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Molecular and Biochemical Approach

Edited by Abdulsamed Kükürt and Volkan Gelen

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Contributors
Abdelmalik Khalafalla, Avishek Mandal, Muawuz Ijaz, Mubarik Mahmood, Muhammad Kashif Yar, Jawad Ashraf, Moiz Ali Younas, Sadia Ilyas, Sana Ullah, Maryam Abdul Sattar, Muhammad Hayat Jaspa, Zayrah Rafique, Iftikhar Hussain Badar, Kanwal Rafique, Basagonda Bhagavanta Hanamapure, Kadir Bozukluhan, Oguz Merhan, Abdulsamed Kükürt, Volkan Gelen

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Aims and Scope of the Series

Paralleling similar advances in the medical field, astounding advances occurred in Veterinary Medicine and Science in recent decades. These advances have helped foster better support for animal health, more humane animal production, and a better understanding of the physiology of endangered species to improve the assisted reproductive technologies or the pathogenesis of certain diseases, where animals can be used as models for human diseases (like cancer, degenerative diseases or fertility), and even as a guarantee of public health. Bridging Human, Animal, and Environmental health, the holistic and integrative "One Health" concept intimately associates the developments within those fields, projecting its advancements into practice. This book series aims to tackle various animal-related medicine and sciences fields, providing thematic volumes consisting of high-quality significant research directed to researchers and postgraduates. It aims to give us a glimpse into the new accomplishments in the Veterinary Medicine and Science field. By addressing hot topics in veterinary sciences, we aim to gather authoritative texts within each issue of this series, providing in-depth overviews and analysis for graduates, academics, and practitioners and foreseeing a deeper understanding of the subject. Forthcoming texts, written and edited by experienced researchers from both industry and academia, will also discuss scientific challenges faced today in Veterinary Medicine and Science. In brief, we hope that books in this series will provide accessible references for those interested or working in this field and encourage learning in a range of different topics.

Meet the Series Editor

Rita Payan Carreira earned her Veterinary Degree from the Faculty of Veterinary Medicine in Lisbon, Portugal, in 1985. She obtained her Ph.D. in Veterinary Sciences from the University of Trás-os-Montes e Alto Douro, Portugal. After almost 32 years of teaching at the University of Trás-os-Montes and Alto Douro, she recently moved to the University of Évora, Department of Veterinary Medicine, where she teaches in the field of Animal Reproduction and Clinics. Her primary research areas include the molecular markers of the endometrial cycle and the embryo–maternal interaction, including oxidative stress and the reproductive physiology and disorders of sexual development, besides the molecular determinants of male and female fertility. She often supervises students preparing their master's or doctoral theses. She is also a frequent referee for various journals.

Meet the Volume Editors

Dr. Abdulsamed Kükürt graduated from Uludağ University, Turkey. In 2019, he obtained a Ph.D. in Biochemistry from the Institute of Health Sciences, Kafkas University, Turkey, where he is currently an assistant professor in the Department of Biochemistry. He has published twenty-nine research articles in academic journals, fourteen book chapters, and thirty-seven papers. Dr. Kükürt has participated in ten academic projects and is a reviewer for many academic journals.

Dr. Volkan Gelen is a physiology specialist who received his veterinary degree from Kafkas University, Turkey, in 2011. From 2011 to 2015, he worked as an assistant in the Department of Physiology, Faculty of Veterinary Medicine, Atatürk University, Turkey. In 2016, he joined Kafkas University as an assistant professor where he has been engaged in various academic activities. Dr. Gelen has sixty journal articles and twenty poster presentations to his credit. His research interests include physiology, the endocrine system, cancer, diabetes, cardiovascular diseases, and isolated organ bath system studies.

Contents

Preface

Cattle Diseases - Molecular and Biochemical Approach is an indispensable reference for veterinary professionals, researchers, and students engaged in the fields of animal health and welfare. The book offers a comprehensive and contemporary understanding of the intricate mechanisms that underlie a spectrum of bovine diseases, thereby providing invaluable insights into the improvement of animal health and productivity. The book features contributions from preeminent scholars and experts in the field who delve into a range of topical issues, including lumpy skin disease, zoonotic diseases, acute phase proteins, hepatic injury, paraoxonase 1, and sustainable livestock practices.

The book's wealth of knowledge and expertise make it an essential resource for anyone seeking to broaden their understanding of cattle diseases and their molecular and biochemical underpinnings. Whether you are a practicing veterinarian, a researcher, or an animal health professional, this book offers unparalleled insights into the complex interplay between bovine physiology and disease.

With its cutting-edge insights and up-to-date research, *Cattle Diseases - Molecular and Biochemical Approach* is a valuable asset for anyone seeking to advance the fields of veterinary medicine, animal welfare, and animal husbandry. The book's contributions provide a vital foundation for future research into animal disease and offer promising avenues for improving animal health and wellbeing.

We extend our gratitude to all the authors who have contributed to the creation of this book.

Abdulsamed Kükürt
Assistant Professor,
Faculty of Veterinary Medicine,
Department of Biochemistry,
Kafkas University,
Kars, Turkey

Volkan Gelen
Assistant Professor,
Faculty of Veterinary Medicine,
Department of Physiology,
Kafkas University,
Kars, Turkey

Section 1

Health and Diseases

Chapter 1

Lumpy Skin Disease: An Economically Significant Emerging Disease

Abdelmalik Khalafalla

Abstract

Lumpy skin disease (LSD) is a severe viral disease of cattle caused by the lumpy skin disease virus (LSDV), a member of the *Capripoxvirus* genus of the poxviridae family. Fever and flat disk-like skin nodules on the skin characterize the disease. It can also lead to death and significant economic losses, especially in herds, that have never been exposed to the virus. Blood-feeding insects, such as specific types of flies, mosquitoes, and ticks, are thought to be the primary vectors of LSDV transmission. Most African and middle eastern countries have a high prevalence of lumpy skin disease. The disease extended to southeast Europe, the Balkans, and the Caucasus in 2015 and 2016 and is still spreading throughout Asia. The World Organization for Animal Health [WOAH] has designated LSD as a notifiable illness due to the likelihood of fast transmission. The rapid spread of disease in formerly disease-free areas emphasizes the need to know the disease epidemiology and the virus's interaction with its host. This chapter aims to provide the latest developments in the etiology, epidemiology, diagnosis, and control of LSD.

Keywords: lumpy skin disease, etiology, epidemiology, diagnosis, control

1. Introduction

LSD is the best example of an emerging infectious disease owing to its recent rapid spread and geographic expansion in disease-free Asian countries. Initially limited to Africa, since 2019, the disease has spread through China and Southeast Asia. In 2021, the disease was confirmed in Pakistan, Mongolia, Vietnam, Thailand, Laos, Cambodia, and Malaysia. Starting from March 2022, it was officially reported by Indonesia, Afghanistan, and Singapore [1]. Many variables could be at play, including the effects of climate change, increased animal and animal product trafficking patterns, and increased illegal animal trade, which could contribute to the spread of the disease [2, 3]. Capripox viruses are considered the most economically significant members of the Poxviridae family of viruses that attack domestic ruminants. LSDV is a host-specific virus genetically related and shares genetic ancestry with the sheep pox (SPPV) and goat pox (GTPV) viruses.

Though the disease has a mortality rate of less than 10%, it leads to animal welfare issues, significant production losses, and substantial trade impacts, indicating the

importance of understanding the epidemiology of the disease. Damaged skins, a decrease in the growth rate of beef cattle, temporary or permanent sterility, miscarriage, treatment and immunization expenditures, and the death of afflicted animals are some additional effects of the disease [4–7].

The present chapter is designed to provide up-to-date information on the various aspects of the disease, such as its etiology, epidemiology, diagnosis, and control.

2. The etiology

Lumpy skin disease virus (LSDV) belongs to the family poxviridae, subfamily Chordopoxviridae, and genus *Capripoxvirus*. This genus is made up of the goat pox virus (GTPV), sheep pox virus (SPPV), and lumpy skin disease virus (LSDV). GTPV infects goats, sheep are infected by SPPV, and LSDV infects cattle and buffalo. There is only one serotype of LSDV, which is phylogenetically distinct but serologically related to SPPV and GTPV. In common with other poxviruses, LSDV replicates in the cytoplasm of an infected cell, forming distinct perinuclear viral factories and the presence of immature spherical virus particles and ovoid or cylindrical mature particles (**Figure 1**) [8].

The LSD virion is large and brick-shaped, measuring 293–299 nm (length) and 262–273 nm (width). The LSDV genome structure is also similar to other poxviruses, consisting of double-stranded linear DNA 25% GC-rich, approximately 150,000 bp in length, and encodes around 156 open reading frames (ORFs). The central region of the LSDV genome contains ORFs predicted to encode proteins required for virus

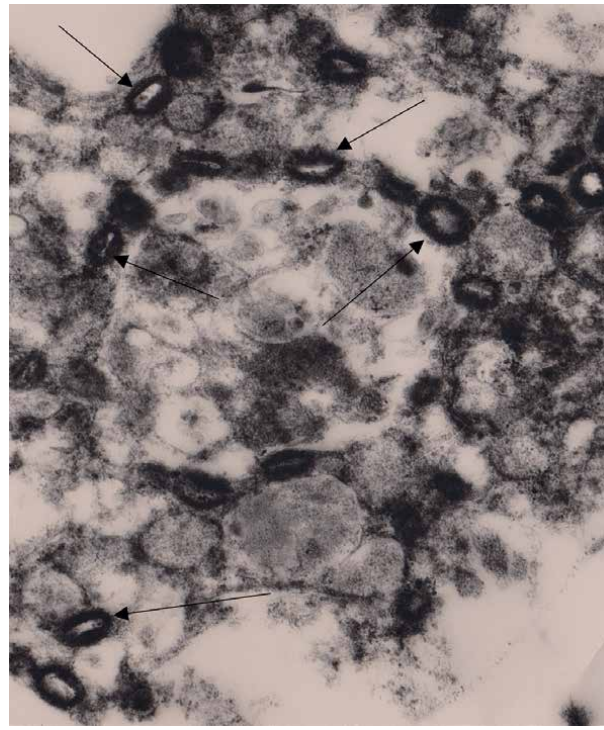

Figure 1.
Electron micrograph of mature lumpy skin disease virus in skin biopsy collected from a sick cow (x 14,400). Arrows point to mature virus particles (Khalafalla et al., [8]).

replication and morphogenesis and exhibit a high degree of similarity with genomes of other mammalian poxviruses. The ORFs in the outer regions of the LSDV genome have lower similarity and likely encode proteins involved in viral virulence and host range determinants [9].

According to recent studies, using homologous live attenuated vaccines cause LSDVs to undergo faster evolutionary changes due to recombination. In Kazakhstan and surrounding countries of Russia and China, multiple vaccine-like recombinant strains of the lumpy skin disease virus (LSDV) were found between 2017 and 2019. Recombinant LSDV strains isolated prior to 2020 were composed of unique combinations of open reading frames. From 2020 onwards, all circulating strains in Russia and South-Eastern Asia belonged to a single lineage radiating out in the region [10]. According to Vandenbussche et al. [11], the vaccine-like recombinant strains can be divided into four groups, and each group has a distinct breakpoint pattern resulting from multiple recombination events. The author claimed that the recent emergence of vaccine-like LSDV strains in large parts of Asia is likely the result of a spillover from animals vaccinated with the Lumpivax vaccine. Furthermore, Suwankitwa et al. [12], in Thailand, by genetic analysis, detected a recombinant LSDV derived from a vaccine strain previously appearing in China and Vietnam. Investigation revealed that the Thailand LSDV possesses a mosaic hybrid genome containing the vaccine virus DNA as the backbone and a field strain DNA as the minor donor.

LSDV can remain viable for long periods in the environment at ambient temperatures, especially in dried scabs. Capripox viruses are highly resistant and can remain viable in infected tissues for more than 120 days. The virus can also be found in blood, nasal discharge, lacrimal secretion, semen, and saliva, which are considered the main sources of direct LSDV transmission [13, 14]. The virus can be inactivated at a temperature of 55°C for 2 hours and 65°C for 30 minutes [15].

3. The epidemiology of LSD

Lumpy skin disease is endemic in Africa, with the first outbreak reported in Zambia in 1929. The disease spread into Botswana by 1943 and then into South Africa in the same year and affected over 8 million cattle, causing significant economic loss. In 1957, LSD reached Kenya, and by 1974 it had spread into Sudan and moved west as far as Nigeria, and in 1977 the disease was reported from Mauritania, Mali, Ghana, and Liberia. The disease reemerged between 1981 and 1986 and affected Tanzania, Kenya, Zimbabwe, Somalia, and Cameroon, with reported mortality rates of 20%. Later, LSD was confirmed for the first time in Egypt in 1988, followed, later, by spread within the middle east identified in Saudi Arabia, Lebanon, Jordan, Iraq, Israel, Turkey, and Iran [16–20]. Between 2012 and 2022, LSD spread into southeast Europe, the Balkans, the Caucasus, and further throughout most of Asia (**Figure 2**). LSD is an economically significant disease. For instance, the economic impact of LSD on south, east, and southeast Asia countries was estimated to be up to US 1.45 billion in direct losses of livestock and production [21].

3.1 Transmission

The transboundary spread of LSD is supported by the traditional system of production and seasonal nomadism, where cattle herds in arid and semi-arid conditions move long distances in search of food and water. The disease can appear several hundred

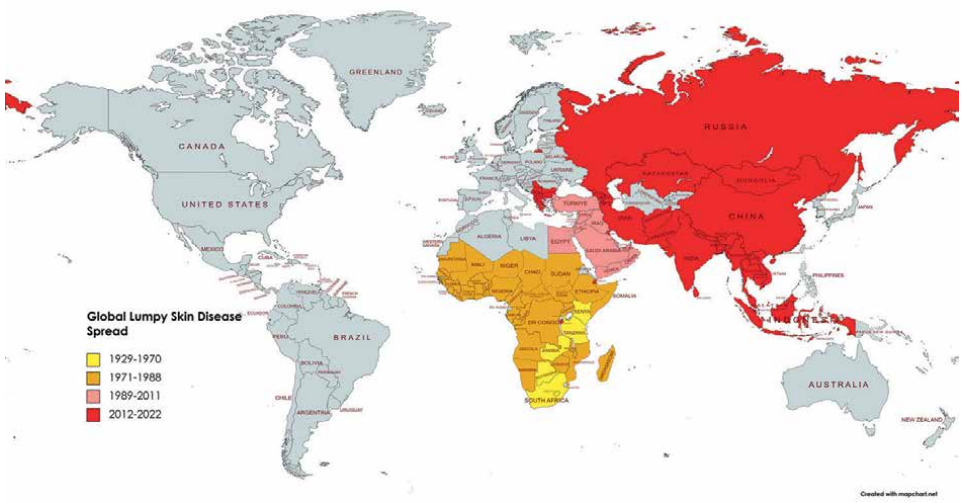

Figure 2.
Lumpy skin disease prevalence worldwide and over time from 1929 to 2022. The impacted nations are shown in yellow between 1929 and 1970, orange between 1971 and 1988, pink between 1989 and 2011, and red between 2012 and 2022. This map was prepared using the MapChart platform (World Map - Simple | MapChart).

kilometers away from initial outbreak sites within a short period, probably via the movement of infected animals. In the past, LSD was known to be mainly transmitted by biting arthropods via a mechanical form of vector-borne transmission without any multiplication of the virus in the vector. However, some researchers suggest that direct contact without vector involvement is a common mechanism of LSDV transmission [22]. Recently, non-vector-borne transmission has been studied in Russia. According to Aleksandr et al. [23], contact transmission mitigates the factor of seasonality, which is linked to insect activity and widens the possibilities for spread regardless of the presence of biting insects. Transmission through contaminated feed and water and direct transmission in the later stages of the disease via saliva, nasal secretions, and semen was also reported [13, 14, 24–26]. The primary infection source is skin lesions, as the virus persists in the lesions or scabs for long periods. The virus is also excreted via the blood, nasal and lachrymal secretions, saliva, semen, and milk [14].

The most likely vectors for LSDV transmission are blood-sucking arthropods, such as stable flies *(Stomoxys calcitrans*), mosquitoes (*Aedes aegypti*), and hard ticks (*Rhipicephalus* and *Amblyomma* species) [14]. Experimentally *Haematopota* spp., horse flies, the biting flies *S. calcitrans*, *Stomoxys sitiens*, and *Stomoxys indica can also transmit the disease to cattle* [27]. Additionally, according to Sprygin et al. [28], a house fly (*Musca domestica*) may also play a role in LSDV transmission.

3.2 Host range, morbidity, and mortality rates

The severity of the clinical signs of LSD is highly variable. It depends on several factors, including the virus's strain, the host's age, immunological status, and breed. Bos taurus is generally more susceptible to clinical disease than Bos indicus; the Asian buffalo (*Bubalus spp*.) has also been reported to be susceptible [9]. Besides, wildlife can also be susceptible, and a recent report described clinical diseases and deaths of giraffes in a Vietnamese zoo [29]. Previously, the susceptibility of springbok, impala, and giraffe to the virus has been experimentally documented [14, 30]. Generally, high

milk-producing European cattle breeds are more susceptible than indigenous African and Asian animals [13, 31]. Morbidity can range from 1% to almost 100%, with mortality most often between 1 and 3%. In European cattle breeds, LSD mortality remains typically below 10%, while morbidity can vary from 5–45% but, in some cases, may be higher (up to 100%) [13, 32]. All animal age groups are susceptible to this viral infection, although calves and animals with impaired immune systems are much more susceptible. The case fatality rate of LSD in adult animals is, in many cases, lower than 10%, although exceptions may occur, and mortality in young animals may be higher.

4. Clinical signs

The disease is characterized by fever, nodules on the skin, mucous membranes, and internal organs, emaciation, enlarged lymph nodes, edema of the skin, and sometimes death [9]. The characteristic skin lesions are multiple, well-circumscribed to coalescing, 0.5–5 cm in diameter, firm, flat-topped papules, and nodules (**Figure 3**).

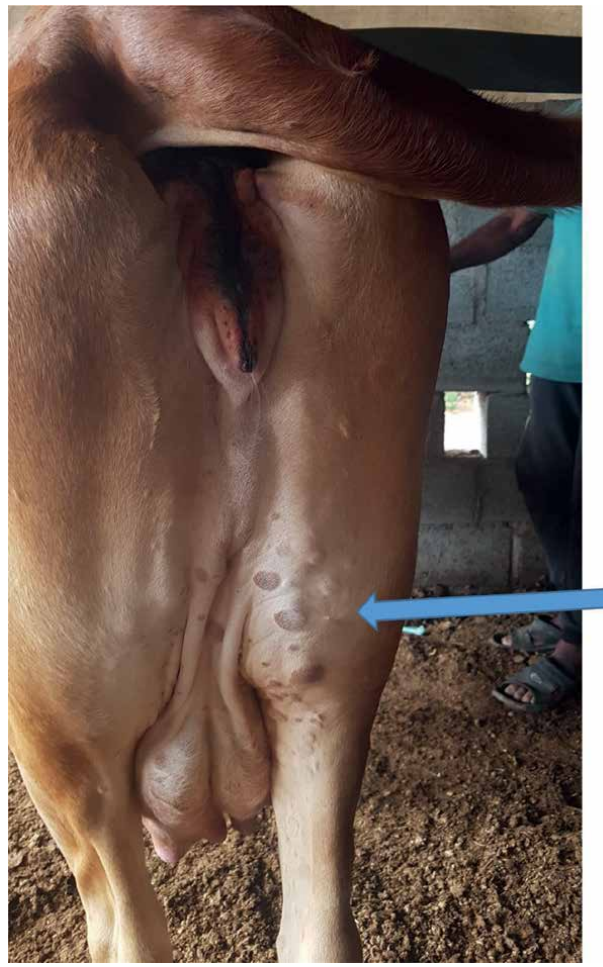

Figure 3.
A cow showing typical lumpy skin disease skin lesions (arrow).

The nodules involve the dermis and epidermis and may extend to the underlying subcutis and occasionally to the adjacent striated muscle. The skin on the head, neck, perineum, genitalia, udder, and limbs are the predilection sites. These nodules have a creamy gray-to-white color on the cut section, which may initially exude serum. However, over the ensuing 2 weeks, a cone-shaped central core or sequestrum of necrotic material/necrotic plug ("sit-fast") may appear within the nodule [9]. As soon as the nodules on the mucous membranes of the eyes, nose, mouth, rectum, udder, and genitalia begin to ulcerate, the virus is present in all secretions, including saliva, ocular and nasal discharge, and the nodules on the genitalia. Many cattle suffer severe emaciation and loss of production for several months. The skin lesions cause permanent damage to the hides. The disease is of economic importance as it can cause a temporary reduction in milk production, temporary or permanent sterility in bulls, damage to hides, and, occasionally, death. LSD can lead to mastitis, orchitis, and abortion. However, nodules were not observed in aborted fetuses [14]. Intrauterine transmission of LSD is possible; pregnant cattle may abort, bulls may become permanently or temporarily infertile, and the virus can be excreted in the semen for prolonged periods [9].

