Digital dermatitis in cattle
Part I: factors contributing to the development of digital dermatitis

Digitale dermatitis bij rundvee
Deel I: factoren die bijdragen tot de ontwikkeling van digitale dermatitis

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ABSTRACT

Digital dermatitis or Mortellaro's disease is a highly prevalent bovine dermatological disorder situated in the foot region that causes lameness and impairs animal welfare.

In this first part of a twin paper, the role of genetics, immunity, bacteria and hygiene in the development of this complex disease are described. There is still no consensus regarding the role of the immune system and the typically isolated *Treponema* spp. in the pathogenesis of digital dermatitis. Moisture and dirt are undoubtedly important for disease transmission in and between dairy farms; furthermore, the genetic component of the disease will be more deeply discussed.

SAMENVATTING

Digitale dermatitis of de ziekte van Mortellaro is een hoogprevalente dermatologische boviene aandoening gesitueerd aan de distale regio van de poot, die aanleiding geeft tot kreupelheid en die het welzijn van het dier aantast.

In dit eerste deel van een tweeledig artikel wordt de rol van genetische factoren, immuniteit, bacteriën en hygiëne in de ontwikkeling van deze complexe ziekte beschreven. Er is nog steeds geen consensus bereikt wat betreft de rol van het immuunsysteem en de typisch geïsoleerde *Treponema* spp. in de pathogenese van digitale dermatitis. Vocht en vuil zijn ongetwijfeld belangrijk voor de ziektetransmissie binnen en tussen melkveebedrijven. Verder zal uitgebreide aandacht besteed worden aan de genetische component van de aandoening.

INTRODUCTION

Despite the abundance of information that is easily accessible nowadays, the knowledge of digital dermatitis remains scarce. Trials based on foot bathing using a large variety of products and topical treatments have been performed, often with variable outcome (Silva et al., 2015; Chiba et al., 2017; Holzhauer et al., 2017; Solano et al., 2017a). However, without knowledge of the exact pathogenesis, it is challenging to establish an adequate, preventive and curative treatment. Many factors, such as hygiene, bacteria, immunological mechanisms and genetic predisposition contribute to the development of the distinctive lesions (Koenig et al., 2005; Evans et al., 2012b; Refaai et al., 2013; Scholey et al., 2013; Klitgaard et al., 2014; Oliveira et al., 2017b). It is unknown to what extent each of these factors matter and at what point in the pathogenesis their role is to be considered crucial. Advances in laboratory techniques made it possible to identify changes in the local skin microbiome and to distinguish treponemal phylotypes (Krull et al., 2014; Zinicola et al., 2015b). Even though digital dermatitis is believed to be infectious, it is yet to be unveiled how it spreads between cows and farms. Moreover, there appears to be individual susceptibility (Capion et al., 2013; Gomez et al., 2015b). As the current treatments, which are mainly directed against the treponemes, cannot cure digital dermatitis, it is uncertain whether solely treponemes play the main role (Berry et al., 2010). Studies indicating the presence of treponemes in pressure sores and in lesions in other animals, have led to the hypothesis that these bacteria might be opportunistic (Clegg et al., 2015; 2016d; Sullivan et al., 2015). Nowadays, more attention is directed to the deviant response of the immune system as a crucial part of the pathogenesis (Refaai et al., 2013; Scholey et al., 2013). Investigating crucial points in the immune response where interference is possible is a scientific path that is worthwhile to take.

Bovine digital dermatitis (DD) is one of the most commonly occurring infectious skin conditions in dairy cattle, causing a significant economic loss worldwide (Bruijnis et al., 2010; Cha et al., 2010; Cramer et al., 2009). Furthermore, it poses a considerable threat to bovine welfare (Bruijnis et al., 2012). These consequences are due to the severe pain caused by the acute stage of this disease. Specific figures for Belgium are currently not available, but digital dermatitis is generally accepted to be a common disease on Belgian farms. In a cross-sectional study in the Netherlands, dairy herd prevalence was estimated to range between 0-83% (n= 383 herds), while on average 21.2% of all included cows (n= 22 545) displayed DD lesions (Holzhauer et al., 2006). Digital dermatitis has also been reported in beef cattle, albeit with a fairly low prevalence in Europe (Sullivan et al., 2013). In a Norwegian study by Fjeldaas et al. (2007), herd prevalence of digital dermatitis observed during claw trimming in beef cattle herds was between 0 and 7.6%. The disease is mostly seen in dairy cattle, especially in Holstein-Friesians (Holzhauer et al., 2006). Currently, the disease is globally and locally so widespread that it is essential to incorporate prevention strategies, such as managing adequate hygiene standards, foot bathing and regular foot trimming, in the routine management of every dairy farm in Belgium to avoid significant problems in terms of animal welfare and herd economics (Read and Walker, 1998; Relun et al., 2013; Solano et al., 2017a; Demirkan et al., 2018; Silva et al., 2018).

Lameness is in the top three of the costliest diseases in the dairy industry, besides fertility problems and mastitis (Ranjbar et al., 2016). Approximately 14-31 % of dairy cattle worldwide is lame when assessing the incidence of lameness at any random given time (Amory et al., 2008; Griffiths et al., 2018). In Germany, culling due to feet and leg disorders has risen from 3.2% (1980) to 9.1% (2000) (Koenig et al., 2005). Whereas the consequences of lameness in general have been examined extensively, research on the economic impact of DD is rather scarce. According to a calculation of Cha et al. (2010), the average cost per DD case in the USA is 132.96 USD. The contribution of treatment costs to the total cost is the most important (42%), followed by losses due to decreased fertility (37%) and milk loss (27%) (Cha et al., 2010). Yearly, subclinical DD cases cost approximately 269 USD (range: 139-403 USD) on a farm with 65 dairy cows held on a concrete slatted floor with access to pasture during summer in the Netherlands. Taking the same farm setting into consideration, the costs rise up to 1249 USD (489-2481 USD) for clinical DD (Bruijnis et al., 2010).

