of the population that are considered at-risk may decrease the impact of AIP on the feedlot's bottom line.

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