5. Risk factors

In general, conditions favoring large vector populations, such as the heavy rainy season, warm, humid weather, and the purchase and introduction of new animals to a herd, are risk factors associated with the spread of LSD. In Bangladesh, LSD attack risk was significantly higher in small herds than in large herds, and the disease was observed in semi-intensive management systems than intensive management systems [33]. Communal grazing, communal water points, the introduction of a new animal, and contact with other animals were identified as significant risk factors for LSDV infection in cattle in Egypt [34]. Kiplagat et al. [35] pointed to raising exotic breeds, outside sources of stock replacement, and large herd size as the main factors associated with LSD outbreaks in Kenya. Calves and young animals (1–2.5-years-old) were at higher risk for LSD cases in Mongolia. At the same time, locations near the tube well and pond water are major risk areas for viral transmission due to the high density of insects [36]. In a study by Sethi et al. [37], grazing of animals and the age of cows (> 3 years old) were potential risk factors for the presence of LSD in India.

6. Diagnosis

Based on the clinical manifestation of the distinctive skin lesions, a provisional diagnosis of LSD can be made in an endemic setting. However, LSD diagnosis is usually tricky in previously unaffected regions because of logistical issues and a lack of familiarity with uncommon diseases.

Although distinctive clinical LSD symptoms allow for a preliminary diagnosis, test confirmation is required. Test methods recommended for diagnosing LSD are available in chapter 3.4.12 (lumpy skin disease) of the WOAH terrestrial manual [9]. The most accurate ways to detect LSDV are molecular techniques, such as conventional or real-time polymerase chain reaction (PCR) and loop-mediated isothermal amplification. The PCR is a sensitive test used to confirm clinical cases, individual animal freedom from infection before movement, and population freedom from disease. The second

diagnostic option is virus isolation, which is recommended for confirmation of clinical cases, followed by transmission electron microscopy to prove a clinical case.

6.1 Pathology and histopathology

LSD nodules are firm and may extend to the underlying subcutis and muscle. Histopathological analysis of infected tissue samples shows pathognomonic eosinophilic intracytoplasmic inclusion bodies in the keratinocytes, macrophages, endothelial cells, and pericytes associated with the ballooning degeneration of spinosum cells. Infiltration of the superficial dermal tissue of affected areas by inflammatory cells, such as macrophages, lymphocytes, and eosinophils, is also seen. In addition, widespread vasculitis and severe coagulative necrosis in subcutaneous muscles may be observed in some cases [14, 38, 39].

6.2 Molecular diagnosis

LSD diagnosis is confirmed by using conventional gel-based PCR [40–42] or real-time PCR techniques that are reported to be faster and have higher sensitivity than conventional PCRs [9, 43, 44]. Besides, a real-time PCR technique has also been established, differentiating between LSDV, SPPV, and GTPV [30].

A new rapid on-site LSDV detection method using an *orf068* gene-based recombinase polymerase amplification assay (RPA) coupled with a CRISPR-Cas12a-based fluorescence assay (RPA-Cas12a-fluorescence assay) has been described to be a specific and highly sensitive detected five copies/μL plasmid DNA [45]. Additionally, a CRISPR-powered platform providing a novel diagnostic tool for portable, ultra-sensitive, rapid, and highly adaptable disease screening of LSD that could identify lumpy skin disease virus from vaccine strains of GTPV and SPPV was recently developed [46]. For genotyping and phylogenetic study of LSDV and other *capripox* viruses, P32, RPO30, and GPCRs, as well as ORF103 genes, were targeted for partial genome sequencing.

6.3 Virus isolation

Virus isolation in cell culture or embryonated fowl eggs is the gold standard for LSDV diagnosis, but it may require several weeks to isolate the virus. LSDV can be isolated in the tissue culture of bovine, ovine, or caprine origin. In contrast to infection with bovine herpesvirus-2, which results in pseudo-lumpy skin condition and induces syncytia and intranuclear inclusion bodies in cell culture, LSDV causes a distinctive cytopathic effect and intracytoplasmic inclusion bodies [9]. According to Wang et al. [47], the most sensitive cell line for the isolation of LSDV, is primary cattle testicular (PCT) cells, while vero cells cannot be used for the isolation of this virus.

6.4 Differential diagnosis

Differential diagnosis is required to distinguish LSD from pseudo-LSD caused by bovine herpesvirus-2 (BoHV-2), dermatophilosis, dermatophytosis, bovine farcy, photosensitization, actinomycosis, actinobacillosis, urticaria, insect bites, besnoitiosis, nocardiosis, demodicosis, onchocerciasis, pseudo-cowpox, bovine papular

stomatitis, cowpox, foot and mouth disease, bluetongue, mucosal disease, malignant catarrhal fever, and infectious bovine rhinotracheitis.

7. Treatment, prevention, and control

There is no specific treatment for lumpy skin disease. Nonspecific therapy using antibiotics, anti-inflammatory drugs, and vitamin injections is typically used to treat secondary bacterial complications, inflammation, and fever, as well as to increase the animal's appetite.

Mass vaccination of cattle is the most efficient method of disease management once it has spread throughout a country. To provide immunization against LSDV in susceptible cattle, several live attenuated homologous (based on the LSDV Neethling strain) and heterologous vaccines (based on strains of SPPV or GTPV have been produced. Attenuated vaccines are widely used and readily available on the market. However, the level of protection they give is still debatable because they may be ineffective or result in moderate side effects. Inactivated vaccines, on the other hand, are safe and stable and allow combinations with different antigens to make polyvalent vaccines, and they can be applied in disease-free countries. Adult cattle must receive a vaccination every year. In addition to other control strategies (such as vector control, quarantine, and biosecurity), mass immunization utilizing live homologous vaccines is presently the most efficient way to control LSD [48–50]. According to the recommendations of the EU's (EFSA) expert panel (20160812.4410864) [51], it is necessary to implement vaccination of the entire susceptible cattle population in regions facing LSDV introduction or already affected. This is in order to minimize the number of outbreaks. High vaccination coverage at animal and farm levels should be achieved. Diseased animals should not be vaccinated. However, it is necessary that the use of live homologous vaccines to protect against LSDV infection requires the use of molecular tools to differentiate between infected and vaccinated animals (DIVA). There are many commercial PCR kits that correctly identify classical field isolates (European lineage) and vaccines (Neethling vaccine) [52].

Additional control measures at the event level involve control of vectors; disinfection; movement control; official destruction of animal products; official disposal of carcasses, by-products, and waste; quarantine; vaccination in response to the outbreak.

8. Conclusions

Due to its recent rapid geographic expansion and widespread distribution, LSD is the best illustration of an emerging infectious disease. The disease is caused by the lumpy skin disease virus (LSDV), a member of the *Capripoxvirus* genus of the poxviridae family. Clinical signs of the illness include fever and flat, disk-shaped skin lesions. Blood-feeding insects are the primary vectors of LSDV transmission, and the disease spread to large distances via movement of cattle and their products. From Africa, where the disease remained endemic until 1989 lumpy skin disease extended to middle east, southeast Europe, the Balkans, and the Caucasus and is still spreading throughout Asia. Understanding the disease's epidemiology is crucial since it affects animal welfare, causes considerable production losses, and has a significant influence on trade.

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Conflict of interest

The authors declare no conflict of interest or delete this entire section.

Author details

Abdelmalik Khalafalla
Veterinary Laboratory Division, Agriculture and Food Safety Authority, Abu Dhabi, United Arab Emirates

*Address all correspondence to: abdokhlf@yahooco.uk

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Chapter 2

Diagnosis and Identification of Zoonotic Diseases Associated with Cattle at Abattoirs: Current Trends and Future Prospectus

Maryam Abdul Sattar, Muawuz Ijaz, Mubarik Mahmood, Muhammad Kashif Yar, Jawad Ashraf, Moiz Ali Younas, Sadia Ilyas and Sana Ullah

Abstract

Zoonoses are illnesses and infections that spread spontaneously from animals to people. They account for over 70% of recently developing infectious illnesses. Meat from cattle is one of the main sources of red meat and essential element of human diet. Meat inspection (MI) is an important aspect to ensure the safety during handling and consuming of meat and meat by-products. Abattoir or modern slaughterhouse is the place where infections are acquired by the workers or veterinary professional as zoonoses. Bacterial zoonotic diseases such as erysipelothricosis, brucella, listeria, and anthrax and viral zoonotic diseases like cow pox, foot and mouth disease, and rift valley fever are causing great economic losses and are important in terms of zoonoses. These zoonotic diseases are mostly diagnosed at abattoir levels using conventional approaches; however, diagnosis and identification of these diseases using latest methods is an important aspect for ensuring meat safety and hygiene. This chapter will discuss the current trends and future prospects about diagnosis and identification of these zoonotic diseases.

Keywords: zoonotic diseases, cattle diseases, meat inspection, human health, abattoirs

1. Introduction

Zoonoses are illnesses that spread spontaneously from vertebrate animals to humans and vice versa [1–3]. Many farm animal species can transmit various zoonotic diseases in the livestock industry. Zoonotic diseases are typically present in killed animals, raw hides/skin, blood, meat, and farm surroundings in the beef industry, but they can be challenging to identify. Additionally, livestock transported for slaughter into metropolitan areas originates from rural communities with ineffective, disorganized, and frequently nonexistent disease control programs. Remoteness, limited infrastructure, a shortage of experienced veterinary staff, poor transportation, and a lack of funding to support surveillance activities or buy reagents and drugs all

contribute to the low quality of animal healthcare services in rural areas. Due to the scarcity of veterinary services, there is a significant risk of widespread sickness in the livestock population and concurrent human exposure to zoonotic disease agents in these areas. Additionally, many of the butchered animals brought to the abattoir run the danger of harboring chronic or subclinical illnesses that are infrequently found during a standard antemortem inspection (AMI).

A lack of knowledge about meat-borne zoonoses can endanger the lives of livestock owners, butchers, and public. There is an even greater risk of meat-borne zoonoses in this facility, given that most home slaughter slabs and abattoirs are not fully controlled and that there is a higher level of interaction with raw meat. The dangers posed by meat-borne zoonoses that are common in certain regions must be clear to cattle owners, dealers, butchers, and policymakers. The information presented should describe how zoonoses are spread to empower persons at risk to decide how to protect themselves best [4, 5]. Many bacterial and viral diseases are frequently seen and described in abattoirs [6, 7].

One of the biggest threats to the security of the world's health is the introduction of novel zoonotic viruses. Our ability to identify and respond to these health concerns more quickly than ever before has been revolutionized by the introduction of increasingly powerful diagnostic techniques. Even yet, the initial detection of new infectious illnesses starts at the local community level, regardless of how advanced these tools have become. Here is where the original human or animal case is located, and early pathogen detection would be most helpful. Unfortunately, many regions with the highest risk of zoonotic disease introduction need to be equipped with a strong enough infrastructure to support laboratory diagnostic systems. Understanding the complex sociological and ecological factors influencing the risk of disease transmission, community involvement, surveillance along high-risk human-animal interfaces, and a skilled laboratory workforce are just a few of the factors crucial for pathogen detection networks. The growing disease paradigm, current technical developments in diagnostic techniques, and plans for comprehensive and long-term methods of quick zoonotic disease detection are all covered in this chapter.

2. Methodology

In many developing countries, disease identification and diagnosis at abattoirs is compromised and a major concern of the meat industry. Bacterial zoonotic diseases such as erysipelothricosis, brucella, listeria, and anthrax and viral zoonotic diseases like cow pox, foot and mouth disease, and rift valley fever are causing great economic losses and are important in terms of zoonoses. These zoonotic diseases are mostly diagnosed at abattoir levels using conventional approaches; however, diagnosis and identification of these diseases using latest methods is an important aspect for ensuring meat safety and hygiene. Consequently, keeping in view this scenario, the current chapter has been developed to highlight the issue and spread the awareness about latest approaches by explaining its zoonotic aspects. Therefore, it is expected that such countries also take interest in proper cattle disease identification and diagnosis by adopting modern techniques in order to avoid zoonoses at abattoirs and to ensure the meat safety and hygiene.

3. Zoonoses occupationally acquired by abattoir workers

Zoonoses are illnesses and infections that spread spontaneously from animals to people. They account for over 70% of recently developing infectious illnesses [8].

More than 300 zoonotic diseases with various etiologies are known to have considerable morbidity and mortality [9]. Zoonotic infections can affect people of either sex, of any age, in any season, in any climatic zone, and both urban and rural settings [9, 10]. Together with the migration of animals across international borders to increase the local supply and the rising demand for meat and meat products, human interaction with animals has reached record levels, raising the danger of zoonotic diseases, particularly in endemic zones [11]. Numerous methods exist for zoonotic infection transmission [12, 13]. But among those who work in slaughterhouses, direct contact appears to be the

Microorganism	**Disease**	**Reservoir**	**Host**
Bacterial zoonoses			
Bacillus anthracis	Anthrax	Soil, animals	Cattle, pig, sheep, and horse
Erysipelothrix rhusiopathiae	Erysipelothricosis	Pig	Cattle, sheep, fish, horse, birds, and reindeer
Brucella abortus, B. suis and B. melitensis	Brucellosis	Animals	Cattle, horse, camel, sheep, goat, and poultry
Listeria monocytogenes	Listeriosis	Plant matter	Cattle, sheep, goat, horse, rabbit, and bird
Francisella tularensis	Tularemia	Tick, rodents	Deer, horse, and calf
Leptospira	Leptospirosis	Rodents	Cattle, camel, sheep, goat, and pig
Staphylococcus aureus	Staphylococcal infection	Cattle	Cattle, camel, sheep, goat, and pig
Clostridium tetani	Tetanus	Soil	Cattle, sheep, and pig
Fusobacterium necrophorum	Necrobacillosis	Soil, animals	Cattle, goat, and pig
Mycobacterium bovis	Tuberculosis	Cattle	Cattle, camel, sheep, goat, and pig
Chlamydophila psittaci	Chlamydiosis	Mammals and birds	Cattle, sheep, goat, and pig
Coxiella burnetii	Q-fever	Cattle, tick, sheep, goat	Cattle, sheep, and goats
Dermatophilus congolensis	Dermatophilosis	Cattle	Cattle, camel, sheep, goat, and pig
Viral zoonoses			
Louping ill virus	Louping ill	Sheep, tick, deer	Cattle, sheep, goat, and pig
Pseudocowpox virus	Pseudocowpox	Cattle	Cattle
Cowpox virus	Cowpox	Rodents	Cattle
FMD virus	Foot and mouth disease	Cattle	Cattle, camel, sheep, goat, and pig
Miscellaneous zoonoses			
Sarcoptes scabiei	Scabies	Animals	Cattle, camel, sheep, goat, and pig
Microsporum, Trichophyton	Dermatophytosis	Animals	Cattle, sheep, goat, and pig
Aspergillus fumigatus	Aspergillosis	Environment	Cattle, camel, sheep, goat, and pig

Table 1.
Diseases, causative agents (microorganism), reservoirsm and hosts of cattle-related abattoir zoonoses.

most typical way for pathogenic agents to enter [14]. Due to their intimate contact with animals and animal tissue during slaughter or processing, workers in the meat industry are particularly at risk of contracting several zoonotic illnesses [9, 10, 15]. The current study focuses on the zoonoses that abattoir employees who kill food animals mainly cattle. The diseases, causative agents (microorganism), reservoirs, and hosts of cattle-related abattoir zoonoses are summarized in **Table 1**.

3.1 Bacterial zoonoses

3.1.1 Erysipelothricosis

Erysipelothrix rhusiopathiae is the causative agent of this contagious bacterial illness. The condition is also known as Whale finger, Pork finger, and Fish finger [9]. Infections in humans are typically acquired from occupational exposure at slaughter-houses for meat, poultry, or fish. *E. rhusiopathiae* is widely distributed, with domestic pigs serving as its primary reservoir. Pigs, sheep, cattle, horses, fish, birds, and reindeer have all been shown to be infected [9]. The most susceptible occupations to disease are those handling and inspecting meat [14].

3.1.2 Brucellosis

This is one of the most significant anthropozoonoses in terms of public health, and it is brought on by *Brucella abortus, Brucella suis, and Brucella melitensis* [16]. Buffalo, cattle, camels, horses, pigs, sheep, goats, deer, and birds have all been recorded to have it [9]. Known as "undulant fever" or "Malta fever," human brucellosis is a severe zoonose that frequently affects livestock. All slaughterhouse employees who handle livestock directly, dress carcasses, or dispose of condemned organs run a higher risk of contracting brucellosis.

3.1.3 Listeriosis

Listeria monocytogenes, a rod-shaped bacterium that is the etiologic agent, was discovered by Murray in 1926 in rabbits and guinea pigs [9]. Buffalo, cattle, goats, sheep, houses, birds, rabbits, and fish are all susceptible to infection [9]. Direct contact with sick animals or contaminated discharges or tissues can cause veterinarians and butchers to develop primary cutaneous listeriosis [14]. The first sign of cutaneous listeriosis is a reddish rash, which progresses to vesicular or pustular lesions that are about 1–2 mm in diameter and have either a dark or light center [14]. It can occasionally result in a more widespread illness.

3.1.4 Anthrax

Bacillus anthracics, a Gram-positive, aerobic, sporulated bacterium, is the source of this occupational disease [17]. All food animals have been shown to have the illness. When conditions are right, the spores can survive in contaminated soil for 40–50 years and in dead host bones for 150–250 years. Between 20,000 and 100,000 cases of anthrax in humans are thought to occur annually on a global scale. 95–99% of all human cases worldwide are of the cutaneous type, also called malignant pustule [13]. It is widespread throughout the world, including Asia and Africa. Most often, an illness spreads to abattoir employees through a skin wound. The hands and arms of

meat handlers appear to be more frequently affected by cutaneous anthrax [14]. The so-called "Malignant Pustule," a tiny pimple that quickly grows into a large blister with a dark necrotic centre, distinguishes it.

3.1.5 Leptospirosis

Weil's illness, mud fever, canicola fever, and rice-field worker's disease are just a few of the many names for this widespread bacterial zoonosis by pathogenic *Leptospira spirochetes* [18]. The illness, widespread in underdeveloped nations and reemerging in the United States [19], affects humans and animals. Numerous food animals, including cattle, buffalo, camels, horses, goats, sheep, deer, and pigs, are susceptible to leptospirosis [9]. Leptospira infection is thought to be resistant in poultry. Direct interaction with infected animals and their tissues can cause transmission, as indirect contact with a contaminated environment, particularly water tainted with the urine of infected food animals [20]. Brown and colleagues [21] investigated the environmental risk factors for leptospirosis in butchers in Jamaica.

3.1.6 Tularemia

Francisella tularensis, a Gram-negative, aerobic, non-sporulated bacterium, is the disease's cause and is often referred to as Deerfly fever or Rabbit fever [9]. Rabbit, deer, horse, pig, and calf cases of the disease have been documented [9]. It affects butchers of rabbits as a profession. The most prevalent way humans become infected is through skinning infected rabbits and hares. The USA annually reports roughly 2000 cases of human tularemia [14]. The first indication in men is typically a papule at the primary infection location, frequently an ulcerated finger.

3.1.7 Tetanus

It is a bacterial illness brought on by the spore-forming, Gram-positive, anaerobic bacterium *Clostridium tetani*. Horses, sheep, cattle, and pigs are all known to get natural infections [9]. The pathogen entered the body when contaminated soil or dust contaminated with *C. tetani* spores infected the incision, injury, or laceration. Incubation lasts 4–10 days. The first sign of tetanus is a tightening of the jaw muscles. The condition known as "Lock Jaw" affects men [9].

3.1.8 Melioidosis

Burkholderia pseudomallei, a Gram-negative, mobile aerobe, is the culprit [9]. Man contracts the virus through direct skin-to-contaminated-soil or water contact. The disease can also be transmitted by inhaling infected dust through the respiratory system. Cattles, camels, goats, horses, pigs, sheep, and kangaroos all contract diseases [9]. In dirt and water, organisms can endure for several months. Vesicles and pustules appear on the patient's hands and feet. There are septicemic, extrapulmonary, and pulmonary types. Australia has a high endemicity of disease in humans and animals [14].

3.1.9 Tuberculosis

Bovine tuberculosis, a severe zoonotic disease, is caused by *Mycobacterium bovis*. The occurrence of *M. Bovis* infection in animals and humans varies

significantly globally. *M. Bovis* causes 5–10% of all cases of human tuberculosis in several underdeveloped nations [22]. Cattle, buffalo, sheep, goats, horses, pigs, and deer have all been recorded to have the disease [9]. Direct contact with an infected animal or carcass in an abattoir results in the spread of bacteria from an animal to a human (occupational exposure). The epidermis, tendons, and regional lymph nodes of people who touch infected carcasses in the slaughterhouse develop tuberculosis sores.

3.1.10 Necrobacillosis

A bacterial infection caused in humans, cattle, and goats. By touching infected animal tissues through a wound or damaged area of skin, a disease can be transmitted from an animal to a human. *Fusobacterium necrophorum*, an anaerobic, Gram-negative, non-sporulated bacteria, is the source of disease. At the location of the organism's injection, necrotic pustules form [9].

3.1.11 Dermatophilosis

Dermatophilus congolensis, a facultative anaerobic actinomycete, is the disease-causing agent. Due to how frequently it appears raindrops have just landed on the skin, the disease is occasionally called "rain scald." Initial symptoms of the illness include pustules, which are frequently disregarded. However, once the longer hairs become entangled in the scab, the pustules quickly clump together to create enormous oval crusts [11]. It affects cattle, goats, sheep, horses, camels, deer, and rabbits [23]. It has a widespread distribution.

3.1.12 Chlamydiosis

Chlamydophila psittaci, an intracellular organism, is the cause of this highly contagious disease that affects people all over the world. Animals, including cattle, sheep, horses, goats, pigs, buffalo, and birds, have been known to be infected [11]. Infection may develop from human exposure to infectious aerosols, dust, bird droppings, nasal discharge, and sheep fetuses and membranes [14, 24]. With good care, the illness seldom results in death. Early diagnosis and awareness are crucial as a result. A bird handler in India was found to have chlamydial infection.

