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Recent Advances in Prevention and Control Strategies for Bovine Respiratory Disease

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Abstract. Bovine respiratory disease (BRD) is a complex and economically significant illness in cattle, with a multifactorial origin involving pathogens, environmental conditions, and management practices. Recent studies highlight a strong genetic component in BRD susceptibility and resistance. From a genetic perspective, key technologies such as high-throughput RNA sequencing, RNA interference (RNAi), CRISPR-Cas9 gene editing, and genomic selection are being widely applied to uncover molecular mechanisms and enhance genetic resistance to BRD. These approaches offer promising avenues for precision breeding and targeted intervention. In addition to genetic strategies, emerging technologies such as nanomedicines and microbial preparations are gaining popularity as innovative tools for BRD prevention and treatment. This article discusses these developments and their potential to reduce antibiotic dependence and promote sustainable cattle health management.

Keywords: beef cattle, disease resistance, prevention and treatment

1. Introduction

Bovine respiratory disease (BRD) is a leading cause of death in North America beef cattle, which not only increase the elimination rate of cattle, but also seriously affect the weight gain of reserve cattle, leading to delayed first mating and reduced conception rate, and even affecting the production performance of dairy cows during lactation or the market time of beef cattle. BRD therefore presents significant challenges for animal health and welfare, as well as the economics of cattle production. Currently, BRD causes huge economic losses to the pasture, annua economic losses caused by decreased production and increased veterinary costs are in the $800 million to $900 million range in the United States.

BRD typically manifests in young, naive cattle because of nutritional changes, poor housing with wet bedding, overcrowding, stress caused by handling and transport, season (summer and winter) or an underlying viral infection. Literature indicates that BRD is a multifactorial syndrome caused by a combination of host-environment interactions, pathogens, and management practices (Figure 1).

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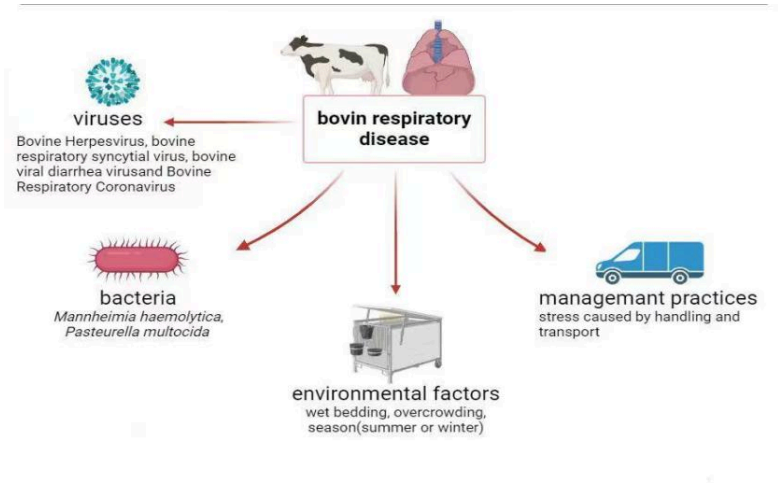


Figure 1: Environmental and pathogenic microbial factors leading to BRD

From a pathogen perspective, the disease is associated with multiple bacteria, including Mannheimia haemolytica, Pasteurella multocida and compounded by viruses, including Bovine Herpesvirus, bovine respiratory syncytial virus, bovine viral diarrhea virus and Bovine Respiratory Coronavirus. Pathogens induce BRD through two main mechanisms: ① Viruses directly damage lung parenchyma and respiratory clearance mechanisms, allowing bacteria to migrate from the upper respiratory tract to cause lung infections; ② Viral infections impair the host's immune response to bacterial infections.

Early detection and treatment are critical, as delayed intervention increases the risk of chronic illness and mortality. Behavioral indicators serve as key pillars for early BRD recognition, with subtle signs like depression, lagging behind the herd, changes in feeding behavior, or social interaction abnormalities often being the first observable symptoms. These are followed by more obvious clinical signs, including ocular/nasal discharge, increased respiratory effort, coughing, depression, ear drooping, head tilting, arched back posture, emaciation, reduced appetite, or complete anorexia. These clinical signs are applicable to all classes of beef and dairy cattle. Several BRD scoring systems (e.g., the DART method for evaluating Depression, Appetite, Respiration, and Temperature) are used to determine if further diagnostic examination is required. Treatment primarily involves injectable antibiotics and antipyretic medications (e.g., flunixin meglumine), with veterinarians and producers collaborating to develop tailored antibiotic use plans. Additionally, vaccination, isolation of sick animals, and improved feeding environments are essential management strategies.

