Differential Diagnosis for Mycotoxicoses in Ruminant



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Differential Diagnosis for Mycotoxicoses in Ruminants, 2023

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Foreword

Working in agriculture has always been a challenge from any given angle. Regardless of the location or the size of an operation, being a farmer requires a complex set of skills such as soil science, animal health, mechanics, building, accounting, meteorology and so many more! However, farmers worldwide are struggling to make profits and continue investing on improving their systems. And what is worse, their average age is increasing because society is failing to attract youngsters to take over the farms of their parents, let alone to start from scratch, without land and equipment.

I dream of a world in which we can farm efficiently not only from an economical perspective but also from a natural resources point of view. We need mechanisms that give farmers fair payment, beyond kilo of meat or milk produced, recognizing the quality of their produce, the biodiversity that is promoted in their lands, the health and longevity of their cows while staying productive, the carbon stockage on their soils and trees and the preservation of cultural heritage, among many other contributions they provide to society. I dream of a world in which your land stewardship and skills are not taken for granted, that they are cherished instead, so that also the younger generations continue this beautiful profession.

This material is dedicated to you farmers. Our goal with the Differential Diagnosis for Mycotoxicoses in Ruminants is to educate and create awareness about the risk of mycotoxins on dairy and beef operations. This topic is not the simplest one and for long it was neglected, but the data is consistent and clear: mycotoxins are present in 60-80% of the crops worldwide (Eskola et al., 2020), and they negatively impact ruminant's health and productivity. We know farmers and technicians might not have time to dig deeply into scientific publications, so our aim was to compile the information in a booklet that outlines some of the most important problems on ruminant farms, explain the possible causes, how to identify them and how to correct them. We hope it is useful for your decision making and promoting healthy conditions for your animals. At dsm-firmenich Animal Nutrition and Health, we can confidently say that we are the experts on mycotoxins and we strive to provide you with solutions and strategies against mycotoxins, so that you have one issue less to worry about.

If you have further questions, please don't hesitate to contact your local dsm-firmenich representative, we will be happy to get in touch.

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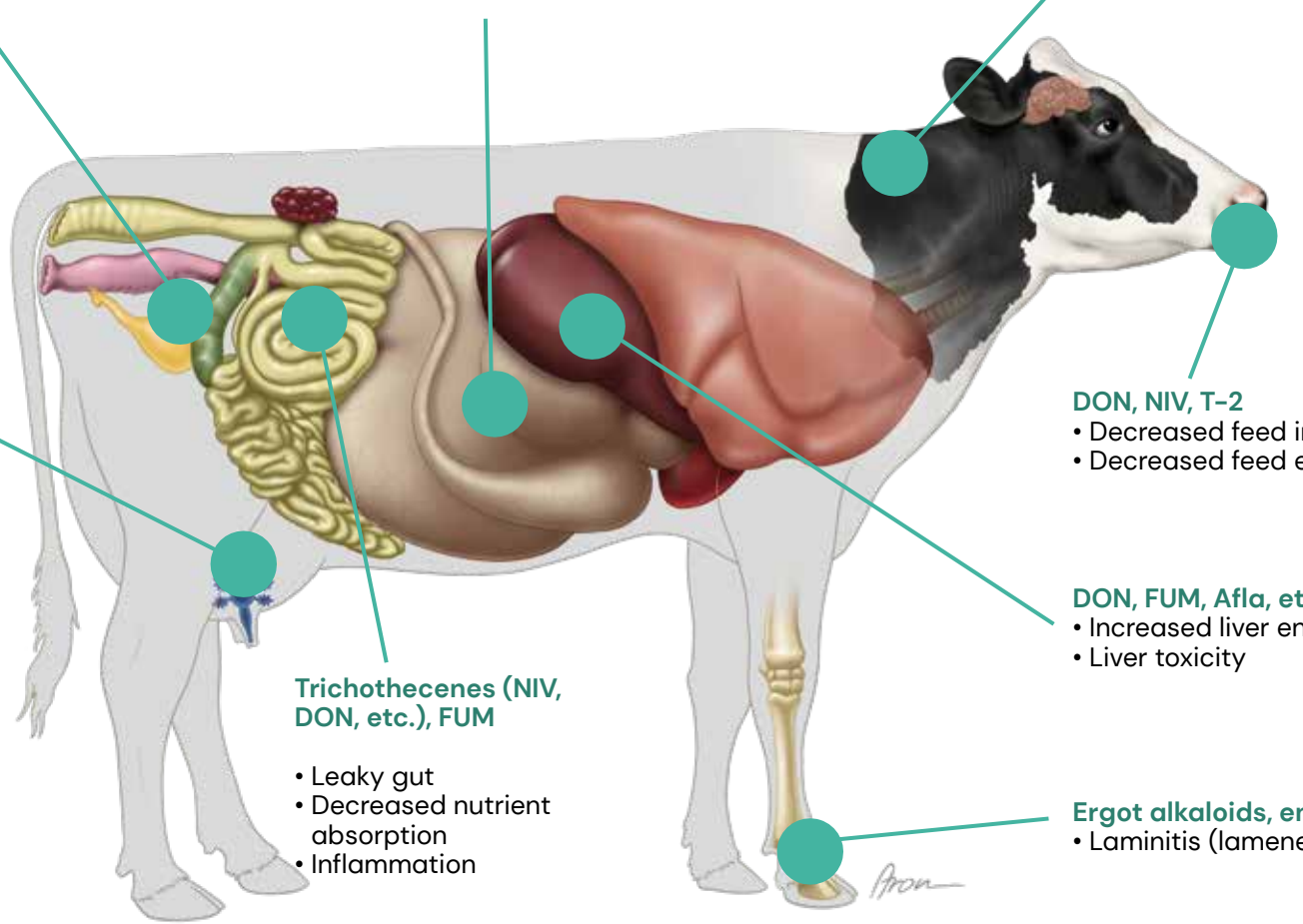


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ZEN, Ergot alkaloids, Trichothecenes (DON, T-2, etc.), Afla
- Irregular heats
- Low conception rates
- Ovarian cysts
- Embryonic Loss
- Abortions
- Low testicular development
- Low sperm production

DON, NIV, T-2, Afla, ZEN, Ergot alkaloids, etc.
- Impaired rumen function
- Diarrhea
- Lower volatile fatty acid production
- Lower microbial protein production
- Decreased rumen pH

Ergot alkaloids
- Impaired thermoregulation
- Convulsions



Afla, DON, NIV, T-2, HT-2, among others.
- Milk contamination
- Decreased milk production
- Mastitis

DON, NIV, T-2
- Decreased feed intake
- Decreased feed efficiency

DON, FUM, Afla, etc.
- Increased liver enzymes
- Liver toxicity

Trichothecenes (NIV, DON, etc.), FUM

- Leaky gut
- Decreased nutrient absorption
- Inflammation

Ergot alkaloids, endotoxins, DON
- Laminitis (lameness)

Meaning of abbreviations:
Afla: Aflatoxins
DON: Deoxynivalenol
FUM: Fumonisins
HT-2: HT-2 toxin
NIV: Nivalenol
T-2: T-2 toxin

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Reproductive Failure

Milk productivity per cow has increased greatly for the last years, partly thanks to genetic breeding. However, this genetic development has happened at the expense of reduced fertility (Veerkamp et al., 2001). Cow fertility plays a very important role on both dairy and suckling cows farm profitability. In the US, the estimated cost of reproductive diseases and conditions (including female infertility, abortions, calving difficulties, retained placenta and metritis) accounts for 1 billion USD (Bellows et al., 2002). An efficient cow should be calving in an interval of 365 days, which includes 9 months of gestation and a specific period of time to be mated and achieve the pregnancy within 90 days after calving. However, most dairy farms struggle to achieve this level of efficiency which becomes an important expense, with every open extra day costing approx. 5.2 USD/ day (Cabrera, 2014).

Additionally, reproductive failure is the most common reason for culling cows, heavily affecting farm economics as it shortens the productive life of cows and requires a replacement heifer. Ensuring reproductive success in suckling and dairy farming is not only relevant to ensure farm profitability but also to reduce the methane emissions per litre of milk, as the emissions from the development until reaching sexual maturity and first calving are spread along a higher number of lactations and less replacement animals are necessary (Grandl et al., 2019).

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How to identify reproductive failure in the farm?

Keeping records is essential to measuring and assessing reproductive efficiency. There are different ways of measuring fertility:

- **Calving interval:** as mentioned before, ideally between each calving there should be 365 days. This way, one calving per year can be obtained.
- **Calving to conception interval:** the time from calving to successful insemination. An ideal CCI of 85 days results in one calf per year. Open days is quite a similar parameter but it counts until cows calved or died
- **Conception rate:** the percentage of cows becoming pregnant after having been bred.

Management

Problem	Check list	Corrective action
a) **Inflammation**, although necessary for uterine involution, restoring damaged tissues and mammary gland involution; when excessive, can lead to feed intake decrease, excessive NEB, poor reproductive performance and lower milk yield. Relevant causes of inflammation are: • Uterus infections after parturition • Mammary gland infections • Bacteria coming through the gastrointestinal tract, especially under leaky gut syndrome (Horst et al., 2021) • Inflammation induced by mycotoxins or endotoxins (Gallo et al., 2020; Humer et al., 2019)	• Keep track of feed intake to identify abnormal reductions • Blood markers of inflammation: » Albumin-to-globulin ratio » Haptoglobin is a very reliable metabolic markers of inflammation (although not so commonly assessed at farm level)	• Ensure adequate management to keep mastitis under control during transition (Check "Mammary gland infections" section) • Increased intestinal permeability: managing risk factors such as ruminal acidosis (Check "Subacute ruminal acidosis (SARA)" section), heat stress, feed restriction (feed delivery and push-up), among others • Minimize sources of stress • Integrate an effective mycotoxin solution against a wide range of mycotoxins
b) **Calving difficulties** may lead to tissue damage, excessive inflammation, subsequent uterine disease and poor reproductive performances (Vieira-Neto et al., 2016)	• Keep track of calving difficulties in the herd, a high frequency of assisted calving may reflect poor management practices	• Ensure that farm workers receive a training on calving procedures and strategies for intervention
c) **Anovular cows**: cows that do not resume ovarian activity soon enough after calving. Main contributing factors are: • Excessive negative energy balance (NEB) (check "Ketosis and fatty liver" section) • Peripartum diseases (retained placenta, metritis, mastitis, among others) (Vieira-Neto et al., 2014)	• Check for cows with no ovarian activity after calving • Evaluate frequently body condition score (BCS) of early lactation cows	• BCS after calving (Check "Ketosis and fatty liver" section) • Minimize infections around parturitions by reducing any factors impacting cow immunity negatively (check "Inflammation & immune suppression" section)
d) **Poor heat expression and detection** can happen because: • Cows can´t exhibit signs of estrus in an observable way. This can be due to: • Low body condition score (BCS), extreme negative energy balance (NEB) • Lameness • Heat stress, among others • Signs undetected by farm staff	• Evaluate frequently BCS, lameness (scoring), heat index and cow comfort in general • Evaluate skills of personnel responsible for heat detection: knowledge on estrus signs	• Minimizing drastic BCS loss (check "Ketosis and fatty liver" section) • Prevent lameness (check "Lameness" section) • Comfortable housing conditions, enough space per cow, heat stress mitigation • Provide trainings on heat detection to the staff • Set warnings on when to expect cows to come/return in heat • Consider using automated activity sensors

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Problem	Check list	Corrective action
e) **Deficient insemination technique:** mistakes at different steps of the artificial insemination routine can lead to failed fertilisation such as semen stocking, handling, placement as well as the timing for insemination (ideally 12 hours after the onset of estrus) (Dalton et al., 2001).	• Ensure adequate training for the inseminator • Make sure that the semen tank is in good conditions and at an adequate temperature • Minimize the time that the straws are kept out of the tank	• Provide adequate maintenance to the semen tank • Implement periodical trainings on artificial insemination to the people responsible for it (Dalton et al., 2021)
f) **Insemination operations:** artificial insemination (AI) should be performed in smooth and non-stressful conditions to maximize chances of conception.	• Check AI conditions for cows: restraint area, time the cow is restrained from group, external stressors • Check AI conditions for AI technician: access to the cow, cow to be properly restrained, behaviour of the AI technician	Restrained cow should: • be placed in a non-stressful environment • not be restrained more than 4h • be provided accessible water • be kept close to some mates AI technician: • must handle the cow with care to minimize stress • should be patient with tough cows
g) **Heat stress** can reduce conception rates and extended open days by: • Reducing estrus expression • Inducing ovarian cysts development • Causing hormonal unbalance (altered follicle development) • Higher embryo mortality (Kelly & Amaral-Phillips, 2016)(Becker et al., 2020)	Monitor temperature and relative humidity during the day. • Consider using ruminating sensors to assess heat stress • Observe breathing rate and overall comfort of the cows	Management strategies: • If necessary, provide artificial ventilation and sprinklers for all animals (including dry cows) • Provide enough access to water • Nutritional strategies: • High NDF digestibility of diet has even higher relevance during hot months of the year • Set supplies of K, Mg and Na to the high thresholds of nutritional guidelines to compensate losses through sweat





A dairy cow herd affected by zearalenone which can be identified by the visual signs of vulva enlargement. Additionally, many cows showed diarrhea, nymphomania (even if pregnant) and no response to hormonal treatment. During the pregnancy check after insemination, many cows were diagnosed as aborted and having cases of cystic ovaries (follicles with diameter over 20 mm, observed with ultrasound). After analysing, the barley hay fed to those cows was contaminated with 1380 ppb ZEN, which was being fed at around 4 kg/cow/day.