3.1.13 Q fever

It is a severe rickettsial illness brought on by *Coxiella burnetii*. The organism has been contagious in farm dust and wool for a long time. Sheep, goats, and cattle are most frequently affected by the disease. Man can become inflected from inhalation, direct contact, or tick bites [9]. Fever, anorexia, chills, frontal headache, myalgia, weakness, cough, chest pain, pneumonia, and excessive sweating are the typical symptoms [9]. Pericarditis, endocarditis, and hepatitis are seen in more severe cases. In a study of employees at an Edinburgh slaughterhouse, 21.1% displayed antibodies to the phase 2 antigen of *C. burnetii* [14]. Infection among abattoir employees has been documented in Australian investigations during the past 20 years [25–27].

3.2 Viral zoonoses

3.2.1 Cowpox

Man can contract this viral zoonosis from infected cattle through close contact, which is how the cowpox virus (DNA virus) that causes it spreads. Acute viral illnesses like cowpox are distinguished by typical vesicular skin and mucous membrane outbreaks. Erythema, vesicles, pustules, and scab development are observed in men [9]. Some lesions on the hands, arms, and face are frequently accompanied by lymphadenitis and fever. The illness is self-contained. The hand of a butcher showed the characteristic cowpox lesions.

3.2.2 Contagious ecthyma

It is an occupational disease caused by Orfvirus (DNA) of family Poxviridae. There are cases of disease in cattle, sheep, goats, and camels. Abrasions or injuries to the skin can allow the virus to enter [3]. Man contracts the disease through direct contact with infected animals. The majority of instances are found in adults, particularly men. Butchers, meat handlers, and employees at abattoirs frequently contract diseases. Papule, vesicle, and pustule occur mainly on the finger, hand, wrist, fore arm, and sometimes on the face [14]. The lesions heal in 15–30 days, and occasionally, ocular lesions may occur [9].

3.2.3 Foot and mouth disease

It is an economically important infectious disease caused by FMD virus (RNA) of the family Picornaviridae and is reported in cattle, buffalo, camel, goat, sheep, pig, and deer [9]. Abraded skin that has been exposed to diseased animals or their excretions comes into close contact and spreads the infection. Viruses can persist for a very long time in animal hides. It is a mild disease in man and vesicles occur on the finger, palm of hand, sole of feet, or oral cavity [9].

3.2.4 Rift valley fever

Rift valley fever is caused by the rift valley fever virus (RNA), which belongs to the Bunyaviridae family and was first identified in Kenya in 1931. Man gets infection by direct contact with diseased animals or infected tissues [28]. A mosquito bite can infect both humans and animals with sickness. There are cases of disease in sheep, goats, camels, and cattle. A mosquito bite can infect both humans and animals with sickness. There are cases of disease in sheep, goats, camels, and cattle.

4. Diagnosis and identification of zoonotic diseases

Different goals are achieved by meat inspection (MI) operations carried out in slaughterhouses. MI activities were initially created with the primary goals of safeguarding consumers from foodborne dangers and assuring food safety and quality [29]. More recently, MI activities have expanded their scope to include, in particular,

the supervision of animal health and welfare status [30]. Regulation (EU) 2017/625 of the European Parliament and the Council [31] and Commission Implementing Regulation (EU) 2019/627 [32] both contain regulations governing MI in Europe. The Competent Authority (CA) of each Member State conducts a series of actions at the slaughterhouse under the auspices of MI that are designed using a risk-based methodology. These actions take place before and after the animals are stunned or killed, and some of them include antemortem inspections (AMI) and postmortem inspections (PMI) [33]. At the European [34–37] and Italian levels, there are a number of recently published studies that mostly focused on lesions produced from PMI rather than AMI [38–40]. The information gathered at the abattoir during PMI is unquestionably crucial because it may be a sign of specific diseases or of subpar welfare [41]. However, the outcomes of AMI can help with a number of pig health and welfare issues as well as recommend what should be done when specific criteria are met at the abattoir.

In reality, although PMI in animals in European slaughterhouses is only visual [38], official veterinarians (OVs) can decide regarding additional procedures like physical examination and incision of organs in cases of a suspected risk for public health, animal health, or animal welfare during the AMI [42]. This is unless otherwise specified by procedures required for exporting meat and meat products in non-EU countries. Therefore, AMI operations may aid OVs in recognizing the batches of pigs that are unsuitable for visual inspection alone and that need more involved inspection techniques [43]. In reality, although PMI in animals in European slaughterhouses is only visual [38], official veterinarians (OVs) can decide regarding additional procedures like physical examination and incision of organs in cases of a suspected risk for public health, animal health, or animal welfare during the AMI [42]. This is unless otherwise specified by procedures required for exporting meat and meat products in non-EU countries. Therefore, AMI operations may aid OVs in recognizing the batches of pigs that are unsuitable for visual inspection alone and that need more involved inspection techniques [43].

In order to apply such measures, both OVs and food business operators (FBOs) need specific and reliable indicators that can facilitate the decision-making process. Little is known concerning the relationship between findings reported during AMI and those found during PMI in abattoirs [44]. To the best of our knowledge, a determination of the predictive value of certain conditions presents during AMI with respect to lesions assessable during PMI in slaughtered animals should be focused.

5. Emerging pathogen detection pathway

As people, animals, and viruses interact more intensely and intricately across local and global environments, there is a greater chance that a zoonotic pathogen with actual pandemic potential could emerge, endangering the life of millions of animals and humans. By necessity, the first signs of this threat must be observed locally, with sick people (or animals) being observed by someone acquainted with the local diseases. This initial discovery is typically never reported outside the surrounding area because the disease is not rare and spreads slowly. However, in some cases, the identification of initial cases or the subsequent chain of multiple events may result in the eventual involvement of the local or national state authorities as well as the potential intervention of international health responders. In many nations, centralized systems have been established, where epidemiologic and laboratory diagnostic capabilities are housed in national-level centers that serve as referrals and are located far from the

majority of the high-risk human-animal interfaces that are the forerunners of disease emergence [45]. In these situations, clinical data on patients or animals, news of mass deaths or other uncommon illnesses, and finally diagnostic samples for examination are pulled up to these referral centers from the local level.

Despite its benefits, this centralized pull method has a number of failure points, since it might be challenging to get information and diagnostic samples from the home to the national level. Delays in the identification, diagnosis, and ultimately control of emerging health threats are caused by a variety of factors, including inadequate transportation or information systems, a lack of trained health workers, inadequate laboratory frameworks, poor multidisciplinary or ministerial communication channels between the animal and public healthcare organizations, mistrust of government officials, and occasionally less-than-ideal national reporting systems.

How to best build robust and durable surveillance networks that can identify the rare and isolated health event at the regional level and correlate those evaluations with highly qualified public health laboratory workers is the main challenge in the early screening of growing zoonoses at a systems level [46]. Is it more likely for a distributed network of local partner-driven surveillance teams with basic laboratory capacity for point-of-care rule-in/out diagnosis to be successful than a highly centralized and concentrated network in national- or regional-level reference institutions or government ministries, or even a combination of both? The sustainability of money, the requirement for training, and the sophistication of laboratory procedures required for pathogen detection are important factors that determine which of these approaches is most suited for a given nation. In various nations, examples of accomplishments from a combined effects of national and local monitoring networks with assistance from international organizations have been produced [47, 48].

The best-positioned disease surveillance systems to quickly identify emerging zoonotic hazards are probably those that strive to connect the animal and human health sectors as closely as is practical. The objective of these combined surveillance operations is to identify novel emerging diseases from susceptible animals and the human population as promptly as feasible. Field ecology teams and human and animal health professionals will collaborate on these activities. It may be best to combine this integrated strategy with initiatives to bring the technical expertise and laboratory facilities required for zoonotic disease detection as near to the local levels as possible. Systems that use a locally driven and distributed component may be more expensive and challenging to manage than exclusively centralized systems, but because they are closer to and more integrated into the local community, they are more likely to be able to quickly identify rare health events for follow-up.

6. Building an effective approach

The development of local or regional surveillance centers is necessary for integrated approaches to be viable. This requires long-term, sustainable financing and investments in human capital, infrastructure, laboratory equipment, and these areas. In response to the SARS outbreak in 2001, 196 World Health Organization (WHO) member countries adopted International Health Regulations (IHR) in 2005, which has accelerated the establishment of integrated animal and human health surveillance systems for zoonoses [49]. The opportunity to more closely link the human and animal disease surveillance sectors has been made possible by these restrictions, together with the growing understanding that the appearance of a disease in one nation might

quickly spread to another through the movement of animals or humans. IHR requires the timely notification (<24 h) of outbreaks "of disease with the ability to cause serious public health impact and to spread internationally" and may constitute a "Public Health Emergency of International Concern" [50]. The regulations do not stipulate the source of the infection (human or animal) and are meant to be applied as broadly as possible by all member nations.

Finding local, national, and regional partners to work with these multinational organizations, create structures with them, and find bright and motivated people is a crucial initial step in this process. To create a knowledgeable and well-coordinated network of people and institutions for zoonotic disease detection, these individuals should ideally come from a variety of scientific backgrounds and work in all fields, including human, animal, and wildlife health specialists, epidemiologists, laboratory and behavioral scientists, and other junior and senior staff.

7. Conclusion

A lack of latest approaches in diagnosis and identification of zoonotic diseases at abattoirs can endanger the lives of livestock owners, butchers, and public. There is an even greater risk of meat-borne zoonoses in this facility, given that most home slaughter slabs and abattoirs are not fully controlled and that there is a higher level of interaction with raw meat. In most of the countries, diagnosis and identification of these zoonotic diseases at abattoirs is performed by conventional ways such as by antemortem and postmortem examinations. However, latest approaches should be adopted to avoid such bacterial and viral zoonoses.

Conflict of interest

The authors declare no conflict of interest.

Author details

Maryam Abdul Sattar[1], Muawuz Ijaz[2*], Mubarik Mahmood[2], Muhammad Kashif Yar[2], Jawad Ashraf[3], Moiz Ali Younas[2], Sadia Ilyas[2] and Sana Ullah[4]

1 Department of Biological Sciences, University of Veterinary and Animal Sciences, Lahore, Pakistan

2 Department of Animal Sciences, University of Veterinary and Animal Sciences, Jhang, Pakistan

3 College of Agriculture, University of Layyah, Layyah, Pakistan

4 Quality Operational Laboratory, International Development and Research Centre, University of Veterinary and Animal Sciences, Lahore, Pakistan

*Address all correspondence to: muawuz.ijaz@uvas.edu.pk

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Chapter 3

Effect of Cattle-Specific Diseases on Carcass Inspection and Meat Quality

Muhammad Kashif Yar, Mubarik Mahmood, Muawuz Ijaz, Muhammad Hayat Jaspal, Zayrah Rafique, Iftikhar Hussain Badar and Kanwal Rafique

Abstract

There are severe cattle-specific viral (foot and mouth, vesicular stomatitis, rinderpest, rift valley fever, malignant catarrhal fever, lumpy skin, rabies, bovine leukosis, bovine viral diarrhea, and bovine spongiform encephalopathy), bacterial (tuberculosis, black quarter, botulism, malignant oedema, leptospirosis, brucellosis, anthrax, hemogenic septicemia, actinomycosis, actinobacillosis, mastitis, and metritis), parasitic (lungworm, fasciolosis, cysticercosis, hydatid disease, and onchocercosis), and protozoal (trypanosomiasis, theileriosis, anaplasmosis, babesiosis, and sarcosporidiosis) diseases that affect the carcass judgment and meat quality. These diseases adversely affect cattle health, welfare, and red meat production. This chapter aims to describe the etiology, mode of transmission, ante-mortem and post-mortem findings, carcass and meat quality judgment, and differential diagnosis of these diseases.

Keywords: cattle-specific diseases, carcass judgment, meat production, meat quality, carcass inspection

1. Introduction

Beef carcasses are commonly inspected to deliver safe and healthy meat for human consumption all over the world. An abattoir is an approved and registered place by the authorities for hygiene slaughtering, inspecting, processing, and storage of meat for human consumption [1]. It also helps to detect economic and public health important diseases [2]. The veterinarians and the meat inspectors are mainly responsible for inspecting the carcasses and the meat at the abattoir phase. The data collected from ante-mortem and post-mortem inspections at the abattoirs are useful to evaluate the disease condition and decide the fate of the carcass either approved for human consumption or should be condemned [3].

Cattle are one of the major sources of red meat all over the world including Pakistan, where the demand for animal protein is increasing with time due to the increase in population [4, 5]. There are severe cattle-specific viral, bacterial,

parasitic, and protozoal diseases that are of economic and public importance [6]. Beef production is one of the most important livelihoods of rural families, especially in developing nations and the condemnation of the carcasses or specific organs causes severe economic losses to the farmers and the livestock sector [7, 8]. Besides carcass and meat inspection, the abattoirs in the most developed nations have helped to detect and eradicate several diseases in cattle [9]. However, in developing nations like Pakistan, the abattoirs are not fully utilized, and carcasses are not properly inspected before defining their fates.

In developing nations, veterinarian and meat checkers often lack the basic guidelines to determine the fate of the carcasses whether it should be approved, conditionally approved or condemned. Therefore, this chapter aims to describe the etiology, mode of transmission, ante-mortem and post-mortem findings, carcass and meat quality judgment, and differential diagnosis of cattle-specific diseases. These guidelines will help the meat inspector to determine carcass fate and prevent the spread of public health important diseases through meat consumption.

2. Carcass and meat inspection procedures

There are two main objectives of meat inspection. Firstly, physically normal, healthy animals should be slaughtered and processed for human consumption. Secondly, the slaughtered animal should be disease free, and there should be no risk to human health. These aims could be attained by performing ante-mortem and post-mortem inspections at the abattoirs.

2.1 Ante-mortem examination

The word ante-mortem examination indicates the examination of cattle "before death". Thus, the examination of cattle before slaughtering is termed as "anti-mortem examination". All the animals presented for slaughtering should receive ante-mortem examination. The purposes of ante-mortem examinations are to screen cattle before slaughter, to ensure the proper rest [10, 11], to get clinical information for disease diagnosis and identifying the reportable diseases, and lastly, to identify the animals treated with antibiotics and other chemotherapeutic agents [12]. Animal should be examined from both sides in both standing and moving conditions. Ante-mortem examination should be carried out within 24 h of slaughtering and perform again if the slaughtering has been delayed over a day. Cattle showing the clinical signs should be separated from the healthy animals and treated as "suspects" and must be held for veterinary inspection and judgment. Ante-mortem examination should be performed in adequate lightening at rest and motion [13]. The general behavior along with the nutritional status, signs of disease, and abnormalities should be observed. The abnormality in behavior, posture, gait, structure, and conformation should be monitored.

2.2 Post-mortem examination

The term post-mortem means "after death". Thus, the inspection of the animals after slaughtering is termed as "post-mortem inspection" [14]. The post-mortem examination majorly comprises head, viscera, and carcass inspection. The post-mortem inspection of the carcass should be carried out just after the dressing of the carcass to notice any abnormality or diseased condition to pass or reject the carcass

for human consumption. The carcass and organs inspections should be corelated before making the final diagnosis. The post-mortem examination is done by viewing, incising, palpating, and using olfaction techniques [15]. The lesions are classified into acute or chronic, localized or generalized and relevancy of lesions to major organs or systems. The ante-mortem and post-mortem findings should be corelated before making the final judgment.

3. Cattle-specific viral diseases

3.1 Foot and mouth disease (FMD)

Foot and mouth disease (FMD) is a highly contagious viral disease of cloven-hooved animals such as cattle [16]. FMD is caused by Aphthovirus, belonging to Picornaviridae family. There are seven serotypes of the virus, termed: A, O, C, Asia 1, and SAT (Southern African Territories) 1, 2, and 3. FMD is spread through direct or indirect contact with infected cattle, their secretions, animal products, and by-products. Ante-mortem examination shows vesicles and erotic lesions on the muzzle, mouth, feet, teats, and udder region. The cattle show high fever, dullness, reduced appetite, dropping milk production drastically, and muscle termers. Post-mortem examination shows a necrotic heart, usually in young cattle and the ulcerative lesion on the tongue, gums, palate, pillars of the rumen, and feet [15]. In the FMD-free countries and zones, the cattle are prohibited to enter the abattoir. If the FMD is diagnosed on post-mortem inspection, then carcass and visceral organs are condemned, and proper measures should be taken as suggested by the regulatory authorities of the country. If the FMD is present in the country, then the judgment should be done by considering the animal health status and public health concerns.

3.2 Vesicular stomatitis (VS)

Vesicular stomatitis (VS) is a viral disease that majorly affects cattle and horses. VS is a viral disease caused by New Jersey and Indiana serotypes of vesicular stomatitis virus [17]. VS is transmitted through aerosol, direct contact, fomites, and also through insects vectors [18]. Ante-mortem examination shows vesicular lesions in the mouth, teats, and around feet. The animal shows a decrease in weight, ending of lactation in lactating cattle, profuse salivation, and lips ribbing on mangers edges in horses. Post-mortem examination shows lesions resembling the lesions of other mucosal diseases; however, like FMD, heart and rumen lesions do not appear in VS. The carcass displaying acute changes and the systematic lesions is condemned. If the animal is not affected by the acute stage and showing no secondary bacterial infection, the carcass is approved; however, the visceral organs are condemned.

3.3 Rinderpest (RP)

Rinderpest (RP) is an acute, viral, highly contagious disease of cattle, buffalo, and some wildlife species [19]. RP is caused by RNA virus of Paramyxoviridae family. RP is spread through air, direct contact, and fomites. Ante-mortem examination shows high fever, nasal discharge, extreme salivation, mouth erosion, decrease in appetite, depression, and bloody diarrhea. Post-mortem examination shows erotic or necrotic lesions throughout GIT and upper respiratory tract leading to the classical

"zebra-striping" in the rectum. Enlarged edematous lymph nodes and necrotic foci are also observed in the Peyer's patches. In the RP-free countries and zones, the cattle are prohibited to enter the abattoir. If the RP is diagnosed on post-mortem inspection, then carcass and visceral organs are condemned, and suitable measures should be taken as recommended by the regulatory authorities of the country. In RP, prevalent countries, if symptoms are mild, then the carcass can be conditionally approved.

3.4 Rift Valley fever (RVF)

Rift Valley fever (RVF) is a viral disease of cattle mostly seen in domesticated animals in sub-Saharan Africa. The disease is caused by the rift valley fever virus (RVFV), a member of the genus Phlebovirus. RVFV is majorly spread through biting insects and mosquitoes [20]. Humans are mostly infected through direct or indirect contact with infected organs. Ante-mortem examination in cattle shows edematous skin, discharge from the nose, weakness, diarrhea, decreased milk production, and abortion [21]. Post-mortem findings show cyanotic visible mucosa, edematous and hemorrhagic gall bladder, and spleen and peripheral lymph nodes are enlarged and edematous and may show petechiae and purple udder with invisible inflammation. The carcass of cattle affected with RVFV is condemned. The carcass of recovered animals can be conditionally approved; however, the affected visceral organs must be condemned.

3.5 Malignant catarrhal fever (MCF)

Malignant catarrhal fever (MCF) is an acute viral disease of cattle. The disease is caused by bovine herpesvirus 6 in cattle [22]. It is transmitted by close contact between cattle and wildebeest, through common water troughs. Ante-mortem examination in cattle shows high fever, lachrymation, erotic lips, tongue, gums, inappetence, and decreased milk yields. Furthermore, the cattle show photophobia linked with corneal opacity and blindness. Superficial lymph nodes might be enlarged and swollen limb joints. On post-mortem, the cattle show erosions and hemorrhages in GIT: contents may be hemorrhagic, white areas in the kidneys and enlarged lymph nodes with varying degrees in different regions of the animal [23]. Typically, "Tiger stripings" in colon region are observed. In mild disease cases, the carcasses can be conditionally approved; however, if systemic signs appear, then carcasses are condemned.

3.6 Lumpy skin disease

Lumpy skin disease is an acute viral disease of cattle. It is caused by the poxvirus. It is transmitted through blood-feeding insects, such as specific species of flies, mosquitoes, and ticks [24]. The diseased cattle show fever, nasal discharge, and hypersalivation skin eruption of different body parts. The nodular lesions are round, firm, and painful. The secondary infection can cause joint and tendon inflammation [25]. The post-mortem inspection shows ulcerative lesions of respiratory and digestive tract mucosa, edema, and nodules in the lungs. In mild disease cases, the carcasses can be conditionally approved; however, if generalized acute infection appears, then carcasses are condemned.

3.7 Rabies

Rabies is an acute lyssaviruses disease, causes encephalomyelitis. It is transmitted through infected saliva or the bite of a rabid animal [26]. It has different forms.

On ante-mortem examination, the furious form shows restlessness, aggression, paralysis, and death. Whereas, the paralytic form shows ataxia leading to paralysis of the throat and masseter muscles, hypersalivation, the inability of swallowing, and death after 48 h of laying down. On post-mortem, the cattle show inflammation of gastrointestinal mucosa. If rabies is present in the country and the animal was bitten eight days before slaughter and within 48 hours of slaughter,then the carcass can be approved after removing bitten tissues.

