An Update on Feedlot AIP

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Abstract

Acute interstitial pneumonia (AIP) has been recognized in feedlot cattle for decades, but the cause is still unknown. AIP is most common in cattle on feed greater than 45 days; heifers may be disproportionally affected. Clinical signs suggest severe respiratory distress, but a definitive diagnosis can only be made at postmortem. At postmortem, the lungs fail to collapse, interstitial emphysema and edema is evident, and a "checkerboard" pattern of light and dark colored, independently movable lobules is commonly seen. Histologically, hyaline membranes, type II pneumocyte hyperplasia, and later, cellular infiltrates are found. No specific treatment is reliably effective. Known causes of AIP outside feedlots include 3-methylindole, perilla mint, and moldy sweet potato toxicity. Bovine respiratory syncytial virus can cause lesions similar to AIP. Bronchopneumonia and histologic evidence of chronic bronchiolar injury have been described in cattle with feedlot AIP, suggesting that chronic airway inflammation may predispose cattle to the disease. Recent research suggests that 3-methylindole, hormonal influences (including the feeding of melengestrol acetate), and bacterial lung infection may influence the development of feedlot AIP; however, no evidence is currently strong enough to support any of these as a single cause. Recent research does not support acute BRSV infection as a cause. Other insults speculated to cause feedlot AIP, such as dust exposure, heat, and allergic reactions, have not been investigated. Currently it seems most likely that feedlot AIP has a multifactorial etiology, and the relative importance of various factors may differ among feedyards. More information is needed before informed recommendations regarding prevention of feedlot AIP can be made.

Introduction

Acute interstitial pneumonia (AIP) can be a frustrating problem for feedlots. Clinical signs can be subtle in the early stages of the disease, but the condition rapidly progresses to cause respiratory distress and death. Death due to feedlot AIP is most common in cattle on feed greater than 45 days,[17,19] thus losses are amplified by the resources invested in animals prior to death. No reliable treatment has been identified, and clinical experience with a similar syndrome in human beings suggests that a treatment that is consistently effective and practical for use in the feedlot is unlikely to be found.[7] Thus, efforts should be aimed at preventing feedlot AIP and decreasing losses due to the disease. Although experienced feedlot staff can often guess when AIP deaths are likely to increase, they can't implement effective preventative measures because so little is known about the cause of the disease. A review of the history of AIP and examination of some recent research may help clarify misconceptions about feedlot AIP, and will establish a basis for understanding the results of ongoing research aimed at identifying preventative measures.

Clinical Signs and Pathology

Clinical signs of AIP include evidence of respiratory distress characterized by a sway-backed appearance with extended head, open mouth breathing, and a wide-based stance in the front limbs.[32] The respiratory rate may be increased or may be relatively slow due to the effort associated with breathing. An expiratory abdominal push, sometimes with an audible grunt, is often evident. Animals with these clinical signs must be moved with care if at all, as it is not unusual for them to die due to the stress and effort of forced exercise.

It is important to note that the clinical signs described above are not perfectly specific for AIP and may also be seen with other types of respiratory disease, or with severe heat stress. Fever is inconsistent in animals with AIP (Woolums *et al*, unpublished data), and lack of fever may help distinguish some cases of AIP from cases of acute pneumonia due to infectious causes.

Gross pathologic findings of AIP include expanded lungs that fail to collapse when the thorax is opened. The lung tissue feels "meaty" or rubbery (heavier and

firmer than normal). Interstitial edema and emphysema is often present. It is important to remember that some emphysema often develops in response to agonal breathing in cattle, thus the finding of grossly apparent emphysema cannot alone be considered sufficient to make a diagnosis of AIP. In some cases of AIP, the cut surface of lung may appear wet or shiny due to interstitial edema, however, this is not a consistent finding. In some AIP cases the surface appears relatively dry. A common finding is that individual lobules appear "freely movable",[26] due to their separation by interlobular edema or emphysema. The color of the lobules often varies, with some dark red and others pale, giving a "patchwork" appearance to the lung. It is possible for individual regions of the lung to be affected with AIP, or for the gross abnormalities to be distributed evenly throughout all lung fields. Animals with AIP may have gross evidence of concurrent bronchopneumonia.

