3rd Annual TVMDL Amarillo
BOVINE RESPIRATORY DISEASE
Conference

July 7, 2018

AIP: What the Heck Causes It?

Amelia R. Woolums, DVM MVSc PhD DACVIM DACVM
Mississippi State University, Mississippi State, MS

Introduction

In feedlot cattle, acute interstitial pneumonia (AIP) is a sporadically occurring respiratory condition that is often fatal. AIP can have a serious negative impact for individual feedlots, because cattle that have been on feed for some time can be affected, because treatment is often ineffective, and because outbreaks leading to death of multiple cattle can occur

Clinical signs and definition

Cattle with AIP have a sudden onset of dyspnea. They stand with the head lowered and neck extended, and breathe with an open mouth, with an expiratory grunt. They may have a base-wide stance in the front limbs. Nasal discharge and coughing are not common. Cattle suspected to have AIP must be moved for examination or treatment carefully, as handling and movement may lead to death. Affected cattle may be found dead without previous signs of disease having been noticed.

"Acute interstitial pneumonia" is a pathologic definition that can only be confirmed by microscopic (histopathologic) evaluation of lung tissue. Therefore, a live animal can only be identified to have signs *consistent with* AIP; without a lung biopsy AIP cannot be definitively diagnosed in the live animal. In humans and other species with AIP, characteristic clinical signs and diagnostic test results are used to confirm a clinical definition of "acute respiratory distress syndrome" (ARDS).[1] A diagnosis of AIP can only be confirmed by histopathologic evaluation of lung tissue collected at postmortem. Experienced feedlot staff may accurately diagnose many AIP cases, but even knowledgeable individuals may misdiagnose some cases when making a judgment based on clinical signs or gross pathology alone. Reports indicated that 67% - 82% of cattle suspected by to have AIP based on their clinical signs were confirmed by histopathologic evaluation.[2,3]

Pathology of AIP

Grossly, lungs from cattle affected by AIP remain expanded when the chest is opened. The lung tissue has a firm, rubbery consistency. Individual lung lobules may vary in color from pale pink or gray to brown, dark red, or purple, giving the lung a "patchwork quilt" or "checkerboard" appearance (Figure 2).[2,4] Emphysematous bullae or interstitial emphysema may be grossly evident.[2,4] However, the presence of grossly evident emphysema, which may simply be a result of agonal breathing, does not alone confirm a diagnosis of AIP. On cross section, the lung surface may appear shiny, due to edema; hemorrhage may also be evident. Manual manipulation of the lung often reveals the lobules to be independently movable, due to their separation by edema or emphysema.[3] Cattle with AIP can have concurrent fibrinous bronchopneumonia, or bovine respiratory disease (BRD) affecting the cranial and/or ventral lung, with firm, dark red, gray, or brown lung that may also have fibrin on the surface.[2,5] In such cases, primary, possibly chronic bronchopneumonia may have predisposed the animal to development of superimposed (secondary) AIP.

Microscopically, the lesions of AIP include alveolar accumulation of pink homogenous material consisting of proteinaceous fluid (sometimes condensed into "hyaline membranes").[2-4] Neutrophils, macrophages, and sometimes eosinophils infiltrate into alveoli and airways. Edema and hemorrhage may be present in some lobules. These may be the only lesions in cattle that die very soon after disease onset (the "exudative phase" of AIP). In cases that live longer, proliferation of alveolar type II pneumocytes occurs, and is seen microscopically (the "proliferative phase" of AIP).[2-4] With more time, inflammatory cells and fibrous tissue may infiltrate the interstitial space. Although AIP is an acute disease, some cattle also have histopathologic evidence of chronic or past airway injury, including bronchiolitis obliterans.[2,4,6] Bronchiolitis obliterans results from injury to the airway epithelium, and could be due to recent or past viral or bacterial infection, or injury from pneumotoxins or inhaled irritants. In humans, the lesion can also result from immune-mediated conditions.[7] The frequent occurrence of bronchiolitis obliterans in cases of feedlot AIP may be a clue to the etiology, but the exact cause of the lesion is not known.