3.8 Bovine leukosis

Bovine leukosis in cattle is caused by the bovine leukosis virus (BLV) [27]. It is found in sporadic or enzootic forms. Between these two forms, the sporadic is observed in young, whereas the enzootic is reported in adult cattle. The infection is spread through the blood and from the dam to the calf through vertical transmission. Ante-mortem findings show weight loss, bloat, fever, tachycardia, and posterior paresis. Moreover, edema in the brisket and intermandibular region is also reported. Cutaneal nodules have also been seen in some cases. The post-mortem findings show lymph node enlargement, splenomegaly, and necrotic lesions in the heart and intestine. Furthermore, ventral edema is also reported. Carcasses are condemned for human consumption in this disease [28].

3.9 Bovine viral diarrhea (BVD)

Bovine viral diarrhea (BVD) is a cattle disease caused by the bovine viral diarrhea virus (BVDV). It is transmitted through congenital infection of the fetus [29]. This disease can lead to abortion or stillbirth. The ante-mortem findings show lethargy, fever, decreased appetite, ocular and nasal discharge, and diarrhea. On post-mortem, BVD shows erotic lesions on the nostrils, mouth, larynx, esophagus, rumen, omasum, abomasum, and caecum [30]. Cecum and colon show stripping similar to the RP. If generalized acute infection appears along with fever and emaciation, then carcasses are condemned.

3.10 Bovine spongiform encephalopathy (BSE)

Bovine spongiform encephalopathy (BSE), commonly known as "mad cow disease", is a fatal neurologic disease of cattle [31]. BSE is caused by prions, an abnormal virus-like protein. Contaminated feed is the major reason for disease spread.

Ante-mortem examination shows behavioral changes, tremors, and abnormal ear position. Hyperesthesia, nervousness, reluctance for milking, and aggression toward other animals are also reported [32]. Post-mortem findings show microscopic lesions including degenerative lesions in the cerebral cortex, medullary region, and central gray matter of the midbrain. The carcass of cattle affected with BSE is condemned.

4. Cattle-specific bacterial diseases

4.1 Tuberculosis

Bovine tuberculosis (TB), caused by the bacterium *Mycobacterium bovis*, is an infectious disease of cattle. It can also cause disease in other mammals including

humans, goats, pigs, deer, and dogs [33]. This infection is mainly spread through inhalation or ingestion of the bacteria. Contaminated water and food are also sources of infection. The ante-mortem examination shows fluctuating fever, chronic intermittent hacking cough associated with pneumonia, weakness, difficulty in breathing, loss of appetite, and emaciation. Post-mortem findings show tuberculous granuloma in the lymph nodes of the head, lungs, intestine, and carcass. Lesions also appear in the lungs, liver, spleen, and kidney. In the country where TB has been eradicated or the eradication program is ongoing, the carcasses will be condemned. In mild cases, carcasses could be conditionally approved.

4.2 Black quarter (black leg)

The black quarter also recognized as black leg is an acute infectious disease of cattle caused by *Clostridium chauvoei* [34]. It causes inflammation of the muscles, toxemia, and high mortality. It is soil-borne infection transmitted through a wound, injection needle, or ingestion (especially when there are oral abrasions). Ante-mortem findings initially show high fever, lameness, with severe depression are classical signs of black quarter disease. Animal stops eating and ruminating. Crepitating and gaseous swelling of the affected muscles of hind quarters and shoulders leading to hot and painful swelling is very characteristic. If not treated immediately, death may occur within 12–36 h due to severe toxemia. On post-mortem, skin over the swelling appears dark with oozing dark-colored offensive-smelling fluid. Crepitating swelling when cut open shows oozing of a dark red fluid with bubbles with a rancid odor. The affected muscles on palpation appear sponge-like with the presence of gas bubbles indicating necrotizing hemorrhagic myositis (due to toxin). Usually, the spleen is enlarged and hemorrhagic. The slaughtering of affected cattle is prohibited, and if the cattle have been slaughtered, then carcass and visceral organs are condemned [15].

4.3 Botulism

Botulism is caused by the toxins produced by *Clostridium botulinum*. It causes paralysis of different muscles. Decomposed flesh and bones are the sources of infection for cattle [35]. Ante-mortem examination shows flaccid muscular paralysis, disturbed vision, difficulty in chewing and swallowing, and generalized progressive paresis. On post-mortem, foreign material in the rumen or reticulum may be found. The carcasses are condemned due to human hazards.

4.4 Malignant edema

Malignant edema is caused by *Clostridium septicum* in cattle. Infection ordinarily occurs through contamination of wounds containing devitalized tissue or soil [36]. On ante-mortem examination, the cattle show anorexia, high fever, depression, weakness, muscle tremors, and lameness. Post-mortem findings show gangrenous skin in the affected area, foul putrid odor, accumulation of sero-sanguineous fluid in body cavities, and darkening of muscles. The carcasses are condemned due to human hazards.

4.5 Leptospirosis

Leptospirosis is a bacterial disease caused by Leptospira genus in cattle. Leptospirosis can be transmitted directly or indirectly between animals and through

the environment, respectively [37]. The ante-mortem examination shows fever, loss of appetite, and mastitis in mild cases; however, severely affected cattle show anemia, jaundice, pneumonia, and abortion with retained placenta. Post-mortem findings show anemia, jaundice, submucosal hemorrhage, interstitial nephritis, and septicemia. In the case of acute leptospirosis, carcasses are condemned, whereas, in the case of chronic and localized conditions, carcasses can be conditionally approved [15].

4.6 Brucellosis

Brucellosis is an infectious and contagious disease of cattle that is caused by *Brucella abortus*. It is transmitted by contaminated feed, pasture, water, milk, an aborted fetus, uterine fluid, and discharges [38]. Ante-mortem examination shows stillborn or weak calves, retained placentas, and reduced milk yield. Post-mortem examination shows an edematous fetus and placenta. Carcasses of affected cattle are approved as *Brucella abortus* remains viable only for a shorter period after slaughter. However, in acute aortic form, carcasses are condemned.

4.7 Anthrax

Anthrax is a noncontagious zoonotic disease. It is caused by *Bacillus anthracis*. Anthrax is transmitted through inhalation, ingestion, and a wound in the skin [39]. Biting flies are also a source of transmission. In per acute and acute cases, no clinical signs are reported as it causes sudden death. On post-mortem examination, the cattle show dark-colored blood discharge from natural orifices, no rigor mortis development, splenomegaly, and rapid decomposition of the carcasses. Carcasses are commended and buried almost six feet below ground with a surrounding layer of lime [15].

4.8 Hemorrhagic septicemia (HS)

Hemorrhagic septicemia (HS) is a systemic disease of cattle. It is caused by specific serotypes of *Pasteurella multocida*. It is spread by the ingestion of contaminated feedstuff. The ante-mortem examination of cattle shows high fever, salivation, difficulties in swallowing, cough, difficult breathing, and pneumonia [40]. The cattle also show edematous swelling of the throat, dewlap, and brisket region. In per acute cases, HS causes death within 8–24 h. The post-mortem findings show subcutaneous swelling and yellowish gelatinous fluid around the throat and brisket areas. Lymph nodes are enlarged hemorrhages in the organs and pneumonia [41]. If the HS is diagnosed on ante-mortem examination, then cattle are not allowed to enter or be slaughter in the abattoirs. The carcasses of HS-affected cattle are condemned.

4.9 Actinomycosis

Actinomycosis is caused by *Actinomyces bovis*. It is a chronic granulomatous disease of cattle. The causative agent is a normal inhabitant of the bovine mouth. The bacteria enter through cuts or abrasions and migrate to the bone, leading to osteomyelitis [42]. The mandible is affected more commonly than the maxilla. Ante-mortem findings show a hard, immobile, bony mass on the mandible, ulceration of cheeks and gums, and wart-like granulations outward on the head. Fever, excessive salivation, and dropping of feed from the mouth are also observed. On post-mortem examination, the

cattle show mandibular lesions (lumpy jaw). Lower part of the esophagus and anterior reticulum also show granulomatous lesions [43]. In severe cases of actinomycosis, the carcasses are condemned; however, in mild cases, carcasses are conditionally approved.

4.10 Actinobacillosis

Actinobacillosis is caused *Actinobacillus lignieresi*, a chronic disease of cattle. The causative agent is a normal inhabitant of the bovine mouth. The bacteria enter through cuts or abrasions. The ante-mortem examination shows salivation, loss of appetite, erosions in the mouth, swallowed tongue, and enlarged parotid and retropharyngeal lymph nodes. Post-mortem findings show an enlarged fibrous tongue (wooden tongue), granular lesion in the lymph nodes, and the thickening of the lower part of the esophagus and stomach wall [44]. The erosions in the mucosa of the rumen and reticulum are also reported. In severe cases of actinobacillosis, the carcasses are condemned; however, in mild cases, carcasses are conditionally approved.

4.11 Mastitis

Mastitis in cattle is caused by bacteria, fungi, and yeasts. It is spread through milk, especially through milker hands. Ante-mortem examination show variable temperature, swallowed painful udder, depression, loss of appetite, and exudate from teats [45]. Post-mortem findings show pale yellow edematous udder parenchyma and enlarged supramammary, iliac, and lumbar lymph nodes. In severe cases, if mastitis is associated with systemic changes, then carcasses are condemned. In case of localized conditions, carcasses are approved for human consumption.

4.12 Metritis

Inflammation of the uterus is termed as metritis mostly originated from bacteria. It occurs majorly due to calving problems such as retention of placenta, abortion, twin births, abnormal labor, traumatic lesions of the uterus cervix, and vagina [46]. Ante-mortem examination of cattle shows high fever, retained placenta, and reddish discharge from the vulva. The post-mortem findings show an enlarged flaccid uterus, an inflamed uterus with foul-smelling exudate, and congestion in muscles. In acute disease conditions, the carcasses are condemned, whereas in case of mild infection and carcasses lacking systemic signs may be approved.

5. Cattle-specific parasitic diseases

5.1 Lungworms

Lungworms (*Dictyocaulus viviparus*) cause verminous pneumonia in cattle. The eggs are engulfed by the host while coughing [47]. On ante-mortem examination, the cattle show high temperature, nasal discharge, labored breathing, and recumbency. Post-mortem findings show hemorrhagic inflammation of the bronchi along with froth, edema in the lungs, enlarged lymph nodes, and lungworms are also present in lungs. In mild cases, carcasses are approved, while the affected lungs are condemned. In severe cases, if lungworm infestation led to pneumonia along with emaciation and anemia, the caresses are condemned.

5.2 Fascioliasis

Fascioliasis is majorly caused by liver fluke (*Fasciola hepatica*). It is a zoonotic and public health important disease. It is spread by the ingestion of cysts by the host cattle [48]. Ante-mortem findings show emaciation, weight loss, anemia, chronic diarrhea, and swallowing in the mandibular region. Post-mortem examination shows anemic, emaciated carcasses, the presence of flukes in enlarged and thickened bike ducts, calcification of bile ducts, and blackish lymph nodes of the liver due to fluke excrement [15]. Carcasses are condemned if heavily infested along with the emaciation. If the condition is mild, then carcasses are conditionally approved.

5.3 Cysticercosis

Cysticercosis in cattle is caused by *Cysticercus bovis*. It is the cystic form of the human tapeworm *Taenia saginata*. Cattle become infested by the ingestion of ova. In human, infection occurs by eating raw or undercooked beef containing viable cisticerci [49]. Cattle may show muscle stiffness on ante-mortem examination only in heavily infested cases. Post-mortem examination shows small white lesions in the muscles and later on calcification also occurs. Carcasses and visceral organs are condemned.

5.4 Hydatid disease

Hydatid disease in cattle is caused by *Echinococcus granulosus*. This disease is also known as hydatidosis or echinococcosis. Eggs are dispersed in the environment via the feces of infected dogs [50]. Cattle become infested by the ingestion of ova. No significant ante-mortem findings are reported. On post-mortem examination, carcasses show hydatid cysts in the heart, liver, kidney, and muscle tissues including the bones. In case of edema, emaciation, and muscular involvement, carcasses are condemned. In mild cases, carcasses may be conditionally approved, however, visceral organs are condemned.

5.5 Onchocercosis

Onchocercosis in cattle is majorly caused by nematode *Onchocerca gibsoni* [51]. The midguts of the Cullicoides are the common vectors. However, the other biting flies may act as the intermediate host. The larvae are developed to the infective stage in the midguts of the Cullicoides. Cattle are infected through the biting flies. Ante-mortem examination show sub-cutaneous nodules in the brisket and buttock areas. On post-mortem examination, cattle show single or clusters of fibrous nodules in the brisket, buttock, and thigh region. The worms may be live, dead, or in the calcified form in nodules. The carcasses are approved by removing the affected parts.

6. Cattle-specific protozoal diseases

6.1 Trypanosomiasis

Trypanosomiasis in cattle is caused by Trypanosoma genus. It is transmitted mechanically by biting flies. Ante-mortem examination of cattle shows intermittent

fever, anemia, weakness, weight loss, enlarged lymph nodes, edema, and opacity of the cornea. Post-mortem examination shows edematous and emaciated carcasses, enlargement of the liver and spleen, and enlarged lymph nodes. The carcasses are condemned in acute cases, showing systemic enrollment. In mild cases, carcasses are conditionally approved; however, affected parts and visceral organs are condemned.

6.2 Theileriosis

Theileriosis in cattle is caused by a blood-borne parasite Theileria parva. It is spread through ixodid ticks of the species Rhipicephalus [52]. Ante-mortem examination of cattle shows high temperature, difficulty in breathing, nasal discharge, and swallowed lymph nodes. One-sided circling and convulsions leading to death are also reported. Post-mortem examination shows pulmonary edema, emphysema, enlarged hemorrhagic lymph nodes, enlarged liver, white spots of lymphoid aggregates in kidneys, and brownish coloration of fat. In mild cases with no systemic involvement, the carcasses and visceral organs are approved. However, in acute cases of theileriosis, showing fever and generalized lesions, the carcasses and affected organs are condemned.

6.3 Anaplasmosis

Anaplasmosis in cattle is majorly caused by a blood cell parasite *Anaplasma marginale*. It is transmitted through Boophilus tick. Whereas, the horsefly and mosquitoes are the mechanical transmitters. Ante-mortem examination of cattle show high fever, jaundice, anemia, and emaciation [53]. Post-mortem examination shows congested splenomegaly, watery blood with poor clotting ability, enlarged, icteric liver, deep orange in color, distended bile ducts, and yellow-colored carcasses. Confirmation can be done by detecting the parasite Giemsa stain. In case of acute infection, carcasses are condemned. In recovered and suspect cases, showing mild or inconclusive signs is conditionally approved.

6.4 Babesiosis

Babesiosis is a tick-born disease, and in cattle, it is caused by different protozoan of genus Babesia [54]. Ixodidae family of ticks serve as vectors in different locations. Ante-mortem examination of cattle shows high fever and dark reddish-brown urine. Post-mortem findings show enlarged liver and spleen, edematous congested lungs, anemia, jaundice, edematous and hemorrhagic lymph nodes, and pink-colored hemorrhages in cattle brain. In case of acute infection, carcasses are condemned. In mind cases, carcasses are conditionally approved.

6.5 Sarcosporidiosis

Sarcosporidiosis also termed as sarcocystosis is caused by different species of Sarcocystis genus. Cattle become infested by ingesting contaminating feed, pasture, or water that contains Sarcocystis spp. cysts. Ante-mortem examination of cattle shows fever, loss of appetite, excessive salivation, anemia, and loss of hair from tip of the tail [15]. On post-mortem examinations, cysts are invisible due to their smaller size, and cysts become associated with eosinophilic myositis. Heavily infested carcasses showing macroscopic cysts are condemned. In mild infestation, unaffected parts of the carcass are approved for human consumption.

7. Conclusion

The purpose of carcass inspection is to ensure meat quality and its suitability for human consumption. Ante-mortem and post-mortem findings are helpful to diagnose any diseased condition and to give final judgment regarding meat consumption. This chapter covered cattle-specific disease and their effect on carcass judgment and meat quality. The recommendation given in this chapter regarding carcass judgment related to cattle-specific diseases will be helpful to find out the suitability of the carcass for human consumption.

Conflict of interest

The authors declare no conflict of interest.

Author details

Muhammad Kashif Yar[1*], Mubarik Mahmood[1], Muawuz Ijaz[1], Muhammad Hayat Jaspal[2], Zayrah Rafique[3], Iftikhar Hussain Badar[2] and Kanwal Rafique[1]

1 Department of Animal Sciences, University of Veterinary and Animal Sciences, Jhang, Pakistan

2 Department of Meat Science and Technology/Faculty of Animal Production and Technology, University of Veterinary and Animal Sciences, Lahore, Pakistan

3 Department of Basic Sciences, University of Veterinary and Animal Sciences, Jhang, Pakistan

*Address all correspondence to: kashif.yar@uvas.edu.pk

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Chapter 4

Paraoxonase 1 in Cattle Health and Disease

Abdulsamed Kükürt and Volkan Gelen

Abstract

Paraoxonase is a family of enzymes with diverse biological functions. This study investigates the role and effects of the paraoxonase enzyme, particularly in relation to cattle health and disease. The findings reveal that the paraoxonase enzyme mitigates oxidative stress, regulates the immune system, preserves liver function, and exerts other biological effects in cattle. Moreover, certain genetic variations associated with the paraoxonase enzyme may be linked to health issues, such as cattle diseases. Therefore, further research aimed at comprehending the relationship between the paraoxonase enzyme and cattle health may assist in the development of novel treatment and prevention strategies in future cattle breeding and veterinary applications.

Keywords: Paraoxonase 1, cattle, oxidative stress, acute phase response, antioxidant

1. Introduction

The Paraoxonase (PON) molecule comprises three distinct subtypes of enzymes: PON1, PON2, and PON3. PON1 is the most extensively studied subtype in humans and is typically the focus of research [1, 2]. The enzyme Paraoxonase 1 (PON1) was first discovered as an organophosphate pesticide-hydrolyzing enzyme in mammalian tissues by Mazur in the 1940s [3]. In 1953, Aldridge identified it as an α-esterase enzyme due to its ability to hydrolyze diethyl p-nitrophenyl phosphate [4]. Subsequently, PON1 was classified as an "aryl dialkyl phosphatase" by the International Union of Biochemistry and Molecular Biology Enzyme Commission owing to its ability to hydrolyze an aryl-dialkyl phosphate into a dialkyl phosphate and an aryl alcohol [5]. Further investigations have revealed that PON1 also functions as a lactonase and an arylesterase [6]. Moreover, PON1 has been shown to exhibit peroxidase-like activity by reducing H_2O_2 produced under oxidative stress conditions and converting lipid hydroperoxides in oxidized high-density lipoprotein (HDL) to hydroxides [7, 8].

PON1 is considered an antioxidant enzyme and is secreted by the liver. It is responsible for hydrolyzing organophosphate pesticides and neurotoxic compounds in the body [9, 10]. Additionally, PON1 has been reported to increase macrophages associated with cholesterol (CHOL) efflux, prevent protein modification by breaking down homocysteine thiolactone, and stabilize free radicals, thereby preserving membrane integrity [11].

PON1 exhibits genetic polymorphisms, with multiple alleles present in humans. As a result, individuals with different genetic variations may exhibit varying levels of activity. These variations play a significant role in many conditions believed to be associated with PON1 and disease risk [12].

Paraoxonase is also considered a negative acute phase reactant protein, which means its levels decrease during inflammation and may be a risk factor for inflammatory and infectious diseases [13–16].

In cattle, we believe that research on paraoxonase enzyme activity is still insufficient. Therefore, the objective of this chapter is to provide an overview of the current research on paraoxonase enzyme in cattle health and disease.

2. General characteristics and structure of Paraoxonase 1

The PON1 protein consists of approximately 355 amino acids and is composed of two distinct regions: the N-terminal and the C-terminal. The N-terminal region of the protein binds a cofactor copper ion, which is essential for PON1's catalytic activity. The C-terminal region, on the other hand, aids in substrate binding [17]. The N-terminal region also contains a hydrophobic signal sequence necessary for binding the enzyme with HDL [5]. The protein contains a central tunnel that houses two Ca^{+2} ions, with one ion necessary for catalytic activity and the other for protein stability. This central tunnel forms the active site of the enzyme. The hydrophobic nature of PON1's substrate is attributed to the hydrophobicity of the enzyme's active site. Among the critical structural features of PON1 are active site amino acids, such as cysteine and histidine, that confer PON1 with the ability to hydrolyze toxic compounds, including organophosphates, which are responsible for PON1's cellular anti-oxidative damage-reducing properties [8, 18].

3. Association of Paraoxonase 1 with oxidative stress

Oxidative stress arises from an imbalance between the generation of reactive oxygen species (ROS), including free radicals, and the body's capacity to detoxify and neutralize them. ROS are highly reactive molecules that can harm cells, proteins, and DNA. Accumulation of ROS due to inefficient neutralization can lead to oxidative stress, resulting in cellular damage and contributing to the development of various diseases, such as cancer, cardiovascular disease, and neurodegenerative disorders. Factors contributing to oxidative stress include environmental pollutants, smoking, alcohol consumption, poor diet, and specific medications [19–23].

Antioxidants are molecules that can prevent or slow down oxidative damage to cells caused by free radicals. Free radicals are unstable molecules that can damage cells and contribute to the development of various diseases, including cancer, cardiovascular diseases, and neurodegenerative disorders. Antioxidants neutralize free radicals by donating an electron, thereby reducing their potential to cause harm. The consumption of antioxidant-rich foods and supplements has been associated with numerous health benefits. Antioxidants can help mitigate ROS and protect against oxidative stress [24–28].

