Liver abscesses—New perspectives on a historic fed-cattle issue*†‡

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HEALTH: *Perspective and Commentary*
New perspectives on a historic issue

Liver abscesses—New perspectives on a historic fed-cattle issue*†‡

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ABSTRACT

Purpose: Our purpose was to provide commentary and new perspectives related to liver abscesses, a historic problem in beef cattle, by describing and discussing documented research, anecdotal observations, and opinions regarding the causation, detection, and prevention of liver abscesses.

Sources: Sources for this article include peer-reviewed, scientific literature; abstracts; proceedings; theses and dissertations; popular press articles; personal communications; and unpublished research data.

Synthesis: Liver abscess (LA) disease in cattle is a multifactorial, polymicrobial disease that has wide-ranging effects on productivity and profitability throughout all stages of the beef production cycle. The interest in and the study of LA has drastically increased in the past several years, driven largely by efforts to identify alternatives to the use of antibiotics for LA control. Although a primary, prevailing theory on LA formation has existed for decades, recent research has led to alternative theories as well as new questions about the role of breed-type specific management, behavior, feed intake patterns, and other factors on LA causation. The inability to detect LA before slaughter complicates research evaluating mitigation strategies and disease etiology. Moreover, the inability to detect LA in live cattle has hindered researcher efforts to understand timing of abscess development or whether an abscess can resolve.

Conclusions and Applications: Although the primary pathogens associated with LA have been identified, an effective mitigation strategy has eluded researchers. Nonetheless, new perspectives and research efforts are needed from both basic and applied perspectives using multidisciplinary, collaborative approaches to successfully combat the challenges faced by the beef industry related to LA.

INTRODUCTION

Liver abscesses (**LA**) have been a persistent problem in the beef industry for over a century. Recent estimates suggest economic losses may exceed $400 million annually across all aspects of beef production and processing. Like other beef cattle diseases such as bovine respiratory disease, the prevalence of LA has remained relatively unchanged for the past 30 years (Lorenzen et al., 1993; Boleman et al., 1998; Herrick et al., 2022). Recent attention surrounding LA has resulted in the procurement and allocation of significant public and private funding designated for the study of all aspects of LA from formation to prevention. Several factors likely play a role in the recent interest in LA, a key one being the industry's concern that in-feed antibiotics could no longer be available for use to control LA (Cazer et al., 2020) as these products are currently the most commonly used prevention strategy (Davedow et al., 2020). Another factor is the increased population of beef × dairy crossbred calves entering the feedlot system, which seem to have a greater propensity for the development of LA (Foraker et al., 2022; Grimes, 2022). Conversely, the increase in concern with LA could simply be the result of economics as the beef industry has trended toward marketing feedlot cattle at a heavier HCW and increased DOF. Pushback from beef proces-

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sors also occurs as LA detract from revenue and production efficiency that can ultimately lead to discounts on cattle with a greater propensity for LA, especially severe abscesses with adhesion to adjacent tissues and organs (A+ abscesses). With an ever-changing economy, drastic fluctuations in commodity prices, increasing inflation, and tighter profit margins, the need to increase growth performance and carcass efficiency highlights the importance of mitigating the effects of LA on the beef industry.

PREVAILING THEORY OF LA FORMATION

The most widely adopted theory of LA formation was described by Nagaraja and Chengappa (1998). When cattle are marketed through the beef system, the final stage of production is the finishing phase, which often occurs in a feedlot. At the feedlot, cattle are transitioned from a forage-based diet to a diet with increasing concentrations of grain. Often, this grain is further processed through methods such as steam flaking to increase starch availability. As cattle consume this primarily grain-based, starch-rich diet, ruminal bacteria rapidly ferment this starch. Thus, acid loads develop in the rumen, and this acidic condition damages the ruminal epithelium, termed "rumenitis." The physical damage from the acid load results in protective barrier dysfunction and provides an indiscriminate pathway for the translocation of bacteria from the rumen. Although this barrier disruption could facilitate migration of most microorganisms, much of the focus on translocation surrounds *Fusobacterium necrophorum* because it is the most commonly isolated bacterium from LA and is believed to be the causal agent. *Fusobacterium necrophorum* is sensitive to acidotic conditions, and it is believed that these bacteria are able to escape acidotic conditions in the rumen by attaching to the epithelial cells in the rumen wall, hiding in folds and protecting itself. Thus, when rumenitis occurs, *Fusobacterium* is in closest proximity to these damaged epithelial cells, facilitating its translocation from the rumen into vascular circulation. Because the entire mesentery is involved in portal circulation, these bacteria that escaped the rumen will eventually wind up in the liver. In the liver, the bacteria proliferate and form encapsulated abscesses that can grow to various sizes (i.e., 1–300 mm in diameter), and some might resolve.