Epidemiology and risk factors

In the 2011 USDA NAHMS survey,[8] 72% of all feedlots reported having cattle with AIP, with AIP affecting 2.8% of cattle placed. For comparison, 97% of feedlots reported having cattle with shipping fever (BRD), with BRD affecting 16.2% of cattle placed. A survey of causes of death in yearling feedlot cattle over a single year in 4 western U.S. feedlots revealed AIP in 5.3% of the cattle subjected to necropsy.[4] Mortality rates ranging from 0.03% - 0.15% of all cattle placed have been reported.[4,9] Compared to BRD, cattle die of AIP relatively late in the feeding period;[10] the average number of days on feed at the time of death for cattle with AIP has been reported to be 114 – 136 days.[2,3,10] Heifers may be disproportionately affected; in one report the odds of an animal with AIP being a heifer were 3.1 times greater than controls.[11] However, in a survey of feedlots to determine risk factors for AIP, feedlots where 50% - 75% of placements were heifers did not always report having cases of AIP.[12] Thus, in feedlots where AIP occurs, heifers may be disproportionately affected, but feedlots placing large numbers of heifers do not always see AIP.

Gastrointestinal problems may predispose feedlot cattle to develop AIP. An analysis of health records for 128,500 feedlot cattle collected over 18 months showed that the incidence of AIP was approximately 70% greater in pens where at least one digestive death occurred, as compared to pens where a digestive death did not occur.[13] However, AIP does not appear to result from acidosis; cattle with feedlot AIP have been found to have higher ruminal pH values than expected for cattle adapted to a high concentrated diet. Ruminal pH in AIP cases ranged from 5.6 to 7.2 in one study[2] and from 4.9 to 7.4 in another,[14] whereas the ruminal pH of cattle adapted to a high concentrate diet is typically about 5.5 to 5.6.[15] Many proteins are relatively basic; therefore the high ruminal pH could be related to abnormal protein metabolism. However, the relatively high ruminal pH could also be caused by anorexia.

A survey of U.S. feedlots[12] found that feedlots in northern states (Nebraska, Utah, Idaho, South Dakota, North Dakota, Montana, and Washington) were less likely to recognize AIP as a cause of morbidity and mortality than feedlots in other states, with 66% of northern feedlots recognizing AIP, versus 94% of feedlots in other regions ($P < 0.01$). Larger feedlots were more likely to recognize AIP; 90% of

responding feedlots that placed 10,000 or more cattle annually reported AIP as a cause of morbidity and mortality, as compared to 62% of feedlots placing fewer than 10,000 head annually ($P < 0.01$). Feedlots that vaccinated over 95% of their cattle against *Mannheimia haemolytica* +/- *Pasteurella multocida* were less likely to report seeing AIP cases, as compared to feedlots vaccinating 95% or fewer of their cattle ($P < 0.001$). The significance of the relationship between *Mannheimia/Pasteurella* vaccination and AIP is not known. Because a trend toward increased recognition of AIP by feedlots placing more yearling cattle was also identified in the survey, the relationship between *Mannheimia/Pasteurella* vaccination and decreased recognition of AIP may have been because AIP was less common in feedlots placing younger cattle, where vaccination against *Mannheimia/Pasteurella* was likely more common.

So…what the heck causes AIP?

Acute interstitial pneumonia occurs following injury to alveolar epithelial cells; therefore cattle with feedlot AIP have been exposed to something that injures these cells. However, the exact cause of this injury may be difficult or impossible to determine. In cattle outside of feedlots, pneumotoxic compounds such as 3-methylindole (3-MI), produced by ruminal metabolism of L-tryptophan in green forage[16] are known to cause bronchiolar and alveolar epithelial cell injury, leading to AIP. Metabolites of 3-MI such as 3-methyleneindolenine (3-MEIN) bind to cellular proteins and nucleic acids, leading to cellular dysfunction and death. Pneumotoxins in moldy sweet potatoes[17] and perilla mint[18] likewise cause AIP by direct cellular injury. Other feeds, including turnip tops, moldy hay, and individual batches of silage, have been associated with AIP outbreaks, but the causative components of these feeds is not known. Toxic gases, such as nitrogen dioxide, zinc oxide, or chlorine gas, can cause AIP, but in most cases feedlot cattle are unlikely to be exposed to concentrations of these gases sufficient to cause disease. Smoke inhalation can also cause AIP, and exposure is usually obvious.

While the exact cause of feedlot AIP is not known, research undertaken to determine the cause has identified the following factors to be associated with the disease in one or more reports:

3-methylindole (3-MI) and metabolites of 3-MI[3,11]
melengestrol acetate (MGA)[19,20]
BRSV infection[2,21]
bacterial pneumonia[2,9]
airway epithelial cell injury (bronchiolitis obliterans)[2,4,6]
hot weather[2-4]
dusty conditions[3,4]

Two or more of the above factors may interact to induce AIP in many cases. This is suggested by the finding that experimental exposure of cattle to BRSV with 3-MI has been shown to cause lung lesions of significantly increased severity compared to those seen in cattle exposed to BRSV or 3-MI alone.[22]

Taken together, the available information suggests that: 1) **factors related to the formulation or delivery of the diet, or rumen metabolism of dietary components**; and/or 2) **viral or bacterial respiratory infection** are likely the most important factors contributing to the development of most cases of feedlot AIP.

