Etiology of Acute Interstitial Pneumonia in Feedlot Cattle: Noninfectious Causes

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ABSTRACT: Acute interstitial pneumonia (AIP) of cattle is a cause of severe dyspnea of acute onset that often ends in death. In feedlots, AIP can be an important cause of morbidity and mortality; however, the cause of feedlot AIP is unknown. In nonfeedlot situations, feed-associated pneumotoxins, particularly 3-methylindole (3-MI, a product of ruminal tryptophan metabolism), are well characterized to cause bovine AIP. A metabolite of 3-MI, 3-methyleneindoline-nine, has been found to be increased in the plasma and lung tissue of animals dying of feedlot AIP in some studies, suggesting that 3-MI contributes to the pathogenesis. In some lots, heifers die of AIP in greater numbers than steers; evidence suggests that melengestrol acetate may contribute to the development of feedlot AIP in these heifers. Although hypersensitivity is often speculated to cause feedlot AIP, the pathology of AIP is not typical of most lung diseases known to be due to hypersensitivity. No research has been conducted to address the role of hypersensitivity in feedlot AIP. Many anecdotal reports associate airborne dust with feedlot AIP, but no research has been carried out to test the hypothesis that dust exposure induces AIP. The toxic gases nitrogen dioxide and hydrogen sulfide have been incriminated in the etiology of AIP, but there is no evidence to suggest that feedlot cattle are likely to be exposed to sufficient amounts of these gases to induce AIP.
surface of the lung, gelatinous edema is evident, with interlobular emphysema and sometimes emphysematous bullae. Histologically, alveolar hyaline membranes are seen, with proliferation of type II alveolar cells and alveolar and interstitial edema and hemorrhage. The various names associated with this syndrome can lead to confusion; use of the terms AIP for the characteristic pathologic changes and ARDS for the clinical presentation of severe acute respiratory distress is both accurate and all-encompassing. 7,8

Acute interstitial pneumonia is a pattern of lesions that may result from a variety of etiologies. The best characterized cause is associated with movement of beef cattle from heavily grazed summer pasture to lush pasture in the fall. 9 This form of the disease, also commonly known as ABPE or fog fever, is due to damage of the lung by pneumotoxins resulting from ruminal conversion of forage-derived L-tryptophan. Bovine AIP can also be caused by pneumotoxic compounds ingested in moldy sweet potatoes, 10 purple mint, 11 rape, turnip tops, or kale. 12 These pneumotoxic compounds induce the final common result of AIP through damage of the alveolar wall.

Acute interstitial pneumonia is less well characterized in feedlot cattle. 13–18 Although often mentioned in reviews of feedlot diseases, very little descriptive or experimental research regarding feedlot AIP has been published. Speculation abounds, but the cause of feedlot AIP is unknown. The small amount of available information provides some clues to possible causes.

Mortality rates due to feedlot AIP are reportedly 0.03% to 0.15% 13,14 of cattle received. AIP has been described as the second leading cause of death due to respiratory disease (the leading cause is bovine respiratory disease [BRD; shipping fever]). 13,15 AIP can also be a cause of sudden death in feedlots. 19 It is generally reported that most cattle that develop feedlot AIP have been on feed longer than 45 days and that disease is most common in the summer and fall 13,16 (although this point has been debated 14). The disproportionate number of deaths in animals on feed longer than 45 days amplifies the losses incurred due to feedlot AIP as relatively more resources have been invested in fatal AIP cases than in fatal shipping fever cases. Some research indicates that heifers are more likely to die of AIP than steers. 18,20

