Interstitial pneumonia in feedyard cattle: risk factors and diagnosis

by

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Abstract

Interstitial pneumonia is an economically important disease in feedyard cattle due to higher incidence in cattle late in the feeding period. Understanding previous research on interstitial pneumonia and refining the field case definition are important to improve knowledge for this disease syndrome, and determining risk factors for interstitial pneumonia early in the feeding period can assist in predicting affected cattle.

A systematic review was utilized with the objective to describe the clinical signs, etiologies, risk factors, pathologies, and treatments of feedyard AIP. The relevant literature was identified using three databases: PubMed, CABI Direct Library, and AGRICOLA with criteria to include only primary literature that took place in North American feedyard cattle. The original search resulted in 807 publications. A systematic screening process was utilized that identified 19 articles that fit the inclusion criteria. Six articles described clinical signs used to diagnose AIP and the most common were severe respiratory distress, increased expiratory effort and grunting when breathing. Eleven articles evaluated various etiologies which included bovine respiratory syncytial virus (BRSV), other infectious pathogens, melengestrol acetate (MGA) and 3-methylindole (3-MI). The most frequently evaluated aspect of AIP was pathology, with 17 articles providing detailed descriptions of AIP pathological and diagnostic features. Frequently used gross pathological characteristics included intralobular emphysema or edema, a "checkerboard" appearance, and diffuse, overinflated lung lobes. The most frequent histopathological features recognized were hyaline membranes, type II pneumocyte hyperplasia and bronchiolitis (fibrosa) obliterans. Eleven publications evaluated various risk factors that may contribute to AIP. Common risk factors analyzed included season, sex, days on feed (DOF) at onset and DOF at death. No primary literature was identified evaluating AIP treatments,

however, one article assessed feather meal and vitamin E supplementation as a preventative for AIP. The literature review identified several knowledge gaps related to AIP in feedyard cattle and the areas where there is limited published research.

The objective of the second study was to utilize gross necropsy and histopathology to determine the frequency of bronchopneumonia (BP), acute interstitial pneumonia (AIP), and bronchopneumonia with an interstitial pneumonia (BIP) and the agreement between gross and histopathological diagnosis. Gross necropsies were performed on 417 feedyard cattle, across six Kansas feedyards in a cross-sectional, observational study. The frequency of each pulmonary diagnosis was determined with descriptive statistics for both methodologies. Generalized linear mixed models were used to evaluate the agreement between histopathological and gross diagnosis. Both diagnostic modalities identified BP and BIP as the most common pulmonary syndromes. Bronchopneumonia was identified in 36.6% of mortalities followed by BIP in 35.8% of mortalities and AIP in 10.0% of mortalities. The histopathological diagnosis revealed 32.3% of lungs had BP, 36.0% of lungs had BIP and 12.2% of lungs had AIP. Histopathological diagnosis tended (*P*-value = 0.06) to be associated with gross diagnosis. Four lung samples were acquired from right cranioventral, left cranioventral, right caudodorsal, and left caudodorsal to determine agreement in histopathological diagnosis. Lung sample location was not significantly associated with the probability of agreement between the overall histopathological diagnosis and each sample diagnosis. Refined mortality diagnostics are necessary to improve understanding of pulmonary pathology in feedyard cattle, which can be valuable for evaluating and adjusting therapeutic interventions.

The objective of the third study was to determine the probability of at least one AIP mortality occurring in a cohort (AIPMort) and potential associations with cohort arrival

characteristics and disease incidence in the first 45 days on feed. A retrospective data analysis was performed using 27,324 cohorts from 20 U.S. commercial feedyards, over a 4-year time span. At least one AIP mortality was present in 5,525 (20.2%) cohorts. The risk factors analyzed included cohort sex, head received, arrival weight, arrival month, BRD morbidity (BRDMorb45), BRD mortality (BRDMort45), digestive morbidity (DigestMorb45) and digestive mortality (DigestMort45). All risk factors were significantly associated with AIPMort. Heifer cohorts were more likely to (19.5% ± 0.048) experience AIPMort than steer cohorts (13.3% ± 0.035). Cohorts that experienced high BRD morbidity (>5%) and mortality (>0.1%) in the first 45 days on feed were associated with higher AIPMort compared to cohorts with less BRD challenge. Further research is still necessary to assess the etiology of this disease, and the individual cattle affected. However, this cohort data guides further research to the specific risk factors of cattle that experience AIP mortalities.

Interstitial pneumonia in feedyard cattle, although rare at the individual animal level continues to have significant negative economic and cattle welfare impacts. Bronchopneumonia with an interstitial pneumonia has been documented for many years but not consistently acknowledged as a separate disease process. Further research is necessary to investigate these two pulmonary diseases, their pathogenesis and the cattle affected in the feedyard setting.

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Introduction

Interstitial pneumonia continues to be a challenging respiratory disease in the feedyard industry that often leads to mortality late in the feeding period. Acute interstitial pneumonia (AIP) has been documented in feedlot cattle for many decades and knowledge gaps exist regarding its pathogenesis. Bronchopneumonia with an interstitial pneumonia (BIP) is not commonly acknowledged as a separate respiratory disease, however, bronchopneumonia (BRD) and AIP have been documented together for many years. Refining interstitial pneumonia diagnosis can provide insight into this disease and if separate management and treatment is warranted.

Chapter 1 summarizes and discusses the current literature on AIP in North American feedlot cattle and highlights the current knowledge gaps regarding this interstitial disease. Limited research is available addressing AIP, along with many informal reviews and summaries on the disease. However, there is not a comprehensive summary of prior research on this pulmonary disease. The objective of this research was to perform a systemic primary literature review to describe the clinical signs, etiologies, risk factors, pathologies, and treatments of feedlot AIP. This review highlights the understood areas of this respiratory disease and also highlights critical gaps in AIP pathogenesis and diagnosis.

Chapter 2 focuses on refining respiratory diagnosis at postmortem examination and the three main pulmonary lesions documented in 417 feedlot necropsies, with a primary focus on BIP cases. The most common respiratory diseases diagnosed in feedlot cattle mortalities include bronchopneumonia, acute interstitial pneumonia, and bronchopneumonia with an interstitial pneumonia. Necropsy is a useful tool to collect information and enhance decision making about the health and management of a pen or lot. The objective of the study was to utilize gross

necropsy and histopathology to determine the frequency of pulmonary lesions from the three major syndromes and agreement between gross and histopathological diagnosis. Refining postmortem diagnosis of feedyard mortalities can be important to understand these disease processes and the cattle affected.

Finally, Chapter 3 is a retrospective analysis that evaluates the probability of experiencing an AIP mortality in a feedyard cohort compared to arrival and health demographics. Understanding risk factors can be an important tool in respiratory disease prediction. Utilizing information available at arrival and health parameters collected in the first 45 days on feed may provide insight to understand the cohorts affected with AIP mortalities. The objective of the retrospective analysis was to determine the probability of at least one AIP mortality occurring in a cohort and potential associations with cohort arrival characteristics and disease incidence in the first 45 days on feed. Individual animal research is necessary to understand the pathogenesis of AIP, however understanding cohorts affected with this respiratory disease guides further research and specific groups of cattle to target.

Chapter 1 - Review of clinical signs, etiologies, pathologies, diagnostics, risk factors, and treatments of acute interstitial pneumonia in North American feedlot cattle

As submitted: *Journal of Veterinary Diagnostic Investigation*

Abstract

Acute interstitial pneumonia (AIP) has been a recognized cattle respiratory disease for many decades, yet sporadic occurrence in feedlot cattle is poorly understood. This systematic literature review aims to provide a comprehensive overview of clinical signs, pathologies, etiologies, risk factors, and treatments associated with AIP in feedlot cattle. A systematic search utilized three databases PubMed, CABI Direct Library, and AGRICOLA including primary literature in North American feedlot cattle focused on interstitial pneumonia. The review identified 19 peer-reviewed articles from 1976 to 2023. Six articles described clinical signs used to diagnose AIP with the most common clinical signs of severe respiratory distress, increased expiratory effort and grunting while breathing. Of the articles reviewed, 17 provided detailed descriptions of AIP pathological and diagnostic features with the most frequent histopathological findings including hyaline membranes, type II pneumocyte hyperplasia, and bronchiolitis (fibrosa) obliterans (in 15, 12, and 9 articles respectively). Eleven articles explored potential etiologies, 7 of those articles specifically explored bovine respiratory syncytial virus (BRSV) infection with only one article finding a statical difference with BRSV more likely in AIP diagnosed cattle compared to negative controls. Risk factors were evaluated in 11 articles with consensus supporting heifers in the summer months more likely to acquire AIP. No primary literature was identified evaluating AIP treatments. Despite the importance of AIP this review

identifies gaps in current knowledge, and highlights the previous research performed on AIP in feedlot cattle.

Introduction

Various factors influence cattle industry profitability, sustainability, and efficient resource management. Acute interstitial pneumonia (AIP) is a respiratory disease of feedlot cattle with significant negative economic impact due to typical occurrence late in the feeding period at a time corresponding to high sunk costs.[26,36] While AIP has been recognized in cattle around the world for many decades,[12] there is not a comprehensive summary of prior research on this pulmonary disease.

The disease referred to as "acute interstitial pneumonia" has been historically described by various names, including atypical interstitial pneumonia, bovine asthma, bovine pulmonary emphysema, dust pneumonia, fog fever, lunger, panter, pneumoconiosis, and pulmonary adenomatosis. Each of these terms has been associated with specific etiologies or feeding practices under which the disease manifests, leading to a lack of consensus on whether these terms are synonymous or indicate distinct syndromes. Interstitial pneumonia in pasture-managed cattle is well-documented, but the occurrence of this condition in feedlot cattle requires further investigation. The varied nomenclature reflects the ongoing struggle to precisely characterize and differentiate the clinical presentation, pathology, and underlying mechanisms of this complex pulmonary disease.

In feedlots, AIP is primarily used to describe a sporadic respiratory disease observed in cattle fed in North America.[38] Overall, AIP has a low incidence compared to other feedlot diseases, such as bronchopneumonia or digestive disease;[37] however, there is relatively high economic loss compared to other diseases due to the close proximity of AIP cases to harvest

date. Identifying risk factors play a crucial role in understanding and analyzing sporadic diseases such as AIP that affected approximately 2.8% of all cattle placed in feedlots according to the United States Department of Agriculture National Animal Health Monitoring 2011 survey.[27] Minimizing negative impact of AIP requires improved understanding of factors associated with diagnosis, disease development, and therapy. While multiple reviews have been written and cited on specific aspects of AIP,[6,11,13,17,26,42] a systematic review of the available primary data to critically evaluate and thoroughly summarize AIP in feedlot cattle has yet to be published. The objective of this research was to perform a systematic primary literature review to describe the clinical signs, etiologies, risk factors, pathologies, and treatments of feedlot AIP.

Materials and Methods

Literature Search Strategy

The relevant literature was identified using three databases: PubMed, CABI Direct Library (CABI Direct), and AGRICOLA (AGRICultural Online Access). The same search string was used for all three databases to ensure uniformity. The search term string utilized within each database was as follows: ((((((cattle) OR (bovine)) OR (bos taurus)) OR (feedlot cattle)) OR (cow)) OR (cows))) AND ((((((((((acute interstitial pneumonia) OR ("atypical interstitial pneumonia")) OR (acute interstitial pneumonias)) OR (acute interstitial pneumonitis)) OR (lunger)) OR (fog fever)) OR (pulmonary adenomatosis)) OR ("bovine pulmonary emphysema")) OR (pneumoconiosis))) OR ("a typical interstitial pneumonia")). These search terms were then used to fit the advanced search criteria of each database. The original search strategy was written by author PHS and reviewed by all authors. The terms “panters”, “bovine asthma” and “dust pneumonia” were included in the original search, however, no results were

found, and these terms were removed from the search string. No search strategies from previous systematic literature reviews were utilized. Each search was refreshed and updated in each database several times. The final search was utilized on all three databases to retrieve articles published as of May 30, 2024, at 5:00pm (United States Central Daylight Time).

The search was used for all three databases to ensure uniformity per PRISMA guidelines.[29] Articles were retrieved and formatted to be copied and pasted from each database. In each database, an automation filter to include only English articles was utilized. In CABI Direct an additional filter called "Only CABI Content I Have Access To" was selected to ensure only accessible articles were reviewed.

Article Management

Results from the final search were recorded in Microsoft Excel[43] and duplicates were removed. Final results were organized with corresponding titles and abstracts for screening, followed by full text review.

Initial Inclusion/Exclusion Process

To be included for this review, literature had to meet inclusion criteria (Table 1.1). Studies were excluded if they did not meet all criteria. For example, if a study was characterizing interstitial pneumonia in adult beef cattle removed from pasture, the article was excluded due the study population not matching inclusion criteria. Only peer-reviewed primary literature was considered; therefore, conference proceedings and other reviews were not eligible for inclusion.

Final Article Selection Process

The first step in selection involved article titles and abstracts being reviewed according to the criteria previously mentioned (Table 1.1). Two reviewers [PHS and ARW] evaluated the article list independently while blinded from the other reviewer's assessment and denoted each article as "Yes" or "No". Any articles with insufficient information in the title and abstract resulted in full text review prior to determining if the article was included or excluded. Articles were excluded after this process if both reviewers assigned "No" to the article after reading the title and abstract. Articles were included if both reviewers assigned "Yes" to the articles. Any disagreement in this process resulted in a list of those articles sent to be reviewed by a third reviewer [BJW] for the final decision. Following this process, no changes were made to the final selection and the articles were read and summarized. After final selection the full-text version of each included manuscript were downloaded and reviewed by each of the reviewers.

Results and Discussion

Search and Selection

The original search of the three databases resulted in a total of 807 articles: PubMed 210, CABI Direct 509, and AGRICOLA 88 articles (Figure 1.1). In each database, a filter was included to identify only articles available in English. This eliminated 20 articles from PubMed, 1 article from CABI Direct, and 8 articles from AGRICOLA. In CABI Direct an automation filter called "Only CABI Content I Have Access To" was selected and eliminated 175 articles. An additional 106 articles from CABI Direct were removed as they required further purchase, or accessibility was not available through the Kansas State Libraries. Once the initial search was

conducted on all databases, 128 duplicated articles were removed. The initial list of articles combined from all three databases with no duplicates included 369 manuscripts.

The screening process was performed by three reviewers [PHS, ARW, and BJW]. Initial reviewers [PHS and ARW] agreed "Yes" on 25 articles and "No" on 280 articles. The initial reviewers disagreed on 63 articles which results in evaluation by a third reviewer [BJW]. This excluded an additional 54 articles and included 9 articles. Eight articles were not able to be evaluated via title and abstract and underwent full-text review. Following initial screening, the 42 identified articles were evaluated via full-text review, 7 of the 42 articles did not have full-text available and were excluded. A full-text evaluation was performed on the remaining 35 articles, however, 5 of the studies were performed in non-feedlot cattle and 11 of the studies were not performed in North America. Therefore, 19 articles met the inclusion criteria and were included in the review.