In our ongoing research we have found that some cases of bronchopneumonia without AIP can have expanded, "meaty"-textured dorsocaudal lung that appears grossly to be AIP, but which is not confirmed histologically. In these cases the gross findings are due to interstitial inflammation that may be related to a generalized inflammatory response in the lung resulting from the primary infectious etiology.

Histopathologic evaluation is necessary to confirm a diagnosis of AIP. A definitive diagnosis of AIP is made based on identification of hyaline membranes (a result of alveolar accumulation of proteinaceous fluid), alveolar type II pneumocyte proliferation, interstitial edema and emphysema (and sometimes hemorrhage), and interstitial infiltration of inflammatory cells, both neutrophils and mononuclear cells.[9,17,26,28] The most acute changes are hyaline membrane formation and interstitial edema and emphysema, which are attributed to leakage of fluid into the alveoli and air into the interstitium as a result of damage to the alveolar-vascular interface. Later, the subacute changes of type II pneumocyte proliferation and inflammatory cell infiltrate are seen. In individual cases of AIP either the acute or subacute changes may predominate. In early reports this difference between cases was attributed to different etiologies,[26] but it is more likely that the difference is due to varying duration of time from the onset of disease until death.

It is interesting to note that changes consistent with chronic bronchiolar injury, specifically bronchiolitis obliterans, have been described in cases of AIP in many reports.[9,17,28] In at least one report[28] bronchiolitis obliterans was present significantly more often in AIP cases than controls. This indicates that chronic airway insult is occurring in animals that go on to develop AIP. The cause of the airway insult is unknown, but could include past infection with *Mycoplasma,* BRSV, or parainfluenza virus (PI3), or irritants such as dust.

It is important to note that not all cases identified as AIP based on clinical signs or gross pathology are confirmed histologically. In one study,[1] 82% of cases identified based on clinical signs and gross pathology were confirmed to be AIP. Our ongoing research has revealed a similar or sometimes lower level of agreement in different feedyards. In our research, animals found not to have AIP have instead been found to have histopathologic changes consistent with chronic bronchopneumonia or chronic bronchiolitis.

It must be emphasized that the pathologic changes of AIP can occur in response to a variety of insults that cause severe acute alveolar damage. Thus the lesion of AIP should not be considered as specific for one particular etiology, but rather a possible result of a variety of etiologies. The challenge for researchers will be to determine which etiologies are the most important causes of AIP in feedlot cattle.

History and Early Research Efforts

In several reports from the 1940's and 1950's, disease consistent with AIP was described in cattle of all ages and in a variety of production settings.[4,5,26,27] Because of the failure of usually reliable treatments to work in animals affected with this syndrome, and also because of what was thought to be unusual pathology compared to that seen in cattle with bronchopneumonia, the disease was considered an atypical pneumonia, and was often referred to as "atypical interstitial pneumonia".[5] We now know the pathology was not atypical, but was actually typical of that seen following acute alveolar injury.[12] A variety of other names were also applied to the syndrome, including pulmonary adenomatosis (due to the histological glandular appearance of the lung), bovine pulmonary emphysema, bovine asthma and "fog fever". The variety of names revealed the general lack of knowledge regarding the exact cause of the syndrome. In many cases feed changes were linked to outbreaks, particularly the addition of moldy feeds such as corn stalks or sweet potatoes. Theories regarding possible causes abounded, and many of the early writers focused on hypersensitivity as a likely cause.

In the 1970's, some breakthroughs were made regarding the cause of at least some cases of AIP. It was found that dietary tryptophan could be metabolized by rumen microbes to indoleacetic acid and then to 3-methylindole (3-MI), which is a pneumotoxin that can damage ruminant lung and lead to lesions typical of AIP.[14] This was determined to be the major cause of AIP associated with an abrupt move of cattle to green pasture. Around the same time it was found that other pneumotoxic compounds were present in moldy sweet potatoes and purple mint.[11,31] In light of this information, AIP outbreaks associated with abrupt diet changes

or introduction of novel feedstuffs are often attributed to dietary pneumotoxins, even when there is not necessarily evidence for this etiology.