It has been repeatedly reported that more AIP cases occur during hot or dusty weather, but it is not clear why this is so. Perhaps hot or dusty weather stresses the respiratory system when it is primed for AIP by one or more of the factors listed above, pushing cattle to a "tipping point" that leads to disease. Exposure of sheep or goats to repeated doses of aerosolized feedlot dust containing microorganisms and endotoxin did not lead to AIP,[23,24] and exposure to *Mannheimia haemolytica* or *Pasteurella multocida* did not induce serious lung disease in goats exposed to aerosolized feedlot dust.[24] Similarly, tracheal instillation of spores of fungi commonly found in feedlot dust did not induce AIP in goats.[25] These studies suggest that feedlot dust exposure alone is unlikely to cause AIP.

Treatment of cattle suspected to have AIP

Evidence-based guidelines for treatment of feedlot AIP are lacking. It is noteworthy that there are currently no specific treatments for humans with the clinical syndrome ARDS, likely due to AIP;[26,27] current recommendations for treatment of humans with ARDS include rigorous supportive care, with certain mechanical ventilation strategies most commonly cited as improving outcomes. In humans, beta-adrenergic agonists, high-dose or moderate-dose corticosteroids, neutrophil elastase inhibitors, and a variety of other therapies have been tested, but have failed to improve outcomes in patients with ARDS.[27] Low doses of corticosteroids appear to be beneficial, but repeated daily treatments for one to four weeks are used;[28] such a regimen is not likely feasible for use in feedlot cattle.

Although no specific therapies are proven to be effective in cattle with feedlot AIP, and no drugs are labeled for the treatment of feedlot AIP, it is rational to treat cattle suspected to have AIP with drugs that address the lesions known to occur in affected lungs, namely, cellular injury, inflammation, and, in some cases, bacterial infection. Additionally, because antemortem case definition is not perfectly accurate, it is prudent to treat apparent AIP cases with antimicrobials, because some may actually have BRD. Treatments most commonly recommended include antimicrobials appropriate for treatment of *M. haemolytica* and *P. multocida,* and
NSAIDs, particularly aspirin. Because cattle with AIP may die suddenly, and because treatment may not be effective, emergency slaughter of AIP cases when they are first identified may be the best course of action.[3,13]

Case fatality and chronic rates for cattle with AIP have not been published, but the reported use of emergency slaughter to handle cases suggests that feedlots do not find therapy to be rewarding. Because it is not possible to make a definitive antemortem diagnosis of AIP in the feedlot setting, it is difficult to know whether cattle that survive an apparent episode of AIP truly had AIP. Humans that survive episodes of ARDS can have long-term debilitation that has a negative impact on quality of life.[26]

Prevention of Feedlot AIP

There is currently no published evidence from controlled trials that supports the development of recommendation to prevent feedlot AIP. Monensin decreases the metabolism of tryptophan to 3-MI by *Lactobacillus* sp. in the rumen; for this reason monensin is sometimes fed to cattle at risk for pasture-associated AIP. Monensin may also help control feedlot AIP; however, feedlot cattle fed rations

containing monensin sometimes still develop AIP.[2,29] Because free radical scavengers can reduce the toxicity of metabolites of 3-MI, both vitamin E[29,30] and the glutathione precursor cysteine (provided as feather meal)[29] have been administered to decrease rates of AIP or to improve growth and health in cattle at risk for AIP. However, no clear beneficial effect of these treatments has been identified.

Likewise, while aspirin is theoretically beneficial because it can inhibit function of prostaglandin H synthetase, which can generate toxic metabolites from 3-MI,[31] a clear protective effect against AIP has not been identified.[30,32] However, it has been claimed that aspirin treatment of cattle with clinical signs of AIP is associated with longer survival.[33]

Removal of MGA from heifer diets has been reported to decrease AIP.[34] In a subsequent clinical trial, these researchers found no difference in death loss in pens of heifers fed MGA compared to pens of heifers not fed MGA; however, rates of emergency slaughter (due to clinical signs consistent with AIP) for heifers fed MGA were over 3 times higher than those for heifers not fed MGA.[20] However, it should be noted that others have suggested that erratic consumption of MGA, leading to estrus, with related hormonal changes, decreased feed intake, and resulting digestive changes, may actually cause AIP.[13] This line of reasoning suggests that *inadequate* MGA consumption leads to AIP. If MGA does contribute to the pathogenesis of AIP its role is not clear; it has been speculated to increase production of 3-MI through multiple possible pathways.