Selected Article Results

The objective of this systematic review was to describe the clinical signs, etiologies, risk factors, pathologies, and treatments of feedlot AIP. Each article was thoroughly reviewed, and information related to AIP in each study were systemically classified to match each portion of the research objective (Table 1.2).

Nineteen individual manuscripts were included; however, there were four instances where the same study population was used for multiple independent projects resulting in more than one manuscript from the same study population included in the final literature review (Table 1.3). In cases where multiple manuscripts were published on the same study population using the same AIP diagnostic classification, both manuscripts were listed in Table 1.2 as separate articles.

Clinical Signs

Six articles listed specific clinical signs used to diagnose AIP in feedlot cattle. The most common AIP clinical signs recognized were severe respiratory distress, increased expiratory effort, and grunting when breathing (represented by 3, 2, and 3 articles, respectively).[2,4,40] Other clinical signs acknowledged by at least one study included open-mouth breathing, sway-back appearance, dyspnea, frothing at the mouth, and non-febrile. Many studies did not describe specific criteria used to diagnose AIP but instead, relied on classification from the veterinarian or feedlot personnel. The clinical signs associated with AIP are non-specific and may also present in other respiratory diseases, traumatic reticulopericarditis, congestive heart failure, or heat stress.

Differentiating AIP from other conditions producing severe respiratory distress poses a significant challenge for veterinarians and feedlot personnel, resulting in potential misclassifications when antemortem clinical signs are the sole method of diagnosis. Bortoluzzi et al. compared clinical diagnosis to gross pathology findings in 360 head and found low agreement (22.5%) between the two diagnostic modalities.[4] This research illustrates the challenges of using non-specific clinical signs to distinguish interstitial pneumonia from similar syndromes; and this potential lack of diagnostic accuracy could prove challenging when interpreting AIP research using diagnosis as the primary method of case identification. The absence of standardizing diagnostic criteria for AIP increases the risk of misdiagnosis, potentially resulting in confusion and the dissemination of inaccurate data when identifying truly affected cattle and assessing specific risk factors associated with AIP. Advancements in chute-side diagnostic technologies are needed to accurately identify cattle affected by AIP, thereby enabling the implementation of appropriate therapeutic interventions.

Etiology

Our search identified 11 articles evaluating AIP etiologies with potential causes categorized into 4 categories: bovine respiratory syncytial virus (BRSV) (7 articles), other infectious pathogens (5 articles), melengestrol acetate (MGA) (1 article), and 3-methylindole (3-MI) (4 articles). Several additional etiologies of interstitial pneumonia have been proposed including tryptophan (lush forage), 4-Ipomeanol (moldy sweet potatoes), perilla ketone (purple mint) toxicity, brassica toxicity, nitrogen dioxide, lungworms, dust hypersensitivity reaction, moldy feed, and paraquat.[1,6,8] Many of these potential AIP etiologies were likely not included in this literature review due to the focus on North American feedlot cattle which would not have exposure to many of the listed potential causal factors.

Bovine respiratory syncytial virus (BRSV) has been a proposed etiology of feedlot AIP for many years. Seven studies evaluated the frequency of BRSV at postmortem examination or emergency slaughter in cattle affected with AIP verse control cattle. However, only 1 found a significant difference in the presence of BRSV in postmortem viral isolation between AIP cases versus cattle with other respiratory diseases, reporting 11/15 cases isolating BRSV from AIP affected lungs, whereas 5/18 cattle with other respiratory lesions had evidence of BRSV infection.[10] Since this study, conducted in 1988, at least 6 studies have not been able to show a significant association between BRSV infection at postmortem evaluation and feedlot AIP. While evidence of BRSV infection in AIP cases is sparse, the virus may still play a role in some cases. Chien et al. evaluated BRSV interstitial pneumonia and “idiopathic” interstitial pneumonia as two separate histological diagnosis because of conflicting evidence associating BRSV infections and AIP cases. Postmortem lung samples were positive by one or more laboratory

tests including polymerase chain reaction (PCR), fluorescent antibody (FA), serum neutralization (SN) assay, and viral isolation. The authors compared histopathological lung lesions in cases with a diagnosis of "interstitial pneumonia" in BRSV- confirmed and BRSV- negative lung samples. Since its publication in 2022, little work has been performed to refine this categorization of interstitial pneumonia in feedlot cattle. Unfortunately, no strong conclusions can be made about the role of BRSV at time of death and feedlot AIP based on this data. BRSV may contribute to the pathogenesis of AIP in the beginning stages of the disease but is not frequently identified at post-mortem examination. Further research evaluating viral isolation of BRSV at onset of clinical signs in AIP cases may provide insight on the role this viral pathogen plays in AIP in feedlot cattle.

Other infectious pathogens have been evaluated in investigations of potential etiology of feedlot AIP. Five studies investigated various bovine bacterial and viral pathogens (other than BRSV), in cattle diagnosed with AIP at emergency slaughter or postmortem examination. Infectious pathogens evaluated included: *Pasteurella multocida, Manheimia haemolytica, Histophilus somni, Actinomyces pyogenes, Mycoplasma spp., Cornebacterium* spp.,*Escherichia coli, Proteus* spp., *Actinobacter* spp., *Streptococcus* spp., *Staphylococcus* spp., *Clostridium* spp., *Fusobacterium* spp., Bovine herpes virus 1, Parainfluenza – 3, and Bovine viral diarrhea virus.[10,21,24,32,39] Woolums et al.2004, found cattle diagnosed at gross necropsy with AIP were more likely to have *Pasteurella multocida* and *Mycoplasma spp* (or both) isolated from lung samples compared to control cattle. The other four studies that evaluated bacterial infections in control cattle or cattle with other respiratory lesions concluded there was no difference between the frequencies of these bacterial pathogens. The lack of bacterial pathogens present at postmortem evaluation may be associated with timing of death relative to disease onset.

Four studies in our search evaluated the effects of 3-methylendole (3-MI) or its metabolite 3- methyleneindolenine (3-MEIN)[22] concentrations in plasma, lung tissue, or urine of cattle affected with AIP. Tryptophan is an amino acid that is found in abundance in lush forages. Once digested by the ruminal microbiome it is converted to a metabolite known as 3-methylindole (3MI) which can be further broken down to the pneumotoxin 3-methyleneindolenine (3-MEIN). Cattle greater than 45 days on feed are at greater risk of AIP compared to cattle recently arrived at a feedlot and this timing coincides with consumption of a highly fermented, predominantly starch diet which is not likely to result in ingestion of high levels of tryptophan. Previous studies have induced interstitial pneumonia in cattle with boluses of tryptophan that undergo conversion into 3-MI.[16] The role of concentration of 3-MI in plasma and lung tissue still remains unknown as 3-MI has not been consistently shown to be higher in lung or plasma in AIP- affected animals.[2,33,34] Due to 3-MI being excreted through the urine, urinary concentrations have been analyzed but no consensus on how urine concentrations correlate with 3-MI metabolism has been reported. Furthermore, one study analyzed 3-MEIN and found a significantly ($P=0.01$) higher level in the plasma in both bronchopneumonia and AIP affected cattle compared to controls.[22] Strong evidence establishes a link of 3-MI and pneumotoxic metabolites with interstitial pneumonia in pasture cattle.[3,15] The four studies captured in this review provided contradicting evidence on the concentration of 3-MI or 3-MEIN in lung tissue, plasma, and urine concentrations in feedlot cattle affected with AIP verse controls. Despite having a role in interstitial pneumonia in grazing cattle, the management practices and ration composition in feedlot cattle do not support a hypothesis for these pneumotoxins as a sole causative agent of AIP.

Melegestrol acetate is a progestogen-like feed additive used to suppress estrus in heifers during the feeding period. Prostaglandin H synthases, along with cytochrome P450, are enzymes responsible for metabolizing 3-MI into the pneumotoxin 3-MEIN.[25] Research has demonstrated a quicker onset and higher concentrations of 3-MI in the plasma of ewes fed MGA verse control ewes.[30] One study which took place over 3 years in southern Alberta heifers evaluated the potential of MGA as a potential etiology for AIP .[33] The natural death loss in MGA-fed heifers verse controls showed no difference. MGA- fed heifers had a 3-times higher rate of emergency slaughter ($P < 0.0001$), however, the AIP-status of all emergency-slaughtered animals was not verified so no conclusions can be made about these results. The pens of heifers fed MGA verse no-MGA were fed at different feedlots, which raises the possibility that different personal and emergency-slaughter protocols could have contributed to the likelihood of heifers going to emergency slaughter being confounded between feedlot and receiving MGA. The AIP status of these animals was not verified during emergency slaughter; therefore, we cannot make any conclusions regarding this statistical significance and have no evidence to support MGA as a contributing factor to feedlot AIP. The direct link between the effects of MGA and heifers diagnosed with AIP has proven to be difficult to support due to the majority of heifers on feed receiving MGA during the feeding period, yet the low incidence of AIP cases that occur in feedlot heifers. Strong evidence has been proposed in other ruminant species but the role of MGA in feedlot AIP remains unknown. The literature review identified 11 studies exploring different causes of feedlot AIP. However, only a few differences were observed when comparing AIP cases with controls or other respiratory conditions to all researched etiologies. As a result, the precise cause of AIP remains unclear, though the current literature suggests it may be a multifactorial disease.

Risk Factors

Eleven studies evaluated various risk factors that may contribute to AIP in feedlot cattle. Season, sex, days on feed (DOF) at disease onset, and DOF at death were common risk factors assessed for association with feedlot AIP. Two studies, published in 2005, utilized a national survey to investigate the perception and characteristics of feedlots experiencing AIP.[40,41] In 1976, it was observed that feedlot cattle were diagnosed with AIP throughout the year, but there was a higher incidence in the summer and fall months.[21] These results were hypothesized to be due to the increase of dust during the fall and summer months, however, dust can induce many types of pneumonia due to respiratory tract irritation and is not specific to AIP.[23,35] The cause for an increase in AIP during the summer months remains unknown, however, three other studies have observed an increase in AIP mortalities during the summer months.[2,37,41] In one survey study, responders reported that 62% of AIP deaths occurred in the summer (June- September) and the remaining causes were split equally during fall, winter, and spring.[41] Vogel et al., reported higher incidence of AIP mortality during the summer months but the difference was not consistent during all years analyzed (2005- 2014).[37] Finally, the third study reported all AIP mortalities over a 2-year period occurred between the months of May and October; however, the distribution differed during the two years.[2] While several studies indicate a seasonal increase in AIP mortalities, particularly during the summer months, the precise cause remains undetermined. Multiple factors could contribute to this observation, however, heifers that are late in the feeding period during the summer months appear to be at a greater risk.

Heifers have been reported as disproportionally more affected than steers since the study performed by Ayroud et al. in 2000. Our analysis identified four subsequent studies that also

identified heifers to develop AIP more frequently than steers.[4,22,33,41] As previously discussed, MGA- supplementation has been thought to contribute to this difference among steers and heifers, however there is no research supporting this hypothesis. Heifers may experience greater metabolic or hormonal stress compared to steers, which could modify their immune status making them more vulnerable to respiratory conditions like AIP. Previous research has demonstrated a higher morbidity and mortality in heifer groups related to BRD.[28] Additionally, heifers often have higher fat deposition, which could exacerbate respiratory issues or alter their inflammatory response. However, the exact reason for this increased susceptibility remains unclear and further research is required.

The final risk factor demonstrated by multiple studies to be significantly associated with feedlot AIP are DOF at disease onset and DOF at death in AIP cases compared to BRD. Days on feed at onset is defined as the days on feed the animal has been at the feedlot when clinical signs of AIP were first identified. DOF at death is defined similarly but with the event being when death occurred. Many studies evaluated the timing of feedlot AIP which resulted in a wide range of DOF. Mean or median DOF at disease onset ranged from 45 to 130 days on feed.[2,14,21,22,33,41] Comparably, DOF at death ranged from 78 to 136 days on feed.[4,14,24,37,39] Both mean or median days at onset and death due to AIP has been documented to be consistently later in the feeding period compared to BRD, but with large non-specific and overlapping ranges. However, DOF may provide minimal insight as a risk factor for when this disease occurs in the feeding period and which specific cattle are affected. DOF is a common metric to classify timing of diseases in the feeding period, however due to the wide range of weight and age at feedlot placement and subsequent wide range in length of time being at-risk for AIP in a feedlot, switching the metric from DOF to days-to-finish (DTF) may better describe the characteristics of cattle with AIP.

Previous research documenting mean or median DTF, reported cattle dying with AIP within 24 ± 12 days of slaughter.[2] Days-to-finish provides a narrower range when considering AIP onset and death compared to DOF. Adjusting the timeline metric for cattle affected with AIP can focus attention on the late phase of the feeding period, as well as the specific treatments, dietary supplements, and management practices employed during this time.

Infrequently identified risk factors included: arrival weight, number of disease treatments prior to death, geographic region of feedlot, treatment interval, liver abscesses, rumen pH, rumen bacteria, vaccine administration, mass treatment and implant administration. These risk factors have been identified as potential contributors to feedlot AIP; however, the significance of each remains unknown. Risk factors that have shown significant association in multiple studies include heifers, clinical onset greater than 45 DOF, death greater than 78 DOF, and summer months. Although the potential causal pathway for these risk factors remains unclear, they offer valuable insights into the cattle most affected by AIP in feedlots.

Pathology/Diagnostics

Despite significant disagreement on the gross and histopathological classifications of AIP, the included literature generally agrees on the criteria used to differentiate AIP cases from controls or other respiratory conditions. Seventeen articles reported or analyzed either gross or microscopic lesions present with AIP cases verses controls. Twelve articles reported on gross lesions present at postmortem examination and 15 articles reported on microscopic characteristics during histopathological evaluation. Twelve manuscripts utilized a "checkerboard" appearance and intralobular emphysema as a classification of gross pathology to diagnose AIP. Furthermore, eleven manuscripts utilized a description of diffuse, overinflated

lung lobes and ten used interlobular edema to classify AIP on postmortem examination. The specific cause for these gross changes is not known, however, the checkerboard appearance is hypothesized to come from the variation in infiltrates of proteinaceous fluid, fibrin, hemorrhage, and atelectasis at the level of the alveolus. A similar gross pattern has been documented in pigs affected with Swine Influenza A Virus due to vascular congestion, edema, cellular infiltrate and hemorrhage from endothelial damage.[20] The underlying cause of the distinct gross pathological findings remains unclear in feedlot cattle. However, there is general consensus for classifying interstitial pneumonia using features such as intralobular emphysema, emphysema, a "checkerboard" pattern, and diffusely overinflated lung lobes.