LA FORMATION AND POTENTIAL CONTRIBUTING FACTORS

The theory that rumenitis is linked to LA, first proposed by Smith (1944) and supported and described by Nagaraja and Chengappa (1998), states that rumenitis is a likely causal or contributing factor to LA. There are other factors that may be involved in LA formation. Lechtenberg and Nagaraja (1991) reported that injecting *F. necrophorum* into the portal vein induced LA within 3 d, providing further credence to the portal route of entry of bacteria into the liver. Nonetheless, the portal circulation drains the entire gastrointestinal tract and associated visceral organs; thus, the potential for bacterial translocation exists across all segments of the gastrointestinal tract and might not be strictly limited to ruminal barrier dysfunction. The discovery of *Salmonella* in LA by Amachawadi and Nagaraja (2015) led to the development of a new theory implicating the potential role of the small or large intestine in LA formation. The presence of *Salmonella* further confirms that LA are a polymicrobial disease. Although, it is still unknown whether *Salmonella* is a causal agent in abscess initiation or whether this bacterium, arriving from lymphatic circulation, is merely present in LA resulting from the indiscriminate translocation of bacteria in areas of compromised barrier function. A recent study in the USDA laboratory in Lubbock, Texas, compared intraruminal infusion of *F. necrophorum* alone or in combination with *Salmonella* and its relationship to LA prevalence (McDaniel et al., 2023). Inclusion of *Salmonella* increased LA prevalence by 22% and drastically increased the percentage of abscesses that were adherent to the diaphragm, thereby implying that *Salmonella* might affect both prevalence and severity of LA, amplifying economic implications via trim loss of valuable carcass components.

Liver abscesses are frequently described as a polymicrobial disease in which several bacterial species can be causally associated with LA formation (Amachawadi et al., 2017). Similarly, LA are associated with a disruption of homeostasis in multiple physiological pathways and resultant changes in protective barrier function across different regions of the gastrointestinal tract. A recent study in our USDA laboratory resulted in an abscess prevalence of 50% following feeding of an acidotic diet combined with ruminal inoculation with *F. necrophorum* and *Salmonella* (McDaniel et al., 2023). Although rumenitis was observed at necropsy, histology samples also revealed damage to the ileum, indicating that barrier function in the hindgut might be involved in bacterial translocation and LA formation. Given the ubiquitous nature of *Fusobacterium*, *Trueperella*, and *Salmonella* in the gastrointestinal tract and environment, it seems likely that protective barrier dysfunction across one or multiple areas of the gastrointestinal tract contributes to bacterial translocation.

From an applied research perspective, there are many factors that producers, feedlot nutritionists, and veterinarians anecdotally identify as contributing to the development of LA. The most common theory is that diet and nutritional management strategies influence abscess prevalence. Decreasing dietary roughage concentration and decreasing bulk density of steam-flaked corn increases LA prevalence without affecting live nor carcass performance (McDaniel et al., 2023), confirming the theory that aggressive feeding strategies increase the potential for LA. Others have theorized that feed bunk management and feed delivery inconsistencies contribute to abscess prevalence, although no differences in LA prevalence was reported by Smock et al. (2021), who fed cattle to a slick bunk or modified *ad libitum* intake where feed was present at

the time of bunk evaluation. Geographical region of cattle finishing location has also been reported to influence LA prevalence (Herrick et al., 2022), with the greatest LA prevalence of fed cattle occurring in the Pacific Northwest (33.8%) and the least (10%) occurring in the Northeast. Although prevalence of LA from cull-beef processors differed geographically in this same surveillance study (Herrick et al., 2022), the greatest LA prevalence was observed in the High Plains (22.6%). However, geographical region is likely confounded by breed type and available feedstuffs within each region, which makes a definitive understanding of how region affects LA prevalence difficult.