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Nutrition

Problem	Check list	Corrective action
a) **Excessive negative energy balance (NEB):** high energy demands and low DMI around parturition result in NEB, a common condition in mammals. However, when too severe and prolonged, NEB can lead to excessive body fat mobilization, ketosis, fatty liver, depressed immune function and relevant hormonal disorders that impair cow fertility.	• Minimize severity of NEB (check "Ketosis and fatty liver" section) • Keep track of excessive BCS loss during the first 6 weeks of lactation	• Balance controlled-energy diets for far-off and close-up groups aiming at a maximum body condition score (BCS) of 3,5 (on a 1-5 scale) before calving • Maximize feed intake after calving through feeding frequency, feed push-up, pen density and particle size • Check "Ketosis and fatty liver" section
b) **High blood urea levels** can result from excessive nitrogen feeding or inadequate protein:energy balance of the diet. High blood urea concentrations can impair oocyte formation at different stages (Jorritsma et al., 2003). This can delay the ovarian cycle or compromise oocyte quality.	Check for protein efficiency (ratio of milk total protein : dietary total protein). Low efficiency is highly correlated with excessive N in milk (MUN) • Monitor fluctuations of MUN or BUN • Monitor other causes or elevated MUN, such as heat stress and local or systemic inflammation	• Balance energy and protein according to a well-established nutritional system • Avoid sudden changes in diet • Re-adjust diet throughout the seasons (changes in grass composition) or when a new silage is opened to avoid mismatch and excess of protein
c) **Mineral and vitamin imbalances** are essential for physiological functions (such as immune function or antioxidant status), inadequate mineral and vitamin supply negatively impact reproductive capacity • **Vitamin A and carotenoids:** oocyte development, necessary for embryo growth, deficiencies can lead to embryo loss • **Vitamin D** • Vitamin E and selenium are the most relevant antioxidants and are essential for hormonal integrity, embryo implantation and immune function enhancement • Cobalt (Co) deficiency can lead to can impair embryo development • Zinc (Zn), manganesum (Mn) and Copper (Cu) have an implication in enzymes mediating the phagocytosis and killing of bacteria by neutrophils. Defficiencies of these nutrients can increase risk of metritis and endometritis (Bicalho et al., 2014)	• Check dietary contents of minerals and vitamins in the mineral mix or premix • Analyze TMR or individual feedstuffs for quality control • Particular focus on Calcium, Phosphorus, Zinc, Manganese, Copper, Cobalt, Vitamin A, b-carotene, Vitamin D and Vitamin E supplies (implications in immune function or antioxidative status) • Consider the fluctuations in nutrient demand for specific stages (dry, transition, lactating)	• Ensure adequate supplementing with the feed formulator/ nutritionist for each of the stages of lactation • Preferably use sources of micronutrients showing the highest absorption in the digestive tract
d) **Phytoestrogens** in forages are plant compounds with similarity to estrogens which can impair normal reproduction function (Wocławek-Potocka et al., 2013).	• Sample feeding material and submit to an HPLC or LC-MS/ MS analysis	• If high amounts of phytoestrogens are found avoid use of this cut or dilute its use in the ration. • There's no practical way to bind or deactivate these components





Jersey dairy cow with a corporal condition 3.5 and 150 days in milk exposed to a concentrate feed contaminated with DON (6140 ppb), FB_1 (330 ppb) and ZEN (434 ppb). The symptoms started by a heavy diarrea and anal prolapse.

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Diseases

Problem	Check list	Corrective action
a) **(Clinical and Subclinical) Uterine infections:** up to 50% of dairy cows are affected by metritis, purulent vaginal discharge, endometritis or cervitis after calving (LeBlanc, 2014). The main causes are: • Impaired immune function, excessive inflammation • Inadequate calving operations, poor hygiene • Calving difficulties, hypocalcaemia, retained placenta	Uterine infections vary in symptoms and can be assessed by: • Urinary test stripes • Cytology tests • Purulent vaginal discharge (observable with vaginoscope, gloved hand or Metri-check device) • Clinical metritis observable through cervical diameter measurement	Treatment: • Discuss with your veterinary about the best antibiotic and anti-inflammatory treatment Prevention: • Uterine lavage with sterile saline solution is recommended (Arias et al., 2018) • Enhance immune function (check "Inflammation & immune suppression" section) • Follow recommendations for calving operations • Ensure hygienic conditions during parturition
b) Different **infectious diseases** can reduce reproductive performance of dairy cows, among the most relevant are: • Bovine viral diarrhea (BVD) • *Leptospirosis* • *Neospora caninum* • *Haemophilus sommus* • Infectious bovine rhinotracheitis/ infectious pustular vulvovaginitis (IBR/IPV) • *Ureaplasma* spp. • *Mycoplasma* spp. • Vibriosis, caused by *Campylobacter fetus* • Trichomoniasis, caused by *T. foetus*	• Consult your veterinarian about the best ways to identify and diagnose any of the potential infections • Request health certificates and vaccination record of newly coming animals before purchase or from bulls before insemination	• Follow a vaccination plan according to the recommendations of your veterinary • Once an infection is identified, the best is to remove the animal from the herd as soon as possible to avoid dissemination in the herd
c) **Lameness** has been related to losses in fertility due to a general alteration of the wellbeing of the cow (Huxley, 2013).	• Check "Lameness" section	• Check "Lameness" section
d) **Mycosis/aspergillosis** infection is caused by several *Aspergillus* spp. (A. fumigatus the most prevalent) and it expresses mainly as a respiratory disease. However, it can also cause abortion (mainly at 6-8 months of gestation), sometimes followed by pneumonia or endometritis.	• Check conditions of the silage or hay. Mouldy feed is more likely to be contaminated with *Aspergillus* spp.	• Procure hygienic storing of feeding materials • Follow good ensiling practices to avoid development of *Aspergillus* spp. in silage • Avoid feeding excessive mouldy materials if possible

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Mycotoxins

Problem	Check list	Corrective action
a) **Zearalenone (ZEN)** can bind to estrogen receptors and cause serious hormonal unbalances that can result in: **In prepubertal heifers:** • Hypertrophy of genitalia and udder development in prepubertal individuals **In cows:** • Difficulties to detect estrus (false heats create confusion) • Changes in uterine morphology • Ovarian cysts • Decreased embryo survival, abortions **In males:** • Decrease in testosterone production, feminization • General infertility • Decreased testicle weight	• Analyse raw materials for mycotoxins • Check for abnormal vulva or genitals inflammations • Sample silage and submit to an HPLC or LC-MS/MS analysis • Sample feed regularly and submit to an HPLC or LC-MS/MS analysis • Monitor number of heat events occurring outside the normal time frame (18-24 days), analyse feed for Zearalenone if the number is higher than usual.	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
b) **Aflatoxins (Afla):** **In females** • General hormonal imbalance leading to general failure in reproduction (Amin et al., 2019) • Follicle atresia and damage. • Ovarian cysts **In males:** • Sperm DNA damage, impaired fertilization (Shan, 2019)	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
c) **Ergot alkaloids:** **Heifers and cows:** • General endocrine unbalance by: » Altering levels of reproductive hormones » They can act as dopamine receptor agonists » (interference with correct ovulation, luteal function and pregnancy maintenance) • They cause vasoconstriction and can limit the transfer of nutrients to the foetus thus impacting negatively on the birthweight and development of foetus. • Can lead to abortion **Males:** • Reduced fertilizing capacity of the semen • Decrease in sperm concentration • Reduced sperm endurance to freeze storage conditions (Klotz, 2015; Rodrigues, 2014)	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis • Check for presence of sclerotia in rye, triticale, wheat, barley and oat • Check for visual signs of ergot contamination: » Diarrhea » Vasoconstriction (ears, tails, feet) can be observable by some degree of necrosis » Lameness » Rough hair coat » Strange nervous reactions like excitability, tremors and inability to cope with heat	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins

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Problem	Check list	Corrective action
d) **Deoxynivalenol (DON)** due to its ribotoxic, antioxidant and inflammatory effect: • May inhibit estrogen and progesterone secretion in granulosa cells • Can inhibit steroidogenesis in bovine granulosa cells and increases cell death rate in vitro (Guerrero-Netro et al., 2015)	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
e) **T-2 toxin,** due to its ribotoxic, antioxidant and inflammatory effect: • can cause delayed ovulation after prostaglandin treated • can exert toxic activity over granulosa and luteal cells (Huszenicza et al., 2000)	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
f) **Mycotoxins in general**, such as Afla, FUM, DON and T-2 have proven to be able to alter and interrupt vaccine-derived immunity in mammals (Oswald et al., 2005). As many diseases can impair reproduction (according to "Reproductive failure" section, Diseases, textbox b) and vaccination is used to immunize or reduce the impact of such diseases; mycotoxin risk management may be of high relevance to ensure the efficacy of such vaccination programs.	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins





Uterine prolapse presumably caused by exposure to zearalenone through a concentrate contaminated with DON (542 ppb), FUM (375 ppb) and ZEN (387 ppb)

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Ketosis and Fatty Liver (Subclinical)

These two conditions can result from fat excessive mobilization that cows undergo in response of excessive negative energy balance (NEB), among other reasons. NEB is a term used to explain when the output of energy (through the development of the calf, gestation, and subsequent milk production) by the cow is exceeded by the input of energy (through feed intake), which is reduced due to lower feed intake, typical around calving. This period lasts from approximately week -2 until week 6 related to the birthdate (week 0). After that period is passed the cow should have recovered intake and supply its energy demands solely from feed. However, cows that suffered excessive body fat mobilisation may take up to 20 weeks to regain a positive energy balance status (Taylor et al., 2004).

Under NEB condition, the organism unleashes hormonal changes which will stimulate the cow to mobilize fat from adipose tissue in form of non-esterified fatty acids (NEFAs) to supply energy. NEFAs will travel to the liver via the bloodstream where they will be oxidized, generating energy and ketones (acetone, acetoacetate and BHB), and any excess will be esterified and converted into triglycerides (TAG) which will pass by the liver. A portion of TAG will be exported from the liver; however, this happens at a very slow rate, thus another portion of TAG will accumulate in the liver. Excessive TAG in the liver impairs its normal functions; among them, the process of gluconeogenesis, which enables the organism to get out of the loop of fat mobilization. A cow under fatty liver syndrome is surely under ketosis but a cow under ketosis is not necessarily under fatty liver conditions. Fatty liver results from a more aggravated level of NEB.

Ketone bodies at high concentrations can decrease the physiological function of organs due to their toxic effect. High ketone bodies and fat circulation in blood decrease the rates of ß-oxidation, gluconeogenesis and the citric acid cycle in liver cells, as well as insulin sensitivity, thus less glucose enters the cell. Under these conditions it is more difficult for the liver to produce and absorb the much-needed glucose for the cow during the transition stage, forcing it to mobilize even more fat. The concentration of ketones in blood will determine the degree of ketosis. NEB is a normal condition during the first weeks around calving, however the typical drop in feed intake has been proven to be more drastic on over-conditioned cows (Body condition score (BCS) >3.5), where a higher amount of fat is mobilized within very few days.

General negative effects:

Immunological:

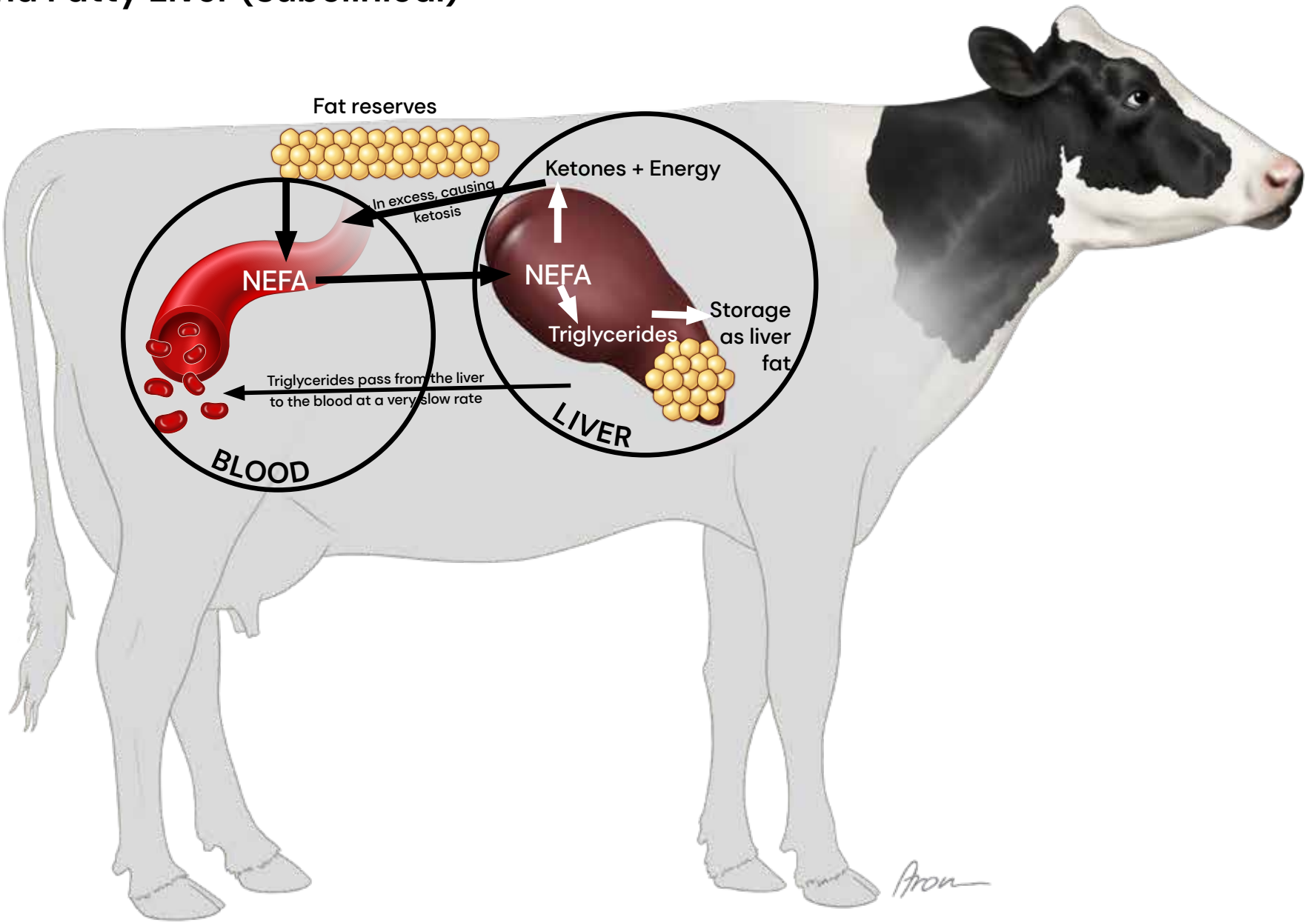
During ketosis and fatty liver, the levels of white blood cells (e.g., leukocytes, lymphocytes, monocytes and neutrophils) are decreased. The accumulation of lipids in the liver directly affects the immune response by altering the ability of the liver to synthesize and degrade the components involved in the immune response and finally their arrival to sensitive areas (ex: mammary gland, reproductive apparatus, etc.). Additionally, during these conditions, a decreased capacity of clearance of toxins and mycotoxins due to an unproperly functioning liver will also expose the animal to endotoxins, mycotoxins, etc.

Reproductive:

Excessive weight loss during the first 30 days of lactation is associated to delayed ovulation. Some of the reasons are that under NEB conditions there is a decrease and delay in progesterone and luteinizing hormone synthesis as well as lower oocyte quality and survival due to toxic NEFA concentrations, among others. Since fatty liver and ketosis disorders decrease immune response in the uterus, a higher incidence and severity of uterine infections may occur (Leroy et al., 2005).

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Ketosis and Fatty Liver (Subclinical)



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How to identify fatty liver and ketosis in the farm?