Current BRD control in feedlots remains challenging. While antibiotics are widely used, they often lead to bacterial resistance and antibiotic abuse. This paper therefore summarizes alternative approaches for BRD management in beef cattle.

2. Main text

Many studies have shown that BRD susceptibility is associated with genetics [5]. High-throughput RNA sequencing (RNA-Seq) is a sensitive methodology for global gene expression analysis, enabling comprehensive evaluation of functional mechanisms and molecular heterogeneity. RNA-Seq studies in post-weaned beef cattle have identified candidate genes and host pathways associated with naturally occurring or experimentally induced BRD. For example, differentially expressed genes (DEGs) in whole blood samples have clearly distinguished BRD-susceptible calves from

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resistant ones, suggesting that bovine respiratory syncytial virus (BRSV) induces specific gene expression changes that may serve as diagnostic markers for BRD. Functional genomics approaches (Figure 2) have also identified BRD-associated genes and biological pathways, providing targets for disease diagnostics and therapies, such as RNA interference (RNAi), gene editing, and genomic selection.

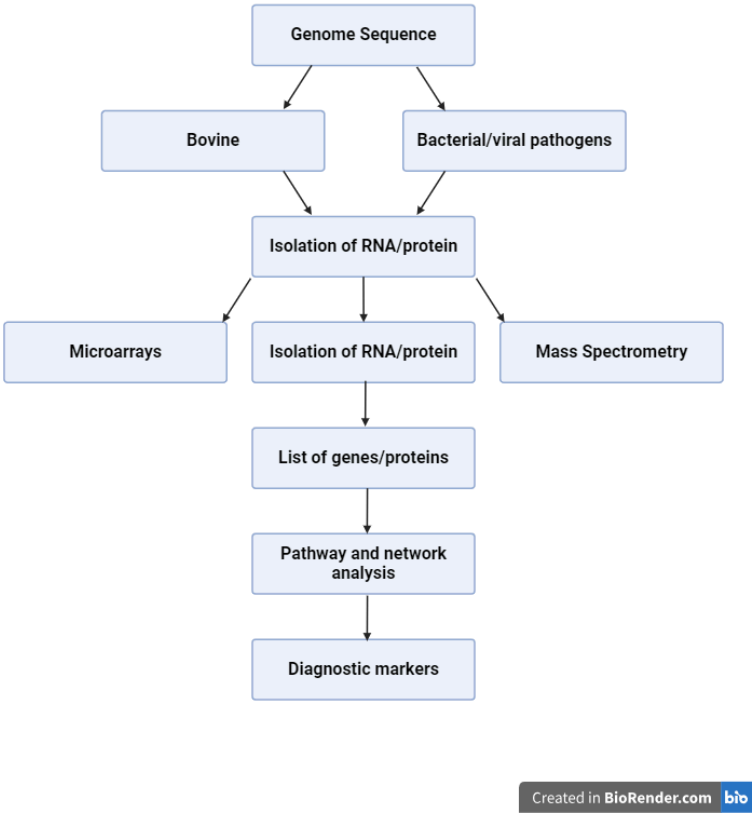


Figure 2: Functional genomics-based approach for identifying BRD associated genes and biological mechanisms

RNA interference (RNAi) is a conserved biological mechanism that mediates resistance to nucleic acid pathogens and regulates gene expression through sequence-specific silencing of protein-coding genes. This natural process holds promise for revolutionizing experimental biology and has practical applications in functional genomics, therapeutic intervention, and agriculture. In BRD management, RNAi is increasingly used to silence pathogen-related genes or enhance host immunity. The availability of bovine and BRD pathogen genomes has facilitated high-throughput analyses (e.g., microarrays, RNA-Seq, proteomics), generating lists of candidate genes/proteins for functional validation.