Digital dermatitis can be defined as an ulcerative-proliferative skin condition with a complex etiopathology situated in the foot region (Cheli and Mortellaro, 1974). The lesions are usually situated on the plantar skin in the proximity of the coronary border of the hind legs. Nonetheless, they can also be found in the distal dorsal region of the foot, on the front legs, near the dew claws, on the interdigital skin and even on interdigital hyperplasia (Read and Walker, 1998; Holzhauer et al., 2008; Rodrigues et al., 2010; Refaai et al., 2013). The most frequently used system for assessing the presence of DD is the clinical M-stage scale proposed by Döpfer et al. (1997) and slightly altered by Berry et al. (2012), going from M0 to M4.1 (Table 1). The acute and painful M2 stage is characterized by a red strawberry-like ulcerative to granulomatous lesion (Figure 1). During the advancement of M2 to M4, the epidermis thickens due to hyperplasia and hyperkeratosis. In some cases, the lesions show long hair-like dyskeratotic projections. In bovines in the USA, the lesions tend to have a more proliferative aspect in comparison to the predominantly ulcerative form seen in Belgium; hence, the term 'papillomatous digital dermatitis' is often used in North America (Read et al., 1998).

This two-fold review provides a brief overview of what is currently known about digital dermatitis in the broad sense.

Table 1. The different M-stages, going from M0 to M4.1 (or M5) (Döpfer et al., 1997; Berry et al., 2012).

Stage	Characteristics
M0	No lesions are present, the skin is considered to be healthy.
M1	Round, well-defined small superficial lesion. The size is less than 2 cm diameter.
M2	Typical moist strawberry-like ulcerative or granulomatous lesion clearly demarcated with erected hairs and white epithelial border. Palpation is usually painful. The lesion is more than 2 cm diameter.
M3	A thick, dry and dark scab covers the healing lesion. The lesion has progressed to a chronic stage and is not painful anymore.
M4	Chronic stage characterized by hyperproliferation of the skin.
M4.1	Chronic stage combined with a recurring active M1 lesion.
M5	The digital skin has normalized, there are no lesions present.

Figure 1. Visual representation of the different stages. The first row: M0, M1 and M2. The second row: M3, M4 and M4.1 (Source photo of M1 lesion: Dairy Cattle Hoof Health).

ETIOLOGY AND PATHOPHYSIOLOGY

Even though DD has been described for the first time by Cheli and Mortellaro in 1974, many questions remain unanswered regarding the primary cause(s), pathophysiology, treatment and measures to eradicate the disease. The rapid spread between animals could possibly be attributed to the bacterial burden on used equipment and in the stall (Wells et al., 1999; Somers et al., 2005). Beside the polybacterial nature of DD, other factors, such as genetic susceptibility, hygiene, specific behavior and physi(ologi)cal mechanisms have been proposed to contribute to this complex disease (Wells et al., 1999; Somers et al., 2005; Holzhauer et al., 2006; Onyiro et al., 2008; Refaai et al., 2013; Zinicola et al., 2015b) (Figure 2). There appears to be an individual susceptibility for developing DD (Capion et al., 2012; el-Shafaey et al., 2017). Some cows are prone to develop DD while others don't seem to be sensitive at all. In a study by Capion et al. (2013), cohousing a small group of naive heifers with severely affected peers in an unhygienic environment did not induce disease transmission between all animals. This clearly indicates an individual variability regarding susceptibility. Factors, like skin characteristics, hoof conformation, immune system properties and behavior, all contribute to the degree of susceptibility (Laven, 2007; Scholey et al., 2013; Krull et al., 2014; el-Shafaey et al, 2017). Cows showing a certain claw disorder run an increased genetic and phenotypic risk of concurrently developing another orthopedic problem (Koenig et al., 2005).

It has been suggested that the gastrointestinal tract, slurry and urine act as a reservoir for the main bacteria associated with DD (Klitgaard et al., 2014; Zinicola et al., 2015b). In skin dye experiments, it has been shown that skin permeability for dye remains the same regardless of whether an animal has DD or not (Palmer et al., 2013). However, contact with slurry for 24 hours significantly increases skin permeability. These findings indicate that slurry potentially facilitates the entry of DD-associated bacteria.

Bacterial consortium

New culture-independent molecular techniques, like 16S rRNA sequencing and 16S-23S intergenic spacer region polymerase chain reaction, have a significant impact on the research on the bacterial community involved in DD (Stamm et al., 2002; Evans et al., 2008; Döpfer et al., 2012). In earlier times, examining the infectious component used to be a challenging issue, as the predominant pathogenic *Treponema* spp. are notoriously hard to cultivate (Walker et al., 1995). Despite the steady presence of anaerobic and motile treponemes in the lesions, DD cannot be reproduced consistently using a treponemal culture on intact skin (Krull et al., 2016). Abrading and moistening the skin prior to inoculation of infectious material has proven to be crucial for successful experimental induction (Krull et al., 2016). The exact mechanism of the initiation of DD has not been elucidated and it is not completely clear yet whether treponemes are primary or secondary invaders. Treponemes tend to have a low abundance during the onset of this disease, implying that the presence of additional synergistic bacteria is needed to pave the way for the treponemes (Krull et al., 2014). In a study by Zinicola et al. (2015b), in which shotgun sequencing was utilized, the abundance of *Treponema* spp. was higher in active lesions compared to the more advanced, chronic stages. It should be remarked that exactly the same range of treponeme phylotypes is not usually identified nor detected among different studies (Rasmussen et al., 2012; Krull et al., 2014; Zinicola et al., 2015b). According to Beninger et al. (2018), the most abundant treponemal species, *T. phagedenis*, *T. medium* and *T. pedis*, are positively correlated with each other but *T. denticola* does not seem to be part of this polytreponemal interaction.