The PON1 enzyme provides protective effects against cellular oxidative stress by reducing the damage induced by free radicals and other oxidant molecules. Specifically, PON1 hydrolyzes toxic compounds, such as organophosphates, thereby reducing oxidative stress and safeguarding cells [9, 29]. Moreover, PON1 is known to

bind to high-density lipoprotein (HDL) in the bloodstream. This binding decreases the risk of atherosclerosis by preventing oxidation of low-density lipoprotein (LDL) or "bad" cholesterol. Decreased PON1 activity can lead to an increase in oxidative stress and an increased risk of atherosclerosis. The antioxidant activity of PON1 is derived from the free sulfhydryl group located on cysteine-284 [30]. It has been noted that the hydrolytic function of PON1 undergoes some degree of inactivation during the prevention of LDL oxidation [7].

PON1 also reduces cholesterol ester hydroperoxides associated with HDL more efficiently than those associated with LDL, likely due to the predominance of PON1 associated with HDL in the body. Thus, PON1 protects HDL against oxidative stress, rather than LDL [31]. The serum PON1 enzyme is found in association with HDL in plasma, and it prevents plasma lipoprotein oxidation [32]. PON1 enzyme is associated with apolipoprotein A1 and apolipoprotein J (clusterin) proteins of HDL [33]. PON1 binds to phospholipids and lipoproteins through the C-terminal hydrophobic termination region [34]. There is a close relationship between circulating PON1 and HDL, and PON1 can only interact with its endogenous substrate and exhibit its biological properties after being released by HDL. In return, PON1 protects HDL from oxidation [35].

PON1 is believed to play a significant role in protecting against oxidative stress by hydrolyzing both H_2O_2 and lipid peroxides, such as cholesteryl linoleate hydroperoxides [36]. As the O-P type ester bond found in paraoxon could also be present in lipoproteins associated with phospholipid peroxides and cholesteryl ester peroxides, the phosphotriesterase property of PON1 may contribute to the protection against oxidative stress [37]. In addition to its protective role against H_2O_2-induced lipid peroxidation, it has been found that PON1 also prevents the accumulation of peroxynitrite ($ONOO^-$) and oxidized phospholipids [38].

4. Paraoxonase-1 enzyme activity in some cattle diseases and metabolic conditions

Paraoxonase, an endogenous antioxidant produced by liver cells [39], plays a crucial role in protecting lipids, particularly HDL and LDL, from oxidative stress [37]. Paraoxonase is also considered a negative acute phase reactant protein [16]. In cattle with paratuberculosis, knowing the changes in acute-phase proteins will be beneficial for diagnosing and controlling the disease [40]. In a study by Akyüz et al. [41], a study was conducted on cows with paratuberculosis and found that PON1 activity was lower in the diseased animals compared to the control group, likely due to liver dysfunction and hepatocyte destruction. The authors suggested that PON1 activity could be used as a new biomarker for this infection. Similarly, in cows with clinical mastitis, Deveci et al. [42] observed a decrease in PON1 activity and HDL levels, and suggested that PON1 activity could be an antioxidant mediator in mastitis-induced inflammation. In addition, PON1 has been proposed as a potential marker for the detection of subclinical mastitis in dairy cows [43].

In lactating cows, PON1 activity has been found to be significantly higher in heifers during lactation compared to lactating cows [44]. However, the PON1 activity was found to be lower in postpartum and dry periods compared to lactating cows [45, 46], which was suggested to be related to changes in the lipid profile. Moreover, the observed low-serum PON1 activity at the end of pregnancy and early postpartum period in dairy cows was suggested to indicate an oxidative stress/antioxidant imbalance affected by reproductive stress and metabolic adaptation during the transition

period [47]. PON1 activity was also found to increase toward the end of the colostrum period in transition period cattle [48].

PON1 activity has also been investigated in relation to fertility in dairy cows. In a study investigating the relationship between pregnancy rates and PON1 activity in dairy cows following synchronization using an intravaginal device protocol for progesterone secretion, the application of an intravaginal progesterone-releasing device was found to affect serum PON1 activity. The study showed a significant difference in PON activity at day 5 of progesterone releasing intravaginal device (PRID) application, which was suggested to be an indicator of fertility [49].

Researchers have also evaluated PON1 activity as a biomarker for fatty liver in dairy cows. They found that serum PON1 activity was lower in cows suffering from hepatic lipidosis and suggested that the addition of serum PON1 activity measurement to the biochemical profile could improve the diagnosis of fatty liver in dairy cows [50]. Future studies should focus on the diagnostic validation of serum PON1 testing for early prediction of fatty liver development and its correlation with hepatic triglyceride content in both healthy and diseased dairy cows. Additionally, the focus on the diagnostic validation of serum PON1 testing for early prediction of fatty liver development in dairy farms could lead to significant clinical impact and greater profitability in the dairy industry.

5. Conclusion

In conclusion, PON1 is an enzyme that plays a crucial role in reducing oxidative stress and safeguarding cells by hydrolyzing toxic compounds, such as organophosphates, in the body. PON1 is also known to bind with HDL, which reduces the risk of atherosclerosis by preventing the oxidation of LDL. Genetic variations in PON1 activity can affect an individual's risk for various diseases, and decreased PON1 activity may increase oxidative stress and the risk of atherosclerosis. PON1 activity has been investigated in various contexts in cattle, including as a biomarker for infectious diseases and inflammation, fertility, and fatty liver. The findings suggest that PON1 activity could serve as a useful diagnostic tool for detecting and monitoring health issues in cattle. In cattle, the research on PON1 enzyme activity is limited, and further investigation is necessary to understand its role in cattle health and disease.

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Author details

Abdulsamed Kükürt[1*] and Volkan Gelen[2]

1 Faculty of Veterinary Medicine, Department of Biochemistry, Kafkas University, Kars, Türkiye

2 Faculty of Veterinary Medicine, Department of Physiology, Kafkas University, Kars, Türkiye

*Address all correspondence to: samedkukurt@gmail.com

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Chapter 5

Clinical Significance of Some Acute Phase Proteins in Cattle

Kadir Bozukluhan and Oguz Merhan

Abstract

Acute phase proteins are proteins synthesized by the liver in response to the acute phase response. While these proteins are insignificant in healthy animals, their concentrations increase rapidly during infection, inflammation, or tissue damage and are used as an indicator of inflammation. Since the blood concentrations and importance levels of these clinically important proteins differ according to the animal species, they are evaluated separately for each animal species. Most of the acute phase proteins have been studied in detail in the field of human medicine and are routinely used in the diagnosis and prognosis of diseases. In the field of veterinary medicine, it has not been used sufficiently. In this book chapter, we will provide up-to-date information about acute phase proteins that are important for cattle, as well as explain that acute phase proteins can be used in the early diagnosis of diseases, in the differentiation of viral and bacterial infections, in guiding the treatment of sick animals and in determining their prognosis.

Keywords: cattle, ceruloplasmin, clinical significance, haptoglobin, serum amyloid A

1. Introduction

Acute phase response (APR) is a response following inflammation, tissue injury, infection, neoplastic growth, or immunological disorders, and this response is characterized by metabolic and systemic changes [1]. APR can be briefly expressed as changes in the concentrations of many plasma proteins that occur in relation to the response of the organism [2]. The function of APR is to protect organs from further injury, to eliminate infectious agents, to clear harmful molecules and residues for the organism, and to restore homeostasis by activating the repair process necessary for the organism to return to its normal function [3]. APR emerges as a complex reaction initiated by inflammatory mediators in the area where tissue destruction occurs and is characterized by local and systemic changes [2, 4]. Increase in capillary permeability, leukocyte migration to the inflammation site, and release of various chemical mediators take place among the local reactions occurring during APR [2]. Among the systemic reactions created by APR, there are changes in the level of acute phase proteins (APP) formed by mediators. Systemic reactions are initiated by mediators such as cytokines, glucocorticoids, and growth factors. Cytokines, which act as intracellular and intercellular signaling molecules and are soluble biological mediators, are in peptide or glycoprotein structure [5–8]. Macrophages and neutrophils arriving

at the inflammation site together with endothelial cells secrete pro-inflammatory cytokines (Interleukin "IL"-6, IL-1β, tumor necrosis factor "TNF"-α, interferon γ, IL-8, and macrophage inhibitor protein-1) [9]. While the production of APPs is accelerated by many cytokines (especially IL-6), it is inhibited by insulin and okadaic acid [10]. Cytokines, which have many different effects such as gene expression, metabolic process, and regulation of oxidation-reduction potential in the cell and ion flow in the cell membrane [9], generally stimulate APP synthesis and corticosteroids regulate cytokine activity. Pro-inflammatory cytokines such as IL-6 and IL-1 activate fibroblast and endothelial cells in the local inflammation area and allow cytokines to be secreted again. Thus, APP is synthesized from the liver as a result of the systemic inflammatory response initiated by the cytokines that enter the circulation [3, 7]. In addition to giving information about the formation of the inflammatory process and being a good marker in the diagnosis of the disease, the use of fast and sensitive measurement methods has made the measurement of APP popular [3, 11].

2. Acute phase proteins

Acute phase proteins are known as proteins whose concentrations change in the blood in cases of inflammation, infection, tissue damage, neoplastic developments, etc. [2, 12]. APPs are species specific and their diagnostic importance varies according to animal species [13, 14]. APPs whose levels change in the case of infection and inflammation are accepted as a nonspecific indicator of the tissue damage [3, 15]. In general, APPs, which can directly destroy inflammatory agents, also contribute to the tissue healing and regeneration. In addition, they have functions such as restoring useful molecules, cleaning residues, transporting cholesterol, preventing oxidation, and activating complement [12, 16].

3. Some acute phase proteins important for cattle

Haptoglobin with positive APP, serum amyloid A (SAA), ceruloplasmin, α1-acid glycoprotein, and albumin with negative APP take place among APPs that are important for cattle [2, 12, 17].

Haptoglobin: Haptoglobin, with a molecular weight of about 125 kDa, got its name from its ability to form a stable complex (haptein = binding) with hemoglobin [18]. In cattle, haptoglobin is found together with albumin as a polymer with a molecular weight of 1000–2000 kDa. It is captured by the reticuloendothelial system when bound with hemoglobin [2, 3, 19]. Haptoglobin is absent or very low (<0.1 mg/mL) in the serum of healthy cattle [20]. As soon as the immune system is stimulated for various reasons, its level in the serum increases up to 100 times [13, 21]. Haptoglobin concentration, which starts to increase within 24 hours after the onset of the inflammation, peaks on the 3–5th day and then decreases and reduces to its normal limits on the 8–21st day [20]. It has been reported that the prognosis is good when the level of haptoglobin used to determine the prognosis in cattle is between 0.1 and 1 g/L, and if this level is >1 g/L, the prognosis is poor and it is necessary to start treatment. In addition, the haptoglobin level can be used to determine the severity of the disease, and a level of 0.2–0.4 g/L is defined as mild infection, while a level of 1–2 g/L is defined as severe infection [20, 22].

Although haptoglobin has many functions, its main function is to prevent iron loss by forming stable complexes with free hemoglobin in the blood [23]. Haptoglobin

binds hemoglobin and the formed haptoglobin hemoglobin complex is transported to the liver and metabolized. The binding of haptoglobin to hemoglobin is very important in terms of the anti-inflammatory property of haptoglobin [24]. However, haptoglobin hydrolyzes the peroxides released from neutrophils in the inflamed region and renders them harmless. It has been reported that haptoglobin, which acts as an immunomodulator in the regulation of lipid metabolism and lymphocyte functions, will be able to be used to monitor the immune functions of cattle [14]. Although haptoglobin is an important APP studied in many species, its serum concentration can be also affected by factors other than APR. For example, in cases where the level of free hemoglobin in the circulation increases, even if haptoglobin synthesis is stimulated by inflammation, its circulating level will be seen as low because hemoglobin binds the existing haptoglobin. Therefore, in cases where the concentration of free hemoglobin in the serum increases, the amount of haptoglobin decreases. The best example of this is the absence of haptoglobin from circulation in acute hemolysis in cattle babesiosis [2].

Measurement of APP levels gives accurate and clear results in the diagnosis of inflammatory diseases in ruminants compared with hematological findings. It has been reported that it can be a helpful parameter in the diagnosis in the diseases such as neonatal diarrhea [25–27], omphalitis [28, 29], pneumonia [30], ascaridiosis [31], besnoitiosis [32], *Trypanosoma evansi* [33], anaplasmosis [34–36], hypodermosis [37], in the bacterial and viral diseases such as brucellosis [38], tuberculosis [39], reticuloperitonitis traumatica [40, 41], foot-and-mouth disease [42], as well as in fatty liver [43] including dystocia [44] and subclinical ketosis (**Table 1**) [45, 46]. In addition, in another study conducted in cattle with endometritis, it has been reported that haptoglobin and TNF-α levels decreased significantly after the treatment compared to the pre-treatment values [47] and that progesterone-releasing intravaginal device (PRID) administration increases haptoglobin and ceruloplasmin levels, but decreases albumin levels in another study conducted by Kuru et al. [48] in cattle.

Serum amyloid A: SAA has a molecular weight of approximately 180 kDa and exists in a complex with lipoprotein. Although SAA is synthesized by the liver with the effect of SAA-stimulating factor during inflammation, it is also synthesized locally in the udder ("milk SAA," MAA) outside the liver [2, 49]. The serum concentration of SAA, which is α globulin, is reported as <24 μg/mL [14] in healthy cattle. SAA, which rises within 2–5 hours after inflammatory stimulation and reaches a peak level within 24 hours, can be used for earlier diagnosis of acute cases [12]. SAA is used to determine the prevalence as well as the activity of inflammatory events, to monitor the course of the diseases and to evaluate the success of the treatment applied [50]. The functions of SAA include transport of cholesterol to hepatocytes, inhibition of oxidative degradation of neutrophil granulocytes, stimulation of calcium mobilization by monocytes, endotoxin detoxification, inhibition of lymphocyte and endothelial cell proliferation, prevention of platelet aggregation, and adhesion of T lymphocytes to extracellular matrix proteins [2, 13]. It has been reported that determining the haptoglobin/SAA ratio will be able to be also used in the differential diagnosis of acute and chronic cases [12]. SAA, one of the important APPs in cattle, has been reported to increase in nonfed for more than 3 days [51] in the infections such as foot-and-mouth disease [42], coryza gangrenosa bovum [52], hypomagnesemic tetany [53], enzootic bovine leukosis [54], subclinical ketosis [46], postpartum [55], mastitis [56–58], subclinical endometritis [59], and pneumonia (**Table 1**) [60, 61]. In addition, it has been reported that it increases in relation to the severity of clinical symptoms in viral respiratory system diseases [2]. It has been reported that there was no significant difference in the levels of APPs between double-infected animals and single-infected

Diseases	APP investigated	Findings of the study
Neonatal diarrhea Hypodermosis Tuberculosis	Haptoglobin, albumin	Infected animals had higher concentrations of haptoglobin, and the level of albumin was lower.
Pneumonia Foot-and-mouth disease	Haptoglobin, SAA, albumin	Infected animals had higher concentrations of haptoglobin, SAA; the level of albumin was lower.
Omphalitis, Ascaridiosis, Besnoitiosis, *Trypanosoma evansi*, Anaplasmosis, Brucellosis, Fatty liver Dystocia	Haptoglobin	Haptoglobin was higher.
Reticuloperitonitis traumatica	Haptoglobin, Ceruloplasmin, α1-Acid glycoprotein	Haptoglobin, ceruloplasmin, and α1-acid glycoprotein levels were higher in diseased animals.
Subclinical ketosis	Haptoglobin, SAA	Haptoglobin and SAA levels were higher in diseased animals.
Nonfed for more than 3 days, Coryza gangrenosa bovum, Hypomagnesemic tetany, Enzootic bovine leukosis, postpartum	SAA	SAA was higher.
Mastitis, Endometritis	SAA, Ceruloplasmin	SAA and ceruloplasmin levels were higher in diseased animals.
Hepatic abscess and leukosis, *Pasteurella haemolytica*, digestive system disease	α1-Acid glycoprotein	α1-Acid glycoprotein was higher.

Table 1.
A brief summary of APPs-related studies on cattle.

animals in a study conducted in dual- and single-infected cattle [62]. In another study conducted in cattle with bovine respiratory disease complex, it has been reported that haptoglobin and SAA levels increased compared to healthy animals, and the level of APPs decreased with the treatment [63].

Ceruloplasmin: Ceruloplasmin, which consists of a single polypeptide chain, is a copper-binding α-2 globulin. The functions of ceruloplasmin is (i) lipid peroxidation, (ii) oxidation of toxic ferrous iron to nontoxic ferric form, (iii) obtainment of increasing immune function by acting on various enzyme levels, (iv) mediation of copper transporting to enzymes such as lysyl oxidase and copper-zinc superoxide dismutase involved in tissue repair, (v) role in the antioxidant system, and (vi) regulation of phagocytosis and antimicrobial activity [13, 64, 65].

It has been reported that ceruloplasmin is very useful in monitoring the inflammatory process in cattle [66]. The studies conducted have reported that APP levels increase in cattle with reticuloperitonitis traumatica [41], endometritis [67], and subclinical mastitis (**Table 1**) [68]. In addition, it has been reported that the level of APPs increases in cattle infected with foot-and-mouth disease and can be used in the diagnosis of the disease [42].

α1-Acid glycoprotein: α1-Acid glycoprotein is a sialoprotein synthesized from hepatocytes, containing 180 amino acids and released at a molecular weight of

41 kDa [69]. This protein has two important functions: drug binding and immunomodulation. α1-Acid glycoprotein, a natural anti-inflammatory agent, increases IL-1 receptor antagonist release by macrophages by inhibiting neutrophil activation. It also inhibits lymphocyte proliferation and natural killer cell activity [2, 13]. When the albumin concentration formed during APR decreases, α1-acid glycoprotein, which has good drug binding properties, helps to maintain the total drug-binding level [13]. α1-Acid glycoprotein, whose concentration in the blood increases moderately and slowly [2], increases in chronic cases rather than acute inflammation [18]. It has been reported that α1-acid glycoprotein, which is of moderate importance for cattle, will be able to be used especially in monitoring the inflammatory process [12]. The studies conducted have reported that its concentration increased in cattle with hepatic abscess and leukosis [12, 20] in traumatic pericarditis [40], *Pasteurella haemolytica* [12], and digestive system disease (**Table 1**) [70].

Albumin: Cattle albumin, a negative APP, is synthesized by the liver and its molecular weight is 67 kDa and consists of 583 amino acids [71, 72]. Albumin is a very important protein that maintains and stabilizes the plasma oncotic pressure. Because it is a small molecule, its extravascular concentration changes are an important indicator of membrane integrity [73, 74]. In addition, the decrease in blood concentration due to the fact that it is produced only by the liver is accepted as an important finding indicating liver failure [75]. Binding and transport, acting as a source for endogenous amino acids, and maintaining plasma pressure take place among its main biological functions. It is reported that its concentration decreases in liver diseases, anorexia during APR, kidney and intestinal diseases, and malabsorption syndrome [8, 76]. It has been reported in the studies conducted that albumin levels decrease in neonatal diarrhea [26], pneumonia [30], hypodermosis [37], tuberculosis [39], and foot-and-mouth disease (**Table 1**) [42].

4. Conclusion

Acute phase proteins, which are nonspecific markers synthesized by the liver as a result of APR in cattle, are very useful in terms of diagnosis and monitoring of diseases, as well as determining the prognosis of patients. In particular, the measurement of APPs is important in terms of distinguishing bacterial or viral infection and guiding the treatment to be applied. When used for this purpose, it strengthens the diagnosis and provides more accurate information in determining the prognosis of sick animals.

Author details

Kadir Bozukluhan[1*] and Oguz Merhan[2]

1 Kars School of Higher Vocational Education, Kafkas University, Kars, Turkey

2 Faculty of Veterinary, Department of Biochemistry, Kafkas University, Kars, Turkey

*Address all correspondence to: kbozukluhan@hotmail.com

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Section 2

Breeding and Genetics

Chapter 6

The Focus on Core Genetic Factors That Regulate Hepatic Injury in Cattle Seems to Be Important for the Dairy Sector's Long-Term Development

Avishek Mandal

Abstract

The cattle during the perinatal period, as well as malnutrition, generate oxidative stress which leads to high culling rates of calves after calving across the world. Although metabolic diseases have such a negative impact on the welfare and economic value of dairy cattle, that becomes a serious industrial concern across the world. According to research, genetic factors have a role or controlling fat deposition in the liver by influencing the biological processes of hepatic lipid metabolism, insulin resistance, gluconeogenesis, oxidative stress, endoplasmic reticulum stress, and inflammation, all of which contribute to hepatic damage. This review focuses on the critical regulatory mechanisms of VEGF, mTOR/AKT/p53, TNF-alpha, Nf-kb, interleukin, and antioxidants that regulate lipid peroxidation in the liver via direct or indirect pathways, suggesting that they could be a potential critical therapeutic target for hepatic disease.