Besides, the clustered regulatory interspaced short palindromic repeats associated protein 9 (CRISPR-Cas9) system, a cutting-edge genome-editing tool, has been widely applied to engineer BRD resistance in cattle. It enables targeted modification of multiple genes in host tissues and cells to directly correct genetic mutations underlying disease susceptibility. CRISPR-Cas9-mediated genome editing offers a powerful strategy to generate disease-resistant livestock by modifying host immune-related genes, though off-target mutagenesis remains a key concern requiring careful

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validation. Figure 3 shows the applications of immunogenomics and genome editing to produce disease-resistant animals.

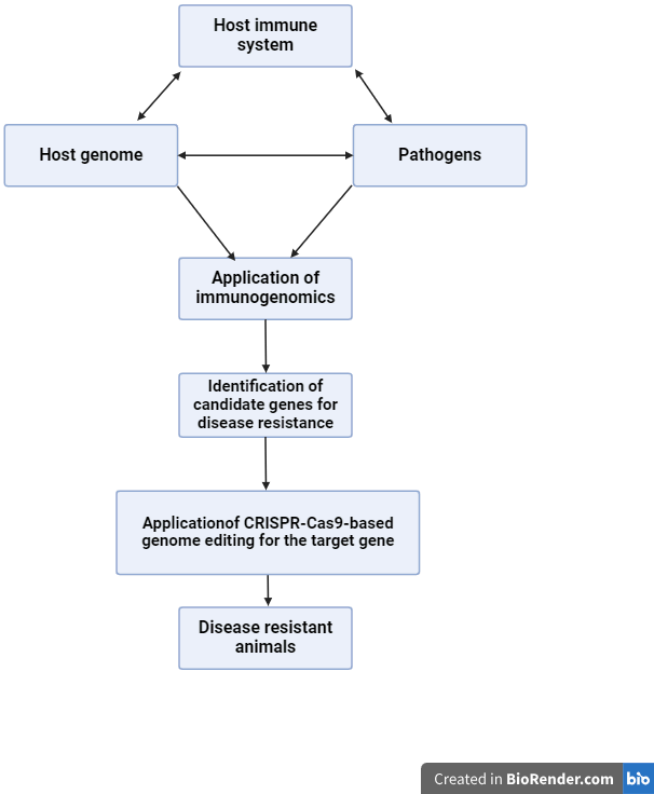


Figure 3: The applications of immunogenomics and genome editing to produce disease-resistant animals

Moreover, artificial selection has proven to be effective at altering the performance of animal production systems. Genomic selection, an advanced breeding strategy, uses genome-wide marker information to predict an animal's genetic potential for economically important traits. Unlike traditional selection methods that primarily rely on pedigree and phenotypic data, genomic selection incorporates dense genetic marker data to estimate genomic breeding values (GEBVs) with greater accuracy. This approach enables earlier and more precise selection, leading to faster genetic improvement and increased efficiency in livestock breeding programs. In the context of beef cattle, genomic selection can be a powerful tool for enhancing disease resistance by identifying animals with favorable genetic variants associated with immune response and resilience. For example, genomic studies have shown that the heritability of BRD resistance ranged from 0.1 to 0.3 and also identified specific regions associated with resistance to BRD. By integrating genomic information with phenotypic data, breeders can develop predictive models that estimate the genetic merit of individuals for disease resistance traits, allowing for the selection of animals with superior genetic potential. Similarly, genetic markers linked to resistance against parasitic infections, such as gastrointestinal nematodes, have been used to guide selection decisions and improve herd health. The application of genomic selection in beef cattle breeding helps reduce economic losses caused by disease outbreaks, lowers reliance on antibiotics, and contributes to the sustainability of production systems by enhancing overall herd health and productivity. However, there are still some questions

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about using the method of gene prediction to prevent some specific diseases. One reason has been our inability to cost-effectively rank selection candidates for all the attributes of interest [6].

