



## Invited review: Udder cleft dermatitis in dairy cows

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### ABSTRACT

Udder cleft dermatitis (UCD) is a common dermatological condition of the udder skin in dairy cows. It is generally considered to be a multifactorial disease, being described in a rather limited amount of literature. Its cow and within-herd prevalence widely ranges between studies depending on the study characteristics, environment and breed. Known risk factors include husbandry practices and environmental factors, such as freestall housing, the use of mattresses as cubicle bases, and foot-bathing. Cow-related elements, such as udder conformation, parity, and lactation parameters are well-known risk factors for developing UCD. Despite being associated with a high incidence of veterinary-treated clinical mastitis and culling due to udder disease, the SCC of the milk is not influenced by UCD. Severe UCD lesions are characterized by chronic and persistent, dysregulated inflammation accompanied by hampered skin healing and an impaired skin barrier. There is a decrease in microbial diversity followed by dysbiosis and a concomitant overgrowth of opportunistic bacteria negatively affecting beneficial commensal bacteria. Concurrently, a shift in virulence factors most likely contributes to the creation of an environment favorable to pathogens. Anecdotally, mange mites have been associated with UCD but current literature refutes this. The role of treponemes remains inconclusive. Multiomics analysis of both transcriptomic and metagenomic severe UCD datasets, revealed the negative interaction of the facultative pathogen *Streptococcus pyogenes* with microbiome-associated virulence factors and the patient's transcriptome. No efficient curative treatments nor prevention strategies have been identified so far, although alginogel products have been described to have a positive effect on the healing process of severe lesions. All in all, UCD is a painful skin disease

for which an array of miscellaneous risk factors have been identified. For the first time we assimilate literature on prevalence and risk factors, and results from recent elementary studies that provide insights into the pathogenesis of this challenging disease.

**Key words:** udder cleft dermatitis, dairy cow, microbiome, risk factors

### INTRODUCTION

Udder cleft dermatitis (UCD) is an inflammatory skin condition with a foul odor, commonly occurring between the udder halves and at the front udder attachment. In early literature, the terminology for this type of udder skin lesion was ill-defined, resulting in the interchangeable use of various terms to describe these lesions such as ulcerative mammary dermatitis, intertrigo, udder dermatitis, foul udder, necrotic dermatitis, udder rot, and udder scald (Beattie and Taylor, 2000; Warnick et al., 2002; Sorge et al., 2019). However, nowadays “udder cleft dermatitis” is mostly used. In cattle, we need to distinguish UCD from udder-thigh dermatitis, which is situated on the skin between the posterior part of the udder and the thigh and is predominantly seen in heifers shortly before calving (Roy et al., 2012). Various classification scales exist, complicating cross-study comparisons but also enabling a standardized diagnosis of different UCD stages. Concrete evidence on the etiology and clinical course of UCD is scarce. A causal mechanism is yet to be determined.

### CLINICAL ASPECTS AND PREVALENCE

Lesions can be categorized according to the macroscopical aspect of the lesion. In mild lesions, the skin remains intact with minor changes such as erythema, papules, and crusts (<5 cm<sup>2</sup>), whereas large ulcerative exudative wounds with necrosis and hemorrhages are characteristic for severe UCD cases (Persson Waller et al., 2014). However, a clinical (0-to-5 scale) scoring sys-

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The list of standard abbreviations for JDS is available at [adsa.org/jds-abbreviations-24](https://adsa.org/jds-abbreviations-24). Nonstandard abbreviations are available in the Notes.

**Table 1.** Cow and within-herd prevalence of UCD lesions in several studies

Cow prevalence, %	Within-herd prevalence, %	Breed and study size	Country	Reference
5.2	0–15	Holstein-Friesian (n = 948 cows; 20 farms)	The Netherlands	Olde Riekerink et al., 2014
52 <sup>1</sup>	32–43 <sup>1</sup>	>95% Holstein-Friesian (n = 457 cows; 5 farms)	The Netherlands	Bouma et al., 2016 <sup>1</sup>
12.7 (mild) 5.7 (severe) 18.4 (total)	0–39	SR, SH, SR × SH (n = 1,084 cows; 30 farms)	Sweden	Persson Waller et al., 2014
19 (mild) 9 (severe) 28 (total)	0–43 (mild) 0–33 (severe) 0–62 (total)	SR, SH, SR × SH (n = 3,479 cows; 98 farms)	Sweden	Ekman et al., 2018
0.3	0–6.2	Simmental, Brown Swiss (n = 6,208 cows; 152 farms)	Germany	Groh et al., 2022

<sup>1</sup>No random selection of herds, leading to a higher prevalence.

tem with 6 severity categories has been proposed by Olde Riekerink et al. (2014), based on skin discoloration, presence of crusts and exudate, skin integrity and hair loss. The system by Olde Riekerink et al. (2014) was unsuitable for the longitudinal study conducted by Bouma et al. (2016) due to overlapping clinical signs between lesion stages. Moreover, Bouma et al. (2016) identified the presence of sebum or transudate as an additional clinical sign of UCD. The authors used a simple system: “healthy” (no skin lesions), “mild” (affected skin but no wound), and “severe” (wound with or without UCD lesions). The characteristics assessed in Bouma et al. (2016) were type and aspect of skin (presence of transudate, sebum, or crust), presence of erythema, granulation tissue, scar tissue, length of affected skin, and the length of the open wound. Hansen and Nissen (2010) suggested a scoring system based on the appearance and lesion size (less or more than 25 cm<sup>2</sup>). The appearance of a grade 1 lesion ranges from hyperkeratosis to hyperemia or small papules or pustules. Grade 2 and 3 represent necrotic dermatitis, whereas grade 4 and 5 describe exudative necrotic dermatitis. The lack of a clear, standardized clinical scoring system makes it difficult to set up an adequate treatment protocol and also poses a challenge to compare studies. Complications such as embolic pneumonia or even death through erosion of the udder vein have been reported (Turner et al., 2017). In a brief case report, 2 Holstein-Friesian cows with UCD lesions displayed general malaise, a drop in milk production and dyspnea (Turner et al., 2017). Despite being diagnosed with chronic suppurative pneumonia, both animals showed poor responsiveness to antibiotic treatment. Postmortem examination revealed signs of embolic pneumonia linked with UCD lesions. In another case report by Capuzzello et al. (2024), UCD is considered as being likely to contribute to a case of renal amyloidosis where no other inflammatory foci could be found.