An extensive array of bacteria including *Fusobacterium necrophorum*, *Dichelobacter nodosus*, *Bacteroides* spp., *Campylobacter* spp., *Mycoplasma* spp., *Borrelia* spp. and *Porphyromonas* spp. has been found in lesions (Blowey et al., 1994; Döpfer et al., 1997; Rasmussen et al., 2012; Krull et al., 2014; Sullivan et al., 2015; Nielsen et al., 2016). These bacteria are possibly actively involved in the pathogenesis or they could be secondary, opportunistic invaders. It has been shown that pathogenic fungi and viruses do not reside in the diseased skin and thus cannot be linked to DD (Krull et al., 2014; Zinicola et al., 2015b). The bacterial diversity of the skin microbiome drastically decreases, along with changes occurring in the bacterial composition throughout the development of DD. While DD progresses from stage M0 to M4, there appears to be a shift in the treponemal phylotypes (Zinicola et al., 2015b). Also, the different species tend to favor a specific depth in the skin to reside: *T. phagedenis-like* and *T. denticola-like* are situated deep in the epidermis, whilst *T. vincentii* can be detected more superficially (Klitgaard et al., 2008). Active lesions are dominated by treponemal phylotypes, like *T. denticola, T. phagedenis, T. medium* and *T. putidum*,

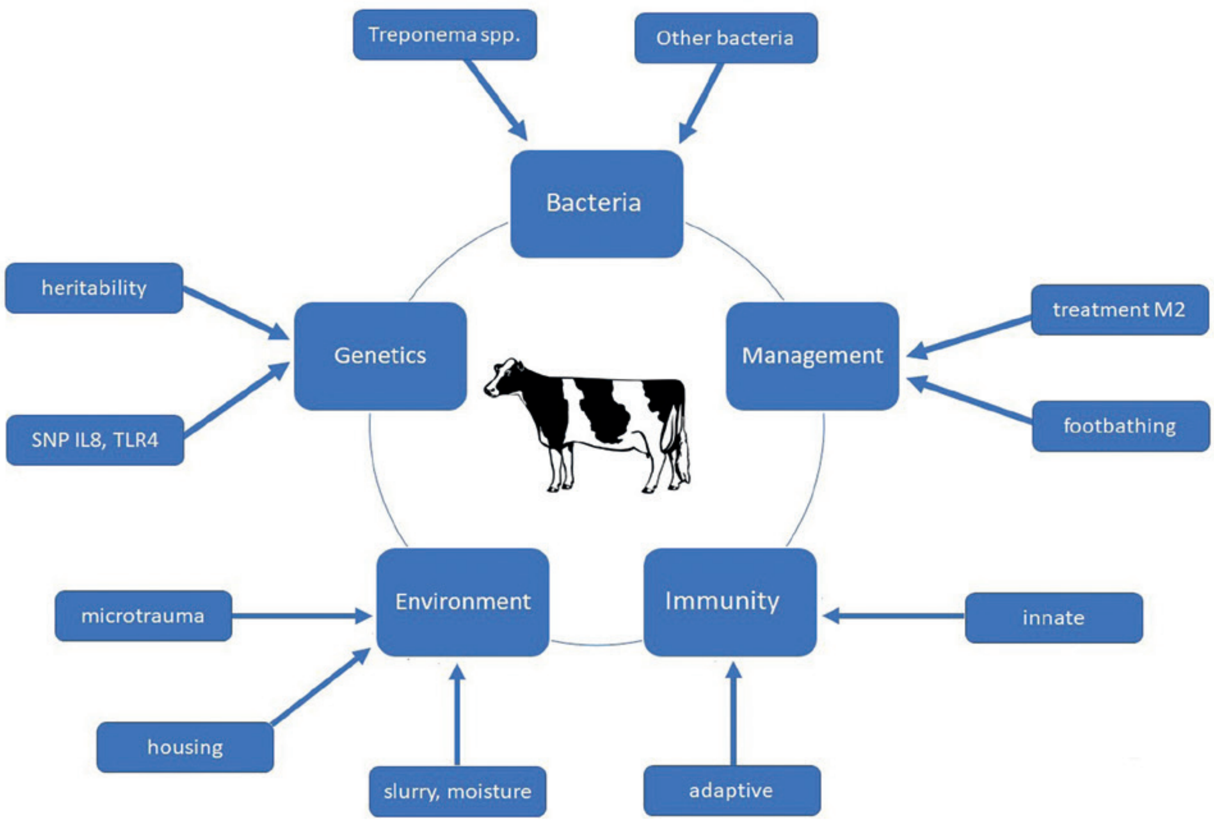


Figure 2. A concise overview of the most important factors contributing to the development of digital dermatitis. This extensive array of factors consists of environmental elements, properties of the immune system, farm management, genetics and an infectious component.

whereas in M3-M4 lesions, the distinct microbiome mainly consists of *Porphyromonas* spp., *Alkaliphilus crotontoxidans*, *Soehngenia saccharolytica* and *Telmatospirillum siberiense* (Zinicola et al., 2015b).