In addition to genetics perspective, there are other new techniques to treat BRD-infected animals. For example, nanomedicine and microbial preparations to reduce the usage of antibiotic in the feedlots. Nanomedicine refers to the application of nanotechnology to develop drug formulations at the nanometer scale (typically 1-100 nanometers) to enhance drug bioavailability, targeting efficiency, and therapeutic efficacy. Nanomedicine delivery systems, including liposomes, polymeric nanoparticles, nanoemulsions, and inorganic nanoparticles, offer unique physicochemical properties such as a high surface-area-to-volume ratio and improved permeability, enabling precise drug delivery within the body. The mechanism of action primarily involves targeted drug delivery, controlled release, and reduced side effects. In the context of BRD, such as BRSV and Mycoplasma bovine infections, nanocarriers can deliver antibiotics, antiviral agents, or anti-inflammatory drugs directly to infected respiratory tissues, penetrating bacterial biofilms and reducing systemic side effects.

Additionally, nanomedicines can penetrate bacterial biofilms, which are often present in chronic respiratory infections, thereby improving treatment efficacy. The sustained release properties of nanocarriers help extend the drug's duration of action, reducing the frequency of administration and improving treatment compliance. As a result, nanomedicine represents a promising approach for the effective management of BRD by enhancing drug delivery precision and minimizing antimicrobial resistance development. Besides, microbial preparations are biological products composed of beneficial microorganisms, such as probiotics (e.g., lactic acid bacteria, Bacillus spp.), or their metabolic byproducts (e.g., enzymes and antimicrobial peptides.), which are widely used in animal health management. The mechanism of action of microbial preparations primarily involves competitive exclusion of pathogenic bacteria, modulation of the respiratory and gut microbiota balance, stimulation of the host immune response, and production of antimicrobial compounds that inhibit pathogen growth. In the prevention and treatment of BRD, microbial preparations can be administered via oral or nasal routes, colonizing the respiratory mucosa and preventing pathogen adhesion and invasion. Certain probiotic strains, such as lactic acid bacteria and Bacillus spp., have been shown to produce antimicrobial peptides that effectively inhibit common respiratory pathogens like Mannheimia haemolytica and Pasteurella multocida. Moreover, microbial preparations can enhance mucosal immunity, promote the production of protective antibodies, and reduce inflammation, thereby improving the overall resilience of cattle to respiratory infections. The use of microbial preparations as a natural and antibiotic-free alternative contributes to reducing antibiotic usage, lowering the risk of antimicrobial resistance, and promoting the overall health and productivity of cattle. As a sustainable approach, microbial preparations offer a promising strategy for the prevention and complementary treatment of BRD. Overall, by using this new technology, we can improve cattle resistance, reduce antibiotic use, and improve treatment efficiency.

3. Discussion

Genetic engineering in livestock is increasingly seen as a commercially viable and innovative approach. However, problems such as regulatory legislation, market pay off, and performance acceptability of users are still unresolved. Global acceptance of gene-edited animal products will hinge on whether these modifications are performed ethically, with proper consideration for animal welfare, and in accordance with national regulations. However, past controversies involving genetically modified (GM) and cloned animals indicate that food from gene-edited livestock may still face public resistance or rejection. Research in consumer psychology suggests that attitudes

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toward GM animals are shaped by perceived risks, potential benefits, and trust in regulatory systems. The public's skeptical view of GM organisms is partly related to the degree of skepticism of both researchers and state policymakers. Off-target mutagenesis seems to be a big problem due to the widespread use of the CRISPRCas9 tool. In relation to disease resistant animals, the problem is/ of more serious concern. The debate on closed animals, stimulated by so many tests, prompted the study of off-target mutation. Exploration of off-target mutations tends to be crucial from the point of view of animal health and ethics to the broader implications of genome-editing techniques in animal breeding. Thus, beyond scientific ethics, prioritizing animal welfare and minimizing off-target mutations is essential to improving public awareness. Such measures could help foster gradual societal acceptance of gene-edited livestock products..