Only a small number of prevalence studies were conducted, and these were limited to a few European coun-

tries. The UCD prevalence varies widely between herds and countries. In 2014, a prevalence study conducted on 30 Swedish herds (n = 1,084 cows) revealed 18.4% of cows were affected, of which most of these cows (69%) had mild lesions. The within-herd prevalence was between 0% and 39%, with a mean prevalence of 18.5% (Persson Waller et al., 2014). In a large-scale study by Ekman et al. (2018), the cow prevalence was 28%: 19% for mild UCD and 9% for severe clinical cases. Within-herd prevalence of UCD lesions (0%–62%), specifically of mild (0%–43%), and severe (0%–33%), exhibited a large variability across the 98 included herds (n = 3,479 cows). In a Dutch study involving 948 cows from 16 different herds, the overall cow prevalence was 5.2%, whereas the within-herd prevalence ranged between 0% and 15% (Olde Riekerink et al., 2014). Only 28 of 6,208 Simmental and Brown Swiss cows from 152 German farms displayed UCD lesions (Groh et al., 2022). The within-herd prevalence for UCD positive farms (n = 16 herds with 914 cows in total) ranged between 0.9% and 6.2% (median = 3.2%). Considering all farms, the herd prevalence ranged between 0.0% and 0.2% (median = 0.0%; Table 1). Contrastingly, the lack of a random herd selection led to a higher within-herd prevalence of 32% to 43% in the study by Bouma et al. (2016). A total of 239 out of 457 cows (52.3%) displayed signs of UCD. Data from non-European countries with different husbandry practices, cattle breeds, environmental conditions, and potential other risk factors are missing, possibly introducing bias. The choice of specific selection criteria such as the presence of a milking parlor or herd size, along with the use of different classification schemes might have contributed to intrinsic differences in prevalence.

## RISK FACTORS

The precise cause of UCD has not yet been elucidated. A multifactorial etiology is highly likely. Nonetheless, several potential factors on cow, herd, and environmental

level associated with the presence (Warnick et al., 2002; Hansen and Nissen, 2010; Olde Riekerink et al., 2014; Persson Waller et al. (2014); Bouma et al., 2016; Ekman et al., 2018; Groh et al., 2022) and the development (Ekman et al., 2020b) of UCD have been identified (Table 2). The inflammation resulting from skin-on-skin friction, intertrigo, commonly presents with secondary bacterial infections and falls under the broader term moisture-associated skin damage (Voegeli, 2020). An analogy between UCD and canine intertrigo can be seen due to the shared combination of skin friction in a moist microenvironment concomitant with microbial overgrowth (Miller et al., 2012). In the case of canine intertrigo, the main risk factors are breed- and weight-dependent skin folds (Paterson, 2017). Udder skin folds and indentations present a potential risk by inducing microlesions through friction, establishing an optimal and moist environment conducive to the colonization of pathogenic microorganisms and the proliferation of opportunistic microbes (Ekman et al., 2018, 2020a,b; Figure 1). Ekman et al. (2018) found that first-parity cows and cows with a smooth udder exhibited a lower risk of having mild UCD lesions compared with cows with skin folds and indentations at the front udder attachment. Udder conformation, parity, and lactation parameters stand out as the most important risk factors identified to date (Warnick et al., 2002; Hansen and Nissen, 2010; Olde Riekerink et al., 2014; Persson Waller et al., 2014; Bouma et al., 2016; Ekman et al., 2018, 2020b). A strong front udder attachment has been established as a protective factor (Hansen and Nissen, 2010). Other identified risk factors include a deep udder in relation to the hock, large front quarters, and a small angle between the udder and abdominal wall (Hansen and Nissen, 2010; Olde Riekerink et al., 2014).

An association between DIM and risk for UCD has been reported in literature (Warnick et al., 2002; Hansen and Nissen, 2010; Bouma et al., 2016; Ekman et al., 2018, 2020b). However, one study found no significant association (Persson Waller et al., 2014). The udder conformation undergoes changes during the lactation, influenced by production levels and increasing parity, potentially resulting in a loose udder attachment, a deeper udder, and reduced skin elasticity (Warnick et al., 2002; Bouma et al., 2016; Ekman et al., 2018). High milk yield is considered an important risk factor at both cow and herd level for UCD lesions (Olde Riekerink et al., 2014; Persson Waller et al., 2014). Production levels possibly influence factors, such as udder conformation, internal udder pressure, and edema. The pressure hypothesis is supported by a multivariable mixed-effects, logistic regression model in a Swedish study that found a significantly lower risk for severe UCD in cows milked thrice instead of twice a day (Ekman et al., 2018). A parity of 2 or higher is considered to be a risk factor, possibly due to the age-related

changes in the udder conformation (Warnick et al., 2002; Hansen and Nissen, 2010; Persson Waller et al., 2014; Bouma et al., 2016; Ekman et al., 2018, 2020b). In aging cows, a loose front udder attachment could lead to increased local skin friction (Jalakas et al., 2000; Hansen and Nissen, 2010). As dairy cows age, similar to other mammals, their skin loses elasticity and becomes thinner. Alongside other morphological changes, this affects the skin's ability to heal. It leads to a longer inflammatory phase, an increase in reactive oxygen species, and a shift toward greater protein degradation during the healing process. These factors collectively contribute to chronic wound-healing issues, potentially accompanied by various complications (Khalid et al., 2022). Most udder conformation traits or other traits such as distance between the tuber ischiae, were not identified as risk factors in Olde Riekerink et al. (2014) (Table 2). Ekman et al. (2018, 2020b) observed that a low milk urea level was associated with a lower risk for severe UCD and the transition from mild to severe lesions. A low urea level might be indicative of a well-balanced protein metabolism and energy balance, suggesting an adequate immune function and tissue repair (Cheng et al., 2015). It is noteworthy that the SCC, and consequently subclinical mastitis, is not correlated with the presence of UCD, neither at the individual cow nor at the herd level (Olde Riekerink et al., 2014; Persson Waller et al., 2014). However, the SCC emerged as a risk factor associated with mild, severe, and all UCD cases in general in a univariable, mixed-effects, logistic regression model (Ekman et al., 2018). Skin lesions potentially have the ideal environment to house pathogens that can cause (sub)clinical mastitis. Although prevalence studies specifically focusing on breed predisposition are lacking, Swedish Red, and Swedish Red × Swedish Holstein cows appeared to be more prone to developing UCD on a cow and herd level (Persson Waller et al., 2014; Ekman et al., 2018).

Hock lesions are possibly associated with the mild form of UCD but further research is needed to explore the connection with leg and hoof disorders (Ekman et al., 2018). The risk for mild UCD was found to increase in herds with a high incidence of culling due to claw and leg disorders (Ekman et al., 2018). Prolonged periods of lying down, as observed in cows with such disorders, could contribute to this association (Chapinal et al., 2010). Additionally, hock lesions might serve as an important reservoir for pathogenic and opportunistic bacteria (Clegg et al., 2016a).

The use of a footbath was positively associated with the UCD prevalence at the herd level (Olde Riekerink et al., 2014). Footbathing is a crucial herd-level measure for preventing infectious foot disorders such as digital dermatitis (DD) and foot rot. However, a clear-cut link between DD and UCD has not been established yet.