One of the hypotheses is that treponemes can transform themselves into an encysted form (partially) responsible for the persistence of DD (Döpfer et al., 2012). Encystation has been observed in other *Spirochaetae*, like *Borrelia burgdorferi* (Lyme's disease), *Leptospira interrogans* (leptospirosis) and *Treponema pallidum* (syphilis) (Czekalowski and Eaves., 1954; Brorson and Brorson, 1998; Döpfer et al., 2012; Ovcinnikov and Delektorskij, 1970).

Immunity

The inflammatory pathway involved in the pathogenesis of DD has not been elucidated yet. The characteristic macroscopic presentation is mediated by a dysregulated inflammatory response and the virulence factors of the pathogenic bacteria present in the skin (Döpfer et al., 1997; Zuerner et al., 2007; Dashper et al., 2011; Refaai et al., 2013). A decrease in the number of peripheral blood T-and B-leukocytes can be noted in dairy cows affected by DD, which slightly improve after lincomycin treatment (Ando et al., 2009). There is a delayed onset of the adaptive immune response, whereas the innate immunity displays a significantly upregulated and continuous response (Refaai et al., 2013). In M2 and M3 lesions, a dramatic increase in keratinocyte-derived interleukin-8 (IL-8) levels is noted (Refaai et al., 2013; Watts et al., 2018). This increase can be attributed to a genetic upregulation and to the keratinocyte proliferation (Tuschil et al., 1992; Scholey et al., 2013). Interleukin-8 is an early response pro-inflammatory chemokine stimulating neutrophils and keratinocytes. In vitro exposure of fibroblast and keratinocyte cell cultures to *Treponema* spp. sonicates has not shown any changes in the IL-8 levels (Evans et al., 2014). However, an increase of chemokine ligand 5 (CCL5/RANTES), tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β), metalloproteinase inhibitor 3 (TIMP3) and matrix metalloproteinase 12 (MMP12) expression has been observed in the fibroblasts (Evans et al., 2014). In a study by Lazarus et al. (2006), a better clearance of the spirochete *Borrelia burgdorferi* in mice with an anti-inflammatory peptide IL-10 deficiency ($IL10^{-/-}$) was described. These $IL10^{-/-}$ mice tended to have a better innate and adaptive immune response than non-IL10 deficient mice. In a study by Watts et al. (2018), the transcription levels of IL-10 in bovine M4 samples were elevated. More research is needed to investigate the role of IL-10 and other cytokines in the possible clearance of *Treponema* spp. (Refaai et al., 2013). In an in vitro study with bovine macrophages, wound repair mechanisms were impaired by the presence of *T. phagedenis*-like spirochetes (Zuerner et al., 2007). This particular strain had a significant immunosuppressive effect. Most of the genes coding for cytokines remained unchanged or downregulated after treponemal exposure. However, the transcription of the IL-10 receptor was enhanced.

A surface-bound protease called dentilisin of human oral *T. denticola* is known to degrade cytokines, like IL-1β, IL-6 and TNF-α (Dashper et al., 2011). Various other virulence factors of *T. denticola* are known, such as toxin-antitoxin systems (TA), transposases, immunodominant major sheath protein (Msp) and outer sheath vesicles (OMVs). All of them aid the treponemes to escape from the host immune response and to invade efficiently in the host tissues. Treponemes seem to lack the typical lipopolysaccharide (LPS) present in gram-negative bacteria (Schultz et al., 1998; Walker et al., 1999). Some treponemes possess a functionally similar molecule lipooligosaccharide (LOS), with some parts also found in lipoteichoic acid in gram-positive bacteria (Dashper et al., 2011); this implicates a possibly weaker stimulation of the immunity.

A tremendous variability regarding antibody levels may be noted within and between groups of affected animals (Moe et al., 2010; Gomez et al., 2014a). This could be explained by the dynamic polybacterial burden, the presumed antigen mismatch in laboratory assays and the fact that the presence of treponemes in the gut possibly induces some degree of immunotolerance (Evans et al., 2011b; Krull et al., 2014). Despite the production of anti-treponeme IgG antibodies, the lesions generally progress into a chronic state and the animals are not protected against relapses (Gomez et al., 2014a). The M1 and M4.1 lesions are not associated with an increase in antibody titer. Even animals that never had macroscopic DD lesions appear to have a consistently low serum IgG titer against treponemes. In a study by Gomez et al. (2014a), a 56%-increase of the antibody titer was seen when heifers were confronted with an acute M2 lesion. Vaccine development has been attempted over the years but has failed so far due to the complexity of the disease (Berry et al., 2003). Besides the fact that there are extensive microbiomial changes, the pathogenesis also entails many non-infectious facets, like genetics and environmental factors (Koenig et al., 2005; Somers et al., 2005; Holzhauer et al., 2006). Moreover, the different treponeme phylotypes reported to be involved, are known to express antigenic variety (Trott et al., 2003).

Metabolism

Postparturient dairy cattle descend into a negative energy balance, putting a tremendous amount of (metabolic) stress on the body. If cows have an excessively high body condition score during the late stage of lactation and the dry period, they are prone to develop fat cow syndrome and insulin resistance in the immediate postpartum period (Roche et al., 2013; Oliveira et al., 2016). Overconditioned cows tend to go into a hyperinflammatory state caused by high amounts of adipose tissue-derived cytokines, like TNF-α, IL-1 and IL-6 (Depreester et al., 2018). Nonetheless, the periparturient metabolic adaptations also have a debilitating effect on other immunological parameters (Lacetera et al., 2005; Depreester et al., 2018). According to Perez-Cabal and Charfedinne (2016), there is no direct association between the presence of digital dermatitis and body weight. However, a study by Schöpke et al. (2013) showed that cows that are overconditioned or have a body condition score that drops below 2.5 at peak lactation, tend to be more susceptible to DD.