Another relevant discovery in the 1970's was a new respiratory virus that was associated with some outbreaks of AIP, particularly those occurring in weaned calves. This virus was bovine respiratory syncytial virus (BRSV).[6,13] BRSV infection causes many of the pathologic lesions also seen in AIP, but histologic identification of syncytial (multinucleated) cells in bronchioles and alveoli is particularly characteristic and is not consistently present in AIP. Moreover, acute bronchiolitis is a hallmark of acute BRSV infection that is not consistently found in AIP. However, the fact that BRSV can be difficult to isolate and often eluded early investigators no doubt led to confusion regarding which outbreaks were due to BRSV infection and which were AIP due to other causes. Further clouding the issue was the observation made by many that BRSV outbreaks seemed to be associated with feeding corn silage. This led to speculation that dietary pneumotoxins and BRSV somehow interacted, a theory that was to be revisited in coming decades.[2,8]

Another theory that has often been raised is that toxic gases, either inhaled from environmental sources or generated in the rumen, cause AIP. This theory has been much discussed but to this date almost no research has been done to test the hypothesis. In one small study, one steer was exposed to large amounts of nitrogen dioxide by inhalation and that animal did develop signs of AIP.[10] However, a second animal that had large quantities of nitrogen dioxide pumped into the rumen for several days never developed AIP. The amount of nitrogen dioxide required to induce AIP in the single animal affected was so large that the investigators considered it highly unlikely that such exposure was the cause of any significant number of natural AIP cases.

The theory that anaphylaxis or hypersensitivity causes AIP has also been much discussed, but studied very little. One group of researchers tested the anaphylaxis theory by inducing hypersensitivity in cattle and sheep to egg protein or horse serum.[18] These animals did develop respiratory distress, and one animal that died acutely did have some of the lesions typical of acute AIP, including interstitial edema, emphysema and hyaline membrane formation. However, the majority of the animals recovered, and when they were euthanized a few days later they did not have the typical subacute lesions of AIP, alveolar type II pneumocytes proliferation with inflammatory cell influx. These findings suggested that AIP is not initiated by a hypersensitivity response. A limitation of this study was that the allergen was delivered by injection, rather than by inhalation. Many people have speculated that inhaled allergens contribute to AIP, but no research has been done to investigate this possibility. It should be noted that extrinsic allergic alveolitis, which is due to type III and type IV hypersensitivity responses to inhaled allergens, is characterized by very different pathology than AIP.[24]

Thus, by the end of the 1970's at least two major causes of the bovine lung lesion typical of AIP had been identified; dietary pneumotoxins, especially 3-MI associated with dietary tryptophan, and BRSV infection.

In 1988, the first published attempt to determine a cause of feedlot AIP was reported.[9] In a small observational study, researchers tested the hypothesis that BRSV was associated with AIP. They found that 11 of 15 cattle with naturally occurring fatal AIP were infected with BRSV, while only 5 of 18 cattle with other types of respiratory disease were infected with BRSV. This association was significant, suggesting that BRSV was the cause of at least some cases of feedlot AIP, however, later research would not support this finding.[1,19,28]

Recent Research

Since the 1990's more research has been carried out that directly or indirectly provides information regarding possible causes of feedlot AIP. In two studies, investigators tested the hypothesis that concurrent exposure to 3-MI and BRSV causes more severe lung disease than exposure to either agent alone. In one study, disease was not enhanced in cattle exposed to both 3-MI and BRSV,[8] but in a later study combined exposure did enhance disease[2]. Failure to induce enhanced disease in the first study may have been related to low virulence of the BRSV isolate used for challenge. These findings raise the possibility that low levels of 3-MI combined with low-level BRSV challenge may together lead to AIP when the dose of each is insufficient to cause disease alone.

A direct examination of feedlot AIP was undertaken by researchers in western Canada[1]. In selected western Canadian feedlots, heifers appeared to be disproportionally affected by AIP. Anecdotal evidence suggested that withdrawal of melengestrol acetate (MGA) decreased the incidence of AIP. Controlled studies indicated that ewes fed MGA had higher baseline levels of a toxic metabolite of 3-MI, 3-methyleneindolenine (3-MEIN), in their plasma than control sheep.[25] Additionally, when sheep fed MGA were challenged with 3-MI, they developed respiratory distress more rapidly than control sheep not fed MGA, and 3-MEIN levels were higher in the lung of sheep fed MGA than in controls. This research supported the concept that MGA exposure could increase levels of pneumotoxic metabolites in the lung following 3-MI exposure.