PATHOLOGY

Early descriptions of AIP often did not differentiate feedlot-associated from pasture-associated AIP, 2,3 but later reports specifically detailing feedlot cases describe pathology similar to that seen in pasture-associated AIP. 13,21 Grossly, lungs fail to collapse (Figure 2) and the texture is firm and rubbery. The lesions of AIP are distributed throughout the lung with the dorsocaudal lung notably affected; the cranioventral lung may be consolidated, which may indicate superimposed bacterial bronchopneumonia. Unless bacterial pleuropneumonia is also present, the pleural surface is free from exudate or fibrin deposition, although it is typically slightly thickened. Affected lobules are dark red to purple, or sometimes grayish, and independently movable; they are interspersed with normal-appearing lobules, giving the lung a variegated appearance. 15 The cut surface of affected lung has interlobular gelatinous edema and emphysema. Hemorrhage into interlobular lymphatics may rarely be evident. 15

Grossly, AIP can be confused with other types of pneumonia; thus definitive diagnosis requires histologic evaluation. The hallmark histologic lesions of AIP,
whether pasture- or feedlot-associated, are fibrin accumulation and hyaline membrane formation in alveolar spaces, alveolar epithelial hyperplasia and congestion, and edema. Histologic lesions may be categorized as either the early exudative phase of the syndrome (marked by fibrin accumulation and hyaline membrane formation [Figure 3] with interstitial edema and hemorrhage) or the later proliferative phase of the syndrome (marked by alveolar epithelial proliferation, inflammatory cell infiltrate, and possibly collagen formation). In the early exudative phase, hyaline membranes (composed of serum proteins, fibrin, and cellular debris) are evident. Strands of deeply basophilic chromatinlike material may be scattered in alveolar spaces and terminal bronchioles. Alveolar edema (which differs from hyaline membranes by being more homogeneous, diffuse, and pale staining) and alveolar hemorrhage may be present. The alveolar wall may be thickened with edema fluid, and the interlobular space is expanded by edema fluid, emphysema, dilated lymphatics, and sometimes hemorrhage.

In the later, proliferative phase of AIP, cuboidal alveolar type II cells proliferate in response to destruction of type I cells, sometimes leading to an almost glandular appearance of the alveoli, which led to the early name pulmonary adenomatosis. Desquamated type II cells, neutrophils, eosinophils, or mononuclear cells may be present in the alveoli. The alveolar wall may be enlarged with edema fluid; mononuclear and sometimes neutrophilic infiltrate may be present and, when extensive, likely represents inflammation of several days’ duration. Bronchiolar and bronchial changes sometimes noted include luminal exudate with edema of the lamina propria and infiltrate of mononuclear and globular leukocytes into airway walls. Bronchiolitis obliterans may be present, indicating chronic bronchiolar inflammation. It is not clear whether this bronchiolar inflammation is related to the pathogenesis of AIP or is an incidental finding related to other superimposed or chronic airway disease.

The pathologic lesions of AIP have been categorized as representative of a dietary form and a hypersensitivity form of the syndrome. Schiefer’s hypersensitivity cases differed from dietary cases in that the lesion was more irregularly distributed, with abnormal lobules interspersed with normal-appearing lobules. Mononuclear cells infiltrated the interstitium, with eosinophils present in the alveoli of hypersensitivity cases. An alternative possible explanation for the differences in these two groups is that they represented acute (the dietary form) versus relatively chronic (the hypersensitivity form) pathologic changes. Alveolar interstitial infiltration with inflammatory cells that are predominantly mononuclear is recognized to be part of the expected progression of pathology in AIP? However, the presence of eosinophils, which have been noted in some feedlot AIP cases, supports an allergic component of the syndrome.