**Table 2.** Potential risk factors contributing to the presence or development<sup>1</sup> of mild or severe UCD<sup>2,3</sup>

Risk factor	Reference
Increased risk	
Cow level	
Udder conformation:	
Front udder attachment	
Intermediate (A, M, S)	Ekman et al. (2018)
Loose (A)	Hansen and Nissen (2010); Ekman et al. (2018)
Udder skin folds and indentations (A, M)	Ekman et al. (2018)
Udder skin folds and indentations at the front udder attachment × parity $\geq 1$ (A, M)	Ekman et al. (2018)
Absence of udder skin folds and indentations at the front udder attachment × increasing parity $\geq 2$ (A, M)	Ekman et al. (2018)
Udder skin folds and indentations in SR, SH or other breeds (A, M)	Ekman et al. (2020b)
Absence of udder skin folds and indentations in SR (A, M)	Ekman et al. (2020b)
Udder depth	Hansen and Nissen (2010); Olde Riekerink et al. (2014)
Large front quarters	Olde Riekerink et al. (2014)
Strong udder support	Hansen and Nissen (2010)
Breed:	
SR with any type of front udder attachment (A, S)	Ekman et al. (2018)
SH × SR with a loose front udder attachment (A)	Persson Waller et al. (2014)
SH × SR with an intermediate front udder attachment (A, S)	
SR, SH × SR (M, S)	
SR	
Lactation parameters:	
Stage of lactation (parity 1)	Warnick et al. (2002)
Increase in DIM (A, M)	Bouma et al. (2016); Ekman et al. (2020b)
181–305 d (S) and $\geq 306$ d (S)	Ekman et al. (2018)
Milk production	Persson Waller et al. (2014)
ECM	
$>39.7$ kg or 29.7–34.0 kg (S)	Ekman et al. (2020b)
$>32$ kg (S)	Ekman et al. (2018)
Milk urea level $>3.7$ mmol/L (A, M)	Ekman et al. (2020b)
Parity:	
Higher	Warnick et al. (2002)
$\geq 2$ (A, M, S)	Ekman et al. (2018)
$\geq 3$	Hansen and Nissen (2010); Persson Waller et al. (2014); Bouma et al. (2016)
Other parameters	
Mild UCD (S)	Ekman et al. (2020b)
Veterinary-treated clinical mastitis $\pm 30$ d from the herd visit	Persson Waller et al. (2014)
Hock lesions (M)	Ekman et al. (2018)
Herd level	
Production level	Olde Riekerink et al. (2014)
$\geq 10,900$ kg/cow	Persson Waller et al. (2014)
High proportion of SR cows ( $\geq 20\%$ )	Persson Waller et al. (2014)
Freestall housing	Groh et al. (2022)
Comfort rubber mats (dry period) as cubicle base	Groh et al. (2022)
Concrete exposed behind mat(tress) at rear curb (S)	Ekman et al. (2018)
Distance from the brisket board to rear curb under the recommendation or as recommended (S)	Ekman et al. (2018)
Use of footbath	Olde Riekerink et al. (2014)
Culling due to hoof and leg diseases ( $\geq 2.7$ cases/100 cows at risk) (M)	Ekman et al. (2018)
Culling due to udder diseases ( $\geq 9$ cases/100 cows at risk) (S)	Ekman et al. (2018)
Veterinary-treated clinical mastitis	Ekman et al. (2018)
0–3.31 and $\geq 10.00$ cases/100 cows at risk (A, S)	
Regular use of a feed adviser (S)	Ekman et al. (2018)
Decreased risk	
Cow level	
Digital dermatitis	Warnick et al. (2002)
ECM $<38$ kg (A)	Ekman et al. (2018)
Milk urea level (mmol/L)	Ekman et al. (2018)
4.3–5.1 (S)	
Strong udder attachment	Hansen and Nissen (2010); Persson Waller et al. (2014)
SH with strong front udder attachment (A, S)	Ekman et al. (2018)

*Continued*

**Table 2 (Continued).** Potential risk factors contributing to the presence or development<sup>1</sup> of mild or severe UCD<sup>2</sup>

Risk factor	Reference
Herd level	
Cubicles:	Ekman et al. (2018)
Combination of eating and lying cubicles (A)	
Distance from brisket board to rear curb as recommended or above recommendation (M)	
Year of cubicle installation, 2001–2005 (A, S)	
Cleaning cubicles 2×/d (M)	Ekman et al. (2018)
Rubber mats (A, M, S)	Ekman et al. (2018)
Other cubicle bases (A, M, S)	
Visit period between December – March (A, M, S)	Ekman et al. (2018)
Herd proportion of ≥ 17% heifers older than 17 mo and not inseminated (A)	Ekman et al. (2018)
Cow mortality ≥5 cases per 100 cows at risk (A, M, S)	Ekman et al. (2018)
≥20% cows with >70 d between calving and first insemination (A, M, S)	Ekman et al. (2018)
≥1.0 veterinary-treated case of feeding-related diseases per 100 cows at risk (M)	Ekman et al. (2018)
Culling of first-parity cows in early lactation (≥2.5 cases/100 cows at risk) (S)	Ekman et al. (2018)
Herd size <75 and >99–125 and ≥126 cows (S)	Ekman et al. (2018)
Milking 3×/d (S)	Ekman et al. (2018)
No risk <sup>4</sup>	
Cow level	
Udder conformation	Bouma et al. (2016)
Strength of median suspensory ligament	Olde Riekerink et al. (2014)
(Relative to tuber ischiae distance) udder width	Olde Riekerink et al. (2014)
Peak milk production	Warnick et al. (2002)
305 d mature equivalent milk production	Warnick et al. (2002)
Stage of lactation (with parity ≥2)	Warnick et al. (2002)
Parity = 2	Persson Waller et al. (2014)
Distance between dew claws – os calcaneus	Olde Riekerink et al. (2014)
Distance between tuber ischiae	Olde Riekerink et al. (2014)
Hygiene score thighs, udder posterior/lateral view and lower legs	Olde Riekerink et al. (2014)
SH × SR	Persson Waller et al. (2014)
Herd level <sup>5</sup>	
Presence of sarcoptic mange	Olde Riekerink et al. (2014)
Digital dermatitis	Olde Riekerink et al. (2014)
Herd size	Hansen and Nissen (2010)
SCC	Olde Riekerink et al. (2014)
Type of bedding	Olde Riekerink et al. (2014)
Use of lime in stalls	Olde Riekerink et al. (2014)
High frequency of alley scraping	Olde Riekerink et al. (2014)

<sup>1</sup>The study by Ekman et al. (2020b).

<sup>2</sup>(M) indicates mild UCD; (S) indicates severe UCD; and (A) indicates all types of UCD.

<sup>3</sup>Only multivariable analyses were included when a study contained univariable and subsequent multivariable analyses (Persson Waller et al., 2014; Ekman et al., 2018, 2020b).

<sup>4</sup>Variables not passing the  $P < 0.05$  threshold were put in the “no risk” category.

<sup>5</sup>Herd-level risk factors were only indicative in Olde Riekerink et al. (2014) due to the small herd sample size.

No association could be found between DD and UCD prevalence in studies of Hansen and Nissen (2010) and Olde Riekerink et al. (2014). Contrastingly, the presence of DD decreased the risk for UCD in another study (Warnick et al., 2002). These latter findings warrant an in-depth analysis on the simultaneous presence of DD and UCD in farms. Additionally, the presence of harsh chemicals in the footbath poses the risk of splashing onto the udder, potentially causing skin irritation and damage. Neglecting to clean footbaths regularly can lead them

to become a source of contamination for infectious foot diseases and udder skin infections.