These researchers extended their studies by measuring levels of 3-MEIN in the tissues of cattle dying of

AIP in western Canadian feedlots. In 31 animals with naturally occurring AIP, plasma 3-MEIN levels were increased compared to control animals. However, 3-MEIN levels were not increased in the lung of AIP cases.[1] In a further study,[1] 3-MEIN levels were measured in the plasma of intact heifers, ovariectomized heifers, and in heifers fed MGA. No differences were found, suggesting that feeding MGA did not cause a baseline increase in 3-MEIN levels in heifers as it had in sheep. In summary, the western Canadian research supports some role for 3-MI in feedlot AIP, but the relationship between 3-MEIN levels and the development of AIP is not straightforward.

Other research aimed at determining the cause of feedlot AIP has been done by investigators at Colorado State University.[19,20] Levels of 3-MEIN were measured in lung tissue taken at postmortem from animals with AIP, animals with bronchopneumonia, and animals subjected to postmortem for nonrespiratory disease. Blood for analysis was also available from a subset of the animals. Levels of 3-MEIN were higher in the blood of AIP cases than in cattle with bronchopneumonia or the control animals. Levels of 3-MEIN were also higher in the lung of AIP cases as compared to control animals, but there was no difference in 3-MEIN levels in the lung of AIP cases compared to animals with bronchopneumonia.[20] These results are interesting because they suggest that toxic 3-MI metabolites may be involved with disease due to both AIP and bronchopneumonia. However, if 3-MI is a unique cause of AIP, it is not clear why 3-MEIN levels are not higher in the lung tissue of cattle with AIP compared to cattle with bronchopneumonia.

In addition to 3-MI, recent research has evaluated the association of infection with respiratory pathogens with feedlot AIP. Bacterial infection was associated with AIP in two reports,[16,28] but not in a third.[19] BRSV infection was not associated with AIP in three recently published studies,[1,19,28] indicating that acute BRSV infection is not associated with AIP, in contrast to the early report by Collins *et al.*[9] To date, our ongoing research has not supported a role for acute BRSV infection. Because evidence of chronic bronchiolar injury is common in cattle with AIP,[9,17,28] and because BRSV causes bronchiolar injury, a role for past BRSV infection cannot be ruled out. Acute infection with PI3, bovine viral diarrhea virus (BVDV), or bovine herpesvirus-1 (BHV-1) was also not found to be associated with development of AIP in one study.[19]

Summary of Current Concepts Regarding the Cause of Feedlot AIP

Reading the available information on feedlot AIP can be nearly as frustrating as dealing with AIP cases in the feedlot. Some hypotheses have been tested several times, with different answers resulting. Other hypotheses have never been tested, although they are still discussed. The available information can be summarized as follows:

3-MI

Animals with AIP have repeatedly been found to have higher levels of 3-MEIN, a toxic metabolite of 3-MI, in their blood as compared to control animals. This suggests that 3-MI toxicity is somehow involved with AIP. However, it is not clear why the toxic metabolites are not higher in the lung tissue of animals with AIP. Researchers do not understand the equilibrium of these metabolites well. It may be that 3-MEIN leaks from damaged lung back into the blood. Some research has suggested that 3-MI contributes to other BRD as well.[3]

If 3-MI toxicity contributes to feedlot AIP, it is important to determine where the 3-MI comes from. Normal cattle produce some 3-MI from rumen metabolism of dietary proteins. Feedlot AIP is particularly a problem in animals on feed for over 45 days, and these animals normally don't experience large, erratic changes in ration that would be likely to lead to large spikes in 3-MI production. However, it may be that some combination of feedstuffs can lead to 3-MI spikes that contribute to the development of AIP. More research is necessary to determine whether specific feedstuffs can be associated with feedlot AIP.

Treatment with vitamin E or aspirin, and feeds containing elevated cysteine levels (for example, feather meal), have all been proposed to decrease incidence due to AIP through various mechanisms.[3,21,22] While some of these interventions have shown promise in small trials, a consistent and cost-effective advantage for these treatments has not yet been confirmed.