These gross pathological findings have been documented consistently since 1962 in cattle affected with interstitial pneumonia on pasture.[3] Despite consistent descriptions of gross AIP pathology, one study compared the agreement between gross necropsy and histopathological diagnosis and reported a low probability (*P*-value = 0.23) of gross diagnosis of AIP being confirmed by histopathology.[31] Furthermore, because AIP is often described as being diffusely distributed throughout all the lungs lobes, this hypothesis was tested by comparing four lung samples, collected from the same lung, and the probability of agreement among those samples.[31] Cases diagnosed with AIP had a 0.89 probability of all four samples agreeing with each other - confirming our gross description of diffuse, overinflated lung lobes.[31] However, it has been reported that depending on the cause of alveolar damage, not all interstitial pneumonia produces a diffuse pattern.[7]

Multiple criteria have been employed to diagnose AIP using histopathological lesions at postmortem examination. Not only is there disagreement among pathologists and researchers, but approach and knowledge gained over time has changed the classification system. The three

most consistently used histopathological lesions were: presence of hyaline membranes, type II pneumocyte hyperplasia, and bronchiolitis (fibrosa) obliterans (in 15, 12, and 9 articles respectively).

Hyaline membranes are collections of fibrin and various proteins that are leaked into the interstitium when endothelial cells are damaged. This microscopic characteristic is seen during initial insult, and some categorize this lesion as being associated with the acute exudative phase. The presence of hyaline membranes is a key finding that defines diffuse alveolar disease; however, this characteristic is only present during the beginning phases of the disease.[7] For this reason, clinical history may be important to consider when utilizing hyaline membranes to diagnose interstitial pneumonia in cattle.

Normal lung tissue is lined with type I and type II pneumocytes along with capillary endothelial cells, interstitial fibroblasts, and alveolar macrophages. Type I pneumocytes line the majority of the alveolar surface and are responsible for gas exchange through the alveolar parenchyma.[8] Type II pneumocytes are responsible for the production of surfactant and replace the alveolar epithelium when damage occurs. The commonly described type II pneumocyte hyperplasia occurs when these cells replicate in great number to repair damaged alveoli. Unfortunately, gas exchange becomes difficult when these cells replicate in abundance and if the injury causing the damage persists, the hyperplastic damage does not reverse. Presence of type II pneumocyte hyperplasia is classified as the subacute proliferative phase. The presence of type II pneumocyte hyperplasia occurs during continued damage of the alveoli, which can stem from multiple potential causes inducing physical injury: septicemia, hypersensitivity reactions, inhaled irritants, or physical injury.[7]

Bronchiolitis (fibrosa) obliterans occurs in chronic cases and was a microscopic classification to confirm cattle affected with AIP in 9 manuscripts. This change, known as the fibrosing stage is characterized by a "polyp" of fibrous tissue that has invaded the alveoli, stops gas exchange by blocking the endothelium and occluding the bronchiolar lumens.[8] Woolums 2004, documented a significant difference in the risk of cattle affected with AIP having microscopic lesions consistent with bronchiolitis obliterans compared to control cattle. Unfortunately, this chronic microscopic lesion is not pathognomonic for interstitial pneumonia and has been documented in bronchopneumonia affected animals. Conversely, Chien 2022, evaluated "idiopathic" AIP lung and BRSV-positive lung samples and found a difference in the degree of bronchiolitis greater in BRSV-positive cattle verse "idiopathic" AIP cattle. The presence of bronchiolitis obliterans in many AIP cases indicates there is a degree of chronicity that contradicts the current name and the apparently acute onset of clinical signs. Furthermore, these bronchiolar lesions are not specific to interstitial pneumonia and have to be used in conjunction with other histopathological findings to support a diagnosis of AIP.

In regard to histopathological diagnosis, the literature presented three commonly used microscopic characteristics to diagnose AIP: hyaline membranes, type II pneumonocyte hyperplasia, and bronchiolitis (fibrosa) obliterans. Multiple other microscopic lesions were used including alveolar septal necrosis, bronchiolar epithelial injury, and inflammatory cell infiltration. Without a consistent case definition for AIP, there is controversy in what microscopic lesions are characteristic of AIP. This complicates the ability to establish accurate diagnostic criteria - leading to challenges in classification for etiological determination.

However, with the understanding of having multiple criteria for diagnosing AIP, one study aimed to diagnose respiratory lesions, including AIP, through automated machine

learning.[5] The researchers evaluated the use of various lateral lung images collected during feedlot necropsies and paired them with gross and histopathological diagnosis. Image classification models utilized machine learning algorithms to differentiate AIP, BRD, and bronchopneumonia with an interstitial pneumonia (BIP) gross necropsy and histopathology lesions.[5] BRD and BIP cases presented higher sensitivities compared to AIP. Acute interstitial pneumonia-diagnosed lungs had the lowest sensitivity for gross (14%) and histopathological (23%) classification. The low sensitivity for AIP lung lesions may have been due to missing diagnostic components such as palpation and lung cross section; furthermore, the "checkerboard" appearance of AIP lungs varies in color distribution which may provide challenges for machine learning models.

Bronchopneumonia with an interstitial pneumonia (BIP)

Two articles were included with a primary focus on bronchopneumonia with an interstitial pneumonia (BIP).[18,19] These were kept in the final inclusion list to document the gross and histopathological lesion criteria for AIP utilized in the studies. Four other articles also acknowledged BIP lung lesions that were distinct from AIP, grossly and histopathologically.[4,5,14,31] However, 6 articles acknowledged bronchopneumonia concurrently with an interstitial pneumonia but categorized these cases as AIP.[2,21,22,24,32,39] Our literature review suggests BIP has been documented for many years, however, until recently this pulmonary lesion has not been considered as a separate syndrome from AIP. At this point, BIP, distinct from AIP, is not an industry accepted diagnosis. Limited knowledge exists about the mechanisms of BIP and its pathology, which presents a significant limitation to our review. Consequently, we recognize the potential for misdiagnosis between these pulmonary diseases.

Treatment/Prevention

The systematic search resulted in no primary literature focused on the treatment of AIP in feedlot cattle. However, one of the selected articles evaluated the supplementation of feather meal or vitamin E in the last forty days on feed for the prevention of AIP.[34] Feather meal and vitamin E, acting as free radical scavengers, were utilized with the hypothesis that free-radicals intensify damage to the pulmonary epithelium. The study concluded that there was no significant difference in risk of death due to AIP in heifers supplemented with feather meal or vitamin E versus controls. No additional studies were identified that examined treatment or prevention of AIP in feedlot cattle. A significant knowledge gap exists in this area of AIP management, highlighting the need for further research on treatment of AIP.

Every systematic literature review has its limitations. Although we attempted to be thorough in our search, there are likely published articles that were not retrieved using our chosen search methods. Our literature review did not explore conference proceedings or other non-peer-reviewed literature. We also limited our search to North American articles and feedlot cattle which eliminated other types of interstitial pneumonia. The goal of our inclusion criteria was to focus on a specific sector of the cattle industry to only encompass interstitial pneumonia in feedlot cattle.

Figures

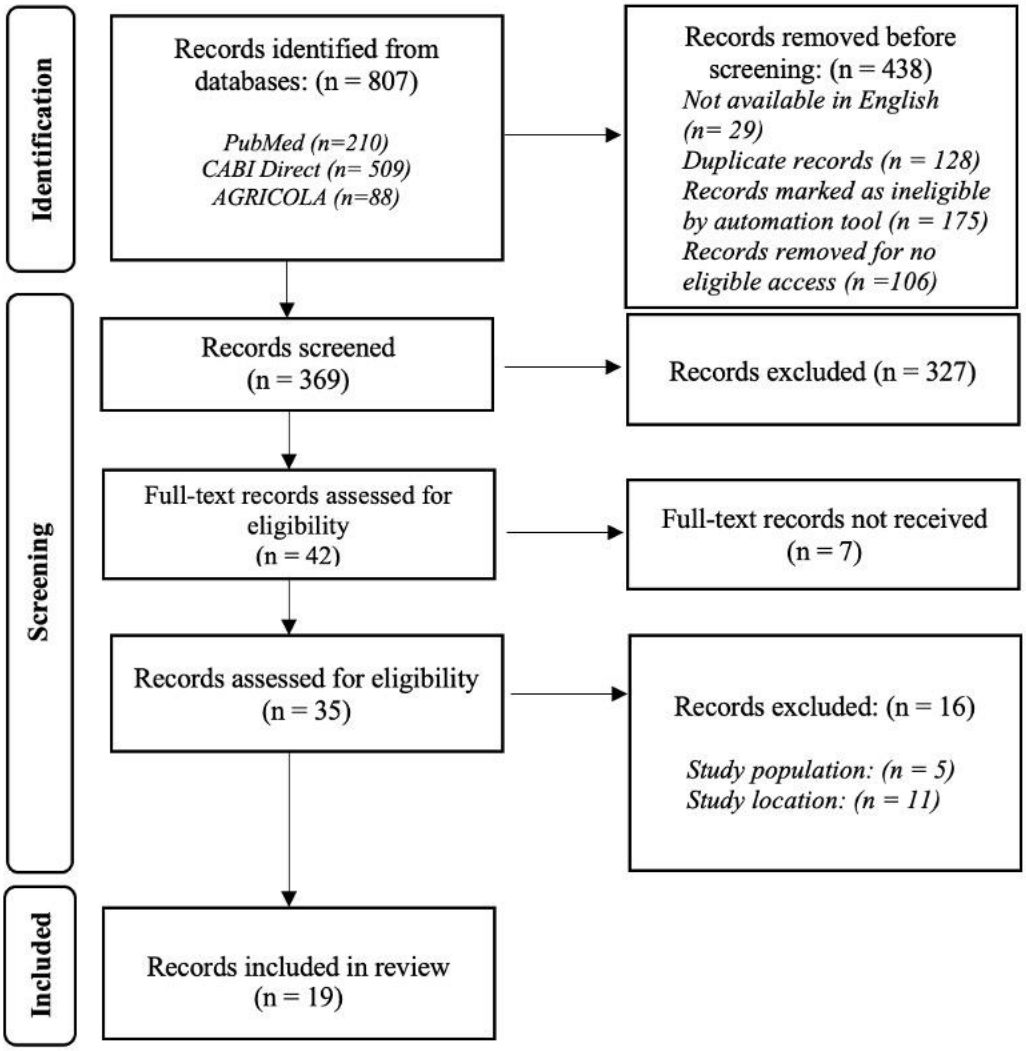

Figure 1.1. Prisma flow diagram*

* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Tables

Table 1.1. Inclusion criteria for initial screening for a systemic review of acute interstitial pneumonia in North American feedlot cattle.

	Criteria
Type of Literature	Peer-reviewed literature representing original research
Language and format	English full text
Study Location	United States and Canada
Study Population	Feedlot cattle
Relevance	Clinical signs, etiology, risk factors, pathology, diagnostics, treatment, prevention

Table 1.2. Characteristics of acute interstitial pneumonia in feedlot cattle and the corresponding articles that studied or described these characteristics of AIP.

Characteristics of AIP	Number of Articles	Referenced Articles
Clinical Signs	6	[2,4,22,24,40,41]
Etiology	11	[2,9,10,14,21,22,24,32–34,39]
Risk Factors	11	[2,4,14,21,22,24,33,37,39–41]
Pathology/Diagnostics	17	[2,4,5,9,10,14,18,19,21,22,24,31–34,39,40]
Treatment/Prevention	1	[34]

Table 1.3. Articles that used the same or similar study population for their manuscripts.

Articles with similar study populations	4,5,31 17,18 22,24 40,41

Conclusion

The current literature addressing acute interstitial pneumonia (AIP) in feedlot cattle has significant gaps regarding clinical signs, etiology, risk factors, pathology, and treatment. The non-specific nature of AIP's clinical presentation poses diagnostic challenges, often leading to misclassification and complicating the understanding of its pathogenesis. Although some potential etiologies, such as BRSV and 3-MI, have been evaluated, no definitive cause has been consistently identified suggesting that AIP may be multifactorial. Risk factors like sex, season, and days on feed (DOF) at disease onset and death have been commonly associated with AIP, though the exact mechanisms remain unclear. Gross necropsy findings were consistently determined based off interlobular edema and emphysema, a “checkerboard appearance, and diffuse, overinflated lung lobes. Microscopic findings, such as hyaline membranes, type II pneumocyte hyperplasia, and bronchiolitis obliterans, provide some diagnostic criteria but lack consistency across studies and are not pathognomonic of AIP. Furthermore, there is little research on effective treatment or prevention, highlighting a critical knowledge gap in AIP management. The absence of standardized diagnostic criteria, along with the lack of research into potential treatments, underscores the need for further study to clarify the causes, diagnosis, and treatment of AIP in feedlot cattle.

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Chapter 2 - Determining Frequency of Common Pulmonary Gross and Histopathological Findings in Feedyard Fatalities

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Abstract

Pulmonary disease is often associated with feedlot cattle mortality, and the most common syndromes include bronchopneumonia, acute interstitial pneumonia, and bronchopneumonia with an interstitial pneumonia. The study objective was to utilize gross necropsy and histopathology to determine the frequency of pulmonary lesions from three major syndromes and agreement between gross and histopathological diagnosis. A cross sectional, observational study was performed at six U.S. feedyards using a full systematic necropsy to assess mortalities during summer 2022. A subset of mortalities had four lung samples submitted for histopathological diagnosis. Gross necropsy was performed on 417 mortalities, 402 received a gross diagnosis and 189 had a histopathological diagnosis. Descriptive statistics were used to evaluate pulmonary diagnosis frequency based on method (gross/histopathology), and generalized linear mixed models were used to evaluate agreement be- tween histopathological and gross diagnoses. Using gross diagnosis, bronchopneumonia represented 36.6% of cases with acute interstitial pneumonia and bronchopneumonia with an interstitial pneumonia representing 10.0% and 35.8%, respectively. Results identified bronchopneumonia with an interstitial pneumonia as a frequent syndrome which has only been recently reported. Histopathological diagnosis had similar

findings; bronchopneumonia represented 32.3% of cases, with acute interstitial pneumonia and bronchopneumonia with an interstitial pneumonia representing 12.2% and 36.0%, respectively. Histopathological diagnosis tended (*P*-value = 0.06) to be associated with gross diagnosis. Pulmonary disease was common and both diagnostic modalities illustrated three primary syndromes: bronchopneumonia, acute interstitial pneumonia, and broncho- pneumonia with an interstitial pneumonia with similar frequencies. Improved understanding of pulmonary pathology can be valuable for evaluating and adjusting therapeutic interventions.

Introduction

Pulmonary disease is a major issue in feedyard cattle resulting in significant performance and economic impacts [1–4]. A variety of etiologic and risk factors contribute to pulmonary disease and an accurate diagnosis impacts effectiveness of prevention and control programs. Necropsy is a useful diagnostic tool to collect information in order to enhance decision making about the health and management of a pen or lot. Respiratory disease contributes to feedyard cattle mortalities throughout the feeding phase [5,6]. Several previous studies have evaluated the timing, infectious components, and economic loss of respiratory disease in feedyard cattle [7,8]; however, limited research has compared gross and histopathological lesions and the linkage to cattle demographics. Improved diagnostics in postmortem cattle will increase knowledge of disease processes, timing, and demographics of affected cattle, ultimately leading to more precise therapeutic interventions and efficiency.