**DIET-RELATED PNEUMOTOXINS**

**3-Methylindole and 3-Methyleneindolenine**

The role of pneumotoxins in pasture- or feed-associated AIP is well characterized. Some evidence suggests that pneumotoxins associated with dietary factors may lead to feedlot AIP. Pasture-associated AIP results from damage to the alveolar wall by pneumotoxins generated by metabolism of 3-methylindole (3-MI) by mixed function oxidases and prostaglandin H synthetase in type II pneumocytes and Clara cells. In pasture-associated AIP, 3-MI originates in the rumen, where it is the product of metabolism of L-tryptophan by rumen microbes, particularly *Lactobacillus*. 3-MI is rapidly absorbed from the rumen into the systemic circulation, through which it travels to the lung and is converted to several toxic metabolites, the most toxic of which may be 3-methyleneindolenine (3-MEIN). While 3-MI is rapidly metabolized and cleared from the body, 3-MEIN can be detected in lung tissue for hours to days following exposure to 3-MI. 3-MEIN covalently binds to cellular macromolecules; the exact mechanism of cellular damage is unclear but likely involves free radical formation, peroxidation of cellular lipids, and degradation and/or inactivation of cellular proteins and DNA (Figure 4). Widespread cellular damage leads to disruption of the alveolar wall, with flooding of the alveoli with protein-rich exudate, recog-
nizable histologically as hyaline membranes, and also edema, hemorrhage, and emphysema.

Evidence that 3-MI contributes to the pathogenesis of feedlot AIP has been gathered by investigators in Alberta. Plasma levels of 3-MEIN were significantly higher in animals with AIP than in those that died from other respiratory tract disease (Table 1). Similar evidence supporting a role for 3-MEIN in feedlot AIP has been gathered in the United States.

Melengestrol Acetate

Evidence also suggests that melengestrol acetate (MGA) may enhance the capacity of 3-MI to induce AIP. MGA is commonly fed to heifers to suppress estrus. In some southern Alberta feedlots, 97% of feedlot AIP cases were heifers. Removal of MGA from feedlot rations was associated with a decrease in the number of emergency slaughters, which were often due to AIP (Figure 5). These data represent approximately 100,000 animal days per treatment and were collected from multiple feedlots. Thus the possibility that management factors other than MGA resulted in differences in AIP incidence cannot be eliminated. Further work demonstrated that MGA did not alter plasma levels of 3-MI in heifers that did not develop AIP.

The interaction of 3-MI and MGA was tested by experimental administration of both compounds to ewes. Ewes were administered 3-MI, with or without MGA added to their feed. Animals in both groups developed pulmonary changes of AIP. Ewes fed MGA at the time of 3-MI administration developed signs of respiratory distress more rapidly and had higher levels of 3-MEIN in lung tissue than did ewes treated with 3-MI alone.

If MGA impacts the development of AIP, the mechanism by which it does so is not clear. Popp and colleagues speculated that MGA may enhance toxicity of 3-MI by increasing levels of the enzymes prostaglandin H synthetase or cytochrome P. These enzymes convert 3-MI to the more toxic 3-MEIN. Increased levels of these enzymes may lead to increased production of toxic metabolites, enhancing disease. Another hypothesis is that changes in feed intake due to environmental factors such as weather lead to altered MGA intake. The resulting change in hormone balance may somehow contribute to AIP. However, while this hypothesis has not been tested, there was no difference in total number of culturable bacteria, lactobacilli, or protozoa in the rumen fluid of heifers that were fed MGA and developed AIP compared with rumen fluid from control heifers also fed MGA. These findings suggest that acidosis associated with abrupt changes in feed intake did not occur in heifers that developed AIP.

Bovine Respiratory Syncytial Virus with 3-MI

In recent work, 3-MI and bovine respiratory syncytial virus (BRSV) were found to exert a synergistic effect to induce severe respiratory disease in cattle. This effect was not seen in earlier work, possibly due to diminished pathogenicity of the BRSV isolate used by Castleman and coworkers. Bingham and colleagues found that signs of respiratory distress occurred earlier (by day 2 after challenge) in calves exposed to both 3-MI and BRSV compared with calves exposed to 3-MI alone (by day 4 after challenge). Cattle exposed to BRSV alone did not show signs of respiratory distress.
At postmortem, emphysematous bullae were larger and more numerous in lungs of cattle exposed to both 3-MI and BRSV than in cattle exposed to 3-MI alone. These results suggest that 3-MI could contribute to the development of AIP in cattle infected with BRSV.