Nanomedicine holds significant promise in the treatment of BRD by offering precise drug targeting, which ensures that therapeutic agents are delivered directly to the affected tissues, potentially improving treatment outcomes. This targeted delivery can also enhance drug penetration into tissues and bacterial biofilms, which are often difficult to treat with conventional therapies. Additionally, the controlled release of drugs, a key feature of nanomedicine, can help maintain therapeutic levels over extended periods, reducing the need for frequent dosing and minimizing side effects [10]. The ability to reduce side effects is particularly important in veterinary medicine, as it helps avoid adverse reactions that could impact the overall health of the cattle. However, despite these promising benefits, nanomedicine faces several challenges, including high production costs that may limit its accessibility for widespread use in the livestock industry. There are also concerns about the potential toxicity of nanoparticles, especially with long-term exposure, which has led to the need for extensive research on their safety and efficacy. Moreover, regulatory hurdles remain, as the approval process for nanomedicine in veterinary applications is still evolving, requiring rigorous testing to ensure the products meet safety and efficacy standards.

On the other hand, microbial preparations present a natural, antibiotic-free alternative for managing BRD, helping to maintain the balance of the microbiota, which plays a crucial role in the overall health of cattle. These preparations can enhance immunity and support the body's natural defense mechanisms, offering a safer option with fewer concerns about promoting antimicrobial resistance, which is a growing problem in veterinary medicineOne major issue is the inconsistent efficacy of these treatments, as their effectiveness can vary depending on the environmental conditions in which they are used. Factors such as temperature, humidity, and the specific microbial strains involved can influence the outcome. Additionally, storage stability remains a significant concern, as microbial preparations often require specific conditions to maintain their potency over time. Lastly, there is a need for more precise formulations tailored to specific pathogens and cattle populations, as the variability in disease-causing agents and cattle health can affect the success of these treatments. This requires further research and development to optimize microbial treatments for different settings and conditions.

We have summarized both advantages and disadvantages of antibiotics, nanomedicine, and microbial preparations (Table 1). Each offering unique benefits such as targeted action and reduced side effects while also presenting challenges like potential toxicity, high production costs, and variable efficacy. This comparison highlights the trade-offs between traditional antibiotics, emerging nanomedicine, and sustainable microbial preparations in the management of BRD, which highlights the need for balanced and tailored therapeutic strategies in treating BRD. Although antibiotics continue to be the cornerstone for preventing and treating BRD, emerging genetic techniques, nanomedicine, and microbial preparations are poised to play an increasingly vital role in mitigating

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BRD. However, to achieve this goal of reducing antibiotic usage, additional efforts are required to lower costs and enhance the effectiveness of these technologies.

Table 1: Comparison of antibiotics, nanomedicine, and microbial preparations in treating BRD

Aspect	Antibiotics	Nanomedicine	Microbial Preparations
Mode of Action	Both bactericidal and bacteriostatic.	Nanomedicine uses nanoparticles to improve drug delivery to specific organs	acting on multiple targets on the plasma membrane of pathogenic bacteria.
Effectiveness	Most effective	Second effective	Least effective
Resistance Risk	strong	medium	weak
Toxicity	strong	medium	weak
Cost	cheap	expensive	Most expensive
Sustainability	Not sustainable, drug resistance	sustainable	sustainable
Application Method	Killing the bacteria or by making it hard for the bacteria to grow and multiply.	Delivering drugs directly to target cells .	harnesses the power of microorganisms.
Regulatory Hurdles	the need to prove value in the face of drug-resistant infections	Lack of global harmonization of characterization and test methods.	assess the quality, safety, and consistency.
Storage Stability	sustainable	sustainable	Not sustainable

4. Conclusion

While antibiotics have traditionally been the primary treatment, growing concerns over antimicrobial resistance and sustainability have prompted the exploration of alternative strategies. Genetic approaches—including high-throughput RNA sequencing, CRISPR-Cas9 gene editing, and genomic selection—offer promising avenues for enhancing disease resistance through the identification and modification of key genes. Nanomedicine enables targeted drug delivery with improved treatment precision, though its application is limited by high costs and potential toxicity. Microbial preparations, such as probiotics, provide an eco-friendly alternative by enhancing immune responses and suppressing pathogenic organisms, albeit with variable efficacy. Each method presents unique advantages and limitations: antibiotics are effective but unsustainable, nanomedicines are precise but expensive, and microbial preparations are environmentally friendly but less consistent. Moving forward, the sustainable management of BRD will depend on an integrated approach that combines these technologies while addressing regulatory, ethical, and economic considerations.

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