Previous studies evaluated gross and histopathological lesions in feedyard cattle at death; moreover, these studies are often limited to cattle with confirmed clinical respiratory disease prior to death [9,10]. Cause of death is often recorded as a singular disease which may restrict

the true estimation of pulmonary lesions when concurrent disease processes are present. Estimating pulmonary lesions in all cattle regardless of clinical diagnosis or concurrent pathological lesions can provide a more accurate estimate of pulmonary disease frequency. Improved classification regarding cause of death seen throughout the feeding phase will allow a clearer understanding of these disease processes and the cattle they affect. Pulmonary disease has been documented in cattle at harvest with no previous signs of disease [11,12], but little work has been done documenting pulmonary disease in cattle that died of other causes.

A major syndrome associated with pulmonary disease in feedlot cattle is bronchopneumonia (BP) which plays a significant role in morbidity and mortality seen throughout the feeding period. Pathological agents associated with BP include viruses such as Bovine herpesvirus 1 (BHV-1), Bovine parainfluenza virus (BPIV-3), Bovine viral diarrhea virus 1 and 2 (BVDV 1, 2), Bovine respiratory syncytial virus (BRSV), Bovine adenovirus A-D (BAdV A), DP and Bovine coronavirus (BCoV), along with bacterial pathogens *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma* spp [13–16]. Depending on etiologic agent(s), gross lesions of BP can have various presentations. Acute interstitial pneumonia (AIP) is a sporadic, rapidly progressing respiratory disease, with high mortality in feedyard cattle [17–19]. Multiple pathogenic processes have been considered for inciting AIP; however, little is known about risk factors for this disease [20,21]. Bronchopneumonia with an interstitial pneumonia (BIP) is a combination of pulmonary lesions consistent with both BP and AIP [22,23]. While a diagnosis of BIP is recorded by some veterinarians, other diagnosticians will attribute cause of death to either BP or AIP. The risk of BIP compared to lesions associated with only BP or AIP is not well documented.

The study objective was to utilize gross necropsy to determine the frequency of pulmonary lesions associated with three major diagnoses: acute interstitial pneumonia (AIP), bronchopneumonia (BP), and bronchopneumonia with an interstitial pneumonia (BIP). Furthermore, we assessed the accuracy of recognizing AIP, BP, and BIP gross respiratory lesions to corresponding histopathological samples and if there was consistency between diagnosis throughout the four samples collected from the right cranioventral, left cranioventral, right caudodorsal and left caudodorsal lobes of each lung.

Materials and Methods

The Institutional Animal Care and Use Committee (IACUC) was contacted, and a protocol was deemed unnecessary due to evaluations only performed on cattle mortalities.

Experimental Design

This cross sectional, observational study was designed to determine gross pulmonary lesions observed throughout the feeding period in feedlot cattle mortalities from all causes. Feedlot cattle were necropsied from 1 June 2022 to 29 July 2022, at six feedyards located in the High Plains region of the United States. Mortalities enrolled in the study were from deceased cattle within eighteen hours of postmortem examination and/or minimal to no gross autolysis. Autolysis was determined by the individual performing the postmortem examination based on external appearance, tissue color, smell, and texture. Individual calf demographics were provided by the feedyard following the necropsy.

Postmortem Evaluation

A full systematic necropsy was performed by modifying previously described procedures [24]. All necropsies were documented, and photographs were collected. Necropsies were

conducted in groups of two veterinary technicians [PHS, MM, RB, MJ] with one technician performing the postmortem examination and determining the gross lesions. Postmortem diagnoses based on gross findings were confirmed by a veterinarian [BJW].

Gross pathological pulmonary lesions were categorized into four areas: BP, AIP, BIP, and Undifferentiated. Diagnosis of BP was based on a variety of characteristics reported in previous research including lung consolidation, interlobular fibrinous material, pulmonary abscesses and firm/rubbery texture of lungs by palpation [10,25,26]. Cattle diagnosed with AIP lesions had diffuse, overinflated lung lobes, interlobular edema and emphysema, and pulmonary lobules varied in color from light pink to dark red leaving a "checkerboard" appearance which has been described in previous research [19,20,27,28]. Lung lesions that expressed characteristics of both bronchopneumonia and an interstitial pneumonia were diagnosed as BIP [16,22,23]. Gross pathological lesions for BIP typically included a diagnosis of BP in the cranioventral lung lobes and a diagnosis of interstitial pneumonia in the caudodorsal regions of the lungs. A line of demarcation was often noted between the two pathological processes within the lungs. Examples of gross lesions consistent with each classification are depicted in Figure 2.1. Respiratory lesions that did not meet the above criteria (AIP, BP, or BIP) were recorded and documented but categorized as an Undifferentiated pulmonary lesion for the purpose of this study (i.e., Embolic pneumonia). The case inclusion strategy was utilized to create a dataset consisting of all animals necropsied with a gross pulmonary diagnosis (GrossDx) as described in Figure 2.2.

Histopathology

To maximize study resources, lung samples were collected from the first 9–11 mortalities at each feedyard each week. Regardless of the number of mortalities and postmortem diagnoses, a maximum of 11 cases were taken from one feedyard in a week. Pulmonary histopathology samples (HistoSp) were collected as a 1 × 1 cm square from four areas of the lung: right cranioventral, left cranioventral, right caudodorsal and left caudodorsal lung lobes. If applicable, samples were obtained at the junction between grossly diseased and non-diseased lung tissue.

Lung samples were fixed in 10% neutral buffered formalin. Individual samples from each case were dyed with one of four different colors of Davidson Tissue Dye for sample location identification. For histopathology processing, standard techniques were utilized to prepare samples. Slides were placed in the Sakura Prisma Plus Stainer, stained with hematoxylin and eosin (H&E), and cover-slipped according to the manufacturer's protocol. Slides were loaded into the Hamamastu NanoZoomer S360 digital slide scanner and read by a pathologist who was blinded to gross diagnosis determined in the field.

An individual sample diagnosis was determined using specific histopathological criteria (HistoSp), and each case could have 4 histopathological diagnoses. Microscopically, the lesions of AIP included an alveolar septum expanded by mononuclear inflammatory cells, alveolar septal necrosis, and hyaline membranes. By definition, all AIP/BIP cases had either hyaline membranes and/or type II pneumocyte hyperplasia. Hyaline membrane are characterized by eosinophilic lamellations of polymerized fibrin and necrotic debris that replace lost type I pneumocytes of the alveolar interstitium. Some cases also had type II pneumocyte hyperplasia and bronchiolitis obliterans [9,27,29]. Bronchopneumonia type lungs were categorized by neutrophils within the bronchi/bronchioles and/or alveoli. Figure 2.3 provides example

photomicrographs for each of the diagnoses. For the purpose of this study, histopathological lung samples that did not meet the above criteria were categorized as Undifferentiated. Individual samples were excluded if histopathological autolysis was noted in one or more lung samples or there was inadequate location identification due to absence of tissue dye.

To allow comparison with the animal-level gross diagnosis, histopathological diagnoses were aggregated to the animal level (HistoDx). Animals were only eligible to be included in the dataset with an animal level histopathological diagnosis if all four lung samples were evaluated from an individual and if none of the samples had autolysis rendering the diagnosis impossible. Each case was classified by combining findings from each of the four lung samples to create a single classification for a case. If the four lung samples were diagnosed with only BP or AIP the case was considered BP or AIP, respectively. All four lung samples did not have to be positive to receive a single diagnosis, but no lesions consistent with AIP were noted in BP cases and vice versa. Cases with both AIP and BP in any combination of the four lung samples were considered to be BIP. In cases where no diagnosis of AIP or BP were attained, samples were considered Undifferentiated. In addition, samples presenting healthy lung tissue were also allocated as Undifferentiated. The sampling strategy resulted in a dataset containing the HistoDx for each animal (Figure 2.2). Grossly autolyzed cases were excluded at the time of necropsy; however, gross autolysis can be difficult to distinguish from true necrosis. Further autolysis was evaluated during the histopathology examination and cases with autolysis in one or more lung sample were excluded.

Statistical Analysis

Descriptive statistics were performed on all cases relative to known demographic factors. Two data sets were created to compute the agreement of: (1) GrossDx with HistoDx; (2) HistoSp with HistoDx. A generalized linear mixed effect model was created to evaluate the probability of agreement between HistoDx and GrossDx using the glmer function from the lme4 package of R Studio (https://cran.r-project.org/web/pack- ages/lme4/ (1 October 2022)). Feedyard was included as a random effect to account for the lack of independence among cases. A second generalized mixed effect model was used to evaluate the likelihood that HistoSp was associated with HistoDx using the glmer function from the lme4 package of R Studio. Feedyard and individual animal case number were used as random effects to account for the lack of independence among histopathological samples. The lung sample location and potential interaction with HistoDx were evaluated in the HistoSp model.

Results

Four hundred and seventeen necropsies were performed. Thirteen cases were excluded due to gross autolysis. Two cases were excluded because an incomplete necropsy was performed due to carcass removal for rendering prior to completion of necropsy. Four-hundred and two complete necropsies from 6 feedyards met the inclusion criteria. Cattle demographics can be seen in Table 2.1. Heifers made up 69.4% of the mortalities, while the remaining 30.6% were steers. This was consistent with the feedyard's live cattle enrollment. Cattle of native origin made up 93% of the mortalities. The remaining cattle included Beef × Dairy, Holstein, or Mexican origin. Arrival weight ranged from 181–453 kg with most mortalities presenting arrival weights between 318 and 363 kg (61.7%). Arrival weights for 5 calves were not obtained due to

record errors. Days on feed (DOF) prior to death ranged from 2–222 days. Cattle less than 100 days on feed comprised 55% of the mortalities examined, followed by 30.3% between 101–150 DOF. Days on feed for 3 calves were not obtained due to record errors.

Gross and histopathological samples were collected each week at 6 different feedyards (Table 2.2). The sampling strategy at each feedyard was to perform gross necropsies on all eligible cattle at each facility and due to variance in animals present at each facility the number necropsied varied by facility and week.

Gross Results

Of the 402 cattle with gross necropsy results, 359 cases showed gross lung lesions (89%). The remaining forty-three cases were not evaluated due to the absence of a lung lesion. Of the 402 cases that were grossly diagnosed, 36.6% (147/402) were classified with BP, 10.0% (40/402) with AIP and 35.8% (144/402) were classified with BIP (Figure 2.4). The remainder of the cases were categorized in the Undifferentiated category, including healthy lungs (17.7%; 71/402).

Histopathological Results

Lung samples were taken from 318 mortalities and submitted for histopathology. Twenty-four samples were lost in transit resulting in 294 cases evaluated by the pathologist. Of the 294 cases, 102 were excluded due to microscopic autolysis in one or more of the four samples collected. An additional three cases were excluded due to inadequate labeling. Thus, histopathological lung samples (HistoSp) from 189 cases were considered for this evaluation.

Similar to the distribution of GrossDx, BIP lesions accounted for 36.0% (68/189) of the lung HistoDx. BP followed with 32.3% (61/189) and AIP was classified in 12.2% (23/189) of the HistoDx. Respiratory lesions that did not fit the above three categories or healthy lungs were categorized as Undifferentiated (19.6%; 37/189) (Figure 2.5).

Gross Diagnosis versus Histopathological Diagnosis

The cases where both HistoDx and GrossDx were known (n = 172) were evaluated for potential associations between the two diagnoses. The HistoDx tended to be (p- VALUE = 0.06) associated with GrossDx. Case classification by each of the two diagnostic methodologies is demonstrated in Table 2.3. AIP GrossDx had a low probability of agreement with AIP HistoDx (P-value = 0.23); many of these cases were classified as BIP with HistoDx (n = 10). BIP GrossDx and HistoDx had the highest probability of agreement (P-value = 0.49). Gross BIP cases that were not classified as HistoDx BIP were classified as exclusively BP or AIP with HistoDx. BP GrossDx and HistoDx had a 0.36 probability of agreement. The majority of BP GrossDx cases that did not agree were diagnosed as BIP with HistoDx. Finally, the lowest probability of agreement was between the Undifferentiated lung lesions (P-value = 0.17). HistoDx classified 18 of the 24 Undifferentiated GrossDx cases as BP.

Histopathological Diagnosis and Histopathological Sample

A generalized mixed regression model was used to evaluate the probability of diagnostic agreement between each individual HistoSp diagnosis (4 per mortality) with the overall HistoDx (n = 189). Sample location was not significantly (P-value = 0.11) associated with the probability of agreement between HistoSp and HistoDx. The potential interaction between sample location and HistoDx was also not significantly (P-value = 0.22) associated with probability of agreement

between HistoSp and HistoDx. In the final model, only HistoDx was significantly ($P < 0.01$) associated with probability of agreement between HistoSp and HistoDx. The highest probability of agreement between HistoSp and HistoDx was seen for Undifferentiated (probability = 0.99) and AIP (probability = 0.89) (Figure 6). The HistoSp diagnosed with BP demonstrated a probability of 0.69 of agreeing with HistoDx, while BIP HistoSp had the lowest likelihood (0.30) of agreeing with HistoDx.

Discussion

Pulmonary diseases continue to be a major issue in feedyard cattle with important performance and economic impacts. Postmortem examinations in conjunction with laboratory diagnostics, such as tissue histopathology, are valuable tools to understand disease processes and the cattle affected. The goal of this study was to evaluate the frequency of three common pulmonary lesions (AIP, BP, BIP) as diagnosed grossly and by histopathology. Both diagnostic methodologies revealed similar findings in frequency of specific syndromes; however, individual diagnostic probability of agreement between the two modalities was less than expected. The potential utility of a single lung sample was evaluated by comparing diagnoses of individual samples (HistoSp) to overall HistoDx and revealed that level of diagnostic probability of agreement varied by HistoDx.

Based on GrossDx, BP was diagnosed in 36.6% of mortalities followed by BIP in 35.8% of mortalities and AIP in 10.0% of mortalities. The HistoDx revealed 32.3% of lungs had BP, 36.0% of lungs had BIP, and 12.2% of lungs were AIP. The frequency of pulmonary lesions varies from previous studies due differences in sample size and selection of cases for specific clinical signs prior to death [22,27]. Both diagnostic modalities revealed that BP and BIP were

the most common syndromes. Etiologic and risk factors for the bronchopneumonia component have been well documented in the literature with many cases involving viral and bacterial pathogens in susceptible animals [14,30,31]. This study revealed that AIP cases comprised a substantial portion of the mortalities. The prevalence observed in this study may have been higher as the study was conducted in the summer months and in a population of predominately heifers, both of which have been previously described as risk factors for AIP [18,27,32,33]. Additional cross-sectional studies at varied times of year would be helpful to more accurately describe ranges in pulmonary disease prevalence among populations and seasons.