Diagnosis of these conditions is complicated to do just by observation, but some signs hinting to clinical stages of ketosis and fatty liver are the following:

- sudden and fast loss of condition (2-4 days)
- reduced appetite
- glazed eyes
- breath with an acetone smell
- exaggerated licking
- excessive salivation and chewing movements

- **in blood:** subclinical ketosis is defined as blood serum BHBA above a threshold (e.g., 1,200 µmol/L) (Enjalbert et al., 2001; Geishauser et al., 1998)
- **in milk (still not so common as a way of diagnosing):** increased concentrations of BHB in milk. The cut-off concentration of BHB in milk set at ≥0.080 mmol/L (AUC=0.91±0.03; p<0.001) is a significant indicator for subclinical ketosis in dairy cows (Ježek et al., 2017).

The following points are all focussing on the reduction of length (amount of days on NEB) and depth (amount of energy mobilized from fat reserves) of NEB to prevent fatty liver and ketosis but also towards supporting the liver health and avoiding other stress factors, especially during transition period. There are some treatment possibilities, but these vary according to the veterinarians advise and severity of the case.

Management

Problem	Check list	Corrective action
a) **Overfeeding during dry period** until peri parturition. Cows above body condition score (BCS) 3.5 will mobilize more fat, reach higher concentrations of circulating fat, and take longer to recover feed intake than cows below BCS 3.5.	• Monitor BCS frequently. Any tendency of over-conditioning should be detected as early as possible to avoid BCS close-up	• Ensure that cows reach BCS 3-3.5 at parturition
b) **Low dry matter intake (DMI) after parturition:** • Due to inflammation processes around parturition, fresh cows reduce feed intake. However, severe and prolonged intake reduction can induce the cow to mobilize higher amounts of fat than normal, increasing the risk of ketosis and potentially fatty liver.	• Keep track of feed bunk emptying to make sure the cow is eating as soon after calving as possible • Monitor body condition score (BCS) in fresh cows´ pen • Assess quality of forage fed to cows	• Stimulate feed intake by feeding highly palatable ingredients and if possible, complement with organoleptic (flavor and smell) enhancers • Oral cobalt sulphate solution and/or B complex vitamins are commonly used to stimulate the appetite (Haass & Eness, 1984) • Make sure the cow can easily access to the feeding area without any stress
c) **Subacute Ruminal Acidosis (SARA)** can be an important factor of risk for the development of ketosis (Pechová & Nečasová, 2018). First through reduced energy uptake during transition by limiting feed digestibility and nutrient uptake, thus inducing the need to mobilize fat reserves. Second, SARA can also contribute by acidifying the rumen and inducing release of endotoxins, which can further cause toxicity to the liver and generalized inflammation.	• Check "Subacute ruminal acidosis (SARA)" section	• Balance diet to source high energy during early lactation but managing risk for SARA • Provide enough effective fibre to ensure proper rumination • Include buffers accordingly to manage rumen pH • For more recommendations check "Subacute ruminal acidosis (SARA)" section
d) **Lack of homogeneity in the herd**: Having too much difference between cows in breed and size, makes it difficult to feed precisely. resulting in either over feeding or underfeeding according to the cows' requirements.	• Important factors here can be breed, number of lactations known or expected productivity of a cow, etc. • Evaluate the possibility of keeping cows in groups to feed them according to their needs	• When possible, keep primiparous and multiparous cows separate to provide conditions according to specific needs • Sort cows at the dry cow's pen or top feed with the required ones • Avoid mixing too much the herd with different breeds
e) **Stressors (e.g., heat, social, handling)** can lead to different effects such as increased respiratory rate, reduction in feed intake and even leaky gut (causing systemic inflammation and liver damage) Additionally, it might affect metabolic pathways within the liver (Skibiel et al., 2018).	• Keep track of heat index daily fluctuations • Evaluate cow comfort • Check the animal handling practices of the farmer and employees	• Condition barns to ensure comfort (ventilation, fresh air, sprinklers, etc.) • Avoid altering the cow grouping too often • Ensure cow comfort in the areas where they lie

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Nutrition

Problem	Check list	Corrective action
a) **Insufficient glucogenic*** components in the diet: if levels of glucose in blood are low, the hormonal response will stimulate fat mobilisation. *Glucogenic nutrients are any materials that act as a precursor of glucose, the most important is starch.	• Discuss with your nutrition consultant if the concentrations of carbohydrates (fermentable and non-fermentable) in the diet formulation are sufficient • Do not overfeed starch in the diet to avoid subacute ruminal acidosis (SARA) • Observe the acceptance of the available feedstuffs by the cow • Analyze mycotoxins as these might induce a lower feed intake (especially trichothecenes)	• To maximize glucose uptake, discuss with your nutrition consultant the levels of glucogenic components included in the ration considering the following points: » Increasing blood glucose will supress fat mobilization » Some potential precursors of glucose are glycerol, propylene glycol, alanine or other amino acids (Allen & Bradford, 2019) » Make use of enzymes that increase starch digestibility
b) **Low quality** (organoleptic, nutrient content or mycotoxin contamination) of feed post parturition	• Observe the acceptance of the available feedstuffs by the cow • Analyze mycotoxins as these might induce a lower feed intake (especially trichothecenes	• Ensure the best quality of feed available is fed to the fresh cows • Prevent mould growth by good silage management practices and use of silage inoculants • Integrate an effective mycotoxin solution against a wide range of mycotoxins
c) **Insufficient antioxidants and vitamins:** This is not a direct cause for fatty liver, but the lack of certain nutrients might add up to the liver function problems (Bobe et al., 2004). Some nutrients of relevance to consider and check their sufficiency are cholin, vitamin E, Selenium, cobalt and B-complex vitamins (Haass & Eness, 1984).	• Review the content of nutrients in the basal diet and the supplements offered	• Consider investing in transition specific supplementation which should have higher inclusion of antioxidants and vitamins
d) **High butyric acid concentration in the silage** can increase the concentrations of plasma BHBA (ketones) as well as limit dry matter intake (DMI)(Oetzel, 2007).	• Assess quality of silage by smell at the opening time • Analyze silage to monitor quality	• Follow guidelines for good silage making and emptying practices. • •Use additives to promote a lactic fermentation and a quick pH decrease

Disease

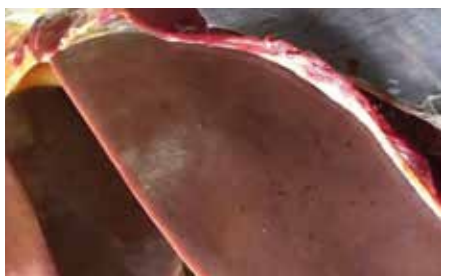
Problem	Check list	Corrective action
a) **Endotoxins or Lipopolysaccharides are** cell wall components from gram-negative bacteria that are released when bacteria die and cause inflammatory effects. Endotoxins might originate from mammary or uterine infections, but greater amounts derive from low rumen pH caused cell death (due to subacute ruminal acidosis (SARA)). Exposure to endotoxins can result in higher fat mobilization, liver damage and decrease of liver function thus can represent a factor of risk for fatty liver (Eckel & Ametaj, 2016).	• Difficult to assess	• Avoid SARA conditions, check "Subacute ruminal acidosis (SARA)" section • Integrate the use of an endotoxins binder to adsorb in the rumen and avoid their negative effects in the animal

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Mycotoxins

Problem	Check list	Corrective action
a) **Aflatoxins (Afla)** cause heavy hepatotoxic effects that would increase the liver damage thus aggravating inability to synthesize hormones according to its needs under complicated metabolic conditions, therefore can promote fat accumulation in the liver.	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
b) **Trichothecenes** (e.g., DON, NIV, DAS, T-2, HT-2, among others) cause ribotoxic stress in all cells of the body but particularly impact very active tissues (high cellular turnover rate) like the liver. These relevant group of mycotoxins provoke oxidation, inflammation and even cell death in the liver cells. Even at lower concentration increased liver enzymes can be expected (ASH and GGT) as well as some increases on markers of inflammation (Duringer et al., 2020; Gallo et al., 2020). Trichothecenes harm liver health and limit its adequate function.	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
c) **Fumonisins (FUM)** can influence concentrations of AST and GGT in blood (liver health markers), which indicates liver damage (Diaz et al., 2000; Hartinger et al., 2022; Mathur et al., 2001). In other species, increased triglycerides and cholesterol concentration in blood were observed after fumonisin exposure (Rauber et al., 2012).	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
d) **Zearalenone (ZEN)** is an estrogenic mycotoxin, with the ability to bind to estrogen receptors. Elevated levels of estrogen are known for inducing lipogenesis in the liver of cows (Grummer et al., 1990) and are considered as contributing factor to lipid accumulation in the liver (Katoh, 2002).	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • • Integrate an effective mycotoxin solution against a wide range of mycotoxins
e) **Many other mycotoxins** are known to be able to cause feed refusal, inflammation and liver toxicity. The result of this is an attenuation of the NEB.	• Sample silage and concentrate and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins





Rounded edge livers observed during the biopsy of an animal affected by a feed contaminated with DON (400 ppb), FUM (1000 ppb) and α-ZEL (2847 ppb)



Constant push up of feed to ensure highest feed intake possible. Referring to Subacute ruminal acidosis (SARA), management, d.

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Lameness

After reproductive failure and mastitis, lameness is the third major problem in dairy farming as perceived by producers. Lameness can stem from both, non-infectious and infectious diseases. The two are often interconnected as bacteria find their way into the organism through mechanical lesions.

Non-infectious: mechanical damages to the hoof and its different components (sole, wall, white line, corium, etc.):

- **Laminitis:** inflammation of the lamina/corium due to vascular disturbances that preclude the normal diffusion of oxygen and nutrients from the blood flow to the corium, resulting in production of poor quality or defective claw tissue. Laminitis also leads to the weakening of the suspensory apparatus of the claw, leading to mechanical stretching that allows the claw bone to rotate and sink in the hoof.
- **Sole ulcers:** highly painful lesions often associated with stone bruises usually when the soft tissues inside the hoof are damaged and the horn becomes softer than normal. If the corium gets exposed through the ulcer, penetration of pathogens can lead to major infections.
- **White line disease:** result from the separation of sole and outside hoof wall, which leaves openings that allow penetration of foreign materials and potential infections.

Infectious: related to infectious organisms, often bacteria.

- **Digital/interdigital dermatitis:** a bacterial disease that affects mainly the skin of the heel. This infection causes inflammation and skin damage which leads to pain and discomfort.
- **Foot rot:** a highly infectious disease characterized by the entrance of bacteria (e.g. *Fusobacterium necrophorum*) through any kind or degree of interdigital skin lesion. This infection then spreads to the different tissues, joints and tendons in the foot resulting in severe pain.

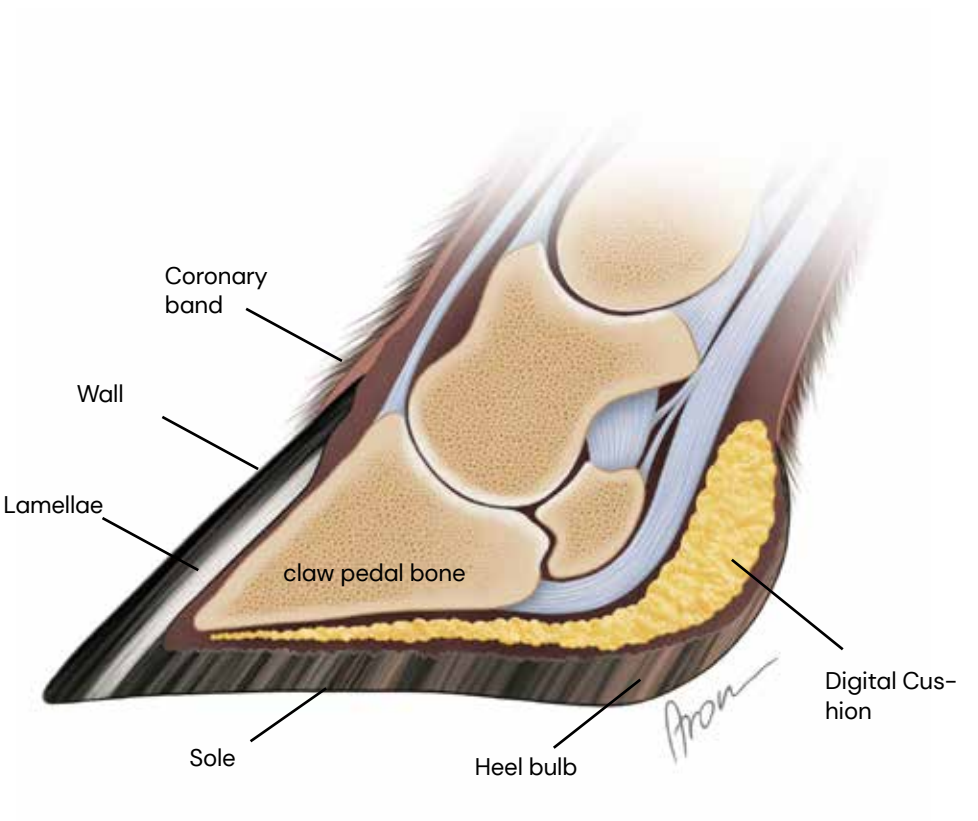
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How to identify lameness in the farm?

There are existing methods to score mobility in dairy cows which are highly recommended to identify from the moment early signs of lameness appear. Consult your veterinarian for the most suitable scoring method to the needs of your farm

General Indicators of lameness include:

- back arching
- legs swinging in an out
- short steps
- head bobbing
- leg joints stiffness
- reluctance to bear weight in one or more hoofs

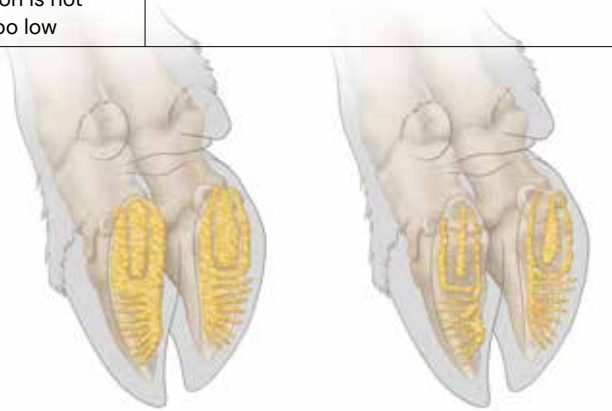


Graphical description of the anatomy of the hoof.