Keywords: cattle liver, inflammation of the liver, gene expression, antioxidant, cytokine

1. Introduction

The "oxygen paradox," which happens when free radicals (RL) are produced during mitochondrial respiration, is supported by a huge body of research that shows that, despite the necessity of oxygen for life, it also has a damaging effect on the body [1]. Now it is interesting to learn what changes oxidation conditions in cattle or bovine liver. Since oxidative stress is the root cause of several illnesses in cattle, such as sepsis, mastitis, enteritis, pneumonia, and respiratory and joint issues, its effects on food are well-known, but they are also, gradually, recognized to have impacts on the organism "in vivo" [2]. Numerous studies have demonstrated the significance of providing antioxidants for animal nutrition and their connection to oxidative stress, taking into consideration the significance at each stage [3, 4]. Consequently, we can state that the

antioxidant impact will not only improve the health of the animals but also raise the quality of the finished product (meat and milk). The large amount of non-esterified fatty acids absorbed by the liver exceeds its ability for oxidation and, as a result, encourages liver-related illnesses including fatty liver and ketosis. Additionally, early breastfeeding cows' livers experience metabolic stress due to high rates of hepatic gluconeogenesis, which produces glucose for lactose in the mammary gland [5, 6]. In addition to this metabolic stress, early-lactating cows experience a variety of inflammatory challenges, including microbial components (lipopolysaccharides, or LPS), pro-inflammatory cytokines (tumor necrosis factor a (TNF-α), interleukin (IL)-1b, and IL-6), and reactive oxygen species (ROS), as a result of infectious diseases like mastitis and endometritis, as well as subacute [7]. As a result, transition dairy cows experience a state similar to inflammation, which is demonstrated by the production of an acute phase response (APR).The production of positive acute phase proteins (APPs), such as serum amyloid A (SAA), haptoglobin (HP), or C-reactive protein (CRP), which compete with the production of negative APPs, or essential liver proteins, such as albumins, enzymes, lipoproteins, transferring or carriers of vitamins (such as retinol-binding protein), and hormones, is a hallmark of the APR [8]. Thus, the creation of an inflammatory process in the liver exacerbates the biologically existing metabolic load in the liver of early nursing dairy cows, which impairs liver function. Decreased milk production and lower reproductive efficiency in dairy cows are both linked to low blood levels of negative APPs, which are a sign of a severe inflammatory reaction in the liver. Additionally, it has been noted that low-level intravenous TNF-alpha injection causes triacylglycerol build-up and hepatic inflammation in dairy cows [9]. In early lactation, cows with a low "liver functioning index" (LFI) have a significant inflammatory response that is characterized by an obvious increase in positive APPs, a notable drop in negative APPs, poor immunological function, and increased clinical issues [10]. Alternatively, cows with a high LFI display a reduced inflammatory response, better liver function, a slower increase in positive APPs, a slower decline in negative APPs, and fewer clinical issues during this phase [11]. This suggests that these cows have a greater ability to handle the inflammatory challenges that arise during the periparturient phase and are less likely to develop liver-related diseases. There is a lack of knowledge on the molecular underpinnings of liver-related disorders and the variations in susceptibility that exist across individuals. A better understanding of the molecular mechanisms underlying liver-associated diseases in transition dairy cows, however, may help to develop ways to avoid the occurrence of liver-associated disorders and increase production in dairy cows given that the occurrence of liver-associated diseases in dairy cows is critical because it impairs the metabolic function of the liver, overall health status, and productive and reproductive performance.

2. Pathogenesis liver disease in cattle

The build-up of excessive levels of free fatty acids (FFA) in blood or triglycerides (TAG) deposited in the liver are the main contributors to the pathogenesis of fatty liver in newborn dairy cows. In animals, the liver, which is an essential organ, controls the metabolic balance of protein, fat, and carbohydrates. Dairy cows' food consumption continues to decline after birthing, but their lactation gradually increases. As a result, the cow's body might quickly experience an inadequate supply of sugar due to the absorption of lactose, which encourages the liver to mobilize fat. The liver serves

as the primary location for the metabolism of both substances and energy [12]. A negative nutritional balance is improved by the rising fat mobilization, which also encourages gluconeogenesis, raises blood sugar levels, and increases blood sugar concentration. The liver's production of non-esterified fatty acids (NEFA), which are partially re-esterified to create triglycerides (TAG), a kind of very-low-density lipoprotein (VLDL) that is seldom ever transported beyond the liver, increases dramatically as a result of the increased fat mobilization. Because dairy cattle lack esterase, TAG accumulates abundantly, making them more susceptible to fatty liver disease [13, 14]. Non-alcoholic fatty liver disease (NAFLD) in people is characterized by aberrant lipid build-up in the liver, raised fasting aminotransferase (AST/ALT), and/or triglycerides (TAG) levels, increased plasma insulin and fatty acid concentration, and metabolic disorder syndromes [15]. Histological evidence of hepatic inflammation brought on by acute inflammation and subacute inflammation is also one of the most significant risk factors. Dairy cows with fatty liver disease are a classic animal model for NAFLD, useful for illuminating its pathology and etiology [16].
A "two-hit" idea has been put out by researchers recently to explain the pathogenic processes of NAFLD. (1) Insulin resistance was the "first hit's" cause (IR). In addition to causing hyperinsulinemia, IR can intensify the lipolysis of nearby tissues. Adipose tissue lipolysis causes the liver's production of TAG and FFA to rise [17, 18]. The FFA is harmful to hepatocellular function, increasing cell membrane permeability and impairing mitochondrial activity by inhibiting associated enzymes [19]. The imbalance between the coexisting oxidation and anti-oxidation processes in the liver was what led to the "second hit." Reactive oxygen species (ROS) are produced persistently as a result of increased lipid peroxidation. Other new or additional variables, such as inflammatory cytokines, adipokines, endotoxins, and mitochondrial inactivation, might boost lipid peroxidation for a second blow to the liver in addition to the pre-existing components associated with the increased oxygen stress. The second hit will eventually result in the advancement of NASH (non-alcoholic steatohepatitis), which promotes oxidative stress, inflammation, cell death, and fibrosis beyond hepatic steatosis [20]. Particularly, the inflammation inhibits lipase activity, prevents the transit of lipids and/or lipoproteins, and results in lipid build-up, which is negatively connected with lipolysis and positively correlated with liver damage [21]. Alternatively, it causes cell apoptosis, IR, and lipid peroxidation, exacerbating the pathophysiology of NAFLD. (3) Hepatocyte cell death and irreversible cell repair constitute a "third hit," in fact. (4) In addition, endoplasmic reticulum (ER) stress is another significant "hit" in the pathophysiology of NAFLD. Obesity and diabetes, two metabolic illnesses, can result in ER stress, which impairs the physiological processes of liver cells by causing an accumulation of improperly folded proteins (unfolded protein response, UPR) [22]. It is important to note that ER stress can cause SREBP (sterol-regulatory element binding protein) to become active. This promotes the transcription of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), which leads to an increase in the production of TAG and fatty acids in the liver [23]. Furthermore, the production of ROS by liver cells under oxidative stress can cause ER stress, which can result in improper protein folding and/or protein modification. Oxidative stress can also be brought on by ER stress. Through many mechanisms, the biological processes of ER stress and oxidative stress interact with one another, causing IR and exacerbating NAFLD. The pathophysiology of NAFLD is largely unknown, though [24, 25]. It was believed that the key route and/or the primary risk factors implicated in the etiology of NAFLD are abnormalities in lipid and lipoprotein metabolism coupled with chronic inflammation and oxidative stress. The prevalence of fatty liver is widely thought to be linked

to biological processes such as disordered glycometabolism, oxidative stress, and intracellular inflammatory response in addition to being directly tied to insulin resistance and fat metabolism issue. Additionally, these processes are connected to and/or coordinated with one another, which accelerates the development of NAFLD [26, 27].

NAFLD's pathophysiology is largely unknown, though. It was believed that the key route and/or the primary risk factors implicated in the etiology of NAFLD are abnormalities in lipid and lipoprotein metabolism coupled with chronic inflammation and oxidative stress. Additionally, these processes are connected to and/or coordinated with one another, which quickens the development of NAFLD. The pathophysiology of NAFLD is influenced by a wide range of variables. In the hepatic lipid metabolism, lipid transport, and secretion, for instance, PPAR (peroxisome proliferator-activated receptor) and/or PPAR, microsomal triglyceride transport protein (MTP), and apolipoprotein (apo B) play crucial roles [28–30]. Tumor necrosis factor, leptin, and adiponectin are examples of adipocytokines. Cytokines include interleukin-6 (IL-6), glucagon-like peptide-1 (GLP-1), fibroblast growth factor 19 (FGF-19), and fibroblast growth factor 21 (FGF-21), growth hormone-releasing hormone (GHRH), and others [31–33]. Toll-like receptors (TLRs) also play a role in insulin resistance. It has been suggested that microRNAs (such as mir-107 and miR-103) control insulin resistance [34–36]. The antagonist against microRNA-103/107, RG-125 (also known as AZD4076), just started a phase I clinical trial to treat NASH (non-alcoholic steatohepatitis) [37]. As a result, aberrant hepatic lipid metabolism, gluconeogenesis, oxidative stress, and inflammation are frequently linked to the etiology of NAFLD. These biological processes' causal connections and underlying molecular mechanisms are yet unknown. However, it would be beneficial to understand the molecular etiology of NAFLD if some significant regulatory factors or genes that control all these biological processes were discovered.

3. Vascular endothelial growth factor (VEGF)

Native VEGF is a homodimeric glycoprotein of 45 kDa that may bind to heparin and stimulate the proliferation of vascular endothelial cells generated from arteries, veins, and lymphatics [38, 39]. It is expressed by a single gene. Even though VEGF primarily targets endothelial cells, studies have shown that several non-endothelial cell types, such as retinal pigment epithelial cells, pancreatic duct cells, Schwann cells, and maybe placental cell functions, are also subject to mitogenic effects. Five distinct VEGF isoforms, with respective amino acid compositions of 120, 145, 165, 188, and 205, are produced [40] as a result of alternative exon splicing. VEGFR-1/Flt-1, or Fms-like tyrosine kinase 1, and VEGFR-2/KDR, or kinase insert domain-containing region, are the two tyrosine kinase receptors that mediate the biological functions of VEGF. Both VEGFR-1 and VEGFR-2 have a single transmembrane region, seven Ig-like structures in the extracellular domain, and a tyrosine kinase sequence that is broken by a kinase-insert domain [41, 42]. Another RTK in the same family, VEGFR-3 or Flt-4, has affinities for VEGF-C and VEGF-D. In addition to RTKs, VEGF also interacts with the neuropilin family of coreceptors [43]. The two different domains of the VEGF molecule, which are found on the opposing terminal of the VEGF monomer, allow VEGF to interact with its receptors, Flt-1 and KDR. While the 120, 145, 165, and 188 isoforms of VEGF activate KDR, VEGF165 and VEGF188 activate Flt-1 [40]. The VEGF system was found in the uterine epithelium, trophoblast, vascular tissue, and uterine glands of placentomes [44]. Bovine VEGF

may have the following traditional roles in angiogenesis and vascular permeability, as well as chemotactic activity in endothelial capillaries, autocrine influence on the migration of giant trophoblastic cells, which promotes maternal-fetal interchange, and modulatory action in trophoblastic function, specifically in steroidogenesis [45–47]. These functions are all suggested by the presence of the VEGF system in the maternal-fetal interface and the vascular system. The improvement of reproductive function and productive efficiency is crucial while growing dairy and meat cattle. Numerous studies have shown that cows, especially those with high milk output, gradually exhibit a rise in reproductive issues, which are reportedly caused by several factors, including poor energy balance and unequal gene expression. In addition to facilitating the transmission of physiological information between the mother and the fetus, the placenta produces and secretes steroid hormones, such as progesterone and estrogens, which are in charge of optimizing the environment for fetal growth. Therefore, the success of gestation depends on its efficient operation. The location of these growth factors and their corresponding receptors in non-endothelial cells, however, suggests that they are involved in other physiological processes, such as the stimulation of hormone synthesis in steroidogenic tissues. NAFLD has been studied using a variety of rat models, each of which mimics one or more characteristics of human NAFLD, including steatosis, NASH, fibrosis, and HCC [48]. Numerous studies have documented how angiogenesis manifests in various models. First, it was demonstrated that mice who were given a high-fat diet (HFD) had higher levels of VEGFR-2 expression and CD31 expression, the most widely used marker of endothelial cells, in their livers [49]. In the livers of rats given a CDAA diet and mice fed an MCD diet, and cattle fed a high-fat artificial diet can cause an increase in VEGF protein was observed. Interestingly, VEGF mRNA levels remained the same in the latter scenario, pointing to posttranscriptional regulatory mechanisms [48]. The global vasculature of the cattle liver with NAFLD was examined using specific imaging methods. NAFLD was linked to an international alteration of the hepatic vascular architecture, which included not only an increase in the number of vessels but also in a visibly different phenotype of vessels, which displayed an enlarged diameter and a disrupted organization, according to research using scanned electronic microscopy of vascular corrosion casts of the liver [50].

4. Practices for consuming more antioxidants

Antioxidants may be produced by the body, obtained through food, or given orally. Some vitamins, such as vitamin K, may be produced by the ruminal and intestinal flora while vitamin D can be produced by UV radiation on the skin in ruminants [51]. Several natural feed ingredients are also high in antioxidants, such as vitamin E or precursors to vitamin A. But, due to the wide range in vitamin concentrations in feeds and exposure to sunshine, depending only on these naturally occurring quantities might put the animals in danger of deficient disorders. Additionally, many dairy farms confine their animals indoors, where they have little exposure to sunlight and fresh fodder and the majority of natural vitamins quickly deteriorate after ensilage. As a result, these animals need to be supplemented with vitamins and trace elements, albeit the needs of grazing cattle may be different from those of cattle-fed preserved forages. Additionally, it is advised to administer an additional supplementation during times of increased need, like right before calving. The addition of vitamins and minerals to the animals' diets is arguably the approach

to antioxidant supplementation that is utilized the most frequently in industrial dairy farms, particularly when premixes are added to the overall mixed ration. The injection of vitamins and trace minerals to these animals, however, facilitates the supplementation without necessitating the creation of a specific management group of cows during this period because the needs for antioxidants are increased in moments of augmented metabolisms, such as the transition period, in farms with several animals not large enough to practically implement a specific diet for similar dry cows [52]. Numerous solutions, either for individual vitamins and trace elements or for a mix of them, are offered on the market for this purpose. The two antioxidants that are most frequently found in dairy cattle diets, either separately or together, are vitamin E and selenium. As a result, the majority of study has concentrated on these compounds' effects. Chain-breaking antioxidant vitamin E, which is highly lipid-soluble, stops the spread of free radicals in plasma lipoproteins and membranes. The effects of this trace element on selenoproteins, such as GSH-Px, are attributed to its function as a cofactor [52, 53]. However, a recent study has emphasized the direct function of selenium (Se) in preventing oxidative stress (OS) and controlling immunity in dairy calves around the time of calving. At the start of lactation, cows frequently have decreased plasma levels of vitamin E [53, 54]. It is unclear why the content of vitamin E a-tocopherol drops near the end of pregnancy. A reduction in the development of various vitamin carrier proteins in the liver of dairy cows during the transition phase causes reduced plasma levels of vitamin E. This may be partly attributed to the usage of antioxidants for colostrum formation. To avoid the reduction in plasma a-tocopherol concentrations around parturition, supplementation with relatively high vitamin E levels is required [55].

5. Transport stress

Feeder's calves are more likely to acquire bovine respiratory disease (BRD) due to transportation stress, which is frequently exacerbated by the stress of weaning. The direct cost of treating BRD was $23.60 per case, according to the USDA (2013) [56], and at some time during the feeding period, 16.2% of feedlot cattle showed indications of respiratory illness [56, 57]. Bruising and dark-cutting carcasses are two additional beef quality issues related to shipping. Cattle can become bruised when they collide with one another during transport or when they come in touch with trailer parts, especially while loading and unloading. 68.2% of the 9860 corpses that were seen at three separate slaughterhouses in the United States had bruises, and 53.5% of those injuries were along the dorsal midline, the area of the carcass with the highest economic value depends [58]. Before slaughter, prolonged stress depletes muscle glycogen reserves, resulting in a condition called dark cutting carcasses. Long-term stress before slaughter depletes muscle glycogen levels, causing a characteristic called "dark cutting carcasses." The possibility that transportation might have a detrimental impact on carcass and meat qualities has sparked interest in transportation beef quality assurance, a program that informs cattle transporters of optimum management practices [59]. A change in the prooxidant-antioxidant equilibrium favouring the former was the original definition of oxidative stress. This condensed definition was eventually expanded to mean an imbalance favouring oxidants over antioxidants, which disrupts redox signalling and causes molecular damage in addition to impairing physiological performance. Under typical biological circumstances, the antioxidant defense mechanism of the cell balances the quantity of oxidants, causing it to vary

within a specific range known as basal oxidative stress or oxidative eustress. Cell death by necrosis, apoptosis, or both may occur when oxidative stress reaches a high intensity, known as oxidative distress. When determining the level of oxidative stress in biological samples, it is crucial to take into account both sides of the equation since oxidative stress is defined in terms of the interaction between oxidants and antioxidants. Direct measurements of reactive oxygen species (ROS), oxidative changes to proteins, lipids, and nucleic acids, antioxidant enzyme activities, antioxidant concentrations, and ROS levels are a few of the indicators that are frequently evaluated.

6. Antioxidant and lipid peroxidation

Endogenous nonenzymatic biological sources and antioxidants received exogenously make up the cellular antioxidant defense system [60]. Since several antioxidants can work together to combat the oxidative offense and a lack of one specific antioxidant does not always signal that the sample's overall neutralizing ability is compromised, quantifying antioxidant components individually does not give a fair picture of the sample's antioxidant capacity [61]. As a result, several techniques have been created to determine the overall antioxidant capacity. This takes into account the overall antioxidant activity of every sample that was analyzed rather than just the total amount of detectable antioxidants [62, 63]. The following are some of the most popular analytical techniques for determining the status of all antioxidants: the overall antioxidant capacity to capture radicals comparable antioxidant power to Trolox capability for absorbing oxygen radicals the sample's ability to reduce iron or the pool of antioxidants that would be severely oxidized by a large dose of hypochlorous acid. It is not unexpected that several endogenous regulatory processes are affected by an external antioxidant supply as a result of this interaction between antioxidant compounds. Recent studies show that these processes may be responsible for some of the contentious conclusions regarding antioxidant supplementation, even if further investigation is necessary to completely understand all the regulatory pathways in dairy cattle: The transcription of genes encoding different antioxidative and cytoprotective proteins is regulated by the nuclear factor E2-related factor 2 (Nrf2), making Nrf2 necessary for the transcription of GSH-Px 2 (and likely GSH-Px 1 as well). Found that a significant increase of Nrf2 target genes with anti-oxidative capabilities occurs throughout the transition from late pregnancy to the start of breastfeeding [64, 65]. Additionally, at this time, the unfolded protein response is triggered in dairy cow livers, activating Nrf2 via the PERK pathway and enhancing the production of antioxidant enzymes and antioxidant capacity [66, 67]. These systems may be physiological defenses against tissue damage brought on by inflammation and ROS generation [68]. They, therefore, serve as crucial benchmarks for ensuring successful adaptation during the period of transition. Additionally, the fact that excessive antioxidant supplementation reduces antioxidant capacity may be explained by the endogenous regulation of antioxidant molecules, as high antioxidant doses may reduce antioxidant capacity by suppressing Nrf2 due to lower ROS levels resulting in decreased expression of antioxidant enzymes [69]. Mastitis, which frequently originates from microbial infection of the mammary gland, is the most expensive inflammatory condition in dairy cows. LPS produced from the bacterial outer membrane is the major pathogen component starting inflammatory reactions if the infection is brought on by gram-negative bacteria.

7. Oxidative stress

Saturated fatty acid excess in the mitochondria causes redox equilibrium to break down and speeds up the production of oxygen radicals. Insulin resistance and non-alcoholic FLD in non-ruminants have been linked to the lipotoxic syndrome known as oxidative stress. As discussed by many authors, the ongoing generation of ROS triggers serine/threonine kinase signalling cascades that prevent the induction of insulin-stimulated insulin receptor substrate [70, 71]. In response, simple steatosis may be promoted by increased intrahepatic lipid accumulation caused by insulin resistance (i.e. non-inflammatory phenotype). The activation of Kupffer cells, which in turn activate redox-sensitive transcription factors like nuclear factor-B and upregulate pro-inflammatory TNF-α, may also be facilitated by oxidative stress. Unfortunately, NADPH oxidase and cytochrome P450 (family 2, subfamily E, polypeptide 1; commonly known as CYP2E1) are also upregulated in inflammatory steatohepatitis, which further reduces antioxidant capacity and promotes hepatocellular damage [72]. Depletion of n-3 long-chain polyunsaturated fatty acids (FA) due to poor fatty acid desaturation and increased peroxidation in the liver are additional effects of excessive ROS formation. Furthermore, polyunsaturated fatty acids (FA) that have been exposed to enzymatic (through cyclooxygenase, lipoxygenase, and CYP2E1) or non-enzymatic (by ROS) oxidation can produce oxylipins with a variety of inflammatory activities [73, 74]. For instance, proinflammatory hydroxyl-octadecadienoic acid and hydroxyl-eicosatetraenoic acid are both oxylipins produced from n-6 arachidonic acid and linoleic acid, respectively [75]. The widespread mitochondrial FA oxidation, albeit incomplete breakdown, that occurs in the transition cow with diminished antioxidant capability is probably a contributing factor in the development of ROS build-up [76]. Adipose tissue lipolysis may be boosted by oxidative stress, which will worsen the oxidant state. Unsaturated FA (fatty acid) produced from lipolysis can undergo ROS oxidation, which produces isoprostane and lipid hydroperoxide [77]. Adipose tissue releases fatty acids that are also utilized by the liver to produce hepatic -hydroxybutyrate, which may trigger p38 mitogen-activated protein kinase activity and increase hepatocyte death. Additionally, nuclear factor B may be induced by lipolytic FA in hepatocytes through ROS-dependent processes that cause inflammation [78, 79]. These results imply that FLD pathogenesis involves oxidative stress. As previously discussed, the buildup of ROS or oxylipids probably affects the immunological responses of cattle. For instance, in peripheral blood mononuclear cells from healthy transition cows, plasma oxylipin levels are associated with the production of interleukin-12 and inducible nitric oxide synthase-2 [80]. Elevations in the arachidonic acid metabolite 15-hydroxy-peroxyeicosatetraenoic acid occur in endothelial cells along with death, caspase-3 activation, leukocyte migration, and the production of inflammatory cytokines [81]. Oxylipids generated from cytochrome P450 and lipoxygenase accumulate in the plasma and adipose tissue of postpartum cows, where they may have an impact on immune cell trafficking and inflammation. Examples of such oxylipids include 5-hydroxy-eicosatetraenoic acid [82]. The significance of oxidized lipids in the development of inflammatory illnesses such as mastitis and metritis has therefore been highlighted. The significance of oxidized lipids has been studied since one of the main characteristics of inflammatory illnesses, such as mastitis and metritis, is inflammatory dysfunction [82]. For instance, hydroxyl-octadecadienoic acid accumulation and breast inflammation are two features of *Streptococcus uberis* mastitis. Oxylipid production and associated health consequences may be influenced by dietary antioxidant intake, trace mineral intake that aids in antioxidant

defense mechanisms, and the kind and quantity of FA supplied to transition cows [83]. Uncontrolled or chronic inflammatory states can be harmful, even though they often result in the recovery from infection after a controlled inflammatory phase. Therefore, after the removal of the infectious agents, a speedy resolution phase is required for a perfect acute inflammatory response. Anti-inflammatory cytokines like IL-10 and n-3 (omega-3) fatty acid derivatives like resolving and protectors are important resolving signals.