Recently, breed type has been spotlighted with respect to LA prevalence. The dairy × beef composites have received greater scrutiny from packers for LA prevalence as this breed type has substantially increased in numbers over the past decade. Dairy-reared cattle often exhibit increased LA prevalence than conventional beef cattle, and this difference has often been considered the result of increased days on feed and thereby a prolonged exposure to a high-concentrate diet. Dairy × beef crossbred cattle seem to have a greater propensity for LA prevalence (Grimes, 2022) at slaughter. Grimes (2022) reported LA prevalence from a post hoc evaluation of over 1.5 million observations and observed LA prevalence rates of 23% in native cattle, 17% in Mexican cattle, 39% in Holstein cattle, and 50% in beef × dairy cattle, further reporting that beef × dairy cattle exhibited the greatest rates for each LA scoring category. Because rearing and management of beef × dairy cattle are practically identical to calf-fed dairy breeds, genetic factors could be a contributing factor for increased development of LA; however, little is known about the role of genetic influences and LA prevalence. It is unclear whether the difference in LA prevalence based on breed type is related to genetics, increased feed intake, increased ruminal volume, growth potential, decreased barrier function, region of finishing, or other factors. Causation of LA, like most complex diseases, is likely multifactorial and could include genetic and epigenetic causal variables.

Behavioral factors related to breed also have been implicated in LA formation. Dairy and beef × dairy crossbreds seem to have continual, nonnutritive oral behaviors in which they lick and ingest non-feed items including hair, soil, rocks, plastics, metals, and any other items present in or around the pen. The rumen functions as a barrier to prevent pathogen translocation (Garcia et al., 2017), and some theorize that these behaviors could irritate the ruminal wall or other parts of the gastrointestinal tract, even the mouth, facilitating bacterial translocation. This mechanical barrier disruption may be one of the reasons that cull cattle not exposed to concentrated feed present with LA but no rumenitis. Additionally, a consistently greater feed intake in beef × dairy crossbreds could be a contributing factor for LA formation as they typically have increased DMI than other breed types. In 2 recently conducted calf trials in our laboratory, dairy × beef crossbred cattle (BW = 110–140 kg; 250–300 lbs.) consumed >4% of their BW on a DM basis compared with another study where Holsteins consumed ~2.5% of their BW on a DM basis (McDaniel et al., 2023). Given that dairy and dairy × beef crossbred calves are reared differently than traditional beef calves, early life management at the dairy and calf ranches likely influences the incidence and prevalence of LA later in life. In the dairy industry, it has been reported that early life management from health and nutritional perspectives can have long-lasting implications (Van Amburgh et al., 2014). For example, insufficient colostrum intake and lack of immune system development early in life can affect health and disease prevalence. We hypothesize that even the quantity, quality, and method of delivery of milk replacer may also influence LA prevalence at slaughter. The value of dairy-type bull and steer calves was limited 20 yr ago; however, given the drastic increase in value of these calves, greater emphasis is being placed on nutritional and health management protocols at the dairy and calf ranch.

BACTERIA ASSOCIATED WITH LA

Historically, the primary pathogens associated with liver abscesses have been *F. necrophorum* and *Trueperella pyogenes*. *Fusobacterium necrophorum* is present in approximately 80% of culturable liver abscesses, whereas *Trueperella* is present in only 10% of abscesses (Herrick et al., 2022). Although the role of *Fusobacterium* and its virulence factors is well documented, researchers have only recently been able to differentiate between subspecies *necrophorum* and *funduliforme*. Ongoing studies to determine the relationship between the concentration and presence of these *F. necrophorum* subspecies and the presence of LA could provide further insight into the relationship between bacterial populations and LA formation and could be a predictor of LA. Although no tylosin resistance in *F. necrophorum* has been published, a recent presentation at the American Registry of Professional Animal Scientists's (ARPAS) liver abscess symposium reported, based on preliminary data, that a strain of *F. necrophorum* exhibited resistance to tylosin. As bacteria have multiple mechanisms to acquire and confer resistance genes within and across species, the lack of resistance exhibited by *F. necrophorum* to tylosin, an antibiotic that has been in use for almost 40 yr, is somewhat surprising.

More recently, *Salmonella* has been isolated from LA and is now commonly cultured from approximately 25% of abscesses (Amachawadi et al., 2017; Herrick et al., 2022). Although the role of *Salmonella* in abscess formation is currently unknown, the virulence factors of *Salmonella* could be involved in LA formation and, as mentioned previously, may influence LA severity and rate of adhesions. Furthermore, the variability in *Salmonella* population concentration and serotype distribution in different regions of the United States coupled with *Salmonella*'s seasonal patterns could also partially explain the regional and seasonal

effects observed in LA prevalence and certainly warrant further exploration.