One novel aspect of this study is recording pulmonary lesions with both broncho-pneumonia and interstitial components as BIP cases. The BIP syndrome has been reported [26,27], but little documentation on the overall frequency compared to other pulmonary disease processes is available. Both GrossDx and HistoDx revealed that BIP occurs frequently in deceased feedyard cattle. One potential reason BIP was identified more frequently was the sampling method used for histopathology. Histopathological samples are often selected from diseased areas; however, in this study all cattle were sampled in the four pulmonary quadrants regardless of gross lesions or diagnosis. Interstitial pneumonic changes were identified in multiple cases, but these may have been present in other cases yet undiagnosed due histopathological focus in other areas. The pathogenesis of BIP is not well described and there have been few studies published evaluating the etiology and demographics of cattle diagnosed with BIP lesions. Cases with BIP could result from an inciting BP case followed by interstitial patterns developing from chronic lung disease or the pathogenesis may be more like the development of AIP in cases recovered from BP. Classifying BIP as a unique diagnosis can

provide further insight and consistency when monitoring changes in pulmonary disease prevalence within populations.

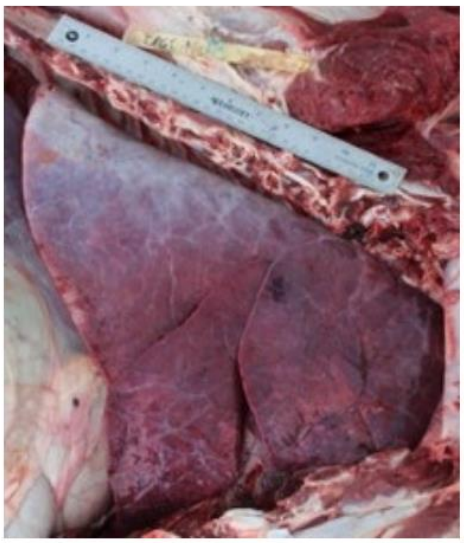
Despite similarities in the overall frequency of syndromes between GrossDx and HistoDx, the two diagnostic modalities only tended to be associated when comparing individual cases. The GrossDx is the most frequent form of diagnosis in deceased cattle. Histopathology is considered the "gold standard" for diagnosis of AIP lesions [28,31] and in this study HistoDx of AIP agreed with only 3 GrossDx AIP, yet 10 of the HistoDx AIP were considered BIP by GrossDx. Thus, the GrossDx should be considered a presumptive diagnosis when trying to identify AIP or BIP with HistoDx used as the final diagnosis. Previous research has reported similar values when comparing gross and histopathological diagnosis agreement [27]. In these 10 cases it is possible the histopathological sample did not contain the BP components observed grossly. The majority of cases diagnosed with BIP agreed between the two modalities and this was a frequent diagnosis. Cattle with GrossDx of BP were often called BP or BIP by HistoDx which is less surprising as the HistoDx may have observed interstitial pulmonary changes unable to be viewed grossly. This finding may indicate that acute interstitial pulmonary changes with BP cases are more common than previously reported. The low probability of agreement between GrossDx and HistoDx may be restricted to the small samples taken for laboratory evaluation.

Clinical diagnoses are often determined solely on gross evaluation with no additional diagnostics, such as histopathology. As this study collected multiple histopathological samples per case, one of the objectives was to evaluate if a single sample would be representative of the histopathological diagnosis and if the location of the sample was important. The statistical model indicated that sample location was not significantly associated with the likelihood of a HistoSp representing HistoDx and there was no significant interaction between sample location and

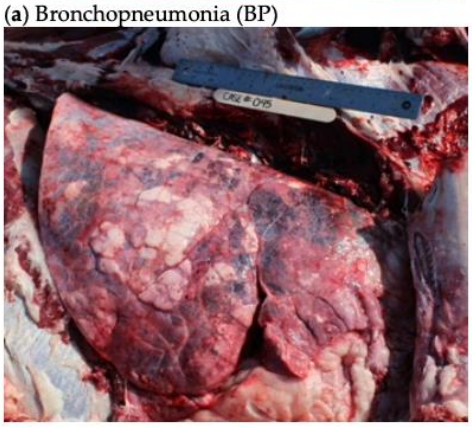
HistoSp. The HistoSp diagnosis was associated with HistoDx, and the level of agreement between probabilities varied by HistoDx. Cases with BIP HistoDx had the lowest probability of agreement indicating that a single HistoSp may not provide the BIP diagnosis. Based on GrossDx, investigators often observed pulmonary areas with distinctly different disease process in BIP cases; therefore, a single sample may not be representative of the entire pulmonary area. This agrees with the current etiology that acknowledges BIP cases to have BP lesions in the cranioventral lung lobes and AIP in the caudodorsal lung lobes [27]. Cases with BP HistoDx had higher probability of agreement (0.71) based on an individual sample, and disagreement may have been due to more localized lesions. If samples were taken from grossly diseased areas our expectation would be higher probability agreement of a single HistoSp with HistoDx. The probability of agreement of HistoDx AIP with a single sample was high (0.91) indicating a diffuse disease process in AIP cases and a single histopathological sample would be diagnostic in most instances. These findings indicate that pulmonary disease is common in feedlot cattle and the specific diagnosis varies by the modality utilized to evaluate pulmonary lesions.

Limitations of this study include that samples were collected based on availability of deceased animals during a limited period of time in 6 different feedyards. The estimated pulmonary disease prevalence may have differed based on season or a varied population of feeder cattle.

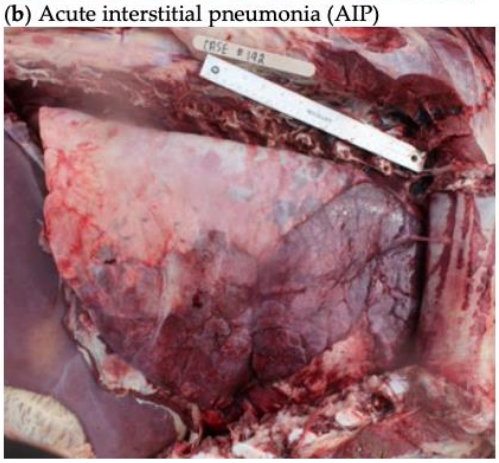
Figures



(a) Bronchopneumonia (BP)



(b) Acute interstitial pneumonia (AIP)



(c) Bronchopneumonia with interstitial pattern (BIP)

Figure 2.1. Right-sided view of gross lesion characteristics representing the three main gross pulmonary pathological diagnoses in this study: (a) bronchopneumonia (BP), (b) acute interstitial pneumonia (AIP), and (c) bronchopneumonia with an interstitial pneumonia (BIP).

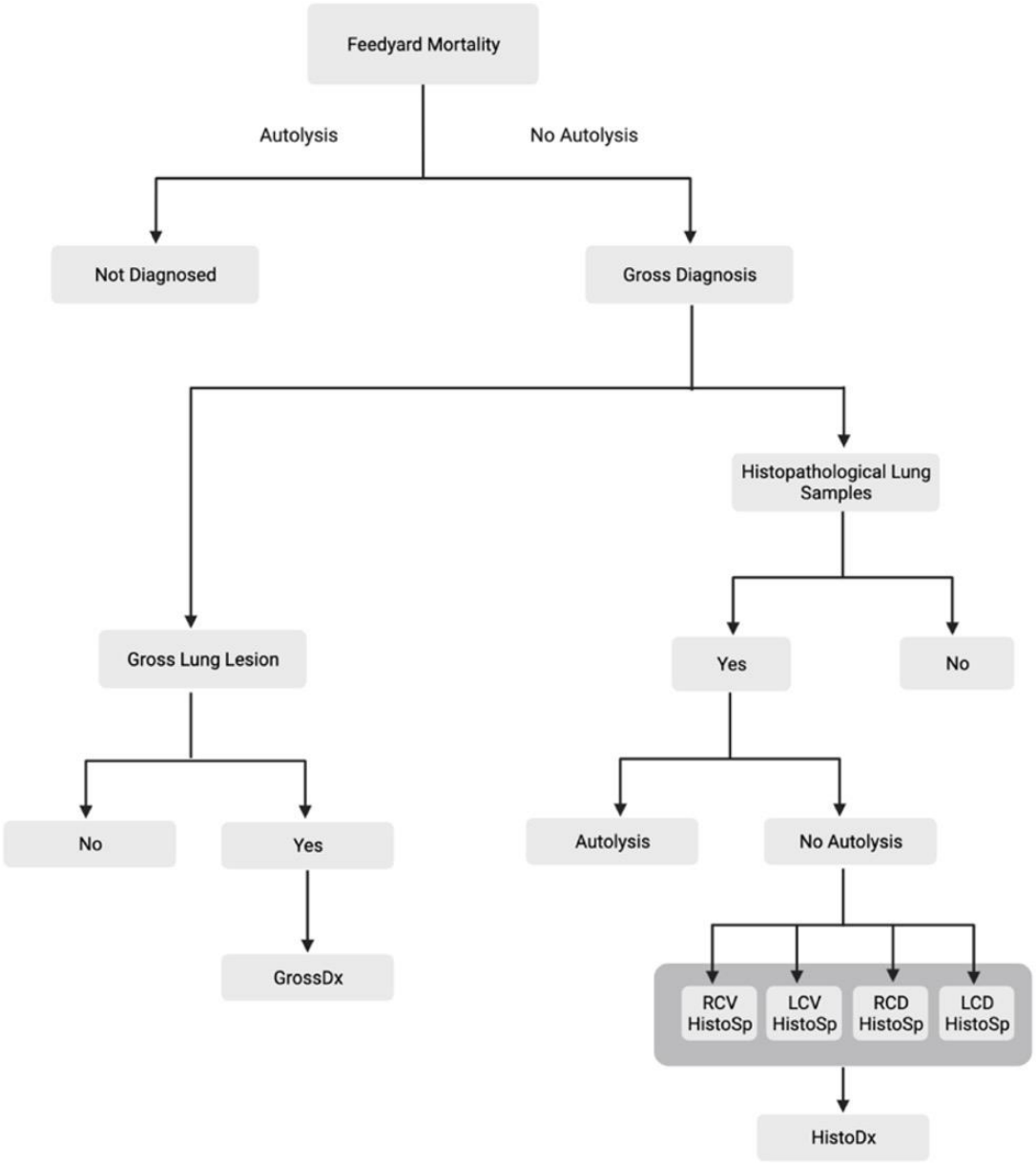


Figure 2.2. Case inclusion strategy to determine feedyard mortalities evaluated for pulmonary lesions by either gross diagnosis (GrossDx) or histopathological diagnosis (HistoDx). Four lung samples were taken from a subset of cases for histopathology. Samples were acquired from the right cranioventral (RCV), left cranioventral (LCV), right caudodorsal (RCD), and left caudodorsal (LCD) lung lobes.

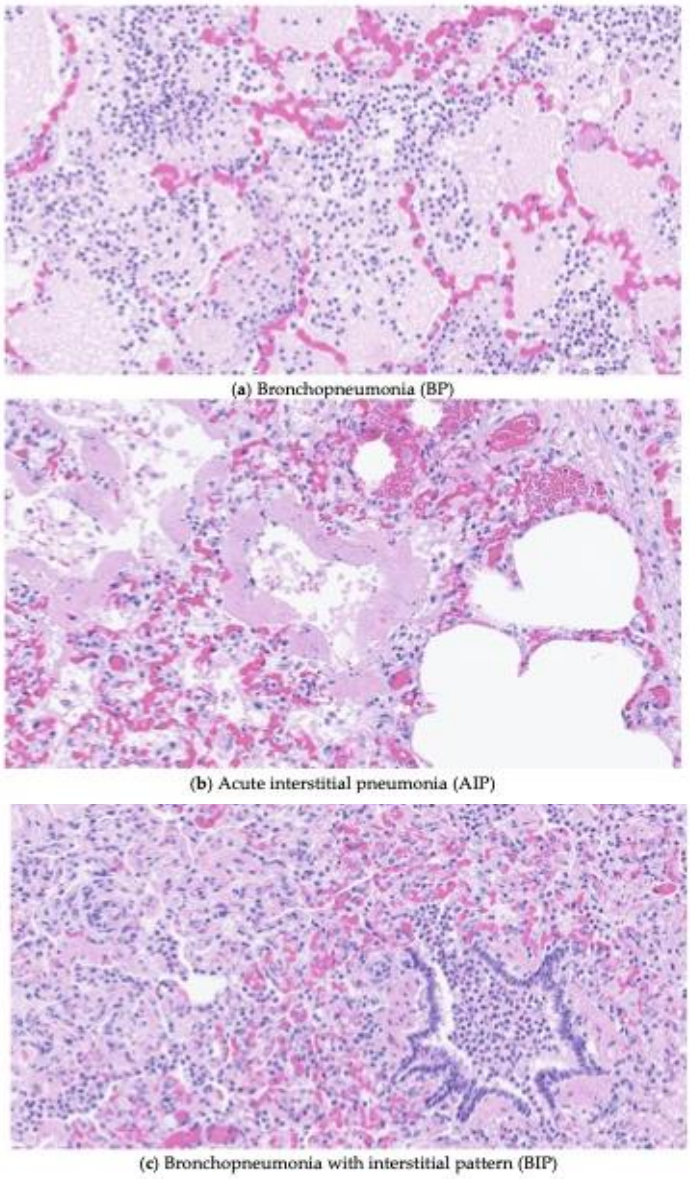


Figure 2.3. Photomicrograph examples from individual cases diagnosed with bronchopneumonia (BP) (a); acute interstitial pneumonia (AIP) (b); bronchopneumonia with interstitial pneumonia (BIP) (c).

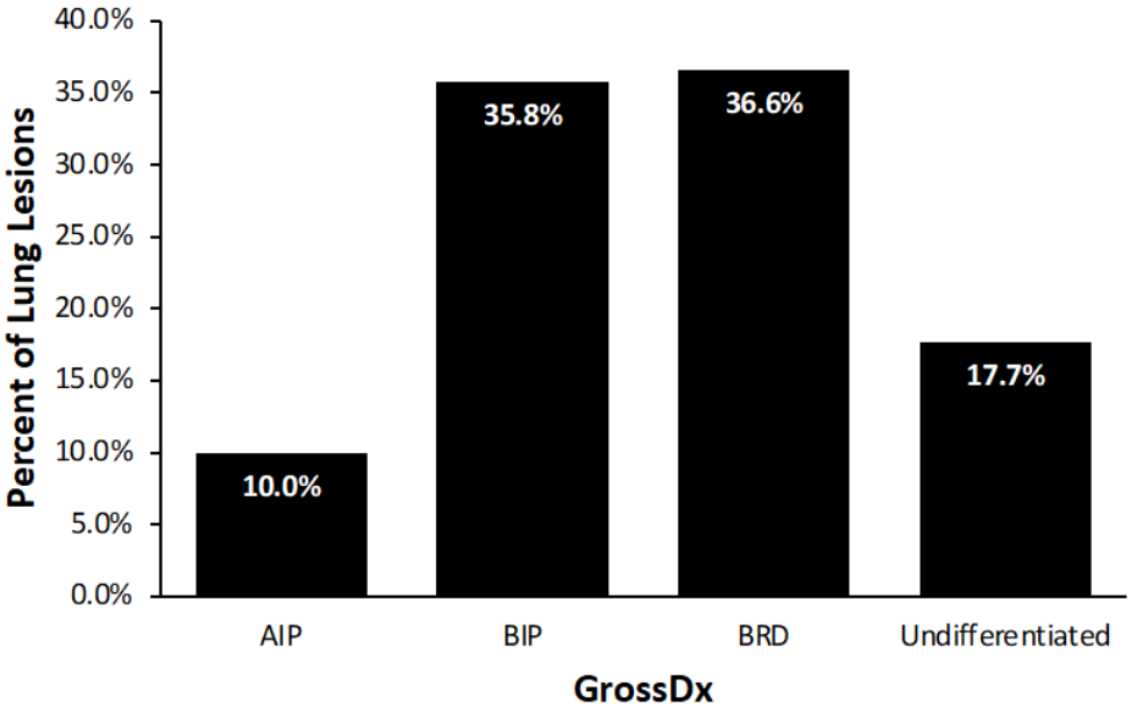


Figure 2.4. Frequency of pulmonary lesions based on gross diagnosis (GrossDx) for individual cattle (n = 402) diagnosed with acute interstitial pneumonia (AIP), bronchopneumonia with interstitial pneumonia (BIP), bronchopneumonia (BP), or Undifferentiated (including healthy).