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Management

Problem	Check list	Corrective action
a) **Lower body condition score (BCS)** cows are more likely to develop lameness problems. The thickness of the digital cushion ("fat pad") decreases as body fat diminishes. This leaves the corium less protected, and more susceptible to damage.	• Regularly assess BCS • Keep track of feed intake	• Promote feed intake to recover BCS at 2.5–3.5 • Avoid excessive body condition loss post-calving, check "Ketosis and fatty liver" section
b) **Excessive standing time**: the longer the cow stands during the day, the higher the risk for sole and hoof lesions. A cow naturally spends many hours of the day lying, and this is important to avoid excessive physical stress on hoof tissues.	• Observe the comfort of the cows at the cubicle, considering lying area, lying material and comfort. • Rule of thumb: >80–90% of cows in the stalls, should be lying or eating • Adequate lying time: > 11–12 h/day (Tucker et al., 2020)	• Ensure at least 5% more cubicles than cows • Provide enough bedding material thickness, temperature and dryness as cows prefer soft, warm and dry lying space • Manage heat stress: cows suffering from it tend to stand longer to dissipate heat • Avoid competition at the feeding line: keep heifers and older cows separated (if possible), ensure 50–60 cm bunk space for each cow
c) **Cows around parturition** are more subjected to hoof injuries due to laxity of tendons and ligaments.	• Put special attention at signs of lameness occurring in pre-calving and early lactation	• Housing comfort should be maximum from 4 weeks before calving to 8 weeks after calving in animals at higher risk
d) **Insufficient or inadequate hoof trimming** • Uneven weight distribution increases chances to develop lameness • Untreated hoof lesions tend to worsen if not treated	• Assess locomotion score regularly (e.g., monthly) • Lame cows need to be re-assessed more often	• Prevention: Schedule trimming for cows without locomotion problems twice per lactation: early dry-off and mid-lactation • Treatment: Trim cows with locomotion score ≥ 3 immediately
e) **Confinement on hard surfaces** (concrete) increases the likelihood of lameness compared to rubber mats or grazing conditions.	• Observe and evaluate the areas were cows lie or move around to identify slippery and dirty areas that can impact hoof health	• Whenever possible, implement the use of rubber mats in walkways, milking station, etc. • Especially on hard surfaces, behave calm and gently when moving animals. Sudden and uncontrolled movements result in more injuries.
f) **Environmental hygiene** • Standing in slurry leads to the spread from cow to cow of the pathogens that cause hoof infectious diseases • Inadequate foot bathing occurs when the foot bath solution is not changed frequently or the disinfectant concentration is too low	• Observe the areas of transit and permanence of the cows and point out the areas that need scrapping or draining • Regularly check the cleanliness of foot bath solution	• Increase scrapping frequency when possible • Reduce stocking density • Implement an efficient foot bathing protocol: optimal schedule and solution vary from farm to farm



Graphic comparison between a healthy (left) and undercontidioned (right) cow, the latter having poor fat reserves which results on weaker digital cushion or "fat pad" (represented on yellow) and potentially causing lameness.

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Nutrition

Problem	Check list	Corrective action
a) **High concentrate diets leading to Subacute Ruminal Acidosis (SARA)** can cause excessive endotoxin release in the rumen, which triggers laminitis. This is a simplified cascade of events: excessive carbohydrate feeding → low rumen pH (SARA) → death of gram-negative bacteria → release of endotoxins → translocation of endotoxins in blood stream → vascular disturbances → laminitis.	• Check "Subacute ruminal acidosis (SARA)" section	• Check "Subacute ruminal acidosis (SARA)" section
b) **Biotin deficiency** could affect cows fed high-grain diet, since microbes responsible for biotin synthesis are sensitive to low rumen pH (Girard, 1998). Biotin supplementation provides benefits to claw health and prevents lameness (Langova et al., 2020).	• Check if biotin is part of the feed formulation, particularly during transition stage	• 20 mg Biotin/cow/day are recommended, according to trials done for preventing lameness (Girard, 1998; Langova et al., 2020)
c) **Trace minerals deficiency** e.g., **zinc and copper** are essential cofactors for enzymes involved in keratin production. Supplementation of these trace minerals could help to reduce the incidence of hoof disorders (Osorio et al., 2016).	• Check trace mineral content and source in through mineral mix and diet in general	• Discuss with your nutritionist the adequate supplementation of an organic form of zinc and copper






Hoof red lines and inflammation apparently induced by exposure to a concentrate contaminated with DON (851 ppb), NIV (105 ppb), FUM (300 ppb) and Ergot alkaloids (250 ppb), being the latter the main toxin responsible for these symptoms.

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Mycotoxins

Problem	Check list	Corrective action
a) **Ergot alkaloids** are vaso-active toxic compounds that can cause severe vasoconstriction of the small arteries. The most affected areas of the body are extremities, ears and tail. This can cause lameness in ruminants and in extreme cases the swelling at hock joints can lead to the loss of hooves or gangrene. This phenomenon is usually called "fescue foot"(Klotz, 2015).	• Sample feed, but mainly pasture and hay and submit to an HPLC or LC-MS/MS analysis • Check for other visual signs of ergot contamination: » Diarrhea » Vasoconstriction (ears, tails, feet) can be observable by some degree of necrosis » Rough hair coat » Strange nervous reactions like excitability, tremors and inability to cope with heat	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
b) **Aflatoxins (Afla)** have been associated to lameness problems although the mechanism of action has not been clearly elucidated (Özsoy et al., 2005).	• Sample feed and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
c) **HT-2 and T-2 toxin** are known to have vasoconstriction effects in mammals (Wilson & Gentry, 1985), therefore can also be a cause for swelling or gangrene.	• Sample feed and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
d) **Mycotoxins in general:** by having a substantial antibiotic effect, mycotoxins are responsible of bacterial death in the rumen and possible subsequent endotoxin release (Baumgard et al., 2020).	• Sample feed and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins





Signs of impaired circulation in ears, legs and nose, as well as lameness and hoof pain induced by exposure to a concentrate contaminated with DON (410 ppb), NIV (155 ppb), FUM (300 ppb) and Ergot alkaloids (324 ppb), being the latter the main toxin responsible for these symptoms.

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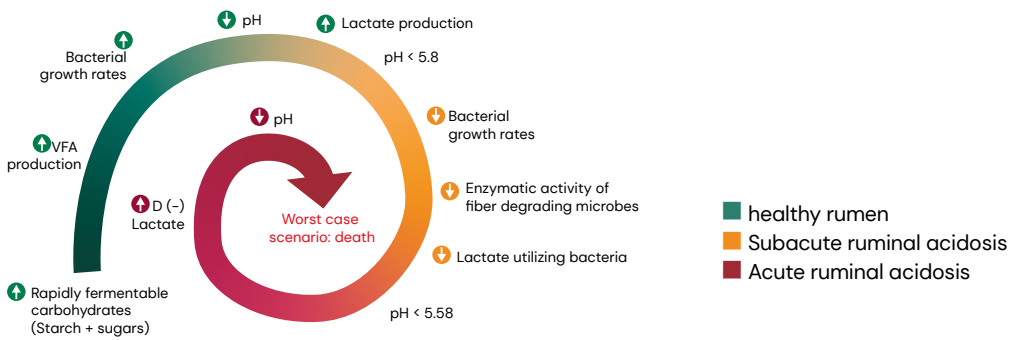
Subacute Ruminal Acidosis (SARA)

SARA is the most important nutritional disease in ruminant farming. In certain developed dairy farming countries, SARA is reported to be present in 11-29% of early lactation cows and 18-26% of mid-lactation cows (Abdela, 2016; Kleen et al., 2013). According to estimations, SARA costs the North American dairy industry between € 500 million and € 1 billion annually, with costs per affected cow estimated at USD 1.12 per/cow day (Mutsvangwa & Wright, 2021).
High yielding cows have a high demand of energy, particularly in the beginning of the lactation, where glucose is very intensively metabolized to supply energy for the increasing milk production. At this point, the best way to provide energy is via glucose precursors such as starch. Nevertheless, starch is a very rapid fermentable carbohydrate and high concentrations of it, accompanied by insufficient chewing activity leads to increased production of lactic acid and a drop of the rumen pH. As a consequence, low ruminal pH reduces the diversity and population of microbiota, thus limiting the adequate digestion of nutrients. Many factors may influence the severity of this condition, such as amount of rapidly fermentable carbohydrates, insufficient fibre causing low saliva production, TMR sorting, among others. Rumen acidosis can be classified in two different levels:

- **Subacute ruminal acidosis (SARA):** no clinical signs are observed; however, pH goes below 5.8-5.6 for 3-5 hours a day, which compromises an adequate function of the rumination and digestion of cows.
- **Acute ruminal acidosis:** the most extreme way, when clinical signs are predominant and ruminal pH depression is most severe, falling below 5.0.

Acidosis predisposes to various other disease conditions such as leaky gut, liver abscesses, haemorrhagic bowel syndrome and lameness, among others. Maximizing milk production and nutrient adequacy without incurring in SARA is a major challenge for the dairy farming industry.

SARA and mycotoxins are closely related problems and the extent of damage that mycotoxins can cause to ruminants varies with the pH of the rumen. Some mycotoxins can be partly degraded by the rumen microorganisms, but this degradation is much lower if the rumen pH is low (especially for trichothecenes e.g., DON, NIV, DAS, T-2 and HT-2) allowing more mycotoxins to be absorbed intact. SARA can increase likelihood of mycotoxin intoxications but in the opposite way, mycotoxins can also have an impact on acidosis in cows (explained in the table).



Description of chain of events from a healthy rumen to a rumen under conditions of acidosis (Adapted from Nocek, 1997)

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How to identify SARA in the farm?

- **Dry matter intake (DMI):** The different degrees of acidosis can be identified by a decrease in DMI
- **Diarrhea – manure assessment:** It is very important to constantly observe and assess the quality of the manure. SARA can be associated to lose, yellowish feces with observable undegraded grains and fibers
- **Milk fat:** depressions can be commonly associated to alterations in the digestibility, especially of fiber and therefore can be linked to SARA.
- **Fat: protein ratio** becomes lower than 1.0

Management

<table>
<tr><th>Problem</th><th>Check list</th><th>Corrective action</th></tr>
<tr><td>a) Fibre particle size in the TMR. If particles are too big, it will allow cows to sort and eat less fibre and more rapid fermentable carbohydrates. If particles are too small, it could limit chewing activity and capacity to ruminate. Larger particle size increases the chewing rate which would increase the production of saliva (much needed for buffering rumen pH).</td><td>• Verify that the fibre sources have a maximum length of 5 cm (Bhandari et al., 2007)
• Observe the eating behaviour and whether the cows are sorting their mixed feed
• Observe the feeding bunk after the cows are finished eating and compare the leftover amount with the initial TMR to understand how much the cows are able to sort at the end of the meal</td><td>• Adjust chopping length of maize and grass silage at harvest moment
• Adjust chopping length of roughages when mixing in the TMR wagon</td></tr>
<tr><td>b) Non-homogeneous TMR allows selective feeding patterns which permits the dominant cows of the herd to consume the more palatable smaller particles while neglecting bigger particles. Thus, animals lower in the hierarchy get access to a lower nutritional value in the TMR left over.</td><td>• TMR homogeneity should be assessed on the proportion of the total which fits into the different particle size fractions
<table><tr><th>Screen</th><th>Pore sizes (mm)</th><th>Particle Size (mm)</th><th>Corn</th><th>Haylage</th><th>TMR</th></tr><tr><td>Upper Sieve</td><td>19</td><td>>19</td><td>3-8</td><td>10-20</td><td>2-8</td></tr><tr><td>Middle Sieve</td><td>8</td><td>8,0-19</td><td>45-65</td><td>45-75</td><td>30-50</td></tr><tr><td>Lower Sieve</td><td>1,18</td><td>1,18-8,0</td><td>20-30</td><td>30-40</td><td>10-20</td></tr><tr><td>Bottom Penn</td><td></td><td>< 1,18</td><td><10</td><td><10</td><td>20-40</td></tr></table>(Heinrichs, 2013)
• Evaluate by observation whether the cows eat the TMR homogeneously (eating from the top) or if they are selecting the particles in the feed</td><td>• Adjust chopping length of roughages
• Use Molasses or water to bind particles together and avoid sorting
• Follow the recommended order of mixing:
» Coarse before fine
» Dry before wet
» Concentrate feed before the last loading of the silage</td></tr>
<tr><td>c) Excessive time of TMR mixing, although intake and palatability may be fine, it can lead to the loss of the structure in the fibrous portion of the diet which will reduce the chewing stimulus, thus less saliva will be produced.</td><td>• Check the mixing time by measuring how long is the TMR mixed from the addition of the last ingredient until the end of mixing</td><td>• The mixing should last 3-5 min from the moment last ingredient was added (Buckmaster, 2005)</td></tr>
<tr><td>d) Distribution of meals during the day and feed push-up. The more often and fresh the feed is served and pushed up to the cows, the more constant the intake will be during the day, resulting in higher dry matter intake (DMI) and more balanced rumen intake and stable rumen fermentation conditions .</td><td>• Evaluate if the feeding times and push-up times per day are allowing the cows to have access to the feed all day
• Expect leftover feed in the bunk to be around 5% of initially provided (Bolsen & Pollard, 2004)</td><td>• Maximize as possible the distribution of meals during the day
• Push feed towards the cows as often as needed to allow permanent access to feed
• Clean the feed bunk regularly to increase the DMI</td></tr>
</table>

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Problem	Check list	Corrective action
e) **Sudden changes in die**t without an adaptation period don't give enough time for the ruminal microbiota to adapt to the new feed. These can lead to a decrease in the diversity and population of microorganisms until balance is re-established.	• Make sure to keep old feed before supplying the new one to be able to make a smooth transition from one to the other	• When switching diets (e.g., dry to milking, or vice versa) or ingredients (e.g., at the opening of a new silage or change of a concentrate formulation), make it progressively considering that it takes ±3 weeks for the rumen to adapt from a high fiber to a high starch diet
f) **Primiparous cows** have shown to be more sensitive to SARA due to a less adapted microbiota, fewer rumen papillae, lower chewing time and a lower hierarchy among the herd which might limit their access to the ration.	• Put special attention on this group of cows and feed them separately from the older cows (Pacífico et al., 2022)	• Reinforce measures of SARA prevention on this group of cows
g) **Insufficient space in the feeding bunk** is a common reason why it becomes hard to provide equal access to TMR for all cows. Higher hierarchy cows get access first and don't allow the other ones. This results in sorting for the first ones and lower quality feed for the second ones or in worse cases insufficient time to eat.	• Observe the collective behaviour of the herd and assess if the lower hierarchy cows are often limited to eat their ration • Avoid overcrowding the feeding bunk	• Extra cubicles and space at the feeding bunk must be provided, when possible





Milking cows with diarrhea and loose, liquid feces after a few days of consuming a concentrate feed contaminated with DON (842 ppb) and FUM (11020 ppb). Shortly after, the cow passed away.