In a multivariable mixed-effects logistic regression model, herds with fewer than 75 cows, as well as those with 99 to 125 cows, and 126 or more cows, are associated with a lower risk of severe UCD compared with herds with 75 to 98 cows (Ekman et al., 2018). Although herd size does not appear to be a risk factor for UCD in a study by Olde Riekerink et al. (2014), a larger sample size in future research could offer more clarity on this matter.

Housing-related factors that pose a higher risk for severe UCD include the use of cubicles not following the standard recommendations in terms of size, and the use of mattresses or comfort rubber mats as cubicle bases instead of rubber mats, concrete, or straw (Ekman et al., 2018; Groh et al., 2022). Also, a German study reported that cows housed in freestalls had 12.6 times higher odds of suffering from UCD compared with cows housed in tiestalls (Groh et al., 2022). Usage of lime in stalls and type of bedding was not associated with the presence of UCD in a study by Olde Riekerink et al. (2014).

Additionally, aside from a high culling incidence due to udder disease, a low culling incidence of first-parity cows in early lactation is considered a herd-related risk factor for severe UCD (Ekman et al., 2018). A high incidence of veterinary-treated clinical mastitis (VTCM) is associated with a higher risk of severe UCD. Furthermore, the risk to develop VTCM within a month is 3.3 times higher after a UCD diagnosis than in healthy cows without UCD lesions (Persson Waller et al., 2014). The risk for severe UCD is lower in herds with a high proportion of heifers over 17 mo old that are not yet inseminated (Ekman et al., 2018). The identification of this risk factor cannot be readily explained and may be a coincidental finding.

### TRANSCRIPTOMIC PROFILE OF SEVERE UDDER CLEFT DERMATITIS LESIONS

A study by Vermeersch et al. (2023) showed a chronic and persistent, dysregulated inflammatory response in severe UCD lesions. Moreover, the skin barrier integrity as well as wound repair mechanisms are severely disrupted (Figure 2). Persistence of severe UCD lesions may be due to a lack of tissue repair and a damaging inflamma-

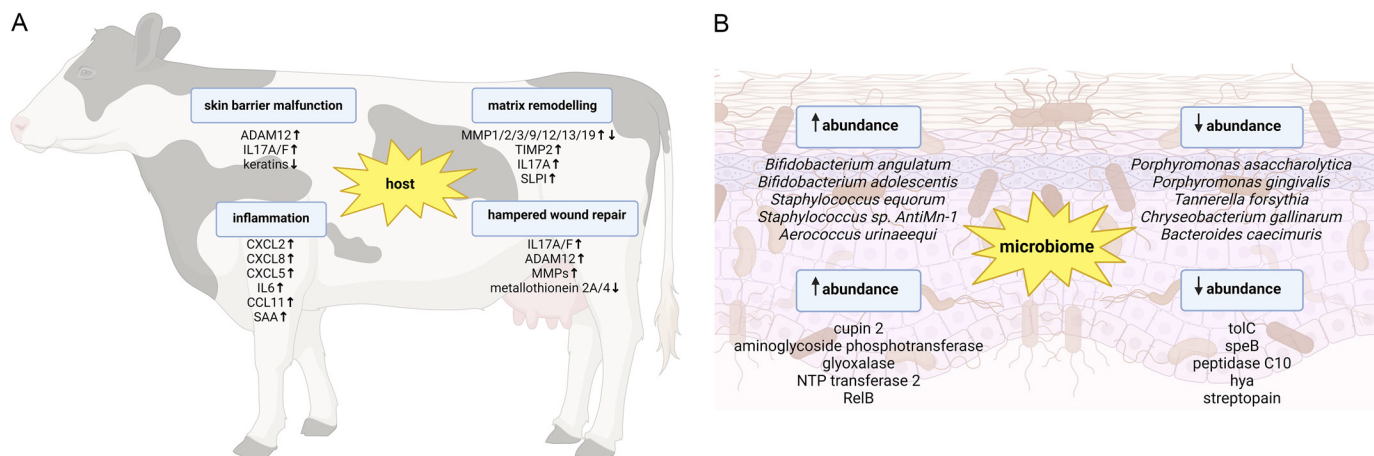


**Figure 1.** The left picture shows a bottom view of an udder suspected of udder cleft dermatitis (UCD). In the right picture, the udder halves of the same udder are pulled apart, exposing a severe UCD lesion.

tory response in combination with an unbalanced matrix turnover. A fulminant cytokine storm is initiated by the elevated expression of C-X-C motif ligand 2 (CXCL2), 5 (CXCL5), and 8 (CXCL8) and C-C motif ligand 11 (CCL11). Keratins and keratin-associated molecules are significantly downregulated, possibly leaving the skin barrier more vulnerable. Moreover, the epidermal keratinocytes might show a decline in migration and faulty differentiation with a postponed re-epithelization of the skin through molecules such as ADAM12 and IL-17A. The concomitant significant upregulation of several matrix metalloproteinases (MMP) and downregulation of metallothioneins could exacerbate the lesion. Furthermore, molecules such as SAA2, IL-17A, and SLPI could intensify the local inflammation. Multiple pro-inflammatory pathways were found to be upregulated, of which the chemokine- and the IL-17 signaling pathway. Curiously, the latter has also been found to be activated during acute and chronic stages of bovine DD (Vermeersch et al., 2022).

### ROLE OF THE MICROBIOME

To gain a comprehensive understanding of the pathogenesis, it is imperative to examine the microbiome in UCD lesions (Table 3). Whether changes in the microbiome are primary or secondary in the pathogenesis, is yet to be clarified. Microorganisms such as mange mites, treponemes, as well as an evident dysbacteriosis, have been indicated as potential key players (Warnick et al., 2002; Evans et al., 2010; Hansen and Nissen, 2010; Sorge et al., 2019; Ekman et al., 2020a). Shotgun sequencing failed to identify specific bacterial species as an underlying cause, and typical mastitis-causing bacteria were not abundant in the lesions (Ekman et al., 2020a; Vermeersch et al., 2024a). The microbial diversity is diminished and the bacterial composition appears to shift in UCD-affected skin, leading to a substantial loss of commensals and an increase of facultative pathogenic anaerobes (Figure 2). An increased proportion of bacteria such as *Corynebacterium* spp., *Brevibacterium luteolum*, *Trueperella pyogenes*, and *Fusobacterium necrophorum* has been observed (Beattie and Taylor, 2000; Warnick et al., 2002; Ekman et al., 2020a; Vermeersch et al., 2024a). Additional metagenomic analyses revealed an increase of other bacteria, such as *Anaerococcus* spp., *Porphyromonas* spp., and *Prevotella* spp. in UCD lesions (Sorge et al., 2019; Vermeersch et al., 2024a). Rather than being a primary cause, the latter are more likely opportunistic secondary invaders. In healthy skin samples, *Bifidobacterium* spp. are more abundant (Sorge et al., 2019; Ekman et al., 2020a; Vermeersch et al., 2024a). Given their beneficial role in skin homeostasis by reducing inflammation and fibrosis while simultaneously enhancing the



**Figure 2.** Currently, only 1 study on the transcriptomic component of the pathophysiology of severe udder cleft dermatitis (UCD) lesions has been conducted (left; Vermeersch et al., 2023). The wound repair mechanisms and skin barrier were hampered, concomitantly with a persistent local inflammatory response. Shotgun metagenomic sequencing of the microbiome was simultaneously applied to samples originating from the same severe UCD-affected population, revealing a dysbiosis and shift in virulence factors (right; Vermeersch et al., 2024a). Figure created with Biorender.com.

skin barrier function, their decline in UCD lesions most probably has a detrimental impact on the local microbiome (Kim et al., 2022; Ma et al., 2023).