In dairy cattle, the relationship between subclinical ketosis and lameness is still unclear. Nevertheless, in a study by Suthar et al. (2013), lame cows tended to have higher β-hydroxybutyrate levels in milk (1.165 mmol/L) than non-lame control cows (0.687 mmol/L) between 2 and 15 days . However, it is unclear whether lameness gives rise to subclinical ketosis or if lameness rather has to be seen as a consequence of this metabolic disease.

Lactation and parity

Cows with a high milk yield and high milk protein percentage are prone to develop claw and foot disorders in the current lactation (Koenig et al., 2005). According to Gomez et al. (2015b), having DD during the rearing period significantly impairs the first-lactation performance in heifers. Heifers that experienced at least one DD event before calving, show milk production losses of 199-335 kgs during the first 305 days in milk due to less persistence after peak yield. This could be explained by the discomfort the animal experiences when facing an acute lesion. The findings suggest more attention needs to be paid to young animals regarding prevention. In a study by Somers et al. (2005), the odds of having DD declined with higher parity. This could be due to a higher culling rate and conformational changes (e.g. lower heels) in older cattle versus the intense periparturient adaptations primiparous heifers are confronted with. Moreover, the immune response against DD might be more efficacious in older cattle. In contrast, Amory et al. (2007) did not see remarkable changes in milk yield in cows affected by acute DD, although they showed a slight increase in production after treatment. Other causes of lameness like sole ulcerations had a negative impact on milk production before and even after treatment. Also, lame animals tend to lie down more often and for longer bouts (Thomsen et al., 2012; Solano et al., 2016). Additionally, lameness causes a decrease in the time spent eating (Solano et al., 2016; Weigele et al., 2018). These behavioral changes undoubtingly have an effect on the productivity as well. In a study by Gomez et al. (2015b), no noteworthy changes in fat and protein percentages, nor somatic cell counts in DD affected first-lactation animals were found. Peak lactation and the first month after calving are two stages in the lactation cycle, in which a dairy cow is considered to be the most susceptible to developing DD lesions (Argaez-Rodriguez et al., 1997; Holzhauer et al., 2006). Besides the drastic metabolic adaptations taking place during those times, cows are put on a high energy diet and as a result, contaminate their hind legs with more liquid feces (Somers et al., 2005).

In mice, it has been shown that the subcutaneous fat layer thickens after inoculating pathogenic *Staphylococcus aureus* due to adipocyte proliferation and hypertrophy (Zhang et al., 2015). The adipocytes produce bioactive substances like the pro-inflammatory and antibacterial substance cathelicidin. This molecule is likely to be involved in the chronic inflammatory response in obese individuals. Dairy cattle tend to go into a negative energy balance after calving, whereby they excessively mobilize fat (Depreester et al., 2018). This presumably has a negative impact on the adipocytes in the skin and the fat cushion in the foot region, leading to less support (Bicalho et al., 2009; Mahendran and Bell, 2015).

Fertility

Pain and acute stress negatively influence the pulses of luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) (Battaglia et al., 1997; Phogat et al., 1999). It has been shown that the ovarian cyclicity is compromised by these hormonal changes (Garbarino et al., 2004). Weight loss associated with lameness inhibits ovarian activity during the first month after calving (Opsomer et al., 2000), nor is estrus expressed in healthy, sound cows making estrus detection challenging (Walker et al., 2008; Morris et al., 2011). The average conception rate is lower in lame cows at first service (Gomez et al., 2015b). On average, it takes a lame cow 28 days more to become pregnant (Lee et al., 1989). Lameness is associated with a higher incidence of ovarian cysts during the first 80 days post partum, hence risking infertility (Melendez et al., 2003). By contrast, in a study by Charfedinne and Perez-Cabal (2017), fertility traits, with the exception of calving-to-first-service-interval for mild lesions, were not influenced by the presence of DD. However, it should be mentioned that the number of included animals with severe lesions was low: severe DD lesions were found in 19 animals, whereas 985 animals had mild lesions and 12,129 animals were unaffected by DD.

Genetics

Claw health index and heritability

The information regarding a certain trait, e.g claw health, can be combined with one value, called the breeding value (BV). An estimation of the aforementioned value is made through the performance of the animal and its relatives. It is possible to reduce the prevalence of claw disorders by selecting animals based on their claw health index breeding value (van der Linde et al., 2010). When a bull scores 104 BV for claw health, the prevalence of digital dermatitis, interdigital dermatitis and sole hemorrhages in the progeny decreases with 3% (CRV, 2017). The more trimmed and approved female offspring a breeding bull has, the more reliable his estimated breeding value (EBV) for claw health index becomes (van der Linde et al., 2010). Claw health on a dairy farm can be improved by using bulls with an EBV >100 for claw health, or by using bulls of other breeds (CRV, 2017; Rinell and Heringstad, 2018)

In the claw health index, six claw diseases in the first and in the following lactations (≥2) are taken into account (CRV, 2017) (Table 2). When using only the claw health characteristics, the reliability is approximately 53%. In order to improve the reliability of this index, the leg exterior characteristics can be added. These characteristics show a low to intermediate correlation with claw disorders. If the index is based on the characteristics of the animal's conformation, excluding claw health data, the reliability is 24% (Stoop et al., 2010).

Koenig et al. (2005) estimated the heritability for DD to be 0.073 (± 0.009), which was lower than the estimates for sole ulcers (0.086 ± 0.006), claw wall disorders (0.104 ± 0.0014) and interdigital hyperplasia (0.115 ± 0.021). These estimates are low to moderate but still worthwhile to be taken into account when breeding cattle (Koenig et al., 2005; Buch et al., 2011). There is a strong genetic correlation between DD and heel horn erosions (0.87) but a low correlation with other claw disorders, such as sole ulcers and claw wall disorders (Buch et al., 2011) (Table 3).