**Effect of Feed Additives**

If pneumotoxicity due to metabolism of 3-MI is related to feedlot AIP, the source of the 3-MI is not clear. Disruption of rumen protein balance may lead to production of 3-MI from certain feed components. Cattle dying of AIP have higher rumen pH than animals dying from gastrointestinal disease. Rumen ammonia levels are higher in cattle with AIP than in cattle with bacterial pneumonia. These findings may indicate a disruption of rumen protein metabolism that could lead to production of 3-MI with subsequent pneumotoxicity in feedlot AIP.

An important question that remains to be answered is whether feed additives such as monensin have an effect on feedlot AIP. Monensin may decrease the pulmonary damage related to tryptophan metabolism. Comments in the literature suggest that monensin does not prevent feedlot AIP, but published data are lacking. Because monensin is included in virtually all feedlot rations, it is likely that animals fed monensin-containing feeds have developed feedlot AIP, and recently collected data support this. Monensin is believed to control pasture-associated AIP through inhibition of *Lactobacillus* species, the primary microorganisms responsible for metabolism of L-tryptophan to 3-MI. Failure of monensin in feedlot rations to prevent 3-MI formation may be due to production of 3-MI by microbes other than *Lactobacillus* or failure of monensin to completely inhibit *Lactobacillus* in cattle fed high-starch diets.

**HYPERSENSITIVITY**

Hypersensitivity reactions have often been speculated to cause feedlot AIP. In early work, this association was made due to histopathologic similarities between some field cases of AIP and pulmonary type III hypersensitivity lesions in humans. Fungal spores, particularly those of *Micropolysporum faeni*, have been suggested to play a role in feedlot AIP.

**Extrinsic Allergic Alveolitis**

Extrinsic allergic alveolitis (bovine farmer’s lung) is the best-characterized pulmonary disease due to a hypersensitivity reaction in cattle. This disease is due to inhalation of spores of *M. faeni* or other antigens; the

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### Table 1. Presence of 3-MI Metabolites\(^a\) (nmol/ml) in Urine and Immunoreactivity to Adducts of 3-MEIN\(^b\) (absorbance/µg protein) in Plasma, Lung Tissue, and Isolated Microsomal Protein from Feedyard Heifers

<table>
<thead>
<tr>
<th>Substance</th>
<th>Negative Control A(^c) (n = 7)</th>
<th>Negative Control B(^d) (n = 17)</th>
<th>Positive (n = 31)</th>
<th>SEM</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>133.3</td>
<td>ND</td>
<td>36.5</td>
<td>21.7</td>
<td>.007</td>
</tr>
<tr>
<td>Plasma</td>
<td>60.1</td>
<td>—</td>
<td>79.4</td>
<td>5.8</td>
<td>.02</td>
</tr>
<tr>
<td>Plasma</td>
<td>—</td>
<td>41.4</td>
<td>79.4</td>
<td>3.4</td>
<td>.01</td>
</tr>
<tr>
<td>Lung tissue</td>
<td>117.6</td>
<td>ND</td>
<td>108.3</td>
<td>7.5</td>
<td>.44</td>
</tr>
<tr>
<td>Microsomal protein</td>
<td>79.4</td>
<td>ND</td>
<td>76.1</td>
<td>8.4</td>
<td>.79</td>
</tr>
</tbody>
</table>

\(^a\) Concentrations of the mercapturate metabolite of 3-MI in urine.

\(^b\) As measured by ELISA.

\(^c\) Samples collected from animals slaughtered after presenting with clinical signs of AIP but confirmed by subsequent histologic examination of lungs to be negative for AIP.

\(^d\) Plasma samples collected from asymptomatic contemporaries (penmates) of animals confirmed to have AIP.

\(ND\) = not determined.
subsequent lung lesion is the result of a combination of type III and IV hypersensitivity and other immune-mediated mechanisms. Cattle with extrinsic allergic alveolitis are identified with signs of either acute or chronic onset:

- **Acute cases** are characterized by moderate to severe dyspnea, tachypnea, and coughing. Clinically, the acute form of extrinsic allergic alveolitis is most likely to be confused with AIP. However, there are significant pathologic differences between the two conditions.
- **Chronic cases** are presented for cough, weight loss, and decreased production.