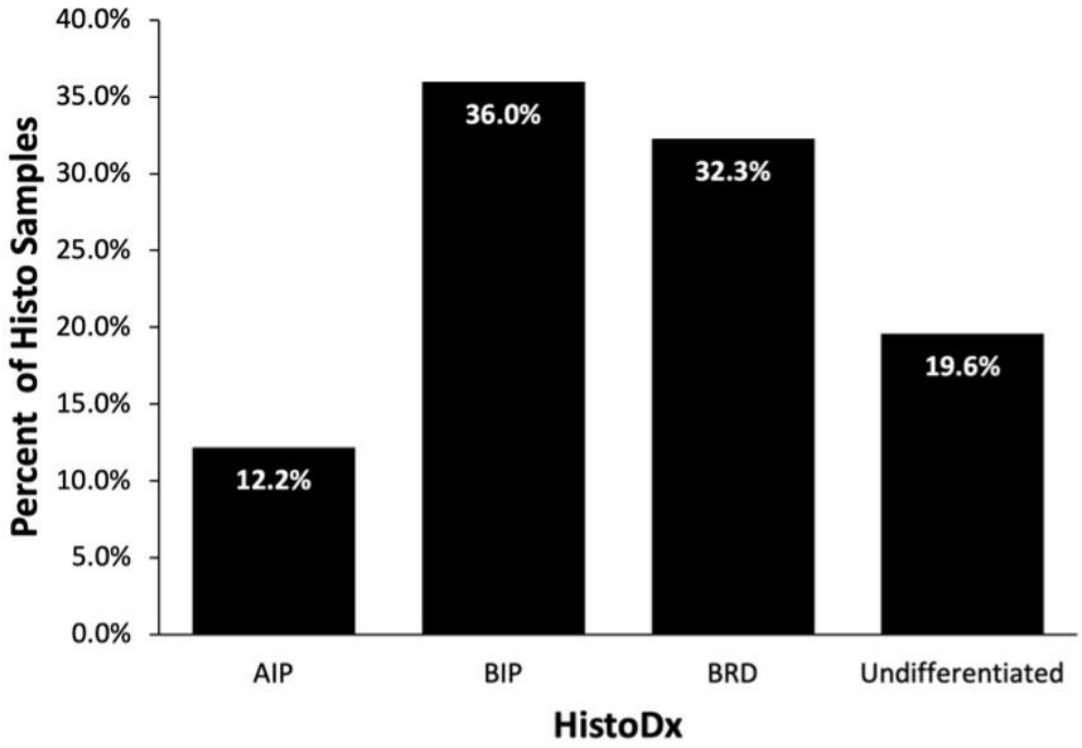


Figure 2.5. Frequency of pulmonary lesions based on histopathological diagnosis (HistoDx) for individual cattle (n = 189) diagnosed with acute interstitial pneumonia (AIP), bronchopneumonia with interstitial pneumonia (BIP), bronchopneumonia (BP), or Undifferentiated (including healthy).

Tables

Table 2.1. Descriptive table of cattle demographics for mortalities evaluated in this study.

Category	Count	Percent Total
Sex		
Heifer	279	69.4%
Steer	123	30.6%
Origin/Breed Type		
Native	374	93.0%
Beef × Dairy	24	6.0%
Holstein	3	0.7%
Mexican	1	0.2%
Arrival Weight (kg)		
181	3	0.7%
227	42	10.4%
272	81	20.1%
318	152	37.8%
363	96	23.9%
408	17	4.2%
454	6	1.5%
Days on Feed		
0-50	114	28.4%
51-100	107	26.6%
101-150	122	30.3%
151-200	51	12.7%
>200	5	1.2%

Table 2.2. Descriptive table of gross necropsies performed at each feedyard (n=417). Mortalities with gross respiratory lesions (n=359) and allocation of histopathological lung samples (n=318).

Week		1	2	3	4	5	6	7	8	9	Total
	Total	0	5	17	22	12	7	14	12	25	114
Feedyard 1	GrossDx	0	5	9	22	10	7	13	12	24	102
	HistoDx	0	5	10	9	11	7	10	11	10	73
	Total	1	5	6	11	10	3	2	2	6	46
Feedyard 2	GrossDx	1	1	5	10	8	3	2	0	5	35
	HistoDx	1	2	5	10	7	2	1	2	5	35
	Total	1	11	8	9	5	4	13	10	10	71
Feedyard 3	GrossDx	1	9	6	7	5	3	10	9	9	59
	HistoDx	0	9	6	7	3	4	9	9	10	57
	Total	2	6	4	5	5	2	1	2	2	29
Feedyard 4	GrossDx	2	5	4	3	5	2	1	2	2	26
	HistoDx	2	5	4	4	4	1	1	1	2	24
	Total	6	14	12	12	6	4	8	9	5	76
Feedyard 5	GrossDx	6	12	10	8	5	4	5	7	5	62
	HistoDx	5	9	9	9	6	4	8	8	4	62
	Total	3	3	13	7	14	9	11	12	9	81
Feedyard 6	GrossDx	3	3	10	9	13	8	9	11	9	75
	HistoDx	3	3	9	7	9	8	10	9	9	67

Table 2.3. Individual case classification based on HistoDx or GrossDx in cases (n = 172) diagnosed with each methodology as either acute interstitial pneumonia (AIP), bronchopneumonia with interstitial pneumonia (BIP), bronchopneumonia (BP), or Undifferentiated (including healthy). Shaded cells represent cases where HistoDx and GrossDx showed agreement.

	Histopathological Diagnoses			
Gross Diagnosis	**AIP**	**BIP**	**BP**	**Undifferentiated**
AIP	**3**	**8**	**1**	**1**
BIP	**10**	**44**	**32**	**3**
BP	**6**	**13**	**21**	**18**
Undifferentiated	**3**	**2**	**5**	**2**

Conclusions

Results from this study indicated that pulmonary lesions are frequent in deceased feedlot cattle with BP and BIP representing the two most common syndromes. Refining mortality diagnostics and creating more specific descriptions of pulmonary lesions at death can facilitate better understanding of pathologic processes and appropriate therapeutic interventions. The BIP diagnosis has been infrequently acknowledged as a specific pulmonary lesion, but an improved understanding of this syndrome may play a role in identifying improved prevention and control measures. The frequency of pulmonary syndrome diagnosis was similar among GrossDx and HistoDx; however, individual case diagnoses were not statistically associated between the two diagnostic modalities. Thus, the GrossDx should be considered a presumptive diagnosis when trying to identify AIP or BIP with HistoDx used as the final diagnosis. This study collected 4 histopathological lung samples in a subset of cases and in this subset a single sample was more likely to agree with HistoDx when the HistoDx was AIP or BP compared to BIP. The three major pulmonary syndromes evaluated were common in mortalities and diagnosed with both diagnostic modalities. Refined mortality diagnostics are necessary to improve understanding of pulmonary pathology which can be valuable for evaluating and adjusting therapeutic interventions.

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Chapter 3 - A retrospective analysis of arrival and health risk factors for the development of acute interstitial pneumonia in feedyard cattle on a cohort level.

As submitted: *Bovine Practitioner*

Abstract

Acute interstitial pneumonia (AIP) in feedyard cattle is a respiratory condition characterized by sudden onset of respiratory distress and, often, rapid mortality. The exact etiology of AIP remains unclear and multiple risk factors are hypothesized to contribute to AIP development. The objective of this retrospective study was to determine the probability of at least one AIP mortality occurring in a cohort (AIPMort) and potential associations with cohort arrival characteristics and disease incidence in the first 45 days-on-feed. Variables analyzed included sex, head received, arrival weight, arrival month, bovine respiratory disease (BRD) morbidity and mortality, and digestive disease morbidity and mortality. Cohort and corresponding individual animal treatment records were acquired from twenty feedyards in the United States, resulting in 27,324 cohorts over four years. At least one AIP mortality was present in 5,525 (20.2%) cohorts. All risk factors were significantly associated with AIPMort. Heifer cohorts were more likely to (19.5% ± 0.048) experience AIPMort than steer cohorts (13.3% ± 0.035). Cohorts with greater than 5% BRD morbidity in the first 45 days-on-feed were more likely to experience an AIPMort (20.2% ± 0.049) than cohorts that had 0% morbidity (8% ± 0.025). Improved understanding of risk factors associated with AIPMort can be valuable for managing cohorts.

Introduction

Acute interstitial pneumonia (AIP) is a well-known respiratory disease in the feedyard industry characterized by sudden, severe onset of respiratory distress with a high case fatality rate with reported ranges from 30 to 100%.[1–4] Previous analyses describe AIP as second only to bovine respiratory disease (BRD) as the leading cause of economical losses in U.S. feedlots. [2,5] While AIP is an important disease syndrome relatively little recent work has been done evaluating potential risk factors leading to this disease in groups of cattle.

Distinguishing AIP from other common syndromes such as BRD is important and often based on a combination of clinical signs and pathologic findings. Commonly described clinical signs of AIP include extended head and neck, wide-based stance, open mouth breathing with abdominal effort, audible grunts or in some cases affected cattle are found dead in the pen prior to evaluation.[4,6–8] Some cattle affected with AIP show signs of aggression due to severe hypoxia.[9,10] Various treatment protocols are utilized, but many cases result in death shortly after diagnosis. On postmortem examination, AIP cases often have diffuse, overinflated lung lobes with visual interlobular edema and emphysema and multiple colorations of pink, white and purple throughout the lobules that result in a "checkerboard" appearance.[8,11–16] Histopathologically, lung samples are well described as having alveolar septum expansion due to inflammatory cells, alveolar septal necrosis, hyaline membranes and occasionally type II pneumocyte hyperplasia and bronchiolitis obliterans.[11,16–18] Although the characteristics of AIP on an individual animal basis are well described, limited research has evaluated this pulmonary disease on a cohort-level to identify risk factors associated with AIP mortalities. Identifying risk factors for AIP early in the feeding period can help feedyard personnel and veterinarians better manage and monitor at-risk cohorts.

Acute interstitial pneumonia in feedyard cattle has been studied since 1962.[19] There is a prevailing industry bias that AIP predominately occurs in heifers during the summer months, particularly late in the feeding period. The pathogenesis and risk factors associated with AIP in pasture cattle are well understood, however, little success has been achieved to induce or characterize a specific causative toxin, agent or environmental characteristic in a feedyard setting. Utilizing information available at arrival and health parameters collected in the first forty-five days-on-feed could provide insight to better define cohort AIP risk. The objective of this retrospective data analysis was to determine the probability of at least one AIP mortality (AIPMort) occurring in a cohort and the associated risk factors from demographics known at feedlot arrival and health challenges recorded in the first 45 days-on-feed. The risk factors analyzed included cohort sex, head received, arrival weight, arrival month, BRD cumulative morbidity risk (BRDMorb45), BRD cumulative mortality risk (BRDMort45), digestive cumulative morbidity risk (DigestMorb45) and digestive cumulative mortality risk (DigestMort45). Distinguishing cohort level risk factors associated with feedyard AIP can complement previous research on individual AIP mortalities to identify specific cohorts that experience these sporadic mortalities.

Materials and Methods

Institutional Animal Care and Use Committee (IACUC) approval was not acquired for this study due to data used for the retrospective analysis being obtained from commercial feedyard's privatized databases. All data utilized for the study were collected as part of normal feedyard operational practices and no health or management changes for the cattle were performed specifically for this study.

Data Source

Cohort records along with corresponding individual animal treatment records were obtained under confidentially agreements from twenty commercial feedyards located in the central High Plains region of the United States. Data were managed and evaluated on a cohort level. A cohort was defined as a group of cattle received, managed and marketed together. However, a cohort did not have to be housed in the same physical pen for the entirety of the feeding period. Data were acquired from individual feedyard systems and further managed in R Software.[a]

Data Management and Enrollment Criteria

Cohort records were categorized by a unique identification number (CohortGroup) to distinguish within and among feedyards. The CohortGroup comprised the feedyard identification number, cohort identification number and arrival year. Individual animal treatment and mortality records were acquired and merged with cohort records using the CohortGroup identification number.

Following the data merge, CohortGroups were categorized by sex, average cohort arrival weight (arrival weight), head received on arrival (head received), and average arrival date (arrival date). Individual animal health records were categorized by cause of death, treatment diagnosis, days-on-feed at death (DOF_Death) and days-on-feed at treatment (DOF_Tx). After categorization of individual animal records these values were aggregated to provide summaries at the cohort level for the first 45 DOF. Variables utilized for the data analysis were refined to include only specific parameters and adjusted to be consistent throughout feedyard databases and terminology (Figure 3.1). Only cohorts designated as heifer (“HF” or “H”), or steer (“ST” or

"S") were included. Arrival date was categorized by month of each year. Continuous variables (arrival weight, head received) were categorized to avoid breaching the assumption of a linear relationship between each covariate and the outcome of interest. Arrival weight was limited to greater than or equal to 300 pounds and less than or equal to 1000 pounds to avoid sparse data. Arrival weight was split into six categories with one-hundred-pound increments (<400, 400 to 500, 500 to 600, 600 to 700, 700 to 800, 800 to 900, and 900 to 1000 lbs.). Head received per cohort was limited to greater than or equal to 50 and less than or equal to 500 head. Head received was categorized into four categories after visualizing the distribution of head received for the included cohorts. These categories included: 50 to 100, 100 to 150, 150 to 200, and > 200 head received on arrival.

Cohort arrival dates were from January 1, 2020, to December 31, 2023. Cohorts were required to be "closed" which refers to cohorts that completed their respective feeding period and were shipped to harvest. In the dataset, unique cohorts may have duplicated records due to shipping or pen movements. Duplicated cohort records were identified, confirmed and removed.