Treponemes are known to play a key role in other bovine skin lesions such as DD (Döpfer et al., 1997), and they have been suspected to be implicated in UCD as well (Evans et al., 2010). Nevertheless, direct scientific evidence linking treponemes to the pathogenesis of UCD is lacking (Evans et al., 2010; Sorge et al., 2019). However, a metagenomic analysis has found an increased yet low abundance of pathogenic *Treponema pedis*, *Treponema denticola*, and *Treponema putidum* (Vermeersch et al., 2024a). Also, multiple treponeme phylotypes have been identified in UCD lesion samples through 16S rDNA-tRNA intergenic spacer region sequence analysis, some of which were closely related to human- and papillomatous DD-associated phylotypes (Stamm et al., 2009). In a UK study, a commensal and pathogenic treponeme PCR assay was positive in 70% of UCD and 75% of normal udder skin samples (Evans et al., 2010). Only one out of 10 UCD samples revealed a positive PCR test for DD-associated *Treponema medium*-like spirochaetes. Immunohistochemistry using DD-associated treponeme antisera was positive in 3 out of 8 UCD skin biopsies. Nested PCR assays showed the presence of *T. pedis* in 80% of healthy udder cleft skin samples ( $n = 25$ ), whereas *Treponema phagedenis*-like sequences have been found in 32% of the same samples (Sobhy et al., 2020). The DD-associated treponemal species *T. medium* and *Treponema vincentii*-like were not detected in this study. *Treponema phagedenis*-like and *T. pedis* were also detected in respectively 40% (10) and 60% (15) of foremilk samples (total  $n = 25$ ) of cows affected by DD. The presence of these treponemes might be attributed to contamination

from DD lesions and the environment in general, or it could indicate an actual treponemal colonization. The variable prevalence of DD between countries, regions, or even herds complicates analyzing the potential effect of DD-associated treponemes on UCD (Holzhauer et al., 2006; Becker et al., 2014; Yang et al., 2019). In a study by Persson Waller (2014) the DD prevalence was very low, ranging between 0% and 0.4%, making it difficult to draw conclusions about its role as a risk factor for UCD (Persson Waller et al., 2014). No statistically significant link could be observed between DD and UCD in another, small-scale study (Hansen and Nissen, 2010). However, DD prevalence might have been underestimated as cows were visually inspected during milking. A broad variety of gastrointestinal tract-associated treponemal phylotypes are ubiquitously present in the dairy farm environment (Evans et al., 2010, 2012; Klitgaard et al., 2014). Although they are likely opportunistic, they have the potential to act as pathogenic invaders. Evidence from other studies indicate DD-associated treponemes are not a part of the environment in dairy farms, with or without clinical DD (Evans et al., 2010; 2012; Klitgaard et al., 2017; Dias et al., 2024). However, the mere presence of treponemes does not necessarily indicate disease might occur. The presence of mange has been mentioned as a possible cause (Warnick et al., 2002) but this hypothesis was later rejected (Olde Riekerink et al., 2014). To date, no solid scientific evidence has been found to indicate the presence of a specific pathogen that causes UCD.

Studying the bacterial community in relation to UCD has revealed significant insights, yet methodological approaches vary greatly in literature. Some studies only included bacterial phyla and genera that represented >1% of the bacteria in the results (Sorge et al., 2019).

**Table 3.** The abundances<sup>1</sup> of microbes in mild and severe udder cleft dermatitis lesions<sup>2</sup> according to studies employing metagenomic sequencing, culture methods, or PCR detection