Grossly, the lungs of animals with extrinsic allergic alveolitis may appear almost normal. Close inspection reveals peripheral hyperinflation of lobules, sometimes with central collapse. In longstanding cases, the lungs may be pale and firm and may fail to collapse; thus the gross appearance is substantially different from that of AIP. Histologically, particularly following acute antigenic exposure, lesions may be similar to those seen in AIP; these include alveolar edema and hemorrhage, with infiltration of neutrophils, eosinophils, and mononuclear cells. However, in both acute and chronic cases of extrinsic allergic alveolitis, microscopic granuloma formation is consistent; these are not seen in AIP cases. Additionally, hyaline membrane formation and alveolar emphysema, which are typical of AIP, are never or rarely seen in cases of extrinsic allergic alveolitis. Thus while animals affected with feedlot AIP may have clinical signs suggestive of acute allergic alveolitis, the pathologic differences in the two conditions indicate that the mechanisms leading to these two diseases are not identical.

**Type I Hypersensitivity**

Type I hypersensitivity (acute anaphylaxis) is similar to feedlot AIP in some ways. Type I hypersensitivity due to milk allergy in dairy cattle can cause severe dyspnea of acute onset. Lung lesions in fatal cases include hyaline membrane formation, alveolar hemorrhage, severe pulmonary edema and congestion, and interstitial emphysema. However, it has been pointed out that type I hypersensitivity is unlikely to play a role in feedlot AIP because the lung lesion associated with acute anaphylaxis is either rapidly fatal or resolves within hours. Feedlot AIP is often fatal within a day, but some cattle may exhibit signs for 1 or more days. No research has been published describing attempts to formally evaluate the role of immune complexes, IgE, or other mediators of hypersensitivity in feedlot AIP.

**DUST EXPOSURE**

Many anecdotal reports associate dust with feedlot AIP; in fact, feedlot AIP is often referred to as *dust pneumonia*. However, feedlot AIP has also been identified in cattle not exposed to significant dust. It has been hypothesized that fungal spores or other antigens in dust may cause AIP through hypersensitivity reactions. It may also be that dust particles cause direct irritation to the alveolar epithelium. The effect of organic and inorganic dust exposure in lung disease is best characterized in humans, in whom dust exposure does not lead to AIP. Inorganic dusts, such as coal dust and silica, induce multifocal pulmonary nodules with fibrosis, which is sometimes extensive. It should be noted that silica exposure causes pulmonary injury through activity of free radicals and also by inducing release of proinflammatory cytokines by macrophages. Both of these mechanisms may be operative in the pathogenesis of AIP. Thus while humans exposed to silica do not develop AIP, it is possible that silica may be an irritant that contributes to the pathogenesis of feedlot AIP in regions with high-silica soils.

In humans, exposure to organic dust generally results in a hypersensitivity reaction, either at the level of the alveolus or at the bronchi or bronchioles (often manifested as asthma; see the Hypersensitivity section). Although no research formally addressing the association of dust with feedlot AIP has been published, the influence of dust exposure and weather on all feedlot respiratory disease was evaluated in one report. Increased levels of 2.0- to 3.3-µm dust particles and increased range in daily temperature were significantly associated with respiratory disease in cattle on feed for 16 to 30 days. However, pneumonia incidence was greatest in cattle on feed for 0 to 15 days. Also, pneumonia incidence was greatest in the first year of the study, whereas airborne dust concentration was greatest in the second year of the study. The results suggested that while 2.0- to 3.3-µm dust particles and temperature fluctuation were associated with respiratory disease in some feedlot cattle, they were not associated with the majority of the respiratory disease in that feedlot.