Dominant cows eating on the portion of the neighbouring (dominated) cow. Referring to Subacute ruminal acidosis (SARA)

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Nutrition

Problem	Check list	Corrective action
a) The **excessive content of rapid fermentable carbohydrates** in the diet (grains) leads to ruminal acid production, inducing quick decreases of pH that alter the environment and the microbiota present in the rumen.	• Consider the ratio concentrate: roughage of the diet fed to the cows and discuss with your nutritional advisor • Often observe and score the faeces of the cows to determine digestive health • Discuss with your nutritionist the inclusion of non fiber carbohydrates (NFC) composed by mainly starch and sugars	• Avoid excessive concentration of NFC in diet (Max. 44%, however high amounts and effectiveness of fiber should be provided alongside, to lactating cows) (NRC, 2001) • If high inclusion of starch in the diet is decided, align a strategy to keep pH on levels that ensure adequate digestion
b) **Low fiber content in diet** will cause under stimulation of the chewing activity. Limited chewing would result in a reduction in saliva production, therefore lower natural buffering capacity within the rumen.	• Consider the NDF, or even better the physically effective fiber (peNDF), which estimates the portion of the fibre which stimulates chewing activity • Discuss the adequacy with your nutrition consultant	• Add roughage or high fiber ingredients in the diet, however it's important to consider that dry matter intake (DMI) will most likely be affected • Ensure a minimum dietary NDF of 25% for lactating cows (NRC, 2001)
c) **Low sodium (Na)** in the diet will limit the saliva production. Saliva contains sodium-bicarbonate, which is the main buffering substance in the rumen, thus keeping pH on adequate levels. Low Na can also be a reason for limited water and feed intake.	• Assess with your nutrition consultant whether Na in the diet is sufficient	• Correct Na inclusion in the ration if needed • Place salt blocks in the stable for ad libitum consumption
d) **Rumen degradability of starch** can vary between the different sources. Not only the content of starch in a diet is important but also the fermentability. Barley, triticale, rye or wheat are more fermentable than corn and sorghum and therefore lead to higher rumen acidification risk.	• Revise the content and sources of starch in the ration and concentrate and discuss it with your nutrition consultant about the options available in your area and their cost	• When the option is available and price is convenient, prioritize the use of corn or sorghum as starch sources over barley, triticale, rye or wheat in the ration
e) **Lactic acid concentration** in the rumen as a result from the soluble carbohydrates fermentation has a strong acidifying effect. **Yeast feed additives** (live yeast, autolysed yeast and other yeast culture products) are capable of reducing pH and increase volatile fatty acid (VFA) concentration by consuming the ruminal lactate, therefore reducing lactate concentrations and shifting towards the production of propionate.	• Observe the list of feed additives included in the diet • Discuss with your nutritionist about the inclusion of yeast-based feed additives	• Include a yeast product to improve the ruminal environment, regulate pH and improve the digestion outputs of the rumen
f) **Supplementation with buffering substances** such as sodium-bicarbonates, calcium carbonates, magnesium oxides or calcareous marine algae, aid to reach a ruminal acid-base balance, but are not enough to ensure a right pH if other factors of risk are not assessed. Each of the different substances has its own advantages and they vary in buffering capacity per unit of weight, reaction time to exert their buffering effect as well as by price.	• Consider buffering products that combine different ingredients as they may have a synergistic effect to modulate the rumen pH • Consult the level of inclusion of buffers in the diet formulation	• Discuss with your nutritionist the right inclusion • Use a combination of buffering materials for achieving buffering at lower inclusion rates

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Diseases

Problem	Check list	Corrective action
a) **Heat stress** is known to decrease dry matter intake (DMI), increase sorting of rations, decrease chewing time and salivary bicarbonate infusion into the rumen. Heat stress also alters the ruminal bacterial composition by favouring lactate producing bacteria (more acidifying) over other bacteria therefore driving down the rumen pH (Zhao et al., 2019).	• Keep track of the Temperature humidity index (THI) in the different areas where the cows spend their time	• If THI is over 68, take measures to regulate the temperature and comfort of the cows by placing them in the shade, using water sprinklers and air fans • Procure comfortable conditions for the cows during day and night





Loose feces with mucus and blood, signs of an unhealthy gastrointestinal tract, presumably as a consequence of consuming a concentrate feed contaminated with DON (425 ppb) and FUM (1150ppb) and ZEN (50ppb).





Manure assessment and evaluation is a relevant practice to assess any digestive disorder. Refering to Subacute ruminal acidosis (SARA)

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Mycotoxins

Problem	Check list	Corrective action
a) **Trichothecenes** (e.g., DON, NIV, DAS, T-2, HT-2, among others) **cause dry matter intake (DMI) reduction** by inducing the production of CCK, a hormone that causes the feeling of satiety. Alterations in DMI impact negatively the constant intake of nutrients. As a result, pH fluctuations and microbiota shifts are more likely to occur (Antonio Gallo, et al. 2015).	• Monitor and observe changes in feed intake and feces every time that there's a change in feed batches or silage bunk • Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
b) **Many mycotoxins** (e.g., trichothecenes) have a stronger **toxic effect on cellulolytic bacteria (fibre degraders)** than other groups of microorganisms in the rumen. They reduce their population, thus fiber digestibility is hampered. This would worsen the SARA scenario where a shift in microbial populations occurs already due to low pH (Kiyothong et al., 2012).	• Monitor and observe changes in feed intake and feces every time that there's a change in feed batches or silage bunk. Mycotoxins can be responsible of diarrhea signs, due to their negative impact in fiber digestion. • Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
c) **Zearalenone (ZEN)**, even at low concentration and duration of exposure can cause negative impacts on ruminal environment by inducing: • Significant reductions of ruminal pH • Lower total volatile fatty acid production • Lower acetate concentration (Hartinger et al., 2022)	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
d) **DON and ZEN**, among other mycotoxins can reduce populations of lactate consuming bacteria in the rumen (e. g., Megasphaera). The activity of Megasphaera is very beneficial because it aids to naturally regulate the pH by consuming lactic acid from the rumen (which is highly acidifying). If these are not present, higher concentrations of lactate could occur, leading to SARA or acidosis (Strachan & Movsesijan, n.d.)	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
e) **Emerging mycotoxins** have antimicrobial effects that negatively impact the ruminal environment, reduce fiber digestibility and despair ruminal environment, contributing to acidosis problems: • **Fusaric acid** can inhibit the proliferation of *Ruminococcus albus*, relevant fiber degrading bacteria (May et al., 2000) • *Aspergillus fumigatus* toxins (e.g., **gliotoxin**) can alter ruminal environment, decrease DM degradation and gas production (Morgavi et al., 2004). • **Patulin** has shown to reduce VFA production and microbal protein efficiency in vitro simulations. Fiber digestibility can be reduced as well (Escoula, 1992; Tapia et al., 2005) • *Penicillium* spp. produced mycotoxins, **Mycophenolic acid** and **Roquefortine C** have proven to be able to reduce VFA production and impair rumen activity due to their antimicrobial activity (Gallo, Giuberti, Bertuzzi, et al., 2015)	• Monitor and observe changes in feed intake and feces every time that there's a change in feed batches or silage bunk. Mycotoxins can be responsible of lose feces, due to their negative impact in fiber digestion. • Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins

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Problem	Check list	Corrective action
f) **Fumonisins (FUM)** have proven to act as a modulator of ruminal microbiota thanks to its antibacterial effects, by reducing microbial diversity and affecting their metabolic pathways, even when fed at low concentrations (Hartinger et al., 2022).	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins

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Inflammation & immune suppression

The immune system is formed by a network of biological processes happening inside the animal to protect it against pathogens, allergens or toxins. When there is no risk of major challenges to the health and wellbeing of the animal, the immune system has rather low energy demands, thus a high proportion of the nutrients available can be converted into bodyweight or milk. When the animal is exposed to a challenge, depending on the level of the insult, inflammatory factors will be produced and the recruitment of circulating inflammatory cells will take place, this is known as the inflammation cascade. The mechanisms of defence can be:

- **Innate immunity:** the first line of defence against pathogen attack, it has a quick reaction and eliminates a wide range of pathogens (regardless of the pathogen)
- **Adaptive immunity:** the mode of action is based on the specific antigen of a certain pathogen. This reaction is slower but very efficient for specific challenges.

Both systems are activated and regulated through the production of several mediators. Generally, the reaction consists of inflammation and proliferation of immune cells that will attack directly at the area of infection or systemically. This process requires a great amount of energy, amino acids and antioxidants, among other nutrients. Additionally, during an inflammatory process, a typical reaction by the animals is to **reduce feed intake.** Therefore, the influx of nutrients to support this inflammation process becomes limited, thus there are less nutrients available to produce milk or to accumulate bodyweight. In cases of advanced infection, veterinarian intervention and antibiotics can help, but by this time, the animal has lost condition and productive potential.

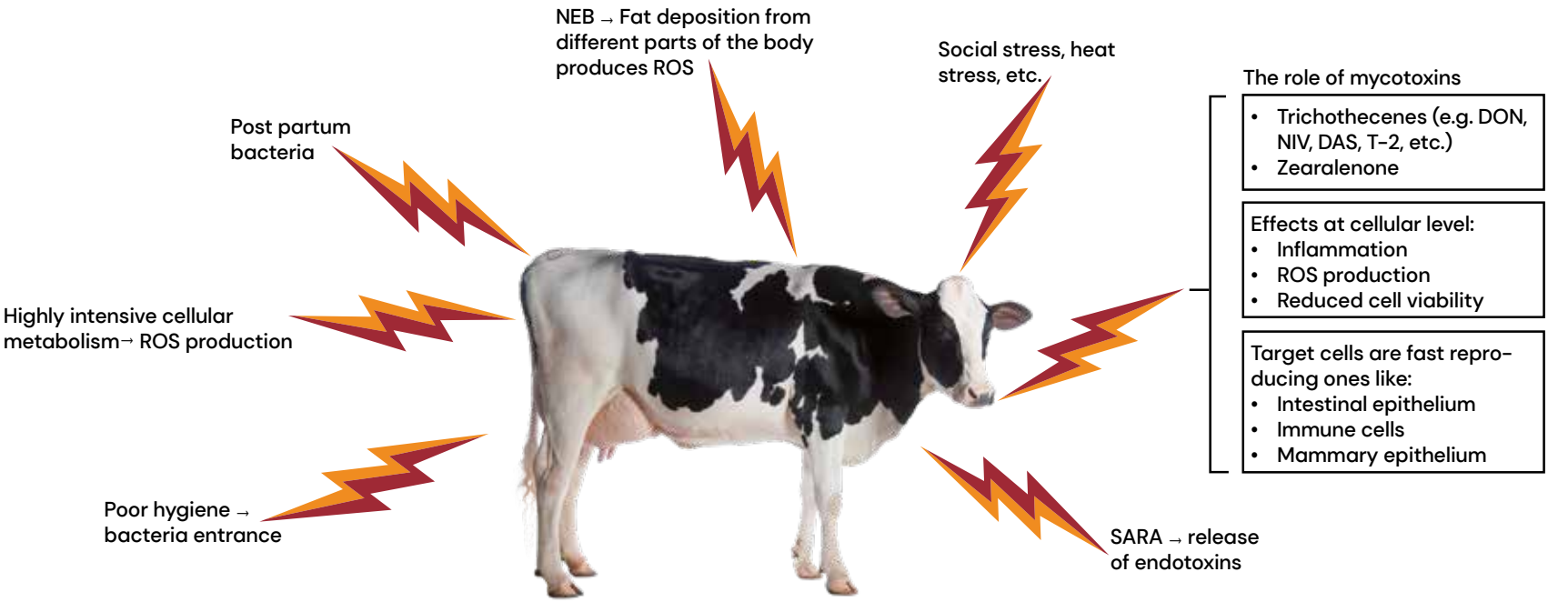
The best strategy to deal with excessive inflammation and ensure that the animals can invest the most energy on production is to minimize the exposure to insults that lead to inflammation. To achieve that, it is necessary to identify and acknowledge the causes that might lead to inflammation and how certain nutrients and management practices can alleviate inflammation or stimulate immune efficacy. Excessive inflammation is a problem of overreaction by the immune system, but the opposite, immune suppression is also highly detrimental. Immune suppression can happen when there is a limited production and efficacy of immune cells to counteract infections and can happen due to scarcity of nutrients needed for immune cells to proliferate or by negative pressure against these cells, like the case of mycotoxins. If pathogens attack the animal, it will not have the capacity to defend against it and therefore, the likelihood of having seriously negative outcomes increases.

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How to identify depressed immune function on the farm?

- Reduced feed intake
- Reduced body condition score (BCS)
- Increased incidence of major diseases e.g., mastitis, metritis, lameness.