Given the list of factors associated with feedlot AIP, it is rational to consider the following interventions to decrease occurrence of the disease:

1. Ensure that rations are formulated, mixed, and delivered consistently.

2. Ensure that monensin is included in the ration at the highest appropriate dose.

3. Review MGA use if AIP in heifers is a problem. Ensure consistent intake, or consider removing from ration (expert views are mixed on the role of MGA).

4. Institute practices to decrease dust and minimize heat stress. Focusing on pens of cattle that have been in the feedlot > 45 days may be most efficient

5. Ensure timely identification and treatment of cattle with signs of BRD, which may predispose cattle to later develop AIP.

References

1. Mukhopadhyay S, Parambil JG. Acute interstitial pneumonia (AIP): relationship to Hamman-Rich syndrome, diffuse alveolar damage (DAD), and acute respiratory distress syndrome (ARDS). *Semin Respir Crit Care Med* 2012;33:476-485. doi:10.1055/s-0032-1325158
2. Woolums AR, Mason GL, Hawkins LL, et al. Microbiologic findings in feedlot cattle with acute interstitial pneumonia. *Am J Vet Res* 2004;65:1525-1532. doi:10.2460/ajvr.2004.65.1525

3. Ayroud M, Popp JD, VanderKop MA, et al. Characterization of acute interstitial pneumonia in cattle in southern Alberta feedyards. *Can Vet J* 2000;41:547-554. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1476195/
4. Jensen R, Pierson RE, Braddy PM, et al. Atypical interstitial pneumonia in yearling feedlot cattle. *J Am Vet Med Assoc* 1976;169:507-510.
5. Panciera RJ, Confer AW. Pathogenesis and pathology of bovine pneumonia. *Vet Clin North Am Food Anim Pract* 2010;26:191-214. doi:10.1016/j.cvfa.2010.04.001.
6. Sorden SD, Kerr RW, Janzen ED. Interstitial pneumonia in feedlot cattle: concurrent lesions and lack of immunohistochemical evidence for bovine respiratory syncytial virus infection. *J Vet Diagn Invest* 2000;12:510-517. doi:10.1177/104063870001200604
7. Barker AF, Bergeron A, Rom WN, et al. Obliterative bronchiolitis. *N Engl J Med* 2014;370:1820-1828. doi:10.1056/NEJMra1204664
8. USDA. In: Feedlot 2011 "Part IV: health and health management on U.S. feedlots with a capacity of over 1000 head. Ft. Collins, CO: USDA-APHIS-VS-CEAH-NAHMS, 2011. https://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_PartIV.pdf
9. Hjerpe CA. Clinical management of respiratory disease in feedlot cattle. *Vet Clin North Am Large Anim Pract* 1983;5:119-142. doi:10.1016/S0196-9846(17)30096-4
10. Loneragan GH, Gould DH, Mason GL, et al. Involvement of microbial respiratory pathogens in acute interstitial pneumonia in feedlot cattle. *Am J Vet Res* 2001;62:1519-1524. doi:10.2460/ajvr.2001.62.1519
11. Loneragan GH, Gould DH, Mason GL, et al. Association of 3-methyleneindolenine, a toxic metabolite of 3-methylindole, with acute interstitial pneumonia in feedlot cattle. *Am J Vet Res* 2001;62:1525-1530. doi:10.2460/ajvr.2001.62.1525
12. Woolums AR, Loneragan GH, Hawkins LL, et al. A survey of the relationship between management practices and risk of acute interstitial pneumonia at U.S. feedlots. . *Bov Pract* 2005;39:125. doi:10.2460/ajvr.2001.62.1525
13. Loneragan GH. Epidemiological characteristics of AIP in feedlot cattle. . *Proc Acad Vet Consult* 2002;Summer Meeting:1.
14. Miles DG, Hoffman BW, Rogers KC, et al. Diagnosis of digestive deaths. *J Anim Sci* 1998;76:320-322. doi:10.2527/1998.761320x
15. Fulton WR, Klopfenstein TJ, Britton RA. Adaptation to high concentrate diets by beef cattle. I. Adaptation to corn and wheat diets. *J Anim Sci* 1979;49:775. doi:10.2527/jas1979.493775x
16. Dickinson EO, Spencer GR, Gorham JR. Experimental induction of an acute respiratory syndrome in cattle resembling bovine pulmonary emphysema. *Vet Rec* 1967;80:487-489. doi:10.1136/vr.80.16.487
17. Peckham JC, Mitchell FE, Jones OH, Jr., et al. Atypical interstitial pneumonia in cattle fed moldy sweet potatoes. *J Am Vet Med Assoc* 1972;160:169-172.
18. Kerr LA, Johnson BJ, Burrows GE. Intoxication of cattle by Perilla frutescens (purple mint). *Vet Hum Toxicol* 1986;28:412-416.
19. Popp JD, McAllister TA, Kastelic JP, et al. Effect of melengestrol acetate on development of 3-methylindole-induced pulmonary edema and emphysema in sheep. *Can J Vet Res* 1998;62:268-274. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1189493/pdf/cjvetres00016-0030.pdf
20. Stanford K, McAllister TA, Ayroud M, et al. Effect of dietary melengestrol acetate on the incidence of acute interstitial pneumonia in feedlot heifers. *Can J Vet Res* 2006;70:218-225. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1477937/pdf/cjvr70pg218.pdf
21. Collins JK, Jensen R, Smith GH, et al. Association of bovine respiratory syncytial virus with atypical interstitial pneumonia in feedlot cattle. *Am J Vet Res* 1988;49:1045-1049.
22. Bingham HR, Morley PS, Wittum TE, et al. Synergistic effects of concurrent challenge with bovine respiratory syncytial virus and 3-methylindole in calves. *Am J Vet Res* 1999;60:563-570.