A positive and moderate genetic correlation between culling due to leg problems and milk, fat and protein yields has been described in a study by Uribe et al. (1995). In a study by Koenig et al. (2005), the genetic correlation between milk yield in early lactation and DD was 0.240 (± 0.145). Cows with a high genetic merit for milk yield tend to be more prone to develop health issues (Johansson et al., 2011). However, the relationship between milk yield and lameness is complex and ambiguous.

There is a moderate correlation between the 56 days non-return percentage and the presence of DD (0.48 ± 0.02) (Onyiro et al., 2008), which implies that DD has indeed an impact on fertility. According to a study by Onyiro et al. (2008), moderate negative correlations with fat (-0.43 ± 0.02), milk (-0.31 ± 0.02) and lifespan (-0.16 ± 0.02) indicate that longevity and productivity improve when taking DD into consideration during bull selection.

Differential gene expression

Scholey et al. (2013) examined the host pathways in M2 biopsies. Curiously, they found a higher expression of a2-macroglobulin-like 1. The related a2-macroglobulin gene has been shown to be crucial for the proliferation of *Treponema denticola* in human periodontitis (Socransky and Hubersak, 1967). These proteins might be decisive for evading the host immune response by coating the treponemes. Also, they seem to inhibit proteases (Galliano et al., 2006). The gene expression of a variety of molecules changes in acute DD lesions (Table 4).

A few single nucleotide polymorphisms (SNP) mutations in the gene coding for IL-8 have been linked to DD resistance (C94T, A220G and T262A). The fol-

Table 2. Heritability, reproducibility and statistical variance for characteristics linked to the claw health index (CRV, 2017). The '1' stands for the first lactation and the '2+' refers to the second and following lactations.

Characteristic	Heritability (h^2)	Reproducibility	Statistical variance (σ^2)
Sole hemorrhage 1	0.07	0.15	0.196
Digital dermatitis 1	0.09	0.36	0.222
Interdigital dermatitis 1	0.08	0.21	0.180
Sole ulcer 1	0.08	0.30	0.116
Interdigital growth 1	0.08	0.42	0.089
White line defect 1	0.03	0.14	0.075
Sole hemorrhage 2+	0.05	0.17	0.165
Digital dermatitis 2+	0.08	0.30	0.190
Interdigital dermatitis 2+	0.11	0.27	0.239
Sole ulcer 2+	0.12	0.30	0.191
Interdigital growth 2+	0.14	0.62	0.184
White line defect 2+	0.03	0.17	0.096
Hind legs rear view	0.18		0.659
Hind legs side view	0.24		0.725
Claw angle	0.20		0.640
Leg use	0.12		0.532
Physique	0.17		1.332

Table 3. Genetic correlations between digital dermatitis and other characteristics. '♦' is the characteristic during the first lactation and '♣' is the characteristic in the ≥ second lactation (CRV, 2017).

	Digital dermatitis ♦	Digital dermatitis ♣
Interdigital dermatitis	♦ 0.77 ♣ 0.82	♦ 0.42 ♣ 0.58
Sole ulcer	♦ 0.00 ♣ 0.09	♦-0.06 ♣ 0.11
Interdigital growth	♦ 0.44 ♣ 0.63	♦ 0.28 ♣ 0.60
White line defect	♦-0.31 ♣ -0.29	♦-0.25 ♣ -0.11
Sole hemorrhage	♦ 0.08 ♣ 0.07	♦-0.12 ♣ 0.03
Hind legs rear view	-0.33	-0.18
Hind legs side view	0.14	0.05
Claw angle	-0.13	0.15
Leg use	-0.56	-0.31
Physique	-0.51	-0.28

Table 4. A brief overview of the altered gene expression for a selection of important molecules in M2 lesions (Scholey et al., 2013).

Molecule	Function	Gene regulation ⇑ or ⇓
Keratin	Skin barrier, keratinocyte activation	⇓, except e.g. keratin 6A (⇑)
Filaggrin 2	Epidermal barrier	⇓
Major histocompatibility class II DY □ and DQ □	Local adaptive immune response	⇓
Matrix metalloproteins (MMPs)	Skin tissue turnover	⇓ and ⇑
Interleukin 24 and 19	Anti-inflammatory proteins	⇑
Interleukin 1□ and 1 □	Keratinocyte activation, early inflammation, MMP-13 stimulation	⇑
SLP 1	Chymotrypsin inhibition	⇑
Hyperactive pyrin (mediterrean fever)	More frequent inflammation	⇑
Monocyte chemoattractant protein	Recruitment of e.g. monocytes, memory T-cells and dendritic cells	⇑

lowing SNPs in the toll-like receptor 4 gene are associated with resistance (C118T) and susceptibility (G349C and C355A) (El-Shafaey et al., 2017).

Other risk factors

A great deal of factors affecting the development of DD have been described in the literature, such as type of housing, environment, hygiene and management (Table 5). They individually do not cause DD, but all have a considerable impact on the development of DD (Wells et al., 1999; Ferguson et al., 2004; Somers et al., 2005; Frankena et al., 2009; Sullivan et al., 2014a). Results from risk factor studies are not easy to be interpreted as many factors are intertwined. A farm owner may have a specific reason for choosing a certain management strategy and may not be able to change certain risk factors.