Summary of the sources of inflammation for ruminants



Managmement

Problem	Check list	Corrective action
a) **Heat and other sources of stress** reduce wellbeing and productivity of animals. It can induce feed intake reduction and systemic inflammation. Intestinal cells (enterocytes) are responsible of ensuring gut integrity, filtering the passage of pathogens and toxins, through the tight junctions to the blood. However, these tight junctions are known to lose their effectiveness feed restriction, heat stress, social stress, among others. The passage of endotoxins, mycotoxins and pathogens to the bloodstream lead to excessive inflammation and immune suppression (Rodriguez-Jimenez et al., 2019).	• Monitor temperature and relative humidity during the day. • Observe breathing rate or panting to assess heat stress • Evaluate overall cow comfort during resting and eating time	• When necessary, provide artificial ventilation and sprinklers for all animals, including dry cows • Avoid any source of stress (changing cows from pens as least as possible), limited access to feed bunk, among others

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Nutrition

Problem	Check list	Corrective action
b) **Excessive negative energy balance (NEB)** leads to disproportionate fat mobilization, which is commonly linked to oxidation, inflammation and depressed immune function, however a clear cause relationship has not been determined (Bradford et al., 2015). It is clear however, that when fat is mobilized in excess out of the reserves in the body, it can't be processed properly by the liver; instead, fat accumulates there and limits liver function. The liver loses capacity to produce glucose (gluconeogenesis), the preferred source of energy for immune cells and alters its capacity to synthesize immune response components (Bobe et al., 2004).	• Check "Ketosis and fatty liver" section	• Check "Ketosis and fatty liver" section
c) **Lack of glucose or glucogenic compounds in the diet.** Glucose is the preferred energy source for immune cells during events of inflammation or immune activation (Ingvartsen & Moyes, 2013). When glucose is deficient, the capacity to counteract infections is reduced due to a lack of energy. Therefore, ensuring enough access to glucogenic components is even more relevant during periods of immune challenges, like transition period.	• When evaluating the content of glucogenic components in the diet consider particularly the cows at transition period, as those are at higher risk of infection and have a high demand of energy for other purposes such as increasing milk production • Check "Subacute ruminal acidosis (SARA)" section for general considerations to avoid SARA when feeding a glucogenic diet	• Discuss with your nutritionist whether there is sufficient supply of glucogenic components in the diet (by stages of lactation) • Check "Subacute ruminal acidosis (SARA)" section to avoid drastic rumen pH reduction meanwhile feeding a glucogenic diet to the cows
d) **Oxidative stress** happens when there is a high production of reactive oxygen species (ROS) and a low access to antioxidant components through the diet, which contribute to a healthy balance. Excessive concentration of ROS leads to immune alterations (activation or depression) and ultimately to cell wall damage and death, particularly affecting immune cells due to their high metabolic activity. ROS are also incremented by inflammation and increased fat circulation. Diets low in fresh forages provide a poor amount of antioxidants.	• Evaluate antioxidant content in the diet with your nutrition consultant or veterinarian. • Special attention to transition cows: the heaviest oxidative stress typically occurs around parturition; when feed intake is reduced, high amount of antioxidants are being excreted through colostrum and stress increases due to metabolic and inflammatory processes naturally occurring during calving and onset of lactation	• If possible, supply fresh forages, as the content of antioxidants is much higher than in dried or ensiled forages • Discuss with your nutritionist the level of antioxidant supplementation required for transition cows (weeks -3 to 3) and rest of the herd
e) **Selenium** is a relevant antioxidant, it makes part of gluthathione peroxidase, an enzyme that detoxifies reactive oxidative species (ROS). Selenium deficiency results in reduced ability to clear out bacteria (Spears & Weiss, 2008), however, when fed in excess can also be toxic. Organic sources of selenium are recommended as they are more bioavailable than inorganic sources (Malbe et al., 1995).	• The recommendation for dairy cows amounts to 0.2 mg Se/kg feed dry matter (DM). Se at high intake is toxic. In the E.U. the maximum content is 0.5 mg Se/kg complete feed, while in the USA, total supplemental Se should not exceed 0.3 ppm in the overall diet • Organic sources of Se are recommended	• Discuss with your nutrition consultant about the sufficiency Se in the diet and balance formulations if necessary
f) **Vitamin E** is the most important lipid soluble vitamin and antioxidant which protects lipid membranes from damage by circulating reactive oxidative species (ROS). It has relevant positive impacts, as it enhances neutrophil function, crucial components of the host defence mechanisms. Vitamin E, in combination with Se, play an important role on preventing mastitis, metritis, retained placenta, among others (Harrison et al., 1984).	• When separate feeding is possible for far-off and close-up cows, a higher dose of vitamin E is recommended for close-up cows based on (Weiss et al., 1997): supplement 1000 IU/day for the first 46 days of the dry period and 4000 IU/day for the final 14 days prior to calving, followed by 2000 IU/day during lactation	• Discuss with your nutrition consultant about the sufficiency of vitamin E in the diet and balance formulations if necessary

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Problem	Check list	Corrective action
g) **Other minerals, such as Zinc, Copper and Chromium** are known to have relevant immune functions and thus must be ensured that their content is adequate in the diet (Spears & Weiss, 2008).	• Discuss with your nutrition consultant the sufficiency of these microminerals in the diet • Organic sources are more recommendable	• Discuss with your nutrition consultant about the sufficiency of minerals in the diet and balance formulations if necessary
h) **Poly unsaturated fatty acids (PUFAs)** are a type of fat that divides in two major groups, the n-3 (commonly present in fish, flaxseed, canola, among others) and n-6 (commonly present in corn, soybean, sunflower, among others). These have been shown to be important immune modulators, with n-6 having pro-inflammatory effects and n-3 alleviating inflammation or enhancing immune response, which is why n-3, also known as Omega-3 fatty acid supplementation has been proposed as dietary strategy to prevent inflammation.	• Discuss with your nutrition consultant the main components on the ration of cows and consider the amounts of n-3 or n-6 PUFAs that these add to the diet	• Consider adding sources of omega-3 fatty acids on cows prone to inflammation (e.g., transition period) or to all cows to reduce likelihood of excessive inflammatory reactions

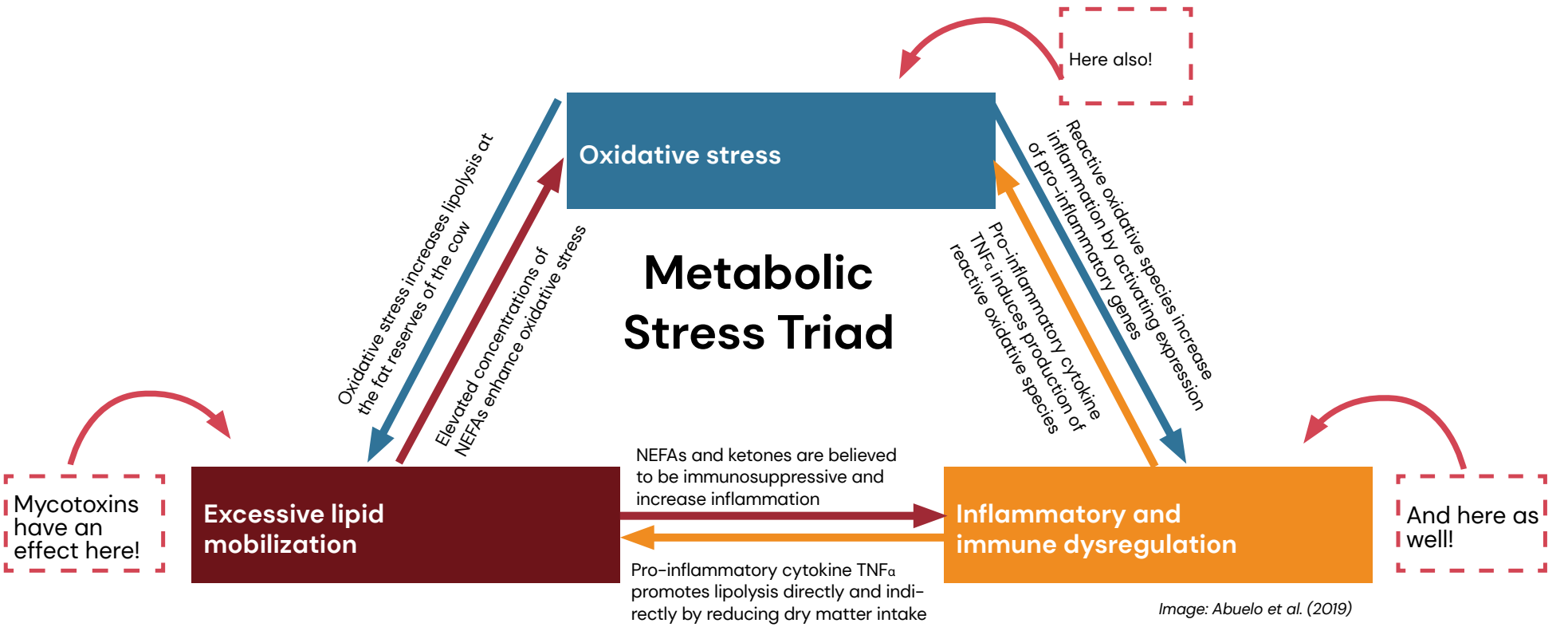


Image: Abuelo et al. (2019)

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Diseases

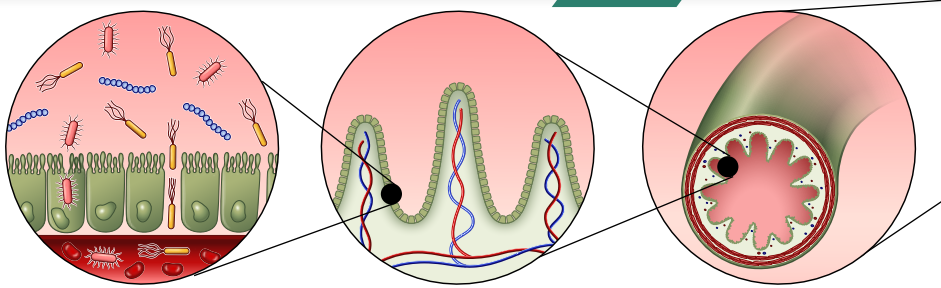
Problem	Check list	Corrective action
a) **Hypocalcemia** is a condition characterized by low calcium concentrations in blood, typically happening around calving. Hypocalcemic cows have reduced content of calcium in their leukocytes (Martinez et al., 2014). Calcium is a mineral of high relevance for immunity, as it participates of the signalling between leukocytes that is required for activation and defence against pathogens. Hypocalcemia is highly correlated with metritis, mastitis, retained placenta and displaced abomasum (Rodríguez et al., 2017).	• Calculate with your nutrition consultant and veterinarian the sufficiency of Ca and the dietary cation anion difference (DCAD) in the diet of dry and transition cows • Analyze your raw materials, especially forages to evaluate the mineral concentrations and how this can influence DCAD • Conduct with veterinarian support the necessary blood analyses to assess hypocalcemia	• Implement with the advice of your nutrition consultant, a feed formulation that takes into consideration DCAD balancing for dry cows, including the usage of anionic salts • Supplement vitamin D in a readily available form to ensure appropriate Ca absorption
b) **Leaky gut syndrome** happens when the intestinal epithelium losses its barrier function and allows the passage of toxic materials (e.g., mycotoxins, endotoxins, bacteria, among others) from digesta into the blood, resulting in systemic inflammation, immune depression and multiple metabolic disorders (Rodriguez-Jimenez et al., 2019). Different conditions can lead to leaky gut syndrome, such as heat stress, cold stress, weaning, acidosis, feed restriction and mycotoxins (Horst et al., 2021).	• Keep track of feed intake • Keep track of overall health condition of the animals • Check for general signs of fever	• Avoid SARA conditions, check "Subacute ruminal acidosis (SARA)" section • Minimize heat and other sources of stress • Avoid periods of restricted feed • Promote intestinal health and enhance mucosal barrier with aid of feed additives, such as plant extracts, probiotics, prebiotics, acids, among others
c) **Endotoxemia or Lipopolisaccharides (LPS) intoxication.** These are gram-negative bacteria cell wall components that get exposed when these bacteria die. They can reach blood circulation from infections like mastitis and metritis but also can come through the intestine. Under "Subacute ruminal acidosis (SARA)" conditions, due to decreased pH a higher rate of gram-negative cell death can occur, thus a much higher LPS concentration in the rumen and in the blood can be observed. Endotoxins elicit inflammatory responses that are followed by the production of reactive oxidative species and fat mobilization (Horst et al., 2021).	• Keep track of feed intake • Keep track of overall health condition of the animals • Check for general signs of fever	• Minimize the pressure of pathogens at the udder level, check "Mammary gland infections and high somatic cell count" section • Minimize likelihood of developing post-calving infections, check "Reproductive failure" section) • Avoid SARA conditions, check "Subacute ruminal acidosis (SARA)" section • Implement the use of an endotoxin binder to adsorb endotoxins in the rumen and avoid passage through the intestine • Promote liver health to ensure adequate response endotoxin induced inflammation, check "Ketosis and fatty liver" section

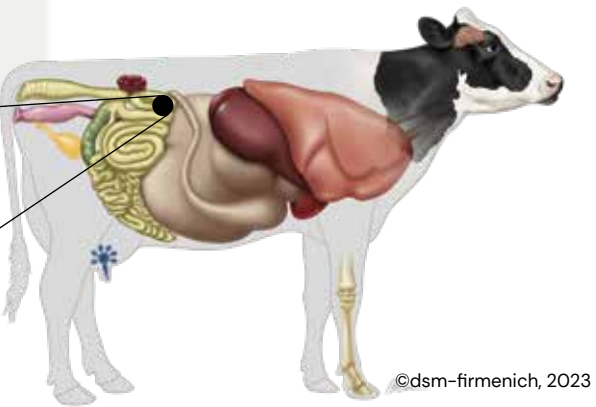
Mycotoxins effects in the intestine

- Gut barrier damage → leaky gut
- Reduced mucin production
- Altered Microbiota composition
- Weaken local immune system

Leading to

- Inflammation and immune suppression
- Decreased nutrient uptake





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Mycotoxins

Problem	Check list	Corrective action
a) **Trichothecenes** have a dose-dependent effect on immune activity. At lower concentrations, they can lead to immune activation and inflammation. Chronic exposure to low levels can deplete immune capacity, leaving animals more susceptible to infections. Additionally, inflammation is very energetically costly for the animal, thus it results in performance losses. At higher concentrations, trichothecenes can cause immune cells to inactivate or die, which limits the capacity of the animal to combat diseases. • **Deoxynivalenol (DON)** can disrupt intestinal barrier function due to its toxic effects against epithelial cells (Reisinger et al., 2019). Once it's on circulation, it can negatively impact immune cells by limiting lymphocyte proliferation from very low concentrations in blood (124 ppb, showing higher sensitivity than swine and poultry lymphocytes) (Novak et al. 2018). • **Nivalenol (NIV)** is less studied than DON but has the same mode of action and has shown to exert a higher toxic effect against bovine intestinal epithelium (Reisinger et al. 2019).	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
b) **Fumonisins (FUM)** disrupt sphingolipid metabolism and cause alterations at the cellular level that limit the production of relevant components like ceramide and sphingosine. These are components of the intestinal epithelial cells, which ensure a good barrier function at the intestine. Sphingolipids are also involved in pathways that control the main stages of development and function of immune cells, thus fumonisins can impair for immune cell synthesis and function, especially when combined with trichothecenes (Gallo et al., 2020; Roberts et al., 2021).	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins.
c) **Aflatoxins (Afla)** have hepatotoxic and immunotoxic properties, among others. Aflatoxins disrupt innate and adaptive immunity by affecting the proliferation and production of immune cells. They can elicit inflammation or lead to suppression of the immune system	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
d) **Zearalenone (ZEN)** can induce inflammatory reactions and impair epithelial barrier function in swine(le Sciellour et al., 2020). Additionally, latest results demonstrate that ZEN at a low dose and time of exposure can cause higher body temperature (fever) than a control diet indicating an activation of the immune system (Hartinger et al., 2022).	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins

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Problem	Check list	Corrective action
e) **Mycophenolic acid** is used in humans for certain treatments due to its immunosuppressive properties. In sheep this metabolite has shown to exert immunomodulatory effects in the liver and ileum (Dzidic et al., 2006).	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
f) Mycotoxins such as Afla, FUM, DON and T-2 have proven to be able to alter and interrupt vaccine-derived immunity in mammals, allowing pathogens impact the animal even if such disease is part of the vaccination protocol. Mycotoxin risk management is of high relevance to ensure the efficacy of the vaccination protocols for diseases impairing reproduction.	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins

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Mammary Gland Infections and High Somatic Cell Counts (SCC)

Mastitis is one of the most prevalent and costly diseases of dairy cows around the world. Mastitis is an inflammation of the mammary gland which is often caused by an intramammary infection (IMI). The economic losses related to this disease arise mainly from decreased milk production, discarded milk due to clinical disease or antimicrobial therapy, the culling of chronically infected cows, veterinary treatment fees, labour costs, penalties in pricing due to high somatic cell count (SCC), or even cow death, in severe cases. Bacteria are the most common etiological agent of IMI, but other pathogens including fungal species (yeast or mould), microscopic algae, and viruses are potential infectious causes. Physical trauma or chemical irritation can serve as non-infectious causes of mastitis. The severity of the inflammation depends on the causative agent as well as the immune response of the cow. A fundamental principle of mastitis control is to limit disease by either minimizing exposure of teat ends to potential pathogens or by increasing cow resistance to infection.