Individual animal treatment records were utilized to assess health events in the first 45 days-on-feed. Individual animal health records were tied to only cohorts that met the inclusion criteria. Days-on-feed at treatment (DOF_Tx) was calculated for individual animals that were treated with a "respiratory" or "digestive" diagnosis with the following equation [DOF_Tx = Treatment date – arrival date]. Clinical signs that resulted in a respiratory diagnosis included but not limited to labored breathing, febrile, increased respiratory effort, depression or anorexia. A diagnosis of digestive disease included but is not limited to bloat, diarrhea, or weight loss. Individual animals treated multiple times for either a "respiratory" or "digestive" diagnosis were counted in the dataset only once. Days-on-feed at death (DOF_Death) was calculated for

individual animals that died with a “respiratory” or “digestive” diagnosis with the following equation [DOF_Death = Death date – arrival date]. Calculated DOF_Death and DOF_Tx was used to calculate BRD and digestive morbidity (BRDMorb45, DigestMorb45, respectively) and mortality (BRDMort45, DigestMort45, respectively) within the first 45 days-on-feed. Each health calculation was not mutually exclusive, allowing an animal to be recorded in multiple categories. For example, if an animal was treated for respiratory disease and digestive disease within the first 45 days-on-feed, that animal would be recorded in both health variables. Animals were only recorded once for each diagnosis regardless of the number of times treated for that diagnosis.

The four health demographics (BRDMorb45, BRDMort45, DigestMorb45, DigestMort45) were evaluated on a percent of cohort basis only in the first 45 days-on-feed. BRDMorb45 was categorized as zero (0%), low (0.1 to 5%), medium (5.1 to 10%) and high (> 10%) risk. BRDMort45 was split into three categories due to a smaller variation: 0%, >0 to 1%, and > 1% mortality. Due to a small percentage of cohorts being affected with DigestMorb45 and DigestMort45, these health demographics were categorized as either 0% or > 0% digestive morbidity and mortality in a cohort.

The primary outcome in this research was to evaluate the presence of at least one AIP mortality in a cohort (AIPMort). Individual animal health records were used to calculate the number of AIP mortalities in each cohort throughout the entire feeding period. Cattle treated for AIP that did not die of AIP later in the feeding period were not included in this analysis to minimize variation between case definitions of individual feedyards and to decrease the impact of misdiagnosed respiratory cases. To create a binominal variable to allow evaluations of risk

factors associated with cohort level AIP mortalities, cohorts were classified as either AIPMort = 0 (experienced no AIP mortalities) or AIPMort =1 (experienced at least 1 AIP mortality).

Statistical Analysis

Data management and statistical modeling were performed in R Software.[a] A generalized linear mixed model was created to evaluate potential associations between cohort level risk factors and the primary outcome of interest (AIPMort). Cohort level risk factors of interest included: sex, head received, arrival weight, arrival month, BRDMorb45, BRDMort45, DigestMorb45 and DigestMort45. The model was specified using the "lme4" package and "glmer" function. Feedyard and arrival year were determined to be random intercepts due to the lack of independence of cohorts within feedyard and each year included in the data set.

Results

Population Demographics

The raw data contained 68,658 initial cohort records and after applying inclusion criteria the final data set included 27,324 cohorts (4,292,674 head) from 20 U.S. High Plains commercial feedyards, over a four-year time span (Figure 3.1). The total population consisted of more steer than heifer cohorts and the number of cohorts were relatively evenly distributed by head received, arrival month and arrival year (Table 3.1). Most cattle (75%) arrived in the 600 to 700, 700 to 800, 800 to 900-pound weight categories. Relatively few cohorts had high BRD morbidity (>10%) or mortality (>1%) within the first 45 DOF. Only 15% and 27% of cohorts had at least 1 digestive morbidity and mortality, respectively.

There were 7,563 individual animals that experienced an AIP mortality which accounted for 0.18% (7,563 / 4,292,674) of the population. Within this data set, there were overall 79,181 mortalities over the entire feeding period, indicating a 1.8% (79,181 / 4,292,674) mortality rate in cattle enrolled. The relative proportion of mortalities attributed to AIP in these data was 9.6% (7,563 / 79,181). The number of AIP mortalities in an individual cohort ranged from 0 to 9 mortalities during the feeding period (Table 3.2). In the final dataset, 20.2% (5,525 / 27,324) of cohorts had at least one AIP mortality (AIPMort).

Outcomes Associated with AIP Mortalities

The probability of AIPMort was significantly associated with sex, arrival weight, head received, arrival month, BRDMorb45, BRDMort45, DigestMorb45 and DigestMort45 (Table 3.3). Heifers had higher AIPMort than steers ($P < 0.01$) and AIPMort increased as head received increased. Cattle in the 500 to 900-pound weight categories had higher ($P < 0.05$) AIPMort compared to cattle in the 400 to 500 and 900 to 1000-pounds categories. Cattle arriving January through May had a higher AIPMort compared to all other months of the year ($P<0.05$). Cohorts that experienced high BRD morbidity (>5%) and mortality (>0.1%) were associated with higher ($P<0.05$) AIPMort compared to cohorts with less BRD challenge. Similarity, cohorts that experienced any digestive challenge had higher ($P<0.05$) AIPMort probability.

Discussion

The current retrospective study evaluated potential associations of arrival and health risk factors on cohort AIPMort. While AIP mortality at the individual animal level is relatively rare, one in five cohorts had at least one AIP mortality. All arrival risk factors tested were significantly associated with AIPMort. Evaluation of other disease incidence in the first 45 days-

on-feed were positively associated with AIPMort. Previous research has described potential individual animal AIP risk factors associated with ration, feed additives, environmental factors and specific characteristics.[2,6,14,16,20,22,23] Other AIP literature has evaluated timing of individual AIP mortalities relative to timing throughout the feeding period.[2,16,23–25]

Our data illustrated the overall AIP mortality on a total head received basis is approximately 2 per 1,000 (0.18%) cattle on feed which is similar to previous research. [5,20,25] Although AIP impacted a relatively small proportion of all cattle, this syndrome represented nearly 10% of the mortality cases when all causes of death were considered. On an individual animal basis AIP is relatively rare, but the incidence becomes more significant at the cohort level with AIPMort present in 20.2% (5,525/ 27,324) of cohorts. Most cohorts had only a single AIP mortality, but the level of cohorts impacted was meaningful. Improved understanding of risk factors could allow managers to focus monitoring efforts on higher risk cohorts.

Arrival characteristics of cohorts entering the feedyard serve as critical variables in cattle management and research, informing decision-making processes and guiding targeted interventions. Arrival data have been used to predict health outcomes, nutritional planning, and performance and economic outcomes.[26–30] Risk factors utilized to predict bovine respiratory disease (BRD) morbidity and mortality are commonly acquired from cattle at the time of arrival.[31–33] Previous research has characterized AIP to affect cattle in the last two-thirds of the feeding period but, arrival risk factors associated with AIP can be useful for disease prediction which could influence the intensity with which each cohort should be monitored for AIP.

Arrival demographics significantly associated with AIPMort in the current study included sex, arrival weight, head received and arrival month. Heifer cohorts had a higher probability of AIPMort compared to steer cohorts. Similar findings on an individual animal basis have been

documented in previous literature, however, the difference in probability between heifers and steers have been recorded previously with as much as a three times higher risk in heifers.[4,14] Previous research speculated this difference due to supplementation of melegrestrol acetate (MGA), however, no difference in the diagnosis of AIP has been found in MGA- fed versus control heifers.[22] The current study had no data available on MGA status of enrolled heifer cohorts although MGA feeding to heifers is a common commercial practice.

One factor regarding differences in sex is heifers tend to have a higher yield grade than steers and the increase in adipose tissue could lead to increased inflammation that targets the lungs, late in the feeding period. AIP is described as an acute inflammatory disease of the interstitium of the lungs. Adipose tissue, specifically visceral adipose tissue, contributes to pro-inflammatory cytokine release.[34,35] Heifers with higher fat deposition could be at higher risk for AIP due to the increase of inflammatory-mediating adipose tissue. However, AIP is likely a complex respiratory disease which likely has multiple etiologies and contributors and the higher yield grade seen in heifers could be one of those contributing factors.

The probability of AIPMort increased by approximately five percent by every 50-head increment in the number of head received. With AIP being a sporadic disease, a greater population size could result in a greater likely of at least one animal in the population would succumb to AIP. Another argument for the correlation in head received is cattle acquired in smaller groups are more accessible and easier for feedyard personnel to closely monitor, resulting in fewer instances of undetected illness among cohorts. Increased AIPMort in larger groups of cattle may influence animal health managers to monitor these cohorts more closely.

Cohorts that arrived January through May had an approximately 8% increased probability of experiencing an AIPMort compared to cattle that arrived the rest of the year. We hypothesize

this is due to cohorts arriving during the first five months of the year are likely to complete the feeding period during the summer, the season associated with an increased incidence of AIP in previous research. Previous AIP timing research has characterized AIP morbidity and mortality to occur more frequently in the summer months, on cattle later in the feeding period.[4,23,25] The current study was aggregated to the cohort-level and probability of AIPMort within a cohort; therefore, the timing of AIP cases could not be assessed. Further research may be useful to elicit potential risk factors associated with AIP timing within a cohort and potential causes of disease seasonality.

Cattle that arrived between 500 to 900 lbs. had a significantly higher probability of having an AIPMort compared to cohort's arriving at greater than 900 lbs. Approximately 85% of cattle arrived within 500 to 900 lbs., reflecting the typical arrival weight for cattle entering the feedyard. Previous research illustrated higher BRD mortality and morbidity in cattle arriving at a lower body weight,[25,36] and the current work displays a relationship between BRD morbidity and mortality with AIPMort. The findings associated with cohort arrival weight could be indicative of increased overall cattle susceptibility to disease. Alternatively, if AIP is truly sporadic based on factors at the feedyard, cattle with lighter weights would spend more days in the feeding period and thus have increased cumulative risk for AIP by virtue of increased time at risk.

The health demographics of feedyard cattle during the first 45 days-on-feed are critically important, as this period is pivotal for assessing early disease incidence. Most BRD cases occur in the first 45 days-on-feed and this time-period also predicts overall risk of digestive disease because of its consistent occurrence throughout the feeding peroid.[37,38] Health outcomes during this period can significantly influence overall feedyard performance, feed efficiency, and health parameters for the rest of the feeding period.[31,39,40]

Bovine respiratory disease (BRD) is the most impactful disease in North American feedyard cattle and has previously been reported in conjunction with AIP.[2,16,20] No previous work has identified if prior BRD infection increases AIP mortality risk in the same cohort. These respiratory syndromes may occur in the same animal and research has identified BRD lesions and AIP lesions found in the same lung (bronchopneumonia with an interstitial pneumonia, BIP) as a distinct disease syndrome, highlighting the need for refining respiratory diagnoses.[11,15,41] Cattle previously treated for BRD have been shown to have greater risk of BIP mortality.[23,41] Cattle with medium BRDMorb45 risk (5.1 to 10%) or higher and BRDMort45 > 0% were associated with a higher AIPMort compared to cohorts with less or no BRD incidence. Cattle challenged with BRD early in the feeding period may be predisposed to other disease challenges later in the feeding period. This retrospective study only identified associations among BRD and AIP risk at the cohort-level and the nature of the analysis prohibits identifying potential causality in the relationship. Prior BRD risk could increase risk of AIP or AIP risk may be more likely in the type of cattle at high risk for BRD; further research should be performed to determine the specific relationship among these respiratory syndromes.

Digestive disorders are hypothesized as predisposing factors to experiencing an AIP mortality, and previous research reported AIP mortality risk almost doubled with the a digestive death in the same cohort.[9] The current research illustrated that while a relatively low percentage of cohorts experienced digestive disease (morbidity or mortality) in the first 45 days, cohorts experiencing digestive disease were more likely to have AIPMort. The lysis and release of lipopolysaccharides (LPS) through the digestive system has been documented to occur in cases of subacute acidosis, and recent research may suggest translocation of LPS across the rumen epithelium or intestinal barrier could be a result of leaky gut.[42] One hypothesis linking digestive

disease to AIP development is the showering of LPS, into the blood stream which can cause an acute inflammatory response in the lungs. Some digestive issues cause subacute acidosis and/or leaky gut syndrome. Then a toxin or pathogen with LPS crosses the rumen epithelium or intestinal barrier such that LPS can become systemic. Leaky gut syndrome refers to a condition where the intestinal lining becomes compromised, leading to permeability to intestinal contents, such that toxins or pathogens, which may contain LPS, become systemic. This condition is triggered by stress factors such as high-grain diets, or heat stress.[43,44] While, there is no evidence linking subacute acidosis or leaky gut with AIP, many hypothesis exist linking these two diseases. Further research is necessary to determine if there is a correlation between digestive disorders and AIP.

Limitations of this study include using retrospective data from various feedyards that may or may not utilize postmortem examinations on all mortalities, therefore, misdiagnosis for AIP, BRD and digestive death may be present. Furthermore, AIP has been documented to occur suddenly often resulting in unexpected mortalities with untreated cattle found in the pen. Various sudden-onset diseases occur in feedyard cattle and unless a postmortem examination is performed, AIP can be misdiagnosed due to limited treatment options and its rapid effects. Potential differences between feedyards were controlled as random effects in the statistical model. This analysis focused solely on AIP mortalities, potentially affecting the total count of cattle diagnosed with AIP, as cattle that were treated or railed with AIP that did not die were excluded. The studied population experienced a mortality rate of 1.8%, therefore, these data can only be extrapolated to feedyard populations that experience similar mortality rates. Our results and conclusions are limited to the data presented and the cattle in the cohorts that fit our inclusion criteria. Regardless of these limitations, the results of this observational, retrospective

analysis demonstrate the complexity of AIP in feedyard cattle and multiple risk factors that were associated with arrival and health characteristics with having at least one AIP mortality in a cohort.