8. Cytokines

Gene activity TNF-alpha is one of the most significant cytokines involved in starting and growing the acute-phase response [84]. TNF-α is necessary for healthy liver regeneration and increases hepatic DNA synthesis by activating NF-B [85]. Numerous cell types, particularly macrophages and mast cells, generate cytokines such tumor necrosis factor (TNF), interleukin (IL)-1, and interleukin (IL)-6. By stimulating the acute phase response and activating leukocytes and endothelial cells, they play significant roles in the inflammatory response. The liver of rats that have experienced chronic starvation maintains its acute-phase reactivity. According to the new research, although the reported rise in TNFA expression between days 14 and there was small, it may have been the result of a systemic inflammatory response that was triggered within the uterus as parturition neared (i.e., higher IL-1 and IL-8 production) [86]. The cows' metabolisms were put under additional stress due to a decreased energy balance brought on by the decrease in energy intake. It is generally known that IL-1 suppresses appetite in humans, but plasma concentrations of TNF- are linked to higher energy expenditure [87, 88]. Early lactation cows were given recombinant bovine TNF- alpha, which raised blood haptoglobin, NEFA, cortisol, growth hormone, and nitric oxide while decreasing feed intake. Some of these symptoms closely reflect periparturient-period reactions that we and others have seen, as well as reactions to endotoxin treatment [89, 90]. Since proinflammatory and signaling genes are upregulated in the liver of mice that have been induced to develop fatty liver and insulin resistance by high-fat diets, TNFA upregulation in liver macrophages may act in a paracrine manner and cause potent upregulation of SAA1 in hepatocytes [91, 92]. Increased inflammation during the formation of fatty livers in transition dairy cows may be caused by NF-B-mediated proinflammatory signals [93]. Bovine recombinant When given to breastfeeding cattle, TNF- raised their blood levels of haptoglobin, NEFA, cortisol, growth hormone, and nitric oxide while decreasing their appetite for food [94]. SAA1's expression has increased by over sixfold, which is partially explained by the fact that TNF- and IL-1 boost the manufacture of positive acute phase proteins like SAA1. The acute-phase reaction causes a 1000-fold increase in SAA1 production in the liver [95]. Furthermore, it has been demonstrated in several reports that pro-inflammatory and signalling genes are upregulated in the liver of mice induced to develop fatty liver and insulin resistance by high-fat diets. This suggests that the upregulation of TNFA in liver macrophages may act in a paracrine manner and result in a potent upregulation of SAA1 in hepatocytes.

In addition to having a deleterious impact on the neurophysiological systems controlling feed intake, IL-8 and IL-1 released from the placenta directly upregulate the expression of SAA1 and TNFA in the liver [96]. Negative energy balance, hyperinsulinemia, increased adipose tissue lipolysis, and decreased feed intake all have an impact on the liver's ability to access nutrients. Blood NEFA and -hydroxybutyrate

levels may be considerably elevated and lipolysis may be further stimulated by cytokines from the liver and/or placenta (BHBA) [97]. Circulating NEFA most likely operate as endogenous ligands for PPARA and HNF4A, upregulating them and activating downstream genes involved in fatty acid oxidation, ketogenesis, and gluconeogenesis (ACSL1, ACOX1, carnitine palmitoyl transferase 1A (CPT1A), ACADVL) (PCK1) [98, 99]. The outcome of metabolic processes that were partially sparked by the overexpression of PPARA and HNF4A is net hepatic glucose synthesis and glucose and amino acids for milk synthesis [100]. Through the direct overexpression of GPAM, fatty acid synthase (FASN), ATP-citrate lyase (ACLY), and Spot 14, activation of PPARA can reduce the expression of the gene strongly connected with lipid synthesis, sterol regulatory element binding transcription factor 1 (SREBF1) (S14) [101]. Higher levels of liver triacylglycerol are correlated with the upregulation of SREBF1 via cytokines or fatty acids and GPAM [102]. Limitations in insulin and amino acid delivery to the liver may suppress IGFBP3, EIF4B, 3-phosphoinositide dependent protein kinase-1 (PDPK1), proteasome (prosome, macropain) 26S subunit, ATPase 2 (PSMC2), and/or PDPK1-dependent protein kinase, resulting in a reduction in hepatic protein synthesis, circulating blood IGF-I, and liver glycogen [103]. Increased lipid peroxidation in the liver may result from the downregulation of GSTM5 expression. The danger for hepatic periparturient health disorder is increased by both less ability to detoxify lipid peroxidation products and larger triacylglycerol build-up in the liver [104].

9. Endoplasmic reticulum stress triggers cytoprotective pathways

It's interesting to note that cryoprotective pathways, including the nuclear factor E2-related factor 2 (Nrf2) pathway, are activated by ER stress brought on by ROS or pro-inflammatory cytokines [105]. This activation is PERK-dependent. Various antioxidative and cryoprotective proteins are controlled by the redox-sensitive transcription factor Nrf2. ER stress causes Keap1 to become disassociated from Nrf2, allowing Nrf2 to move into the nucleus and activate antioxidant and cytoprotective genes by binding to antioxidant response elements in the promoter regions of its target genes. In the absence of ER stress-inducing stimuli, Nrf2 is inactive and retained in the cytoplasm by interaction with Kelch-like ECH-associated protein 1 (Keap1) [106]. The activation of Nrf2 also lowers pro-inflammatory signalling, attenuates inflammatory damage, and neutralizes ROS generated under pro-inflammatory situations, which decreases the vulnerability of tissues to oxidative damage and cytotoxicity [107]. Thus, it has been proposed that ER stress-induced activation of Nrf2 is a method for reducing oxidative damage that is brought on by ER stress.Following the presence of enhanced ROS and pro-inflammatory cytokines in the liver of transition dairy cows, we have recently noticed Nrf2 activation as demonstrated by overexpression of Nrf2 target genes, including catalase, glutathione peroxidase 3, microsomal glutathione S-transferase 3, haem oxygenase 2, metallothionein 2A, NAD(P)H dehydrogenase, quinone 1 [108]. Furthermore, it's been proposed that Nrf2 is a physiological target to preserve liver function and enhance overall health in high-yielding dairy cows. It is not unlikely that interindividual variations in the effectiveness of activating the Nrf2 pathway in response to ROS or inflammatory stimuli explain the molecular level for variations in the susceptibility to develop liver-associated diseases between early-lactating dairy cows with similar NEB and milk yield [109]. This is because Nrf2 plays a crucial role in preventing liver damage.

10. Tnf-α and NF-kb

The pattern-recognition receptor toll-like receptor 4 (TLR4), which recognizes endogenous ligands and external pathogen-associated molecular patterns, is crucial in the development of the inflammatory response [110]. The production of pro-inflammatory cytokines and the activation of nuclear factor kappa B (NF-B) signalling pathways in a variety of cell types are both correlated with TLR4 activation. In rat models of cardiac ischemia-reperfusion, it has been found that TLR4 expression positively correlates with the levels of tumor necrosis factor (TNF) and interleukin-6 (IL-6) [111]. In dairy cattle, disease -affected cows' milk and intra-mammary epithelial cells showed elevated NF-B activity. Lymphocyte antigen-96, also known as MD-2, and CD14 form a complex when lipopolysaccharide (LPS) binds to TLR4 [112]. This complex then triggers TIR (Toll/IL1 Receptor domain) intracellular signalling through adaptor molecules, primarily myeloid differentiation actor 88. (MyD88) [113]. This TLR4 and damage signalling causes downstream kinases to become active, which in turn causes IKB to degrade, releasing NF-B to go to the nucleus [114, 115]. In the promoter region of genes encoding pro-inflammatory cytokines, such as IL-1B and IL-6, it binds B sites [116]. Bovine mammary epithelial cells (bMEC) react differently to diverse pathogenic stressors, according to some researchers. While the reaction to *Staphylococcus aureus* culture supernatant (SaS) was linked to an AP-1 and IL-17A signalling route, crude LPS from *Escherichia coli* was linked to an NF-B and Fas signalling network [117]. The impact of intra-mammary cephapirin therapy, either alone or in combination with prednisolone, on gene expression patterns in experimentally induced mastitis in Holstein Friesian cows was examined [118]. In comparison to challenged, untreated areas, they discovered that both treatments led to a down-regulation of gene transcripts implicated in chemokine and TLR-signaling pathways. It is widely known that TLR4 is a key cell surface receptor for the inflammatory response because it recognizes LPS from the cell wall of gram-negative bacteria and starts the MyD88-IKKNF-B pathway response [119]. The MyD88-dependent pathway is activated by TLR4 regulation of LPS (Mediated by TLR-IL-1 receptor domain containing adapter protein/TIRAP), which triggers the immediate activation of NF-B and the subsequent induction of a number of pro-inflammatory cytokines [120, 121]. Additionally, it was shown that thymol may suppress NF-B activation and down-regulate the mRNA production of tracheal antimicrobial peptide and -defensin, hence reducing the internalization of *S. aureus* into bMEC (BNBD5) [122].

11. AKT and mTOR

A subset of genes involved in lysosomal biogenesis and function, as well as those involved in the creation of autophagosomes, are controlled by transcription factor EB (TFEB), a master transcription regulator [123]. Lysosome-associated membrane protein (LAMP1) and the V0 domain of the vacuolar ATPase (ATP6V0A1) are two examples of the hepatic lysosome-regulated genes that were abundantly expressed in mice after TFEB activation or overexpression. Furthermore, TFEB overexpression in HeLa cells increased the expression of autophagy-related genes including genes such sequestosome-1 (SQSTM1) and microtubule-associated protein 1 light chain 3 (MAP1LC3) (ATG12) [124]. It's important to note that studies have shown that the livers of mice and people with non-alcoholic fatty liver disease had decreased

TFEB transcriptional activity and lysosomal function [125, 126]. Furthermore, low levels of the genes MAP1LC3, SQSTM1, ATG7, and ATG12 in the liver of ketotic dairy cattle propose a reduction in the formation of autophagosomes, suggesting that impaired TFEB transcriptional activity may exist in the liver of dairy cows with ketosis and result in elevated aminotransferase enzyme levels [127]. Mechanistic target of rapamycin kinase complex 1 (mTORC1) phosphorylates the transcription factor TFEB at Ser 211 in nonruminants to prevent its subcellular localization and activity [128]. Other kinases, such as protein kinase B (Akt), glycogen synthase kinase-3 (GSK3), and extracellular signal-regulated kinase (ERK1/2), which phosphorylate TFEB at Ser 467, Ser 138, and Ser 211, respectively, also influence TFEB nuclear localization [129]. These other kinases work in conjunction with mTORC1 to affect TFEB nuclear localization. In the livers of dairy cattle in ketosis, changes in the activity of Akt, GSK3, and ERK1/2 have been observed [130, 131]. The upstream substrates of mTORC1 that are activated support anabolic pathways while blocking catabolic ones. RPS6KB, EIF4EBP1, and TFEB were more heavily phosphorylated in the current research, which is suggestive of an overactive hepatic mTORC1 state during ketosis [132]. It's probable that a similar process operates in dairy cows with ketosis as hepatic overactivation of mTORC1 lowered TFEB transcriptional activity and compromised lysosomal function in mice with fatty liver. Therefore, the decrease in molecules related to lysosomal function that researcher found in ketotic cattle may have been brought on by an overactive mTORC1 that inhibits the transcription of TFEB. It has been observed that Akt, GSK3 and ERK1/2 cause TFEB to become more phosphorylated and less likely to go into the nucleus [133]. Accordingly, in line with earlier research, phosphorylated Akt, GSK3, and ERK1/2 were reduced in the liver of dairy cows in ketosis, which decreased their impacts on TFEB transcriptional activity regulation [134].

12. Conclusion

The environment and dietary habits have a substantial influence on the health of cattle and their hepatic condition in the future. Climate change may encourage the formation of poisons or poisonous spores, which cattle are exposed to when grazing diseased grass. Using mechanical or natural methods, senescent rough dog's tail grass contaminants might be moved to a neighbouring palatable pasture. The specific toxin(s) and their source, however, are still speculative, and it is uncertain if they are stable in the environment. The analysis of tissues from dead animals may thus be able to shed some light on this scenario, even if the concentration of the toxic substances that cause disease would be higher in feed source materials. Any unusual components may reveal information about the type of poison, according to a theory (s). Additionally, it is suspicious that there were many types of insects and regularly contaminated food present during an outbreak of liver injury. As a result, it is suggested that the source of the relevant toxin(s) may be one of numerous factors linked to increased liver damage in the cattle.

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Declaration of interest

The authors declare that there is no conflict of interest for this manuscript.

Informed consent statement

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Author details

Avishek Mandal
Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India

*Address all correspondence to: avishek7477@gmail.com

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Section 3

Sustainability

Chapter 7

Organic, Economical and Environment Friendly Clean, Green, Ethical (CGEEE) Strategy in Livestock

Basagonda Bhagavanta Hanamapure

Abstract

"Throughout the ages, our farming ancestors have chosen system with a high output per unit of land that no longer contain enough of certain needed nutrients such as essential minerals and natural immune-enhancing secondary plant metabolites (phytochemicals)". Balanced Nutrition is a basic source for the Excellent "Immunization Vaccine, Hormone, Antimicrobial Agent" and that is, Natural Self-Cure is the best modern method of health care clean, green, ethical, economical and environment friendly (CGEEE) strategy considered to be the most appropriate means to counteract as an immunomodulatory substances sidesteps these concerns by controlling the proper nutritional status effectively during the nutritional mismanagement and microbial susceptibility. The ascending inflammatory multifactorial complex diseases and metabolic disorders of lactating livestock treatment routes, with antimicrobial agents with or without non-steroidal anti-inflammatory agents, hormones, low intensity radiation, enzymes, multivalent vaccines, disinfectants, are available but the results did not demonstrate any beneficial effect on clinical cure rate, inflammatory parameters or elimination of bacteria, metabolic disorders, infertility, and reduction GHG production. Animal husbandry has entered the era when the use of antibiotics or other pharmaceutical products is increasingly unwelcome as antimicrobial-resistant pathogens which may endanger both the animal and public health and farm land.

Keywords: balanced feed supplement, metabolic disorders, ascending inflammatory diseases, animal husbandry, livestock

1. Introduction

Historically it has been universally accepted that "Food is our most basic need, the very stuff of life and first born amongst all beings" [1]. Human beings are nature's wonderful creature who never thought about the planet and its resources are for all including themselves but tried hard to destroy at any cost by different means such as agricultural land, food source, food quality, natural survival system (pollution,

resource depletion, extinction of species), clean air, water, etc., by intervention (anthropogenic influences) instead of knowing nature's self-cure system to strengthen internal immunity to prevent susceptibility to changes. It is well known that "Nutrition is the best vaccine" [2] and "balanced nutrition is the excellent immunization vaccine, antimicrobial agent and hormone", i.e. Natural Self-Cure is the best modern method of treatment.

It has been scientifically observed that there has been a dramatic reduction or elimination of critical and essential minerals and natural immune-enhancing secondary plant metabolites (phytochemicals) from fields due to convention industrial agriculture produces, over harvesting as well as by using highbred seeds, chemical fertilizers, and other harmful farming practices; stripping soil's minerals show proportionally lower mineral concentrations in varieties bred for higher yields [3] and at rising environment temperature and atmospheric carbon dioxide. Most of the beneficial phytonutrients have bitter, sour or astringent taste. Conventional farming system favored plants that were relatively low in fiber and C, H, O based high energy dense sugar, starch and oil, are responsible for poor crops and in turn for pathological conditions in animals' health that fed such crop [The New York Times explains it well]. Dr. Linus Pauling, two-time Nobel Prize winner stated that "You can trace every sickness, every disease and every ailment to a mineral deficiency." "Sick soils mean sick plants, sick animals and sick people." "Our Immunity Very Much Parallels the Immunity of the Land" — Empty Harvest by Dr. Jensen. Crops grown with malnutrition, attack by insects, bacteria and fungi, weed takeover and general loss of mental acuity in the population, leading to degenerative metabolic disease and early death [4]. Feed or food crops deficient in essential nutritional composition might exacerbate the problem of 'hidden hunger' around the world [5] starving us -no matter how much we eat of them even if they consume enough calories [6].

Grazing livestock are eating a diverse array of plants on pasture, additional health-promoting phytonutrients—terpenoids, phenols, carotenoids, and antioxidants—found in meat and milk known to have beneficial anti-inflammatory, anti-carcinogenic, and cardioprotective effects are absent in monoculture pastures. Therefore, the importance of medicinal plants and their products is increasingly recognized and the public confidence in their use is constantly strengthened [7].

The large-scale production of animals, crops, and forages [8] uses synthetic pesticides, herbicides, and fertilizers while in livestock production uses vaccines, antibiotics, medicated feeds, and growth hormones which may endanger the animal health and also contributes to global greenhouse gas emissions, loss of plant biodiversity, soil organic matter, degradation of natural resources, natural water bodies, and public health [9–14].

Nutritional imbalances, deficiencies, or erratic management of feeding programs for dairy cows can create large numbers and various metabolic diseases. Compounding the problem are the ever-changing nutritional needs of the cow, her lactation/dry period needs, feed quality changes, and the producer's personal management practices. Clean, green, ethical, economical and environment friendly (CGEEE) dietary methods for the treatment, prevention, and control of disproportional energy metabolism (fatty liver, ketosis, subacute, acute ruminal acidosis); disturbed mineral utilization (milk fever, sub-clinical hypocalcaemia); and perturbed ascending inflammatory disorder's immune function (retained placenta, metritis, mastitis) and cystitis, urethritis, pyelonephritis etc. Nutritional management (Ketosis and acidosis) are often blamed for the etiology for innate immunity, metritis, mastitis, milk fever, lameness, abomasal ulcers, gastrointestinal disorders, ruminal bloat

and lesions, diarrhea, displaced abomasum, liver abscesses, pulmonary hemorrhage, poor pregnancy rate, retained placenta, abortions, uterine prolapsed, sperm quality, laminitis, milk quantity and quality, heat stress is in need of the present situation. Current methods are of high cost, not always reliable, labor-intensive, require skill and experience and have negative impact on a dairy farmer's profitability.

Considering the antimicrobial resistance and failure of the current treatment therapy, author has tried his best in explain new dietary feed supplement with mineral source, non-protein nitrogen source and salt (NaCl) and nutrient source as Clean, Green, Ethical, Economical And Environment Friendly Self- Cure strategy considered the most appropriate means to counteract (i.e. "prevention is better than cure")as an immunomodulatory substance sidesteps these concerns by controlling the negative energy balance and enhanced innate -immunity.

2. Role and importance secondary metabolites from plant in human and animals

Since ancient times, plants were the only source of medicine for all organisms. Today, various pharmaceutical combinations (antibiotics, pain killers, fever reducers, etc.) are derived from plants that produce these chemicals naturally. Several reviews describe the many health promoting properties of (plant secondary metabolites) PSMs to animals, including humans [15–19]. The opportunity is to reconsider the fundamentally important roles these compounds played in health before the advent of modern medicine, [20] while integrating plants with diverse PSMs back into our crops and forages. In that context, improved valorization of grassland secondary metabolites (GSMs) is of interest [21–23]. Secondary metabolites named by A. Kossel in 1891 have got great attention due to their potential role in human nutrition, cosmetics, drugs and their indispensable role in plant defense. British Nutrition Foundation [24] classified grassland secondary metabolites into Terpenoids (e.g., carotenoids, sterols, cardiac glycosides and plant volatiles etc.), Phenolics (e.g., lignans, phenolic acid, tannins, coumarins, lignins, stilbenes and flavonoids etc.), Nitrogen containing compounds (e.g., non-protein amino acids, cyanogenic glucosides and alkaloids etc.) and Sulfur containing compounds (e.g., GSH, GSL, phytoalexins, thionins, defensins and lectins etc.) [25, 26].