23. Purdy CW, Straus DC, Chirase N, et al. Effects of aerosolized feedyard dust that contains natural endotoxins on adult sheep. *Am J Vet Res* 2002;63:28-35. doi:10.2460/AJVR.2002.63.28
24. Purdy CW, Straus DC, Chirase N, et al. Effects of aerosolized dust in goats on lung clearance of Pasteurella and Mannheimia species. *Curr Microbiol* 2003;46:174-179. doi:10.1007/s00284-002-3821-7
25. Purdy CW, Layton RC, Straus DC, et al. Virulence of fungal spores determined by tracheal inoculation of goats following inhalation of aerosolized sterile feedyard dust. *Am J Vet Res* 2005;66:615-622. doi:10.2460/ajvr.2005.66.615
26. Carlucci M, Graf N, Simmons JQ, et al. Effective management of ARDS. *Nurse Pract* 2014;39:35-40. doi:10.1097/01.NPR.0000454981.96541.e6
27. Boyle AJ, Mac Sweeney R, McAuley DF. Pharmacological treatments in ARDS; a state-of-the-art update. *BMC Med* 2013;11:166. https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-11-166
28. Tang BMP, Craig JC, Eslick GD, et al. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. *Critical Care Medicine* 2009;37:1594-1603. doi:10.1097/CCM.0b013e31819fb507
29. Stanford K, McAllister TA, Ayroud M, et al. Acute interstitial pneumonia in feedlot cattle: effects of feeding feather meal or vitamin E. *Can J Vet Res* 2007;71:152-156. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1829179/
30. Loneragan GH, Morley PS, Wagner JJ, et al. Effects of feeding aspirin and supplemental vitamin E on plasma concentrations of 3-methylindole, 3-methyleneindolenine-adduct concentrations in blood and pulmonary tissues, lung lesions, and growth performance in feedlot cattle. *Am J Vet Res* 2002;63:1641-1647. doi:10.2460/ajvr.2002.63.1641
31. Bray TM, Emmerson KS. Putative Mechanisms of Toxicity of 3-Methylindole - from Free-Radical to Pneumotoxicosis. *Annual Review of Pharmacology and Toxicology* 1994;34:91-115. doi:10.1146/annurev.pa.34.040194.000515
32. Bingham HR, Wittum TE, Morley PS, et al. Evaluation of the ability of orally administered aspirin to mitigate effects of 3-methylindole in feedlot cattle. *Am J Vet Res* 2000;61:1209-1213. doi:10.2460/ajvr.2000.61.1209
33. McAllister T. Characterization of atypical interstitial pneumonia in feedlot cattle in southern Alberta. *Proc Acad Vet Consult* 2007;Spring Meeting:13 - 22.
34. Woolums AR W, McAllister TA, Loneragan GH, et al. Etiology of acute interstitial pneumonia in feedlot cattle: noninfectious causes. . *Compend Cont Educ Pract Vet* 2001;23:S86-S93