Housing and hygiene

Full access to pasture, especially during the summer, has a protective effect against infectious foot diseases, like digital and interdigital dermatitis (Wells et al., 1999; Somers et al., 2005; Ambrecht et al., 2017), whereas concrete floors in the stable and differences in dietary characteristics, e.g. higher levels of concentrate being fed in the barn, apparently have a negative effect (Somers et al., 2005). A floor that is too abrasive, will cause the horn to wear excessively. Furthermore, concrete that is polished too much, poses a risk for injuries due to slipperiness (Wells et al., 1999). If the stable is not cleaned regularly, the buildup of manure provides a moist and dirty environment. As a result, the skin weakens, which possibly reduces the speed of healing of microtraumata and lesions. Moreover, manure may serve as a nidus for bacteria like treponemes (Evans et al., 2012b). Using a manure scraper more than eight times a day (in order to make the floor drier and cleaner), reduces the odds for DD (Oliveira et al., 2017b). However, in a study by Cramer et al. (2009), the prevalence of DD increased when using a manure scraper more than three times a day. The type of floor the scraper is used upon is considered to be of great importance. Using a manure scraper on a solid floor causes more buildup of manure than on a slatted floor (Cramer et al., 2009); nor should leg cleanliness be underestimated (Relun et al., 2013). The cubicle design of a freestall is of great importance: the cubicle should be long and wide enough, so cows can lie down comfortably and thus spend less time standing in slurry (Faull et al., 1996; Algers et al., 2009). Poor cubicle design, like a misplaced head-rail or lying beds with unsuitable dimensions, put the cow at risk of developing claw abnormalities and/or lameness (Faull et al., 1996). A short lying bed may cause the cow to stand with the hind legs in the (dirty) walking alley, posing the risk of developing (non-) infectious claw diseases (Dippel et al., 2011). The design of the alleys should also be taken into account as a possible contributing factor to the development of foot disease. In a study by Somers et al. (2003), dairy cattle housed in straw yards showed a lower prevalence of claw disorders such as, digital dermatitis and sole hemorrhages, than cattle housed on solid concrete or slatted floors. The number of cows showing lameness in straw yards is lower than for instance animals housed on concrete due to a higher level of comfort and reduced claw loading (Onyiro et al., 2008; Frankena et al., 2009). The hardness of the claws is important for decreasing claw disease prevalence (Ambrecht et al., 2017). The hardness can be improved through a balanced diet and by keeping the claws dry and clean.

An important concern in terms of biosecurity is the hoof trimming practices. In a study by Sullivan et al. (2014a), DNA from different treponeme phylotypes was detected on hoof knives after trimming a herd of sheep and cattle (97% positive samples). Disinfection of the knives with an iodine disinfectant drastically reduced the PCR detection rate. Nevertheless, 35% of the blades remained positive (Sullivan et al., 2014a). These findings highlight the importance of implementing on-farm hygienic measures at levels which are not directly obvious, especially during claw trimming. Cloths for cleaning the feet should be changed between different cows, even between feet of the same cow.

Introducing new cattle, like the replacement of heifers from external farms into the herd, implies a significant risk of bringing in DD, as well as other infectious diseases (Wells et al., 1999). An increase in herd size is also a known risk factor (Wells et al., 1999). Susceptibility also seems to be correlated with parity (Somers et al., 2005; Holzhauer et al., 2006). Pregnant heifers are more at risk for developing DD than cows with a higher parity, because they are confronted with many changing periparturient circumstances. On the other hand, cows in the dry period display less sensitivity to DD (Somers et al., 2005; Holzhauer et al., 2006). They are fed a different ration making their manure more solid and thus making the floor and their hind legs less wet (Holzhauer et al., 2008; Somers et al., 2005). In a study by Somers et al. (2005), housing dry cows together with lactating herdmates before calving notably increased the risk of developing DD. In the same study, it was shown that housing calves and heifers together with the lactating cows is associated with a decrease in susceptibility to DD. The authors hypothesized that, in this way, a certain adaptation period before calving is provided, making the periparturient period less stressful.

Table 5. Summary of the most important risk factors and how to solve them.

Risk factors	Solution	References
Lack of a prevention strategy	Preventive claw trimming, regular footbathing, hygiene, diagnosing and treating acute stages and other strategies.	Somers et al., 2005
Housing and stable design	Access to pasture, non-slippery and not too rough floor, avoid sharp bends, adjust lying beds.	Onyiro et al., 2008; Dippel et al., 2011; Smits et al., 2015; Ambrecht et al., 2017
Moisture and manure	Regular cleaning (e.g. manure scraper), improving general hygiene, adequate ventilation. Score leg cleanliness and take action accordingly.	Algers et al., 2009; Oliveira et al., 2017b; Solano et al., 2017
High productivity	Breeding (genetic selection)	Koenig et al., 2005
Contact with new cows	Disease screening program, respecting a quarantine period and preferably keeping the farm closed off.	Wells et al., 1999; Palmer et al., 2015
Claw trimming hygiene	Cleaning and disinfecting knives in between cows and farms, cleaning the trimming chute.	Sullivan et al., 2014; Palmer et al., 2015

Conformation

Toussaint (1989) advised a dorsal wall length of 7.5 cm for dairy cows. Nowadays, most dairy cattle tend to be larger and heavier, which also implies changes at claw level. The minimal dorsal wall length is estimated to be approximately 8.5 cm for young cows (parity ≤2) and 9.0 cm for adult cattle (Archer et al., 2015). In a study by Laven (2007), DD-affected heifers had significantly lower heels than their healthy herdmates 24 weeks post calving. It is unclear whether low heels are a risk factor for developing DD or if it is rather a consequence of the feet being affected by DD. It is more plausible to assume the long toes and low heels of the heifers in the study by Laven (2007) were a risk factor. The presence of long toes possibly explains the reduced functional heel height. Painful DD lesions result in putting more weight on the toe region and less on the heel, which is in contradiction with the findings in the aforementioned study. In a longitudinal study performed by Gomez et al. (2015a), heifers affected by DD had higher heels, an increased claw angle and more extensive heel horn erosions. Having a sickled conformation of the hind legs increases the odds for suffering from DD and sole ulcers (Perez-Cabal and Charfedinne, 2016). The prevalence of foot and leg problems tend to decrease when the cow's legs are straighter than midrange (Koenig et al., 2005). Digital dermatitis is more likely to develop when interdigital dermatitis or heel horn erosions are concurrently present (Smits et al., 2015). By not applying herd trimming at regular intervals, the herd is more at risk of developing various claw disorders (Somers et al., 2005). Beside treatment of acute DD lesions, hoof trimming improves claw conformation, supposedly making the animals less prone to DD and claw abnormalities.