Microbial abundance	Reference
<i>Treponema</i> spp. ↑	Vermeersch et al., 2024a (S)
<i>Treponema</i> spp. ↓ NS	Sorge et al., 2019
<i>Treponema</i> spp. (7/10 samples)	Evans et al., 2010
<i>Brevibacterium flavum</i> , <i>Brevibacterium linens</i> ↓	Vermeersch et al., 2024a (S)
<i>Fusobacterium nucleatum</i> , <i>Fusobacterium hwasookii</i> ↑	Vermeersch et al., 2024a (S)
<i>Fusobacterium necrophorum</i> ↑	Ekman et al., 2020a (S)
<i>Fusobacterium necrophorum</i> (4/5 samples), <i>Fusobacterium mortiferum</i> (1/5 samples)	Warnick et al., 2002 <sup>3,4</sup>
<i>Fusobacterium</i> spp. ↑	Sorge et al., 2019
<i>Trueperella pyogenes</i> ↑ (16/26 samples)	Vermeersch et al., 2024a (S); Ekman et al., 2020a (S); Van Engelen et al., 2021 <sup>3</sup> (S); Beattie and Taylor, 2000 <sup>3,4</sup>
<i>Trueperella</i> spp. ↑ (1/13 samples)	Ekman et al., 2020a (S); Sorge et al., 2019
<i>Porphyromonas gingivalis</i> ↑	Vermeersch et al., 2024a (S)
<i>Porphyromonas</i> spp. ↑	Sorge et al., 2019
<i>Porphyromonas asaccharolytica</i> ↑	Vermeersch et al., 2024a (S)
<i>Tannerella forsythia</i> ↑	Vermeersch et al., 2024a (S)
<i>Staphylococcus</i> spp. ↓	Vermeersch et al., 2024a (S)
<i>Staphylococcus</i> spp. (3/13 samples)	Beattie and Taylor, 2000 <sup>3,4</sup>
<i>Staphylococcus</i> spp. ↓ NS	Sorge et al., 2019
<i>Staphylococcus simulans</i> (6/13 samples)	Beattie and Taylor, 2000 <sup>3,4</sup>
<i>Bacillus fragilis</i> , <i>Bacillus</i> sp. LM4–2, <i>Bacillus</i> sp. FJAT-14266, <i>Bacillus</i> sp. YP1, <i>Bacillus subtilis</i> , <i>Bacillus cytotoxicus</i> ↑	Vermeersch et al., 2024a (S)
<i>Bacillus infantis</i> , <i>Bacillus glycinifermentans</i> , <i>Bacillus paralicheniformis</i> ↓	
<i>Bacillus</i> spp. ↓	Sorge et al., 2019
<i>Prevotella</i> spp. ↑	Vermeersch et al., 2024a (S); Sorge et al., 2019
<i>Prevotella melaninogenica</i> (2/5 samples); (11/13 samples)	Warnick et al., 2002 <sup>3,4</sup> ; Beattie and Taylor, 2000 <sup>3,4</sup>
<i>Helcococcus</i> spp. ↑	Sorge et al., 2019
<i>Anaerococcus</i> spp. ↑	Sorge et al., 2019
<i>Anaerococcus prevotii</i> ↑	Vermeersch et al., 2024a (S)
<i>Bacteroides</i> spp. ↑	Vermeersch et al., 2024a (S); Sorge et al., 2019
<i>Bacteroides</i> spp. (2/5 samples)	Warnick et al., 2002 <sup>3,4</sup>
<i>Bacteroides pyogenes</i> ↑ (14/26 samples)	Van Engelen et al., 2021 <sup>3</sup> (S)
<i>Bacteroides melaninogenicus</i> (3/5 samples)	Warnick et al., 2002 <sup>3,4</sup>
<i>Corynebacterium</i> spp. ↑	Vermeersch et al., 2024a (S); Ekman et al., 2020a (S); Beattie and Taylor, 2000 <sup>3,4</sup>
<i>Corynebacterium</i> spp. (1/13 samples)	Beattie and Taylor, 2000 <sup>3,4</sup>
<i>Corynebacterium minutissimum</i> (9/13 samples), <i>Corynebacterium jeikeium</i> (4/13 samples), <i>Corynebacterium ulcerans</i> (3/13 samples)	Beattie and Taylor, 2000 <sup>3,4</sup>
<i>Corynebacterium lactis</i> , <i>Corynebacterium urealyticum</i> ↑	Ekman et al., 2020a (S)
<i>Corynebacterium jeikeium</i> , <i>Corynebacterium</i> sp. LMM-1652,	Ekman et al., 2020a (M,S)
<i>Corynebacterium resistens</i> ↑	
<i>Corynebacterium</i> spp. ↓ NS	Sorge et al., 2019
<i>Bifidobacterium</i> spp. ↓	Vermeersch et al., 2024a (S); Ekman et al., 2020a (S); Sorge et al., 2019
<i>Bifidobacterium angulatum</i> ↓	Vermeersch et al., 2024a (S); Ekman et al., 2020a (S)
<i>Mycoplasma</i> spp. ↑	Vermeersch et al., 2024a (S)
<i>Mycoplasma</i> spp. ↓ NS	Sorge et al., 2019
<i>Brachybacterium</i> spp. ↓	Ekman et al., 2020a (S)
<i>Ruminococcus</i> spp. ↓	Sorge et al., 2019
<i>Weissella</i> spp. ↓	Sorge et al., 2019
<i>Peptostreptococcus</i> spp. (2/5 samples)	Warnick et al., 2002 <sup>3,4</sup>
<i>Actinomyces</i> spp. (1/5 samples)	Warnick et al., 2002 <sup>3,4</sup>
<i>Geotrichum</i> spp. (5/13 samples)	Beattie and Taylor, 2000 <sup>3,4</sup>
<i>Candida</i> spp. (2/13 samples)	Beattie and Taylor, 2000 <sup>3,4</sup>

<sup>1</sup>↑ and ↓ respectively indicate an increased and decreased abundance of bacteria. “NS” together with an arrow refers to a nonsignificant decrease or increase in abundance ( $P > 0.05$ ).

<sup>2</sup>In the Reference column (M) indicates mild lesions, (S) indicates severe lesions.

<sup>3</sup>No arrows are used when referring to studies employing culture methods or PCR detection.

<sup>4</sup>Only severe lesions were sampled in Warnick et al. (2002) and Beattie and Taylor (2000). No healthy skin samples were taken, in contrast to the other studies mentioned in this table.

Excluding low abundant species might be problematic as the relevant microbes are not always the most abundant ones, as has been proven with the low abundance of *Dichelobacter nodosus* in ovine footrot (Maboni et al., 2017). At present, the precise role of the lowly abundant treponemes in the development of UCD lesions remains unclear.

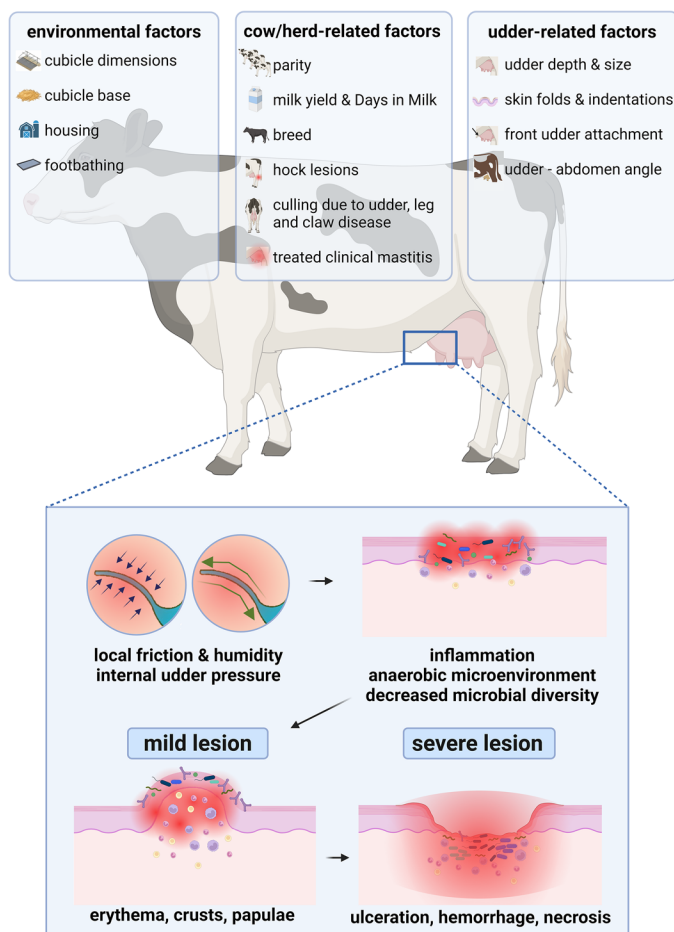
By constructing networks based on co-occurrence patterns of microbial species, the underlying structure of the microbiome and a potential shift toward a more commensal or pathogenic community can be revealed. Network analysis has led to the discovery of a network consisting of mainly commensal bacteria such as *Bifidobacterium* spp. and *Aerococcus* spp. in healthy udder cleft skin, whereas the network in UCD lesions contained anaerobic bacteria such as *Bacteroides* spp. (Vermeersch et al., 2024a). The streptococcal cysteine protease *speB*, the outer membrane efflux protein pump *tolC* and hemolysins *shlA* and *shlB*, are among the key virulence factors in severe UCD lesions (Vermeersch et al., 2024a). The concurrent lower abundance of the *Staphylococcus*-associated toxin *entC* is in line with the decreased abundance of staphylococci. Contrastingly, *cupin 2* and aminoglycoside phosphotransferase are the most abundant virulence factors in healthy udder skin. The shift in virulence factors potentially creates the ideal wound environment favorable to the UCD-associated microbiome. Only one study has investigated the virulence factors as a part of the microbiome in severe UCD lesions, showing a high correlation (88%) between the microbiome members and virulence factors by using sparse partial least squares analysis (Vermeersch et al., 2024a). It has revealed a cluster of potential pathogens such as multiple *Treponema* species together with *Mycoplasma* spp., and ADP-ribosylating toxin (*spvB*), filamentous haemagglutinin B (*fhaB*), and haemagglutination activity domain associated factor. Concomitantly, the commensals *Bifidobacterium indicus* and *Butyrivibrio proteoclasticus*, and virulence factors hydrogen cyanide synthase B (*hcnB*), hydrogen cyanide synthase C (*hcnC*), *relB*, glyoxalase, and *cupin 2* formed a cluster characterizing healthy bovine udder skin. In-depth, longitudinal analyses on the function and interaction of these virulence factors could provide essential insights into their influence on the local skin microbiome, and their role in the UCD pathogenesis.