Hygienic and comfortable conditions at the calving pen are very important for minimizing stress during the vulnerable transition period. Referring to the Mammary gland infection and high SCC section, management, A.

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How to identify mammary gland infections on the farm?

	Subclinical Mastitis	Clinical Mastitis
 Signs on the udder	Appears normal, there are no visible signs of inflammation	Visible signs of inflammation in the gland, such as redness, heat, swelling or hardening and/or pain
 Signs in the milk	Appears normal	Physical changes or abnormalities e. g. flakes or clots to purulent exudate, watery consistency, discoloration, or presence of blood, etc.
 Overall symptoms	No apparent or clinical symptoms	Systemic signs of illness including fever, depression, reduced feed intake, decreased reticulorumen motility, shock, or death in severe cases
 Diagnosis in the farm	• Somatic cell count (SCC) higher than 200,000 cells/mL • California Mastitis Test (Score T or 1) • Milk cultures to identify specific pathogen	• Observation of symptoms • Very elevated SCC • California Mastitis Test (Score 2 or 3) • Milk cultures to identify specific pathogen
 Kind of pathogens associated	Contagious mastitis pathogens: those which survive in infected udders and are spread cow-to-cow via milking equipment, milkers' hands or towels, or by vectors such as flies	Environmental mastitis pathogens: those which survive in the cow's environment including bedding materials, manure, soil, etc.
 Common causing pathogens	*Staphylococcus aureus* coagulase-negative *Staphylococci* (CNS) *Corynebacterium bovis* certain *Streptococcus* spp., among others.	*Escherichia coli* Klebsiella spp. *Enterococcus* spp. certain *Streptococcus* spp., among others.

(Carrillo-Casas & Miranda-Morales, 2012; Dufour et al., 2011; Gooder, 2014)

Mastitis cases often can originate from an intramammary infection (IMI) acquired during a previous lactation or during the dry period. Traditionally, it was recommended to treat all dry cows with antibiotics in a preventive manner but today, wide range use of antibiotics is discouraged or illegal in certain countries. Instead, a selective dry cow therapy (SDCT) is advised, where only cows with evidence of recent or existing IMI (based on records of mastitis, SCC or microbial testing) are given intramammary antibiotics at dry-off. It is important to work in collaboration with the veterinarian to determine the best option for dry cow therapy and work to develop protocols that clearly outline how cows should be managed at dry-off. Finally, the best strategy against mammary gland infections is to prevent and minimize the exposure to pathogens and any insult that might lead to inflammation.

Management

Problem	Check list	Corrective action
a) Maintaining **cow and housing hygiene** is essential to avoid udder health problems, as environmental mastitis pathogens survive in the cow's environment. Manure can be transferred to the udder through four ways: via direct contact, by the leg, by splash and via the tail. Many studies have found a correlation between clean cows and lower SCC (Dufour et al., 2011).	• Evaluate the cleanliness of cows and observe where the debris comes from, by considering the four mechanisms of manure transfer to the udder. Various tools and scoring systems are available to help guide cow and stall hygiene evaluations • Evaluate the cleanliness of holding pens, calving pens, alleyways, outdoor lots, and other areas where cows spend time to determine if these are sources of udder contamination	• Correct causes of poor hygiene and conduct periodic cleaning tasks • Regularly remove manure from areas where cows lie and maintain good amount of clean bedding material • Consider use of sand bedding instead of organic materials such as sawdust, straw, etc (Hogan & Smith, 2003) • Removal of udder hair can reduce accumulation of manure and pathogens

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Problem	Check list	Corrective action
b) **Hygiene in the milking parlour**, including clean milking equipment and use of proper milking procedures are crucial to limit contamination of the teats with mastitis-causing bacteria.	• Ensure the parlour is well cleaned after every milking • Evaluate milking routine. Make sure that milking procedures are posted and proper milking technique is followed and that hygiene is kept	• Maintain a clean parlour and milking equipment to reduce the presence of mastitis-causing bacteria • Carry out periodic deep cleanings • Use of gloves is recommended, and must be changed every time they become soiled
c) **Proper milking procedures** will help minimize udder health issues and maximize yield of quality milk.	• Evaluate milking procedures used in the parlour including timing, hygiene and consistency • Consult with your veterinarian or trusted udder health advisor to determine what are industry recommended best milking practices	• Implement best milking practices based on industry recommendations • Ensure farm protocols are available to staff and review with employees on regular basis • Provide a low stress environment for cows prior and during milking
d) **Pre-milking teat** disinfection has proven its efficacy in preventing new intramammary infections. It is important to clean and dry the teats prior to attaching the milking unit, in order to minimize the entry of pathogens into the teat canal during milking.	• Determine if fore stripping is always practiced by the milking responsible personnel • Evaluate cleanliness of pre-milking teat disinfection equipment (e.g., dip cups, sprayers, etc.) • Determine if complete teat coverage is achieved when applying pre-dip/spray and ensure contact time prior to wiping teats dry is at least 20 seconds	• Fore strip each quarter to identify clinical mastitis and potential milk discard or intervention • Implement a proven pre-milking teat disinfectant • Use single use paper or cloth towels to dry teats
e) **Post-milking teat disinfection** is mentioned to be the most effective way to prevent the colonization of the teat skin and the entrance of contagious mastitis pathogens such as *S. aureus or S. agalactiae* through the teat canal.	• Consult with your veterinarian or trusted udder health advisor about the best post-milking teat disinfection to use • Determine if achieving complete teat coverage when applying post-dip/spray	• Implement a proven post-milking teat disinfectant after every milking • Deliver fresh feed or push up feed while cows are in the parlour to encourage them to eat at the return to their pen after milking. This allows time for the teat sphincter muscle to close prior to cows lying down and can help limit pathogen infiltration into the mammary gland.
f) Routine **milking machine maintenance** is important to ensure milking equipment is working properly and not acting as a vector for bacteria or causing any physical damage in the teat ends.	• Routinely evaluate milking machine function (consult your parlor equipment company/service provider) • Evaluate teat end condition to identify potential issues with milking equipment such as vacuum level and automatic take-off settings	• Conduct routine preventive maintenance of each component of the milking system • Keep a maintenance log notebook to track all milking system service and repairs (follow guidelines indicated by parlor equipment provider)
g) Sometimes after dry-off, cows may fail to produce the **keratin plug**, a physical barrier with natural antimicrobial properties that seals the teat canal and prevents pathogens from entering during dry period. The lack of a proper keratin plug increases the risk of IMI (Bradley and Green, 2004). Internal teat sealants (ITS) can be used to create a synthetic plug. In combination with antibiotic or by its own, they can significantly reduce the incidence of IMI in the subsequent lactation (Rabiee & Lean, 2013).	• Evaluate the different teat sealants available in your region and consult your veterinarian for advice. • Only use this strategy in cows that are free of infection after assessing IMI status by CMT or when SCC is below the threshold (150,000 cells/mL for heifers and 250,000 cells/mL for multiparous cows)(Scherpenzeel, 2017)	• Consult your veterinarian about the use of ITS and the conditions required for the cows to be able to receive it

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Nutrition

Problem	Check list	Corrective action
a) **Excessive negative energy balance (NEB) leads to disproportionate fat mobilization**. At the udder level, cows that mobilized excessive fat were reported to be at higher levels of inflammation, oxidative stress and even cell death, in comparison with healthy cows (Sun et al., 2021). Excessive fat mobilization can impair udder defence mechanisms by: • Reduced phagocytosis capacity and oxidative burst of immune cells • Reduced production of cytokines and concentration of leukocytes (O'Rourke, 2009) • These conditions are known to increase the risk of mastitis (Ingvartsen & Moyes, 2013)	• Check "Ketosis and fatty liver" section to understand better about NEB and how to avoid it from becoming severe	• Check "Ketosis and fatty liver" section to avoid excessive NEB and ensure adequate liver function
b) **Oxidative stress** happens when there's high production of reactive oxygen species (ROS) and a low access to antioxidant components through diet, which contribute to a healthy balance. Oxidative stress leads to inflammation and cell wall damage and death; particularly affecting high metabolic activity tissues like the mammary gland. These conditions are detrimental to udder health, impede proper defence against infections in the udder and reduce the capacity to produce milk (Sun et al., 2021). Diets low in fresh forages provide a poor amount of antioxidants.	• Evaluate antioxidant content in the diet with your nutrition consultant or veterinarian • Special attention to transition cows: the heaviest antioxidative stress typically occurs around parturition; when feed intake is reduced, high amount of antioxidants are being excreted through colostrum and stress increases due to metabolic and inflammatory processes naturally occurring during calving and onset of lactation	• If possible, supply fresh forages, as the content of antioxidants is much higher than in preserved forages • Discuss with your nutrition consultant the level of antioxidant supplementation required for transition cows (weeks -3 to 3) and rest of the herd
c) **Vitamin E** is the most important lipid soluble vitamin and antioxidant. It protects lipid membranes from damage by circulating reactive oxidative species (ROS). Enhanced supplementation focused on higher doses of vitamin E during transition can reduce the incidence of clinical mastitis during the lactation, among other benefits (Weiss et al., 1997).	• When separate feeding is possible for far-off and close-up cows, a higher dose of vitamin E is recommended for close-up cows based on (Weiss et al. 1997): supplement 1000 IU/day for the first 46 days of the dry period and 4000 IU/day for the final 14 days prior to calving, followed by 2000 IU/day during lactation	• Discuss with your nutritionist about how to supplement the required vitamin E through the feed formulation and additional mineral mixes during transition • Consider allowing access to fresh grass consumption, as vitamin E concentrations are higher than in preserved forages
d) **Selenium (Se)** is a very relevant antioxidant and plays an important role in inflammation and immunity. Adequate Se dosage can improve mammary cell survival, (Grasso et al., 1990), minimize mastitis occurrence, duration, and severity as well as reduce somatic cell count (Weiss et al., 1990). However, can be toxic when fed in excess.	• The recommendation for dairy cows amounts to 0.2 mg Se/kg feed dry matter (DM). Se at high intake is toxic. In the E.U. the maximum content is 0.5 mg Se/kg complete feed, while in the USA, total supplemental Se should not exceed 0.3 ppm in the overall diet • Organic sources of Se are recommended	• Discuss with your nutritionist to make sure that selenium supplementation is optimal
e) **Zinc (Zn)** is required for optimal skin integrity and keratin formation lining the teat canal, the first barrier of protection against udder infections. Zinc has proven benefits for reduced SCC (Kincaid et al., 1984).	• Discuss with your nutrition consultant the sufficiency of these microminerals in the diet • When possible opt for organic sources	• Balance diet properly

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Diseases

Problem	Check list	Corrective action
a) **Bacterial pathogens** are divided between those which survive within infected mammary glands, **contagious** pathogens, and those that thrive in the cow's environment, **environmental** pathogens. • ***Staphylococcus aureus*** is a contagious mastitis pathogen that adheres to teat skin and colonizes the teat canal. Treatment with antibiotics often has limited efficacy. Intrammary infection (IMI) by S. aureus can become chronic and is often considered as untreatable • ***Streptococcus uberis*** is often present in the environment, but has also been associated with contagious spread. Infections by S. uberis can be very acute, but this Gram-positive pathogen, tends to be quite susceptible to intramammary antibiotic treatment • ***Escherichia coli*** is the most common environmental cause of mastitis, it's present in fecal material and survives in the soil. IMI by *E. coli* are often acute and cause painful quarters. It produces very strong toxins that quickly lead to severe systemic symptoms and can be fatal if therapy is not provided on time	• Consult your veterinarian or trusted udder health advisor to develop a decision tree to guide mastitis treatments based on the presentation of disease and pathogen present • Monitor SCC (at the cow level or bulk tank) as an indicator of udder health • Use California Mastitis Test (CMT) to identify quarters of cows with elevated SCC • Utilize milk cultures or PCR analysis to identify the causative pathogen(s) of mastitis cases and determine suitable treatment options with your veterinary • Follow recommendations of management listed in "Mammary gland infections and high SCC" section concerning hygiene, milking practices and bedding materials • Discuss with your veterinarian or trusted udder health advisor options for implementation of mastitis vaccinations as part of the overall herd health program.	• Reinforce good post-milking teat dip application to avoid the spread of contagious pathogens such as *S. aureus*. • Reinforce good pre-milking teat dip application to help limit environmental mastitis cases • Good dry cow management including consideration for the use of intramammary antibiotics and internal teat sealants as well as providing clean, dry facilities post-dry off • Make adequate use of antibiotic treatment according to your veterinarian's advice
b) **Hypocalcemia** is a condition characterized by low calcium concentrations in blood, typically happening around calving. Calcium plays a relevant role on immunity and when its concentrations are low, overall immune capacity is compromised, which has a direct impact in mammary gland infections. Calcium is also very important for proper muscle contraction, and therefore cows under subclinical hypocalcemia have been found to have a less functioning teat sphincter (Barragan et al., 2018). This increases the likelihood of pathogens entering and causing infections in the udder.	• Calculate with your nutrition consultant and veterinarian the sufficiency of Ca and the dietary cation anion difference (DCAD) in the diet of dry and transition cows • Analyze your raw materials, especially forages to evaluate the mineral concentrations and how this can influence DCAD • Conduct with veterinarian support the necessary blood analyses to assess hypocalcemia	• Implement, with the advice of your nutrition consultant, a feed formulation that takes into consideration DCAD balancing for dry cows, including the usage of anionic salts • Supplement vitamin D in a readily available form to ensure appropriate Ca absorption



California mastitis test is a tool to aid cow side mastitis diagnosis.