Bacterial or viral infection, including BRSV

Three recent studies have found no association between BRSV and feedlot AIP, making it seem unlikely that acute BRSV infection causes most feedlot AIP cases. However, repeated studies have shown that animals with AIP also have evidence of chronic bronchiolar inflammation, more than seen in control animals. It may be that past BRSV infection, or infection with other viruses or bacteria that cause bronchiolar inflammation, contributes to the development of AIP. Perhaps such infections result in changes in local inflammatory mediators that then contribute to the development of AIP. Acute respiratory distress syndrome (ARDS) in human beings is a syndrome very similar to AIP, and it has been shown that human ARDS is associated with high levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β).[15,29] Infection with *Mannheimia haemolytica* in cattle has been shown to cause production of high levels of TNF-α and IL-1β.[23,33] It seems possible

that increased production of such cytokines in response to chronic airway infection could contribute to feedlot AIP in at least some cases, particularly those with concurrent evidence of bronchopneumonia.

One of the problems with past research is that bacterial cultures were taken from animals that may have been treated with antimicrobials before death, making the results of bacterial culture less reliable. Along with colleagues at other universities, our laboratory is currently involved in a study of viral and bacterial pathogens in feedlot AIP cases that have not received antimicrobial treatment. The results from the untreated AIP cases are being compared to healthy controls taken from the same pen. We believe this research will give a clearer picture of the true role of bacterial infection in AIP. To date we have found that significant bacterial pathogens can be found in the lung of some animals with AIP; however, bacteria are not isolated from many AIP cases even when they have not received antimicrobial treatment. These results suggest that bacterial infection is related to the development of AIP in some cases, but not in others.

Hormonal influences

Multiple studies have shown that heifers are affected disproportionately with AIP. MGA feeding may play a role in the occurrence of AIP in heifers. Some investigators feel that MGA increases a heifer's risk for developing AIP. Others feel that hormonal changes associated with erratic cycling in heifers that ingest inconsistent amounts of MGA during hot weather may be to blame. Some have suggested that MGA levels should actually be increased during periods of hot weather to assure that heifers receive an effective dose even when feed consumption is decreased. More research into this area is needed before recommendations can be made regarding MGA and AIP.

Environmental dust exposure or other hypersensitivity

As discussed above, the lung lesion of AIP is not the same as that seen in acute anaphylaxis. Moreover, the lesions of AIP are not similar to those of extrinsic allergic alveolitis, which is due to type III and type IV hypersensitivity to inhaled allergens.[24] Thus it is unlikely that inhalation of airborne allergens alone causes AIP. However, it is possible that inhalation of allergens could contribute to the development of an inflammatory environment in the lung which then, in the presence of other triggers, leads to AIP. No research has been done directly addressing how hypersensitivity or dust exposure are associated with AIP.

Heat

In many reports, AIP cases are linked with hot weather. Multiple AIP deaths are expected in many feedlots during times of hot, dusty weather. It has been speculated that irritation or inflammation in the lung associated with the rapid, open-mouth breathing typical of overheated cattle contributes to the induction of severe airway inflammation and AIP. Perhaps changes in pulmonary blood flow due to hyperthermia contribute to AIP. No research has been done investigating the role of ambient temperature in the pathogenesis of AIP.

In any consideration of possible causes of feedlot AIP, it is important to remember that the lesion in the lung is not specific for a single etiology. Based on currently available information, it seems likely that AIP is a multifactorial disease, with some causative factors predominating in some yards, and other factors predominating in other yards. Perhaps a combination of two or three insults is necessary to induce feedlot AIP. If this is the case, the key to helping producers will be to determine the causative factors most prevalent in their yard. Strategies aimed at mitigating one or two factors might then significantly decrease deaths to AIP. Current research supports the concept that dietary factors leading to production of 3-MI, hormonal factors, bacterial pneumonia, and insults that cause bronchiolar inflammation contribute to the pathogenesis of at least some cases of feedlot AIP.

A recent NAHMS survey of feedlot operators showed that AIP was the second leading cause of morbidity, behind BRD.[30] This suggests that AIP is a real problem for some yards. Because AIP can be induced by many different insults, it is unlikely that the disease will disappear entirely even with the most vigorous research. However, it is reasonable to expect ongoing research to determine the major etiologies in yards where the disease is a particular problem, so that losses due to AIP morbidity and mortality can be significantly decreased.

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