### USING AN INTEGRATED MULTIOMICS APPROACH TO GAIN INSIGHTS INTO THE PATHOGENESIS OF SEVERE UCD

A biological system with its unique microbe-host-environment interactions can be fundamentally investigated through an integrative approach to omics analyses (Rohart

et al., 2017; Singh et al., 2019). Highly dimensional data such as transcriptomic and metagenomic datasets can be integrated through methods such as (sparse) partial least squares, and bring forth novel biomarkers. The application of this multiomics approach has been successful in psoriasis, atopic dermatitis, and COVID-19 research (Fyhrquist et al., 2019; Su et al., 2020). A multilayered investigation expands our current knowledge on UCD as its pathogenesis entails multiple components such as the microbiome, host characteristics, and environmental influences (Figure 3). Multiomics-driven exploration of transcriptomic and metagenomic data sets of severe UCD lesions has revealed mainly positive associations ( $r = 0.85$ ) between the healthy skin-associated host transcriptome, microbiome, and its associated virulence factors (Vermeersch et al., 2024b). Genes coding for essential components of the host skin, membranes and the immune system such as *GATA3*, *KRT73*, *RETREG*, and *GJB4* positively correlate with virulence factors, such as antitoxin *relB*, hydrogen cyanide synthase coding genes (*hcnB*, *hcnA*), and glyoxalase, and microbiome members *Adlercreutzia equolifaciens*, *Roseburia hominis*, and *Butyrivibrio* species. Although the above-mentioned enzymes are classified in databases as virulence factors, they don't seem to play a role in the pathogenesis of disease, but they are mostly expressed by saprophytic bacteria providing a competitive advantage and thus stabilizing the beneficial microbiome of healthy skin (Loo et al., 2023).

Surprisingly, in this multiomics analysis *Streptococcus pyogenes* has emerged as the sole factor negatively correlated with the host genes and virulence factors mentioned above, but not with udder skin commensals (Vermeersch et al., 2024b). In the metagenomic analysis of severe UCD lesions, *Streptococcus*-associated *speB* emerged as highly abundant, potentially exerting both pro- and anti-inflammatory functions (Egesten et al., 2009; Vermeersch et al., 2024a). This finding warrants further in-depth research into the role of *Strep. pyogenes* in UCD lesions, supported by recent findings in the human skin disease yaws (Griesenauer et al., 2021). Yaws, a neglected tropical disease, causes skin ulcers associated with *Treponema pallidum* subspecies *pertenue* and *Hemophilus ducreyi* (Marks et al., 2015). The cutaneous manifestation of yaws resembles the macroscopical appearance of another presumably treponeme-driven disease, acute DD, as well as severe UCD lesions. Noteworthy, the initial “mother yaw” lesion typically manifests on the lower legs of children (Marks et al., 2015). A recent yaws eradication campaign revealed the presence of *Strep. pyogenes* in human idiopathic ulcers failing to respond to a mass azithromycin treatment, mirroring the lack of response to treatment observed in UCD lesions (Griesenauer et al., 2021). *Streptococcus pyogenes* is able to impair the host



**Figure 3.** Suggested pathogenesis of udder cleft dermatitis (UCD). The risk factors involved in the pathogenesis of UCD, simultaneously combined with the presence of internal udder pressure (bottom left; black arrows), friction (bottom left; green arrows) and humidity between the local skin folds, initiate an inflammatory response. The local skin damage creates a predominantly anaerobic microenvironment, potentially favoring pathogenic bacteria. Figure created with Biorender.com.

immune response by degrading host immune molecules and neutrophil extracellular traps (Egesten et al., 2009; Johansson et al., 2010). Additionally, as a host-adapted human pathogen *Strep. pyogenes* has been implicated in the initiation and exacerbation of human psoriasis (Yousefi et al., 2021), and in human intertrigo (Chiriac et al., 2017). Moreover, *Strep. pyogenes* is a facultative anaerobe, a trait which is now considered a selective advantage for pathogens to establish infection (André et al., 2021). In 2017, the World Health Organization published a list with 12 antibiotic-resistant priority pathogens that pose a probable threat to human health, of which 8 were facultative anaerobes characterized by a wide range of aerotolerance and anaerotolerance strategies (Tacconelli et al., 2018). Chronic wounds tend to have an inadequate blood and nutrient supply in addition to being oxygen-deficient (Bowler et al., 2001). The latter impairs

wound healing and promotes the colonization of distinct (facultative) anaerobic microbes while simultaneously negatively impacting the growth of beneficial aerobes in a less diverse microbiome. The shift from a healthy to a hypoxic wound environment gives the microbiome members the opportunity to become pathogenic and to interact with co-occurrent microbes.

Based on the available literature about the risk factors involved and the recent studies about the reaction of the host and the change of the microbiome, including their mutual interaction, we propose a pathogenesis as illustrated in Figure 3. Close to parturition, the udder is enlarged and eventually swollen by peripartal edema. The latter potentially causes the development of intertrigo, known as an inflammatory skin disorder that occurs due to skin-on-skin friction as a result of moisture becoming trapped due to poor air circulation (Romanelli et al., 2023). Initially, intertrigo presents as a mild mirror-image erythema, but progresses with increasing DIM to a more severe inflammation. The local skin damage creates a predominantly anaerobic microenvironment, favoring pathogenic bacteria including *Bacteroides* spp., *Treponema* spp., and *Strep. pyogenes* associated with skin ulcerations in case of severe UCD (Vermeersch et al., 2024b), over skin commensals such as *Bifidobacterium* spp. and *Staphylococcus* spp.