Figures

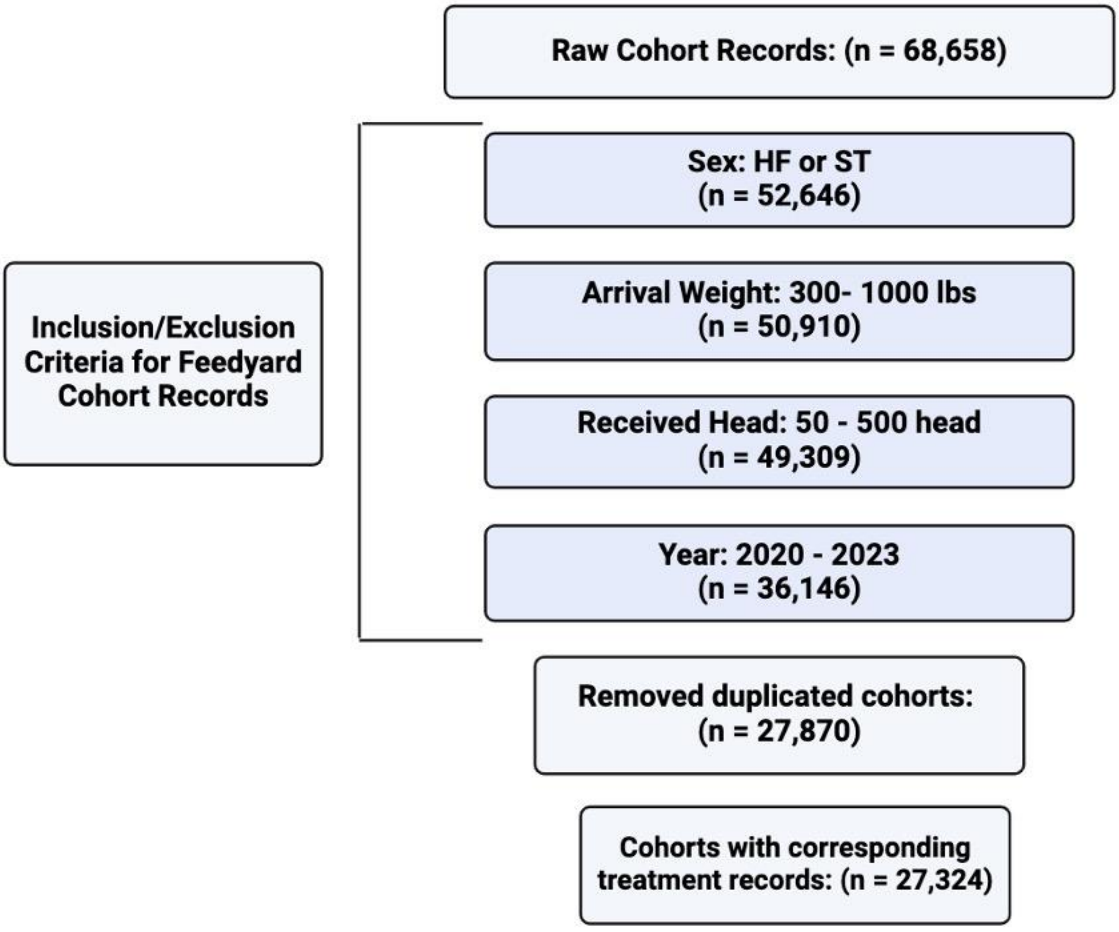

Figure 3.1. Flowchart demonstrating data filtering applied to cohort-level data from 20 U.S. central high plains feedyards used to create a working data set. HF = Heifer; ST= Steer. The n represents the number of cohorts remaining after each stage of data filtering.

Tables

Covariates	Category within Covariates	Cohorts within Covariates	AIP Mortalities
Sex	Heifer	11,309 (41.4%)	2,919 (52.8%)
	Steer	16,015 (58.6%)	2,606 (47.2%)
Year	2020	5,691 (20.8%)	1,048 (19.0%)
	2021	7,322 (26.8%)	1,669 (30.2%)
	2022	7,302 (26.7%)	1,576 (28.5%)
	2023	7,009 (25.7%)	1,232 (22.3%)
Arrival Weight (lbs)	<400	91 (0.3%)	23 (0.4%)
	400-500	806 (2.9%)	141 (2.6%)
	500-600	2,278 (8.3%)	549 (9.9%)
	600-700	5,653 (20.7%)	1,405 (25.4%)
	700-800	8,630 (31.6%)	1,956 (35.4%)
	800-900	6,690 (24.5%)	1,132 (20.5%)
	900-1000	3,176 (11.6%)	319 (5.8%)
Head Received	50-100	6,892 (25.2%)	897 (16.2%)
	100- 150	7,738 (28.3%)	1,527 (27.6%)
	150 – 200	6,052 (22.1%)	1,460 (26.4%)
	>200	6,642 (24.3%)	1,641 (29.7%)
Arrival Month	January	2,602 (9.5%)	791 (14.3%)
	February	1,915 (7.0%)	555 (10.0%)
	March	2,137 (7.8%)	557 (10.1%)
	April	1,854 (6.8%)	500 (9.0%)
	May	2,348 (8.6%)	589 (10.7%)
	June	2,154 (7.9%)	438 (7.9%)
	July	2,410 (8.8%)	379 (6.9%)
	August	2,725 (10.0%)	350 (6.3%)
	September	2,377 (8.7%)	266 (4.8%)
	October	2,386 (8.7%)	318 (5.8%)
	November	2,194 (8.0%)	346 (6.3%)
	December	2,222 (8.1%)	436 (7.9%)
BRD Morbidity (%)	0	2,861 (10.5%)	276 (5.0%)
	0.1-5	13,450 (49.2%)	2,762 (50.0%)
	5.1- 10	6,381 (23.4%)	1,417 (25.6%)
	>10	4,632 (17.0%)	1,070 (19.4%)
BRD Mortality (%)	0	16,361 (59.9%)	2,841 (51.4%)
	0.1-1	6,082 (22.3%)	1,504 (27.2%)
	>1	4,881 (17.9%)	1,180 (21.4%)
Digestive Morbidity (%)	0	23,103 (84.6%)	4,675 (84.6%)
	>0	4,221 (15.4%)	850 (15.4%)
Digestive Mortality (%)	0	20,030 (73.3%)	3,628 (65.7%)
	>0	7,294 (26.7%)	1,897 (34.3%)

Table 3.1. Descriptive table of covariates by category from cohorts with retrospective data collected from 20 US High Plains feedyards from 2020 to 2023 and filtered by inclusion criteria. Cohorts within covariates column indicates distribution of all cohorts (n=27,324) within each category. The AIP mortalities column indicates the distribution of covariates in cohorts with at least one AIP mortality (n = 5,525).

Table 3.2.Frequency table of cohorts by number of individual AIP mortalities using retrospective data collected from 20 US High Plains feedyards from 2020 to 2023 and filtered by inclusion criteria.

AIP Mortalities per Cohort	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Count	21,799	4,117	980	306	72	32	11	4	1	2
Percent (%)	79.8	15.1	3.6	1.1	0.26	0.12	0.04	0.015	0.004	0.007

Table 3.3.Statistical analysis of covariates by category from cohorts and the probability of having an AIPMort during the feeding period. Retrospective data was collected from 20 US High Plains feedyards from 2020 to 2023 and filtered by inclusion criteria. Coefficients are denoting significant between categories in each covariate.

Covariates	Category within Covariates	Probability	Standard Error
Sex	Heifer	0.195[a]	0.048
	Steer	0.133[b]	0.035
Arrival Weight (lbs.)	<400	0.182[abc]	0.059
	400-500	0.103[a]	0.030
	500-600	0.175[bc]	0.044
	600-700	0.200[c]	0.049
	700-800	0.191[c]	0.047
	800-900	0.170[b]	0.043
	900-1000	0.132[a]	0.035
Head Received	50-100	0.090[a]	0.025
	100- 150	0.147[b]	0.038
	150 – 200	0.198[c]	0.049
	>200	0.249[d]	0.057
Arrival Month	January	0.239[a]	0.056
	February	0.244[a]	0.057
	March	0.232[a]	0.055
	April	0.239[a]	0.056
	May	0.210[a]	0.051
	June	0.160[d]	0.042
	July	0.124[b]	0.033
	August	0.106[bc]	0.056
	September	0.093[c]	0.026
	October	0.110[bc]	0.031
	November	0.121[bc]	0.032
	December	0.156[d]	0.041
BRD Morbidity (%)	0	0.089[a]	0.025
	0.1-5	0.170[b]	0.043
	5.1- 10	0.202[c]	0.049
	>10	0.215[c]	0.052
BRD Mortality (%)	0	0.141[a]	0.037
	0.1-1	0.169[b]	0.043
	>1	0.178[b]	0.045
Digestive Morbidity (%)	0	0.147[a]	0.038
	>0	0.178[b]	0.045
Digestive Mortality (%)	0	0.144[a]	0.085
	>0	0.182[b]	0.045

Conclusion

Acute interstitial pneumonia in feedyard cattle, although rare (0.18%) continues to have a significant negative impact economically and individually on the cattle affected. Furthermore, our lack in understanding this complex pulmonary disease and the etiology provides significant challenges to prediction, detection and treatment. Cattle in the feedyard are managed on a cohort level. Changing the evaluation parameters of AIP from an individual animal to a cohort level has provided insight to cohorts that experience AIP mortalities based on their arrival characteristics and health metrics regarding BRD and digestive disease in the first 45 days-on-feed. Heifer only cohorts were more likely to experience an AIPMort than steers and as head received increases, the probability of AIPMort increased by 5 percent. Health challenges in the first 45 days-on-feed are commonly monitored on a cohort level. Our data suggests that cohorts that experienced BRDMorb45 and BRDMort45 greater than 5% and 0.1%, respectively exhibited a higher probability of having an AIPMort. Further research is still necessary to assess the etiology of this disease, and the individual cattle affected. However, this cohort data guides further research to the specific groups of cattle that experience AIP mortalities.

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End Note

[a]R Studio Version 2022.07.2+576. R Studio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA http://www.rstudio.com/

Conclusions

Interstitial pneumonia in feedyard cattle continues to be a constant contributor to morbidity and mortality with little understanding about its pathogenesis and the cattle it affects. Further emphasis towards AIP is present due to its higher frequency in cattle later in the feeding period when economical resources are maximized. Bronchopneumonia with an interstitial pneumonia has been documented to affect more cattle than AIP but consistent documentation of this respiratory diseases provides many challenges. The purpose of this thesis was to evaluate interstitial pneumonia in feedlot cattle and the varying types of interstitial disease that may need refining to fully understand this classification of pneumonia.

Acute interstitial pneumonia (AIP) in feedlot cattle remains poorly understood, with gaps in knowledge about its clinical signs, causes, and risk factors. Its non-specific presentation makes diagnosis challenging, and potential etiologies like BRSV and 3-MI have been inconclusive, suggesting a multifactorial disease process. Commonly associated risk factors include sex, season, and days on feed (DOF), though their exact role is unclear. Necropsy findings like interlobular edema and emphysema are consistent, but microscopic indicators lack consistency across studies. Effective treatments and standardized diagnostic criteria are lacking, highlighting the need for further research into AIP's causes, diagnosis, and management.

Pulmonary lesions continue to be the most frequently documented mortality lesions, particularly bronchopneumonia (BP) and bovine interstitial pneumonia (BIP), in feedlot cattle mortalities. Better diagnostic methods and detailed lesion descriptions could improve treatment and prevention strategies. While gross and histopathological diagnoses (GrossDx and HistoDx) were similar overall, individual case results did not always match, with HistoDx serving as the

final confirmation. Refining mortality diagnostics is key to advancing understanding of pulmonary conditions and determining if BIP and AIP are related or separate pulmonary lesions.

Acute interstitial pneumonia (AIP) in feedyard cattle, though rare (0.18%), poses significant economic and individual impacts. The unclear etiology complicates prediction and treatment, particularly as cattle are managed at the cohort level. Analyzing cohorts has revealed patterns, with heifer-only groups and cattle arriving between January and May more likely to experience AIP-related mortalities. Cohorts with higher rates of bovine respiratory disease (BRD) and digestive disease within the first 45 days on feed also showed an increased risk of AIP. While more research is needed, this data highlights potential key risk factors for AIP in specific cattle groups.

Supplemental Chapter 1 Material

Characteristics of AIP	Category Descriptions	Number of Articles	Article Reference Number
Clinical Signs			
	Severe respiratory distress	3	4,40,41
	Grunting when breathing	3	2,40,41
	Increased expiratory effort	2	2,4
	Nonfebrile	2	22,24
	Open mouth breathing	2	40,41
	Sway-back appearance	2	40,41
	Dyspnea	1	2
	Frothing at the mouth	1	2
Etiology			
	Bovine Respiratory Syncytial Virus (BRSV)	7	2,9,10,14,24,32,39
	Other pathogens	5	10,21,24,32,39
	3- Methylindole (3-MI)	4	2,22,33,34
	Melengestrol acetate (MGA)	1	33
Risk Factors	DOF at onset	6	2,14,21,22,33,41
	Sex	5	2,4,22,33,41
	DOF at death	5	4,14,24,37,39
	Season	5	2,21,37,40,41
	Arrival weight	2	4,37

	Treatment count prior to death	2	4,14
	Region of feedlot	2	40,41
	Feedlot management practices	2	40,41
	Treatment interval	1	14
	Liver abscess	1	39
	Number of antibiotic treatments	1	14
	Rumen pH	1	39
	Rumen bacteria (cellulolytic, lactobacilli and protozoa)	1	2
Pathology/Diagnostics	***Gross Pathology***		
	Intralobular emphysema	12	2,4,5,10,17,18,21,31,32,39-41
	"Checkerboard" (variation in color)	12	2,4,5,10,17,18,21,31,32,39-41
	Diffuse, overinflated lung lobes	11	2,4,5,10,17,18,21,31,39-41
	Interlobular edema	10	2,4,5,10,17,18,21,31,32,39
	Heavy, shiny lungs with firm consistency	4	32,39-41
	Bulge on cut lung surface	3	17,18,21
	Interstitial hemorrhage	2	21,39
	Rubbery consistency on palpation	2	2,21
	Frothy fluid in airways	1	2
	Normal bronchial and mediastinal lymph nodes	1	21
	Microscopic Pathology		
	Hyaline membranes	15	2,4,5,9,10,17,18,21,22,24,31-34,39
	Type II pneumocyte hyperplasia	12	2,4,5,9,10,17,18,31-34,39
	Bronchiolitis (fibrosa) obliterans	9	2,4,5,10,21,31,33,34,39

	Alveolar septum expansion by mononuclear inflammatory cells	5	4,5,9,31,39
	Alveolar septal necrosis	5	2,4,5,9,31
	Acute alveolar damage with exudation	4	2,17,18,39
	Multifocal lobular to diffuse flooding of alveolar spaces with eosinophilic, proteinaceous fluid	4	2,21,33,34
	Bronchiolar epithelial injury	4	2,9,33,34
	Suppurative inflammation with erosion/ulceration of epithelium	3	17,18,39
	Edema/emphysema	3	2,9,21
	Inflammatory cells: neutrophils, lymphocytes, and syncytial cells	3	21,33,34
	Lymphocytic bronchiolitis	2	9,39
	Dilated alveolar lumen and thickened walls	2	2,10
	Dilated and congested capillaries	2	10,21
	Strands of fibrin and chromatin	2	10,21
	Alveolar septal edema	2	22,24
	Serofibrinous exudation into alveolar spaces	2	22,24
	Type II epithelial hyperplasia	2	22,24
	Intra-alveolar inflammatory cells: macrophages, neutrophils and syncytial cells	2	2,21
	Peribronchovascular fibrosis	1	39
	Alveolar histiocytosis	1	9
	Multinucleated giant cells	1	9
	Bronchiolitis	1	9
	Bands of dense homogenous eosinophilic material	1	32

	Alveolar and bronchiolar lumens infiltrated with macrophages, neutrophils and syncytial cells	1	2
	Bronchiolar epithelial squamous metaplasia	1	2
	Alveolar epithelialization	1	21
	Focal interalveolar hemorrhage	1	21
	Dilated lymphatics with gas, fibrin and erythrocytes	1	21
	Bronchopneumonia with an interstitial pneumonia	6	4,5,14,17,18,31
	Diagnostics		
	Automated machine learning	1	5
Treatment/Prevention	Feather meal	1	34
	Vitamin E	1	34