Hot weather is also anecdotally associated with feedlot AIP. It is not clear whether the temperature change induces AIP or whether it causes dusty conditions that contribute to AIP. As noted previously, increased range in ambient temperature was associated with respiratory disease in cattle on feed for 16 to 30 days in one study. Also possibly relevant is that AIP has been identified during hot weather in foals treated with antimicrobials for bacterial pneumonia.
TOXIC GASES

The evidence that toxic gases contribute to bovine AIP has been reviewed. Nitrogen dioxide, which can form in silage, and hydrogen sulfide are the gases most commonly incriminated in the pathogenesis of bovine AIP. Cattle that inhale nitrogen dioxide develop pulmonary edema and emphysema with alveolar epithelial proliferation. It has been speculated that these gases, from either environmental sources or from the rumen, might induce AIP. However, introduction of nitrogen dioxide into the rumen did not lead to pulmonary pathology. Additionally, high sulfur intake, which may lead to ruminal hydrogen sulfide production, was not identified in feedlots where AIP was identified. In summary, there is no firm evidence that toxic gases, particularly nitrogen dioxide and hydrogen sulfide, cause feedlot AIP. It seems unlikely that feedlot cattle are exposed to enough of these gases to cause pulmonary damage, but more research directly addressing the question might shed more light on the issue.

REFERENCES


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1. The cause of feedlot AIP is
   a. insufficient monensin in the finishing ration.
   b. an allergic response to dust in the environment.
   c. currently not known.
   d. a hypersensitivity reaction to vaccination at feedlot entry.

2. Although there is little published information describing the epidemiology of feedlot AIP, most of what is reported indicates that feedlot AIP most commonly causes death in
   a. cattle within 2 weeks of entry.
   b. cattle on feed longer than 45 days.
   c. Holsteins.
   d. cattle receiving multivalent vaccines containing BRSV at entry.

3. Confirmation of a diagnosis of AIP requires histologic identification of
   a. necrotizing bronchiolitis with syncytia formation.
   b. massive infiltration of eosinophils.
   c. microscopic granuloma formation.
   d. hyaline membrane formation, type II alveolar epithelial cell proliferation, congestion, and edema.

4. AIP is recognized by many to cause death primarily in
   a. summer and fall.
   b. fall and winter.
   c. winter.
   d. spring.

5. Which compound travels in the blood to the lung, where it can be metabolized by pulmonary cells to toxic compounds capable of causing cell damage and inflammation?
   a. tryptophan
   b. 3-MI
   c. 3-MEIN
   d. prostaglandin H synthetase

6. Which pulmonary cells metabolize 3-MI to more toxic metabolites?
   a. type I alveolar epithelial cells and Clara cells
   b. type II alveolar epithelial cells
   c. endothelial cells
   d. alveolar macrophages

7. Recent research suggests that 3-MI may play a role in feedlot AIP. This is based on the finding that
   a. higher rumen concentrations of 3-MI are found in cattle that die from AIP than in control cattle.
   b. blood levels of tryptophan are higher in cattle that die from AIP than in control cattle.
   c. a toxic metabolite of 3-MI, 3-MEIN, has been identified in greater amounts in plasma and lung tissue of cattle that die from AIP than in control cattle.
   d. diets of cattle that die from AIP contain more tryptophan than diets of control cattle.

8. Recent research indicated that lung disease was more severe in animals exposed to 3-MI and which respiratory virus?
   a. respiratory coronavirus
   b. BRSV
   c. infectious bovine rhinotracheitis
   d. parainfluenzavirus 3

9. In a study of southern Alberta feedlots, which group of animals was at greatest risk of dying from AIP?
   a. Holsteins
   b. *Bos indicus* breeds
   c. steers
   d. heifers

10. Although hypersensitivity is often speculated to lead to AIP, which of the following is the only hypersensitivity-mediated disease known to cause lung lesions similar to those seen in AIP?
    a. acute anaphylaxis
    b. bovine farmer’s lung
    c. tuberculosis
    d. diffuse fibrosing alveolitis