## TREATMENT, PREVENTION, AND RECOVERY

To date, there is no consensus about efficient curative treatment strategies for UCD. Few treatment studies and anecdotal reports on topical products have been published, warranting further extensive studies to identify effective treatment strategies for both mild and severe UCD. The healing of particularly severe lesions presenting with ulcerative wounds, tends to be slow. Cases of spontaneous recovery have been described scarcely. In a Dutch study, 61% of dairy cows (175 of 289) recovered from UCD episodes, with 18% (44 of 239) cows relapsing (Bouma et al., 2016). The median duration of an untreated UCD case was determined to be 16 wk. The likelihood of recovery was 3 times higher for mild lesions compared with severe ones (Bouma et al., 2016). The recovery rates did not significantly differ between herds (Bouma et al., 2016). In a study by Ekman et al. (2021), 38% of 329 cows enrolled in a 1-yr long longitudinal study recovered spontaneously. Of the 102 cows with mild UCD, 71% recovered within 4 to 8 wk after the first observation of UCD. Only 2 cows with severe UCD that had a known starting point recovered within the latter time frame but if the starting point was unknown, recovery was seen in 22 cows over 4 to 26 wk. A short duration and mild clinical course gave a higher recovery rate compared with longstanding severe lesions. Also,

cows with a parity of  $\geq 3$  had a lower chance of spontaneous recovery. Almost half of affected cows experienced a recurrence episode after recovery. Due to the use of different study designs, such as using a different interval between visits, it is challenging to compare the results of Bouma et al. (2016) and Ekman et al. (2021). However, it is clear that even if cows make a spontaneous recovery, lesions can reoccur.

Early detection of UCD is imperative to prevent the progression to poorly healing severe lesions and secondary infections, which could have potentially catastrophic consequences such as septicemia and even death (Turner et al., 2017). In studies by Ekman et al. (2021) and Eikeland and Paulsen (2018), no positive effect on the recovery from UCD could be seen by applying a spray containing chelated zinc and copper for 2 to 4 wk and 2 wk, respectively. Moreover, the spray seemed to cause discomfort in multiple cows (Ekman et al., 2021). Contrastingly, Lammers et al. (2017) reported a positive effect of this spray on severe lesions in several case studies. The zinc component stimulates skin regeneration whereas copper eliminates secondary wound infections. In a randomized clinical trial, attempts to treat mild lesions thrice per week with a non-sting-barrier film proved unsuccessful (van Werven et al., 2018). Conversely, daily treatment of severe lesions, particularly in lower parity animals, with an enzyme alginogel resulted in a 3.4 times higher improvement within a 12-wk period (van Werven et al., 2018). This specific type of topical wound treatment possesses antimicrobial, debriding, and absorbent properties, while also maintaining a moist microenvironment (Cooper, 2013; Strohal et al., 2017; van Werven et al., 2018). The continuous debridement of the wound is facilitated by the presence of polyethylene glycol and water in the alginogel. The enzymatic complex contributes to an antimicrobial defense system and, inhibits and prevents biofilm formation (Cooper, 2013). However, an *in vitro* study indicated that the biomass of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus* biofilms could not be reduced by employing an enzyme alginogel (Cooper, 2013). In human medicine, the application of a similar gel has demonstrated significant improvement in wound-healing rates and pain sensation in leg ulcers and burns of varying degrees of severity (Lacarrubba et al., 2005; Kyriopoulos et al., 2010). Multiple studies have also observed a reduction in the size, and pain of treated acute and chronic wounds (Lacarrubba et al., 2005; Kyriopoulos et al., 2010). Although the molecular mechanisms of the gel's wound-healing effects are not fully elucidated, an improved balance between metalloproteases and their inhibitors has been identified (Grzela et al., 2014). Topical glucocorticoid creams are used in veterinary and human medicine for their anti-inflammatory properties

(Lourenço et al., 2016; Romanelli et al., 2023). Topical anti-inflammatory treatment has been recommended for conditions such as canine intertrigo and atopic dermatitis (Lourenço et al., 2016). A clinical trial exploring various treatments and preventive strategies for UCD lesions is warranted.

Despite the lack of knowledge about effective treatments, it remains beneficial to maintain regular wound cleanliness and prevent wound infection, while simultaneously promoting skin healing. Cows with severe lesions that underwent thorough cleaning but no further treatment during the treatment trial of Ekman et al. (2021) showed a higher rate of improvement compared to cows with untreated severe lesions. This finding highlights the importance of wound debridement and warrants further investigation. In human medicine, moisture-wicking textiles are used to prevent intertrigo by keeping the skin dry (Kennedy-Evans et al., 2007). Additionally, they also reduce skin-on-skin friction and can contain broad-spectrum antimicrobial silver. Routine screening in the milking parlor by the farmer or herdsman aids to detect UCD cases. During foot-trimming sessions, the udder skin health can be assessed as well, particularly in a hydraulic tipping crush, providing a complete and secure visualization of the abdomen and udder. Early detection could possibly prevent the transition of mild to chronic severe lesions with an extended healing period. Moreover, it is essential to recognize that within-herd prevalence is often underestimated by farmers (Bouma et al., 2016; Ekman et al., 2018). In a study by Ekman et al. (2018), 83% of randomly selected herd owners participating in the study did not perceive UCD as an issue in their herds. In the Netherlands, farmers estimated a within-herd prevalence between 10% and 15% yet the recorded prevalence was much higher (Bouma et al., 2016). This might be due to the stoic nature of ruminants, which often conceal signs of pain and discomfort (Hyde et al., 2016). Several risk factor analyses give us insights into short- and long-term measures that can be taken to prevent UCD. Adequate housing conditions (e.g., to prevent hock lesions), and maintaining a low milk urea level by optimizing the dairy herd's ration could also help prevent UCD (Ekman et al., 2020b). Breeding programs that prioritize optimal leg and udder characteristics may produce cattle that are less susceptible to UCD. Risk factors such as a high milk yield are crucial characteristics for a dairy herd that, in contrast, come along with unfavorable traits, such as reduced longevity, fertility issues, and health problems (Brito et al., 2021). Also, footbathing is a measure that is valuable, and in many cases indispensable, for foot health yet emerged as a risk factor for UCD (Olde Riekerink et al., 2014).

## CONCLUSIONS

Udder cleft dermatitis is a widespread disease in dairy cattle, possibly leading to impaired animal welfare. There is a plethora of risk factors at both herd as well as cow level involved in the multifactorial development of UCD such as parity, lactation parameters, and udder conformation. Recent advances in omics have revealed critical insights into the molecular landscape of UCD. Metagenomic research points toward the presence of a grave dysbacteriosis of the eroded skin, with loss of beneficial bacteria, paving the way for facultative pathogens. Notably, this dysbacteriosis goes hand in hand with a remarkable shift in virulence factors and antibiotic resistance genes. Although the local application of an enzyme alginate product has shown to have a curative effect on lesions, clear-cut treatment and prevention strategies are not defined yet, though rigorous wound treatment is strongly advised. Conducting large-scale prevalence and risk factor analyses globally on farms with diverse characteristics (e.g., different breeds, varying herd sizes, and DD status), could provide more clarity to develop effective prevention strategies. Harnessing the power of cutting-edge omics technologies holds promise to revolutionize the management and treatment of UCD. In-depth integrated research on the host genome and the link with changes in the microbiome and environmental factors is necessary to identify further key points in the pathogenesis, which hopefully may pave the way for innovative treatment strategies. A longitudinal omics approach could enable a comprehensive understanding of UCD and identify early biomarkers, potentially enabling a pro-active intervention.

## NOTES

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**Nonstandard abbreviations used:** DD = digital dermatitis; MMP = matrix metalloproteinase; UCD = udder cleft dermatitis; VTCM = veterinary-treated clinical mastitis.

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