A detailed study of PSMs, functional roles in agroecology, may help producers better manage their soil quality, reduce inputs, and minimize negative environmental impacts. In pastures and rangelands, animal health benefits and production increases when animals ingest forages with different PSMs (plant secondary metabolites), which has implications for enhancing the biochemical richness of meat and dairy products for human consumption. Balanced nutrition is essential in preventing metabolic disorders, such as bloat (pathology often associated with feeding highly fermentable protein-rich forages to ruminants) and acidosis (increased acidity in the blood and other body tissues due to incorrect diet or feeding). Bloat generally occurs when plants degrade too fast in the rumen [27]. For example, Rosaceae, Onagraceae, Polygonaceae, and Dipsacaceous plants source fodder controls the production of CH4 and NH3-N (marker of nitrogen use efficiency) [28], bloat by tannins (CTs) [29] SMs (secondary metabolites) e.g., saponins or essential oils helps to improve N metabolism by manipulation of rumen microflora [30, 31].

Historically, researchers and producers have focused on wheat, maize and rice etc. like species which contribute the most to intake of energy and protein for livestock, but grazing animals will eat without any limitations and have maximum secondary

metabolites available in a meal, and play crucial and important role for the health of livestock and humans through the meat and dairy products we derive from them [32]. Some PSMs are poisonous potential to animals, therefore herbivores respond by reducing their intake because of concentration of the metabolites in plants [32–34]. As Paracelsus (1493–1541) wrote, "All substances are poisons; there is none which is not a poison, their right dose differentiates a poison from a remedy." e.g., many alkaloids are bitter in taste, can be toxic to ruminants [35–38]. However, by offering animals either supplement [39–41] or diverse forages containing different PSMs, [42–46] biochemical complementarities can reduce the negative effects of alkaloids in plants either by binding or through other diluting or other suitable known methods [47–52]. Phenolic compounds have antioxidative and anticarcinogenic benefits that also aid digestion [53, 54]. Condensed tannins reduce internal parasites and nematodes in ruminants and, due to their protein binding characteristics, also enhance the absorption of amino acids in the small intestine, analogous to by-pass proteins popular in ruminant nutrition [55, 56]. Like tannins, saponins can precipitate proteins [57] while lowering cholesterol in animals [58]. Saponins may improve growth and feed efficiency, reduce protozoa in the rumen, and increase efficiency of rumen-microbial protein synthesis [59]. The emphasis on planting monocultures, combined with the influence of PSMs on reducing intake of any one forage, is why these metabolites have historically been bred out of plants used for crops and forages. Diverse plant species with differing PSMs enhance balanced eating habits while also offering health benefits to herbivores and humans [60–62]. Foraging animals eat more and perform better when offered a variety of forages with different kinds and amounts of PSMs [62–64] which at appropriate doses offer numerous health benefits to foraging animals [65–68] including biochemical richness, flavor, and quality of cheese, milk, and meat for human consumption [69–72]. Our health is thus linked with the diets of livestock through the chemical characteristics of the plant species they eat and play a crucial role as PSMs have anti-inflammatory, immunomodulatory, antioxidant, anti-bacterial, and anti-parasitic properties, which protect livestock and humans against diseases and pathogens [73]. Those compounds may confer the same benefits to us as to livestock, dampening oxidative stress and inflammation linked with cancer, cardiovascular disease, and metabolic syndrome.

The current agricultural systems, agriculture scientists with the good intentions to feed the exponentially growing human population by cultivation of monoculture high yielding seeds, and using synthetic chemical to protect the plants has produced various negative impacts too numerous to overlook [74–77] resulting in a need for change. Increasing multicrop agricultural systems offers ecosystem benefits from the soil, to plants and animals, to the atmosphere, enhancing agroecological sustainability. PSMs play a crucial role in defending belowground against root -eating larvae while tannins and terpenes slow mineralization and soil microbial biomass thus increasing carbon sequestration potential in agriculture soil. Aboveground, PSMs aid plants and act as insecticides when defoliation pressure develops. Recent results suggest that the concentration of tannins in cattle defecates is proportional to the concentration of tannins in the forage consumed [78]. Further, methane emissions are reduced when cattle graze forages containing tannins [79–83]. Thus, planting forages containing different PSMs may reduce greenhouse gasses by influencing rumen fermentation and soil mineralization [72, 84].

It has been scientifically confirmed that if the plant is under stressed management practices, reducing inputs of water, fertilizers and insecticides to prevent herbivory by insects can increase the production of functional plant secondary metabolites

which typically increase with environmental stressors [85–87]. It is ironic that we have selected against PSMs in crop and pasture plants that we are now intent on genetically engineering back into plants [62]. Enhancing plant biodiversity and associated phytochemical diversity offers a logical progression to improve agricultural resilience while providing ecosystem services that also benefit the health of herbivores and humans. Natural sources of secondary metabolites (SMs) from permanent grasslands might contribute to limit pharmaceutical input and improve animal health. In that context, especially grassland those with high dicotyledonous plant species, present a large, pharmacologically active reservoir of secondary metabolites (GSMs) (e.g., phenolic compounds, alkaloids, saponins, terpenoids, carotenoids, and quinones) [88] could offer an alternative way to support to livestock health. The improvement of livestock breeding diets has focused on primary metabolites for rapid production and simplification of agricultural practices [89]. The term "forage quality" encompasses nutritive value, including high digestibility or metabolizable energy, crude protein content [90, 91] and amounts of fiber and minerals, as well as forage sanitary status linked to the absence of dust, allergens, noxious weeds, nitrates, prussic acid, ergot alkaloids, and insect infestation.

Numerous studies have shown the involvement of GSMs, have wide range of pharmacological activities, such as anti-inflammatory, antimicrobial, anti-cancer, cardio-protective, neuro-protective, anti-osteoporotic, estrogenic/anti-estrogenic, anxiolytic, analgesic, and anti-oxidant activities in laboratory animals and/or herbivores [92, 93]. A new focus of the study grassland species for animal health concerns their anti-oxidant activity. In fact, current breeding conditions are well known to create unbalanced oxidative stress [94] and complications in metabolic pathologies that have been linked to many diseases [95]. It is currently accepted that intake of phenolic anti-oxidants improves health by reduce oxidative stress [96–102].

3. Balanced minerals as source of feed supplement and its applications in controlling metabolic disorders and ascending inflammatory diseases

The dietary compositions for the treatment, prevention, and control of disproportional energy metabolism (fatty liver, ketosis, ruminal acidosis); disturbed mineral utilization (milk fever, sub-clinical hypocalcaemia); and perturbed immune function (retained placenta, metritis, cervicitis, pneumo-vaginitis, mastitis, cystitis, urethritis, pyelonephritis etc.). Lactating livestock are fed a ration including roughage, and concentrates. The nutritional composition of the ration varies considerably over a period of time, harvesting time, crop growing season, losses in nutrients during storage, and the wide variation in soil nutrient contents. During the physiological state of negative energy balance, the animals meet out their normal requirements by mobilization from its body reserves for a shorter period. For longer duration of nutritional imbalances, deficiencies or in excess or erratic management of feeding programs can create large numbers of various types of health problems generally categorized as metabolic diseases like fatty liver syndrome, clinical ketosis, and displaced abomasum, retained placenta, metritis, and mastitis through impaired immune function etc [103, 104]. There are no nutritional supplements or technologies currently available that will be maintaining cattle in proper nutritional status effectively during the nutritionally mismanaged cattle. There is a need for nutrition strategies which reduce susceptibility to production diseases and our understanding of the interactions between nutrition and immunity remains superficial [105]. Veterinary therapeutic treatment with

antibiotics or other pharmaceutical products is increasingly **unwelcome** as antimicrobial resistant pathogens which may endanger both the animal and public health and farm land. Ruminal Microorganisms must have energy and carbohydrates to use urea to make protein. Therefore, it is important to have ammonia released simultaneously with available energy and carbon skeletons for ammonia to be converted to microbial protein. Urea with starch or cereal grains are included in rations in the rumen for good use of urea by bacteria.

The dietary feed supplement mineral source, non-protein nitrogen source, salt (NaCl) and energy source as SELF CURE strategy considered to control infections and metabolic disorders of livestock particularly domesticated ruminant animals and non-domesticated animals. The present author explained about compositions and the methods for the treatment, prevention, and control of disproportional energy metabolism (fatty liver, ketosis, subacute, acute ruminal acidosis); disturbed mineral utilization (milk fever, sub-clinical hypocalcaemia); and perturbed immune function (retained placenta, metritis, mastitis) and cystitis, urethritis, pyelonephritis etc.

Therapeutic treatment with antibiotics or other pharmaceutical products is not preferred in animal husbandry as antimicrobial resistant pathogens which may endanger both the animal and public health and environment. Therefore, there is an urgent need to have replacement therapeutic method to and cure by CGEEE strategic method to provide balanced feed supplement with plant secondary metabolites to the cattle. This synergic combination which helps to provide healthy atmosphere in rumen. Rumen micro-flora must have energy and carbohydrates, ammonia simultaneously to be converted to microbial protein. The dietary feed supplement mineral source, non-protein nitrogen source, salt (NaCl) and energy source as SELF CURE strategy considered to control infections and metabolic disorders of livestock particularly domesticated ruminant animals and non-domesticated animals. The present author explained about compositions and the methods for the treatment, prevention, and control of disproportional energy metabolism (fatty liver, ketosis, subacute, acute ruminal acidosis); disturbed mineral utilization (milk fever, sub-clinical hypocalcaemia); and perturbed immune function (retained placenta, metritis, mastitis) and cystitis, urethritis, pyelonephritis etc.

3.1 Therapeutic methods and its impact

The ascending (clinical/subclinical) inflammatory multi-factorial complex diseases of lactating livestock (cattle and buffaloes etc.) are caused by aerobes and anaerobes, gram +/− bacteria, including mycoplasmas, viruses, fungi/yeast, and algae. These ascending inflammatory complex diseases such as local or systemic with antimicrobial agents such as antibiotics with or without non-steroidal anti-inflammatory agents, hormones, low intensity radiation, enzymes, multivalent vaccines, and disinfectants are available but the results did not demonstrate any beneficial effect on clinical cure rate, inflammatory parameters or elimination of bacteria, fertility and metabolic disorders. In such a clinical state, the body of the cow is under sever immunity suppressed and may not be strong enough to fight new infections [106–109]. Antimicrobial peptides (APs, bacteriocins) in vivo activity is decreased and are cytotoxic to mammalian eukaryotic cell and are considered to be poor drug candidates and their synthesis is often challenging with high associated research and inventory costs [110, 111]. Antimicrobial resistance is threatening humans and animals worldwide [112–115] and animal husbandry has entered the era when the use of antibiotics or other pharmaceutical products is increasingly **unwelcome** as

antimicrobial resistant pathogens which may endanger both the animal and public health. Additionally, the presence of antibiotic residues in the environment, associated with overuse of antimicrobial agents, may adversely influence the manure treatment systems by inhibition of biogas production and the soil beneficial community to establish persistent reservoirs of resistant bacteria [116].

3.2 Effect of parenteral administration of trace minerals

The parenteral nutrition administration the ruminal interactions can be bypassed entirely by supplementing TM, through injectable TM, which provides TM directly to the tissues. This treatment is beneficial in severe and acute deficiency, and restores normal concentrations rapidly to a functional level in the animal's tissues. Advocate parenteral treatments if alimentary absorption is impaired or at times of increased mineral demand, such as late pregnancy, but is wary of toxicity [117] and antagonistic with other mineral elements and the clinical signs may vary from poor growth and feed utilization to neurologic disorders [118]. Due to the complicated interactions/antagonistic effect between minerals and trace minerals, it is not recommended that trace elements are supplemented separately [119]. Repeated trace mineral injections during development and gestation may increase trace mineral status and milk production and benefits for immunity-related parameters; however, also contributed to the decrease in digestive efficiency. The average productive life of dairy cows in the United States decreased from 35.0 to 28.2 months between 1970 and 2013 [120] no improvement in beef calf health and performance, and resulted in decreased AI pregnancy rates [121, 122] and health did not translate into improved growth performance and reduced mortality [123].

The success of the modern dairy industry in achieving high production is offset by its dismal record of animal health and longevity. Most dairy cows do not live long enough to complete two lactations and 50% calve with either an infectious disease or a metabolic disorder such as ketosis and clinical or subclinical milk fever [124]. There is also lack of proper acts and regulations for monitoring their quality for commercial marketing [125]. Commonly almost all minerals interfere with other mineral utilization and bioavailability. An excess of Calcium may interfere with the utilization of Zinc. Two major elements, Calcium and phosphorus, affect the utilization of most other elements. A high intake of calcium decreases intestinal zinc absorption, while an excess intake of zinc can decrease copper absorption. Similarly, selenium bioavailability is reduced by dietary sulfur, high dietary molybdenum in combination with moderate to high dietary sulfur results in formation of thiomolybdates in rumen. Thiomolybdates greatly reduce copper absorption. Independent of molybdenum, high dietary sulfur reduces copper absorption and high dietary iron also reduces copper bioavailability. Manganese is poorly absorbed in ruminants, and limited research suggests that high dietary calcium and phosphorus may reduce manganese absorption [126].

It has been well established thought that all the living organisms required balanced nutrition at various stages of life cycle. The large-scale production of animals, crops, and forages uses synthetic pesticides, herbicides, and fertilizers while in livestock production uses vaccines, antibiotics, medicated feeds, and growth hormones which may endanger the animal health and also contributes to global greenhouse gas emissions, loss of plant biodiversity, soil organic matter, degradation of natural resources, natural water bodies, and public health. Therefore, there is an urgent need of the well balanced nutritional dietary supplement itself has a capacity to control the negative energy balance and related metabolic and infectious disorders with the low-cost static feeding in a period of short duration.

Infertility is the single largest reason for culling female animals from a herd in India with 41% of total animals being culled due to infertility [127, 128]. Currently, the average meat intake for someone living in a high-income country is 200–250 g a day, far higher than the 80–90 g recommended by the United Nations. Switching to a more plant-based protein diet could save $1.5 trillion by 2050 per year [129]. According to the World Organization for Animal Health, 30% of the production of animal products is currently lost due to diseases, infectious or not, at the farm level in Europe as well as around the world [130]. The average annual herd cull rate remains at approximately 36% and cow longevity is approximately 59 months [131]. The OIE (World Organization for Animal Health) estimates that morbidity and mortality due to animal diseases cause the loss of approximately $300 billion globally per year [132]. During ascending inflammatory disease of mammary gland, bacterial toxins released influence the production of PGF2α, which subsequently causes luteal regression, thus, potentially causing the loss of an established pregnancy and due to hormonal imbalance, the probability of conception decreased by 44%, by 73%, and by 52% when mastitis occurred the week before, the week and the week after insemination respectively. The daughters born to such suffering during gestation have reduced reproductive efficiency and in non-pregnant cows could decrease the number of healthy follicles in the developing fetus and compromise future fertility. Anti-Mullerian hormone, a reliable bio-marker for potential fertility, is severely decreased in the developing fetus as the number of mastitis events during gestation of their dams increase [133]. In an estimate from the USA, it is reported that each case of metritis leads to loss of $304 to $354 to the producer due to losses in production and performance. In buffaloes, it has been reported that the milk yield decreased by 239 kg in retained fetal membrane, 181 kg in stillbirth, 173 kg in dystocia, and 98 kg in metritis in a single lactation with increased number of services per conception [134].

The most interesting observation with regards to the occurrence of metabolic disorders is that they are highly associated with each other in the subclinical state of the animal when it is negative energy state. For example, cows affected by milk fever are more prone to mastitis, retained placenta, metritis, LDA, dystocia, udder edema, and ketosis; cows affected by acidosis are more prone to laminitis, LDA, milk fever, mastitis, and fatty liver. Although these associations have been known for years by animal scientists, the reason behind these associations is not very well understood. All these cascades of disorders are commonly occurring in nutritionally mismanaged cattle.

3.3 Treatment of ascending inflammatory diseases and its sequel

Feed supplement composition for regular feeding to sequel and enhance immunity and control metabolic disorders after treatment:

Mineral source and non-protein nitrogen = 73 wt.% Mineral source and salt (NaCl) = 81.37 wt.% Non –protein nitrogen source and salt (NaCl) = 45.63 wt.%.

Feed supplement composition for treating and controlling Ascending Inflammatory Disease:

Mineral Source and Non-Protein Nitrogen = 71 wt.%; Mineral source and salt (NaCl) = 68 wt.%; Non –protein nitrogen source and salt (NaCl) = 67.90 wt.%.

3.4 General method for feeding the dairy or beef cattle

50.00 g of feed supplement based on the animal condition and physical state formulation product mixed with approximately ≈1.0 kg feed concentrate minimum.

and mixed properly for uniform distribution with or without molasses etc. sweetening agents like if necessary and or this whole mixed with feed/fodder also in wet or dry conditions two to three times daily for static or regular maintenance of the animal in good health conditions depending on the health status and milk yield.

For regular feeding the above feed supplement premix as directed, assists in controlling following disorders successfully. India will save total economic loss (Tn₹) 1.14328791 from dairy industry as shown in **Table 1**:

- Buffering agent, improve rumen micro-flora, excessive salivation, gastrointestinal disorders, low fiber acidosis (SARA), bloat ketosis, control heat stress, pica, anorexia, displaced abomasum, colic, bloat, liver abscesses, fatty liver, jaundice, red urine etc.

- Muscular-Skeletal deformities and stiffness, stunted growth, debility, downers syndrome, lameness, laminitis, digital dermatitis and with abnormal eating habits (stone and soil eating, urine drinking etc.), etc.

- Pre-pubertal uterine development, infantile genital, reduction in voluntary waiting period, polycystic ovary, recto-genital prolapsed, cyst control, regularizing uterine tuning, after insemination healthy uterus.

- Milk quality and milk yield enhancer, hypocalcemia (milk fever), hypomagnesemia (grass tetany), udder edema, SCC and mastitis teat muscle relaxing.

- Para tuberculosis, diarrhea, dysentery, coccidiosis, deworming agent etc.

SN	Particulars	Amount
1	Milk produced in 2013 (132.4Mn tonnes)	–0-
2	[1]Milk loss due to anoestrus& repeat breeding Cr. (₹59/kg)	123507.47
3	Number of Female animals after loss of 30–40% (303.310 Mn)	–0-
4	Total number of female animals (505.502Mn)	–0-
5	Total number of infertile females' animals culled (202.210Mn)	–0-
6a	Economic value of total healthy fertile females (₹65,000/animal)	1314365.00
6b	Economic value of total culled females (₹16,500/animal)	333645.50
6c	Economic loss to the country	980718.50
7	Economic loss due to mastitis (clinical & subclinical)	13163.74
8	[2]FMD production loss + vaccine	320.0
9	Thermal stress milk loss (3.2Mn tonnes)	5000.00
10	Stray animals	11607.00
11	Total economic losses for country (India) approximately(2 + 6c + 7 + 8 + 9 = 10 + 11) (Cr)	1143287.91
12	Total economic loss to dairy Industry (Tn₹)	1.14328791

[1]*Cattle and buffalo 30–40% of total population of the cattle i.e., 20–30 mn tonnes = 50000 Cr (National Academy of Agricultural Science New Delhi June 2013).*
[2]*http://doi.org/10.1016/j.prevetmed.2021.105318.*

Table 1.
Estimated economic loss due to health status in India (₹) 2022 year.

- Build up overall immunity towards heat stress, SARA, Jaundice, downers syndrome, FMD and sequel, BQ etc.

For the treatment of inflammatory productive and reproductive diseases in broad view (inflammatory complex diseases such as cystitis, cervicitis, metritis, endometritis, pyometra pneumo-vaginitis, mastitis, and kidney disease for seven days, and the animal is getting improved physically with the health progress with increased daily dry matter intake and milk yield (see **Table 1**).

4. Conclusion

This article describes the various implications and effects of dairy cow metabolic disorders, their effect on clinical and subclinical ascending inflammatory diseases, and management recommendations for prevention. More than 36% the cattle are culled globally as non-productive animals within 59 months of productive life due failure to achieve as the target set by human, not by natural lifespan of the animal. As the industrialization for over production in quantity with negatively impact on health and immunity of the animals by using synthetic medicines, growth promoting hormones and energy dense feed irrespective of the health status of the animal. Antimicrobial resistance is threatening humans and animals worldwide and animal husbandry has entered the era when the use of antibiotics or other pharmaceutical products is increasingly unwelcome as antimicrobial resistant pathogens which may endanger both the animal, public health and environment. Additionally, the presence of antibiotic residues in the environment, may adversely influence the manure treatment systems by inhibition of biogas production and the soil biomass community to establish persistent reservoirs of resistant bacteria. Here we tried to enhance the health and immunity of the cattle by using balanced phytometabolites and minerals supplements in proper proportion with feed concentrate keeping the rumen microflora at its best level to have better digestion and absorption of the nutrient absorption at proper pH without metabolic disorders, therefore having best quality of animal-based protein and milk products and other by-products.

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Conflict of interest

There is no conflict of interest.

Note

The product details of CGEEE strategy in livestock will be provided to concerned after request.

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Author details

Basagonda Bhagavanta Hanamapure
Shree Renuka Vetmin, Bijapur, Karnataka, India

*Address all correspondence to: rudra_dsi@rediffmail.com

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