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Mycotoxins

Problem	Check list	Corrective action
a) **Multi-mycotoxin contamination** is common and presents synergistic effects among combinations of mycotoxins. The mycotoxin negative effects against the animals at the systemic level results in decreased capacity to fight against pathogens. In a long-term field survey, milk SCC were more elevated in cows exposed to different combinations of the mycotoxins DON, FUM, ZEN, Afla and T-2 (Křížová et al., 2016). Increased SCC can happen due to "excitement" of the immune system following exposure to mycotoxins, which has been shown in multiple scientific cases (Kiyothong et al., 2012; Zouagui et al., 2017).	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
b) **Deoxynivalenol (DON)** has been tested in vitro to evaluate its effects on mammary epithelial cells and has been proven to exert toxic effects by causing oxidative stress, inflammation and cell death (Wang et al., 2019). Although it is not known at which rate mycotoxins reach the mammary epithelium, these damaging effects are very important given that this tissue is naturally under stress due to high metabolic activity to achieve high milk yields. Oxidation and inflammation at the level of the mammary epithelial cells can weaken immune capacity, increase SCC and increase intramammary infection rates.	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
c) **Zearalenone (ZEN)'s** impact on mammary epithelial cells has been tested in vitro, where ZEN proved to reduce cell viability, induce oxidative stress and cause cell death (Fu et al., 2019). Although it is not known at which rate mycotoxins reach the mammary epithelium, these damaging effects are very important given that this tissue is naturally under stress due to high metabolic activity to achieve high milk yields. Oxidation and inflammation at the level of the mammary epithelial cells can weaken immune capacity, increase SCC and increase intramammary infection rates.	• Sample feed regularly and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins



Observable reddening in the infected quarters due to a clinical case of mastitis.

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Reduced Growth Performance

Feed efficiency and growth performance are two metrics used across many species to determine profitability. Whether it is in calves, replacement heifers, bulls, or feeder cattle, growth performance is dependent on proper nutrition, management and health. In dairy farming, the time between the birth of a calf and until its first calving, is rather long and expensive. Raising dairy heifers requires a great amount of resources, such as labour, feed, special facilities, among others. It can take up to 25% of the total cost of dairy production. The main goal after this period is to raise healthy heifers that reach their first calving at 22–24 months of age, to achieve cost efficiency without risking the health and productive life of the animal. The recommended weights for the animal to have at breeding, pre-calving and post-calving are 55%, 94% and 85% of the mature bodyweight, respectively (van Amburgh & Meyer, 2005). Similarly relevant it is for beef cows to soon enough start calving. Any delay on growth and development should be avoided to ensure farm profitability.



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How to identify reduced growth performance on the farm?

It is recommended to monitor weight and height of heifers regularly to compare against breed averages per specific age group. Although most veterinarians, nutrition consultants and dairy farmers can recognize an over conditioned or underconditioned animal from a normal one, subjective judgement can easily lead to mistakes. Weighing with a scale would be ideal but in the case of not having one, weighting tapes are also very functional and accurate (when measuring animals over 150 kg) (Heinrichs & Jones, 2016).

Management

Problem	Check list	Corrective action
a) **Estrus in heifers** causes energy losses due to a higher physical activity.	• Estrus behaviour (riding or allowing to be ridden) • Poor feed intake and weight gain	• Consult with your veterinarian about the use of feed estrus suppressants (e.g., MGA) • Sorting animals
b) **Poor gut health (leaky gut):** The intestine is formed by villi that are composed by epithelial cells. This tissue is very sensitive to inflammation and damage by bacteria, mycotoxins or endotoxins. Such harm allows passage of toxic compounds from the intestine to the bloodstream, increasing infections and inflammation events. Ensuring gut health is highly relevant for a good barrier function and for adequate nutrient absorption. Other factors like ruminal acidosis, stress (moving animals, heat stress and weaning, etc.) can be relevant contributors.	• Assess health by observation of feces (diarrhea) • Keep track of weight gain in a periodic basis • Keep track of feed intake and refusal • Evaluate signs of morbidity or general discomfort • Evaluate if there's an increased incidence of diseases	• Consider the use of probiotics and prebiotics to ensure a stabilized population of healthy microbes • Consider the use of phytogenics to avoid inflammation and promote epithelial health • Avoid SARA conditions, check "Subacute ruminal acidosis (SARA)" section. • Avoid stressful conditions such as environmental and heat stress
c) **Poor immune function and inflammation:** • Excessive inflammatory reactions that result in great investment of energy at the expense of productive performance • Poor immune response: due to different metabolic disorders or deficiencies, the production and efficacy of antibodies can be reduced, leaving the animal vulnerable against infections. Some influencing factors can be antioxidant status, fatty liver, energy availability in the diet, mycotoxins and endotoxins, among others.	Check for signs of an inflammation process, such as: • Loss of body condition score (BCS) • Reduced feed intake • Morbidity • Increased incidence of diseases • Check "Inflammation & immune suppression" section	• Discuss with your nutrition consultant about sufficiency of antioxidants in the diet, the use of immune and liver health enhancers such as yeast wall derivatives and other natural products. Check "Inflammation & immune suppression" section • Avoid SARA conditions to minimize endotoxin exposure and use a binder that can adsorb them, check "Subacute ruminal acidosis (SARA)" section • Integrate an effective broad-spectrum mycotoxin solution
d) **Heat stress** occurs at high temperatures, lack of ventilation and high relative humidity. It leads to reduced feed intake and welfare, which results in health and performance losses.	• Monitor constantly temperature humidity index (THI) • Observe cow comfort, e.g., open mouth, heavy breathing, panting and/or salivating	• If THI is over 68, take measures to regulate the temperature and comfort of the cows by placing them in the shade, using water sprinklers and air fans

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Nutrition

Problem	Check list	Corrective action
a) **Energy deficiency** due to poor intake or insufficient energy in the diet, relative to energy requirements at different stages of production.	• Keep track of weight gain in a periodic basis • Keep track of feed intake and refusal • Evaluate signs of morbidity or general discomfort (inflammation demands great amounts of energy and reduces feed intake)	• Analyze feed ingredients • Balance diets to meet growth requirements • Adjust diet throughout the season to account for changes in ingredient composition and availability • Insure maximal feed intake
b) **Protein deficiency** in the diet will limit the availability of amino acids to provide the requirements for microbial protein production as well as for the animals' absorption for tissue growth. Not only protein amount is of relevance but also: • Rumen degradable protein (RDP): Rumen undegradable protein (RUP) balance • Energy available	• Keep track of weight gain in a periodic basis • Keep track of feed intake and refusal	• Analyze feed ingredients • Assess with your nutrition consultant an adequate protein: energy ratio • Adjust diet throughout the seasons to account for changes in ingredient composition and availability • Ensure maximal feed intake
c) **Mineral and vitamin imbalance** can decrease development even if only one of the minerals or vitamins is missing. Adequate balancing of diets is necessary to meet the requirements of each specific period of development of the animal, for it to be healthy, fertile and resistant to diseases.	• Keep track of weight gain in a periodic basis • Keep track of feed intake and refusal • Evaluate signs of morbidity or general discomfort • Observe hair coat conditions • Observe hoof health conditions	Discuss with nutrition consultant: • Understand animal nutrient requirement depending on stage of production • Analyze feed ingredients • Balance diets to meet requirements • Adjust mineral and vitamin source/quality to ensure nutrients are available for absorption • Ensure maximal feed intake
d) **Nutrient antagonisms** might limit the availability and absorption of the required nutrients. For example, in ruminants, Cu uptake is known to be inhibited by Mo, S and Fe, and high levels of Ca can inhibit Zn uptake. Additionally, certain heavy metals and other compounds originated from feed or water, can bind certain minerals such as Cu, Zn, Mn (López-Alonso, 2012).	• Same points as mentioned above: Mineral and vitamin imbalance	• Analyze feed and water for heavy metals and other antagonists • Adjust mineral source/quality to ensure nutrients are available for absorption

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Diseases

Problem	Check list	Corrective action
a) **Respiratory diseases** can be caused by a variety of viral, bacterial, and parasitic pathogens, such as Bovine Respiratory Disease Complex (BRD), Bovine Respiratory Syncytial Virus (BRSV), Parainfluenza Virus Type 3 (PI3), Mycoplasma and Acute Interstitial Pneumonia (AIP). They affect the respiratory tract and can cause fever, depression and lack of appetite. Behavioural stress is an important contributor to respiratory diseases.	• Evaluate sources of stress, such as weaning, diet changes, transport, environmental/weather and the potential ways to mitigate it • Evaluate clinical signs: Fever, depression, reduced appetite, dullness, coughing, nasal and eye discharge, salivation, heavy breathing, among others	• Consult your veterinarian for adequate treatment and vaccination programs • Reduce stress (handling, transport, weather) • Improve pen conditions (hygiene, ventilation, density, among others) • Ensure optimal immune function, check "Inflammation & immune suppression" section
b) **Clostridial** disease is caused by bacteria family Clostridium which produces potent toxins that affect the health of the animal, most commonly causing gut distress.	• Assess health by observation of feces (diarrhea) and checking for bloated rumen • Keep track of feed intake and refusal • Often leads to sudden death	• Consult with your veterinarian about the right vaccination program (best way to avoid clostridial diseases) • Treatment possibilities are usually unsuccessful • Ensure optimal immune function, check "Inflammation & immune suppression" section
c) **Lameness** has been related to losses in performance and reduced feed intake. A lame animal spends less time eating and more energy on inflammatory processes than a healthy one.	• Check "Lameness" section	• Check "Lameness" section
d) **Coccidiosis** is a protozoan disease that usually affects young cattle (1–12 months old) causing damage to intestinal cells and reducing feed efficiency even in subclinical cases.	• Check for bloody and/or loose feces • Check for signs of dehydration, like sunken eyes and by pinching a fold of skin and observing the time it takes to flatten (widely known method)	• Consult your veterinarian for the best treatment and preventive measures • Exhaustive cleaning of drinking systems, water throughs and feeders • Ensure hygienic conditions and a ventilated environment • Avoid high animal densities
e) **Liver abscess** is a not fully understood condition, however it is an important problem in beef lot production during the highest grain feeding period. The metabolic stressful conditions caused by high grain feeding open the way for pathogens to proliferate, most commonly Fusobacterium necrophorum and Actinomyces pyogenes (Reinhardt & Hubbert, 2015).	• Limited clinical signs • Keep track of weight gain in a periodic basis • Keep track of feed intake and refusal • Reduced carcass value • Increased incidence of other infections • Death	• Consult with your veterinarian for the best treatment possibilities • Balance diet to Increase roughage portion • To prevent, supplement with feed additives that promote immune and liver health • Check "Inflammation & immune suppression" section
f) **Mycosis/aspergillosis infection** is caused by several Aspergillus spp. and it expresses mainly as a respiratory disease, resembling tuberculosis (Taboada, 2018).	• Check conditions of the silage or hay. Mouldy feed is more likely to be contaminated with Aspergillus spp. • Can be asymptomatic, some possible signs are » fever » heavy, loud and/or rapid breathing » nasal discharge » moist cough	• No treatment available • Procure good feed storing practices • Follow good ensiling practices to avoid development of Aspergillus spp. in silage • Avoid feeding excessively mouldy materials

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Mycotoxins

Problem	Check list	Corrective action
a) **Trichothecenes (DON, NIV, T-2, HT-2)** are known to impact health and productivity in many different ways: • Suppression of the appetite via release of CCK, the hormone of satiety • Alteration of the ruminal environment resulting in reduced digestibility, gas production and microbial protein production • Decreased intestinal, reducing nutrient absorption and gut barrier function, thus allowing the passage of pathogens and other mycotoxins to the bloodstream • Immunomodulation effects that can result in inflammatory responses that are very energetically costly; or lower immune cell proliferation, leaving the animal unprotected against pathogens	• Sample feed regular and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants. • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
b) **Aflatoxins (Afla)** are highly toxic. An exposure to this mycotoxin, even at low concentrations can harm the animal due to its carcinogenic, mutagenic, immune suppressive effects, among others.	• Reduced feed intake and retarded growth • Diverse severe symptoms • Sample feed regular and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants. • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
c) **Fumonisins (FUM)** can have negative impacts in: • Ruminal environment by affecting the bacterial compositions • FUM can elicit the breakdown of gram-negative bacteria, incrementing the proinflammatory LPS concentrations in the rumen (Hartinger et al., 2021) • Disrupts sphingolipid formation, important components of cell membranes and can affect the intestinal epithelium integrity and barrier function (Reisinger et al., 2019). • FUM exposure leads to increments of liver enzymes even at low and short-term contaminations which can compromise the health of the animal in multiple ways (Gallo, 2020 and Hartinger, 2021)	• Sample feed regular and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants. • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
d) **Zearalenone (ZEN)** is mainly known for its estrogenic effects, but it also has antimicrobial, oxidative and inflammatory effects: • Can cause impairment and alteration of ruminal environment by altering volatile fatty acid (VFA) production and particularly reducing acetate production (hints of fiber digestibility reduction) • From low doses can induce significant increases in body temperature by activating the immune system, an energy costly process for the animal (Hartinger et al., 2022)	• Check for abnormal vulva or genitals inflammations • Check for signs of impaired ruminal functions like diarrhea • Keep track of weight gain in a periodic basis • Keep track of feed intake and refusal • Sample feed regular and submit to an HPLC or LC-MS/MS analysis	• Prevent mould growth by good silage management practices and use of silage inoculants. • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins

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Problem	Check list	Corrective action
e) **Ergot alkaloids** can affect growth performance in different ways: • Alteration of ruminal environment, lower digestibility and reduction of volattile fatty acid (VFA) production (Sarich et al., 2021) • Inability to deal with heat: animals exposed to ergot fall into nervous problems that limit their ability to deal with heat stress, which reduces their intake and performance • Lameness can result of vasoconstriction induced by ergots which will limit wellbeing and performance	• Check for visual signs of ergot contamination: » Diarrhea » Vasoconstriction (ears, tails, feet) can be observable by some degree of necrosis » Lameness » Rough hair coat » Strange nervous reactions like excitability, tremors and inability to cope with heat • Sample feed regular and submit to an HPLC or LC-MS/MS analysis	• Understand and be aware of seasonable variations in grass and other feeds • Prevent mould growth by good silage management practices and use of silage inoculants. • Purchase mould and mycotoxin free raw materials • Integrate an effective mycotoxin solution against a wide range of mycotoxins
f) **Emerging mycotoxins** have antimicrobial effects that negatively impact the ruminal environment and reduce digestibility and volatile fatty acid (VFA) production: • **Fusaric acid** can inhibit the proliferation of *Ruminococcus albus,* relevant fiber degrading bacteria (May et al., 2000) • *Aspergillus fumigatus* toxins (gliotoxin among them) can alter ruminal environment, decrease DM degradation and gas production(Morgavi et al., 2004) • **Patulin** has shown to reduce VFA production and microbal protein efficiency in vitro simulations. Fiber digestibility can be reduced as well (Escoula, 1992; Tapia et al., 2005) • *Penicillium* spp. produced mycotoxins, **Mycophenolic acid** and **Roquefortine C** have proven to be able to reduce VFA production and alterate rumen due to their antimicrobial activity (Gallo, Giuberti, Bertuzzi, et al., 2015)		



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