The discovery of *Fusobacterium varium* as a dominant *Fusobacterium* species in the rumen and its presence in LA present new questions about the role of this bacterium in LA formation. Schwarz et al. (2023) indicated that *F. varium* grows abundantly under selective conditions commonly used to isolate *F. necrophorum*, implying that mischaracterization of *Fusobacterium* species might have occurred over the past few decades in previous studies. *Fusobacterium varium* also has been reported to harbor invasive virulence genes and displays resistance against tylosin phosphate and monensin. If *F. varium* has been mischaracterized for decades and is resistant to tylosin phosphate, this could help explain why LA are still noted even when feeding tylosin phosphate. This indicates that further exploration of the role of *F. varium* and its relationship to LA formation may be warranted in concert with other bacteria frequently implicated in LA.

Pinnell et al. (2022) not only reported a strong association between *Fusobacterium* spp. and LA, but also noted the presence of *Bacteroidetes* in LA. Although no link has been causally established, an association with *Bacteroides* in distal regions of the hindgut and LA was noted. With the fields of microbiology and molecular characterization techniques constantly evolving, it is important to continually use new technological advancements to explore bacterial communities and their role in LA formation.

DETECTING LA

There is one effective, definitive method to detect LA in cattle, which is visual examination of the liver at slaughter. One potential option for diagnosing LA before slaughter is the use of ultrasonography; however, given the depth of the liver and thickness of the body wall and rib cage, this technique may not correlate with visual confirmation of LA at slaughter (Liberg and Jönsson, 1993). In addition, ultrasonography may only be able to assess a portion of one side of the liver as the liver is positioned on the right side and other viscera occlude observation of the back side, thereby lending itself to a high rate of false negatives, or low sensitivity. Conversely, if a LA is observed via ultrasonography, it is usually always present unless misidentified as a scar or other abnormality on the liver. Furthermore, given that abscesses may form and resolve over time, the timing of ultrasound should be considered. Just because no abscesses are present at the time of scanning does not mean that the animal never experienced a LA throughout its life. As ultrasound technology continues to improve, there is potential for this method of detection to become viable in live cattle.

Many attempts to determine biomarkers that indicate the presence of an abscess have been explored, but, to date, no one single biomarker or combination of biomarkers has proved reliable in detecting the presence of LA. Herrick et al. (2020) collected blood at slaughter to measure complete blood cell counts and chemistry profiles and evaluated their relationship to LA prevalence. Increased platelets and decreased hemoglobin and hematocrit concentrations were noted in cattle with more severe abscesses as well as some changes in serum chemistry profiles. Ongoing model development research trials in our laboratory are also evaluating hematological parameters before slaughter and are noticing similar trends in red blood cell concentrations. Nonetheless, further epidemiological examination is required to determine a consistent correlation that could be predictive of LA prevalence. Identifying predictive biomarkers with a definitive link to LA could prove difficult as some metabolites could be confounded by an unrelated disease. Studies evaluating the entire blood plasma metabolome might provide further insight, as these biomarkers in combination with mathematical models might be able to identify a single analyte or combination of markers that would allow for more accurate diagnosis of LA.

LIVER SCARS AND ABSCESS RESOLUTION

Liver scars are an off-white, often starfish-shaped area of tissue in or on the liver. Although not proven, they are often considered to be areas from resolved LA. These scars are not only identified in fed cattle at slaughter, but they have also been observed in newly weaned calves in recently conducted studies. If liver scars are truly the result of a resolved abscess, and scars are present in young calves, one must question how long it takes a LA to form and the associated length of time for abscess resolution. Likewise, if these scars are observed in newly weaned calves without rumenitis and that have not consumed a diet containing highly fermentable starch, one must question how the bacteria were translocated to the liver. Similarly, cull cattle that have not been fed grain may also have scars resulting from LA occurring throughout their life. Some hypothesize that these abscesses are the result of mechanically induced barrier dysfunction from rough or sharp feedstuffs or nonnutritive oral behaviors that cause damage in the oral or esophageal region. In this scenario, protective barrier damage in other areas of the gastrointestinal tract may be responsible for the bacterial translocation. For instance, an abscess was reported in a preweaned 17-d-old heifer calf that also had an umbilical infection; thus, it was concluded the LA was secondary to the umbilical infection (Sato et al., 2021).

Our collaborative, multidisclipinary, multilocation team has been working to develop an experimental, nutritional model to induce liver abscesses. As part of this process, we have conducted a gross pathology and bacteriological evaluations of liver during necropsy. In these studies, liver scar tissue yielded *F. necrophorum*, which was the bacterium orally inoculated to induce LA. This implies that an abscess developed and then resolved to become a scar within 21 d (which was the length of time between intraruminal inoculation and necropsy). This observation could change the way we think about LA prevalence at

slaughter. We frequently refer to LA prevalence, which is a snapshot of the presence or absence of LA at slaughter. Prevalence evaluations at slaughter are meaningful as the presence of LA is unknown before slaughter, and this is the point in time in which a tangible loss in product and profitability is realized. Nonetheless, it may be more appropriate to consider LA through the lens of the term "incidence," which is the rate or frequency of LA throughout the life of the animal. It is likely that abscesses are formed and resolved on multiple occasions throughout not only the finishing period, but the entire lifespan of an animal. Although tangible costs are not realized before slaughter, LA occurrence at any stage of production could contribute to production inefficiencies. The ability to detect abscesses before slaughter would be a valuable tool and could lead the industry to develop targeted preventive measures.

CONTROL OF LA

Currently, the primary tool used for the control of LA is the macrolide antibiotic tylosin. With increased scrutiny on the use of in-feed antibiotics, producers are exploring novel intervention strategies that could help further mitigate LA with or without tylosin inclusion. Vaccines have been previously used to control liver abscesses, but results have been variable (Amachawadi and Nagaraja, 2016). Hence, vaccines for the control of liver abscesses have not been widely adopted given their minimal effectiveness relative to antibiotics. Currently, many in-feed additives such as pre- and probiotics, phytochemicals, minerals, enzymes, and other supplements are being evaluated for their ability to prevent or decrease the severity of LA (Meyer et al., 2009; Latack et al., 2021). Before adoption, new interventions, whether they be an in-feed additive, vaccine, or other management strategy, will need to show efficacy in LA prevalence and severity reduction. Furthermore, new interventions may be more readily adoptable if they also provide an economic benefit such as improvement in growth or carcass efficiency, reduction in morbidity and mortality, or be equivalent to the cost of tylosin to offset product costs.

LA MODELS

Development of models that consistently produce LA will be an important tool to test novel prevention strategies. Different feeding operations have varying LA prevalence rates, and the potential confounding variables across operations create nonidealistic conditions for the controlled study of LA. Currently, we are aware of 2 controlled experimental models that consistently produce LA in cattle. This first is the ultrasound-guided, portal-vein-infusion model noted previously (Lechtenberg and Nagaraja, 1991). The second model is a repeatable, minimally invasive model that combines intraruminal inoculation with cycles of high- and low-starch diets (McDaniel et al., 2023). These experimental inoculation models are valuable, in that each animal receives bacterial cultures at the same time, thereby allowing researchers to evaluate the progression of disease on a similar timeline across all animals as opposed to relying on endemic infections in which the timing and pathogen concentrations are unknown and the results are more variable. Other noninvasive nutrition studies exist that use diet manipulation through high-starch availability, decreased NDF, or both with or without with irregular feeding patterns and different bunk management strategies. Two recently published studies demonstrated that decreased bulk density of steam-flaked corn can influence LA prevalence (Smock et al., 2021; McDaniel et al., 2023). Further development of existing models and the creation of new experimental and applied models to induce, study, or observe LA will indefinitely be created in the near future as a tool to test preventive measures.

In conclusion, LA result from a complex, multisystem, multifactorial, polymicrobial disease that has negative effects on growth and carcass efficiency. Although rumenitis from acidosis and *F. necrophorum* have been implicated as the primary causal factors, recent data suggest that other bacteria and barrier dysfunction in the hindgut may also play a role. Furthermore, little is known about the influence of genetic and epigenetic components on the incidence of LA formation. However, recent increases in research activity related to LA will continue to provide new insights into the etiology and prevention of this costly disease. Furthermore, development, understanding, and adoption of preslaughter detection and predictive technologies are warranted to further advance our knowledge with respect to the formation and our ability to control LA across all segments of the beef industry. Moreover, further exploration of pathogens associated with LA is needed to fully understand microorganism involvement in abscess development. Finally, development of controlled, repeatable, experimental models to test novel intervention strategies is necessary to explore mitigating solutions. Both basic and applied research using multidisciplinary, collaborative approaches is needed to successfully combat the challenges of LA in beef cattle.

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