Feed ration

Currently, there is a lack of studies linking dietary characteristics to DD. In a study by Somers et al. (2005), it has been shown that increasing the concentrate levels too fast after calving (<2 weeks to maximum amount) is a relevant risk factor. In the same study, feeding residual products from, e.g. breweries, seemed to strongly increase the odds for developing DD. In 2014, a research on the effect of trace mineral premix supplementation on the incidence of DD lesions was published (Gomez et al., 2014b). Nonetheless, the results were inconclusive and speculative due to the lack of power and statistical significance, the possible presence of an observer bias and because the steers enrolled in the 'natural exposure phase' never developed DD.

Trace minerals (e.g. zinc, manganese and copper), calcium, phosphorus, vitamin A and D and sulphur-containing amino acids (methionine, cysteine) play a significant role in skin integrity, wound healing and the regulation of the immune system (Elias, 1986; Nocek et al., 2000; Landsdown, 2002; Ibs and Rink, 2003; Lippolis et al., 2011; Osorio et al., 2013). This implicates their quantity in feed is of unquestionable importance. Daily supplementation for one year of zinc methionine, copper lysine, manganese methionine and cobalt glucoheptonate reduced the incidence of papillomatous DD in an experimental trial (Nocek et al., 2000). In a study by Ferguson et al. (2014), organic trace mineral supplementation in the dry period significantly reduced the claw lesion prevalence in the subsequent lactation. On the other hand, parameters, such as lactation number and stage, had a far greater influence on claw lesions. The effect of biotin supplementation has been well studied in horses but not in cattle. In the literature on equine hoof quality, a positive effect of long term biotin supplementation has been described. In a study by Zenker et al. (1995), 20 mg/kg biotin per day for 38 months improved equine hoof horn quality, specifically the tensile strength and histological features. Biotin is a water-soluble vitamin that needs to be added to the daily diet for a prolonged period of time before any significant changes can be noticed.

Moreover, the effect of the rumen and diet on biotin bioavailability should not be underestimated. A diet rich in grains (>50% DM) leads to an acidification of the ruminal content, causing a decrease in the local bacterial biotin synthesis (Seymour, 1999). It has been indicated that supplementing 20 mg biotin daily for 45 days has no effect on the DD healing rate (Silva et al., 2015). In other studies, it has been shown that daily 10-20 mg supplementation for eight months during two years has a positive effect on the healing rate and incidence of claw lesions (e.g. vertical fissures, white line disease, heel horn erosions, sole ulcers), and additionally increases milk production (Seymour, 1999; Campbell et al., 2000; Hedges et al., 2001; Lischer et al., 2002). In a study by Bergsten et al. (2003), the incidence of sole hemorrhages was significantly lower (24%) in the group of animals receiving biotin supplementation than in the control group (50%).

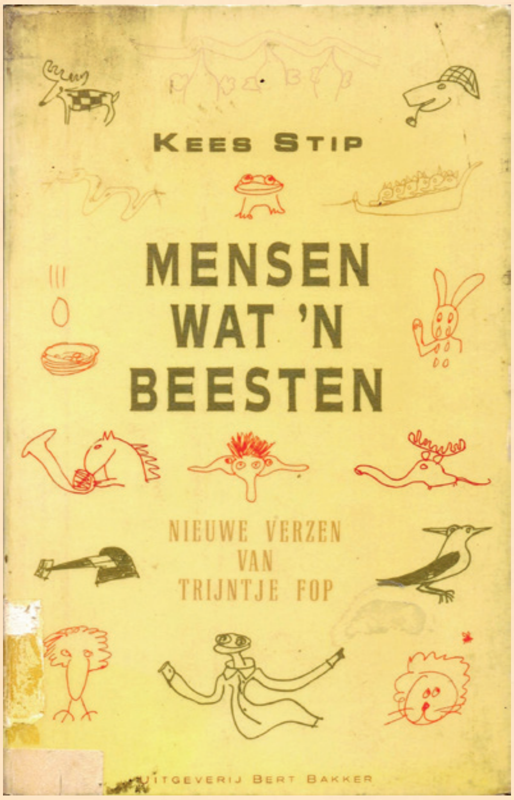
CONCLUSION

One of the most common infectious foot diseases in cattle is digital dermatitis. Its pathogenesis is yet to be elucidated but numerous factors that play a role have been identified. Changes of the local microbiota composition, e.g. an increase in the number of treponemes combined with the possible synergistic action of other bacteria, are considered to be one of the most important elements in the development of the disease. A dysregulation on the level of the innate and adaptive immunity is present. Although antibodies are formed when confronted with an acute lesion, they do not seem to fully protect the animal as the lesions may progress to a chronic stage. Moreover, the animal may relapse at any time. The influence of the daily ration and diet supplements, such as biotin, on the presence of digital dermatitis is under-researched. It may be worthwhile to take digital dermatitis into account when breeding, as every cow has a certain genetical susceptibility. The leg and foot conformations of the individual cow can make an animal more or less prone to develop (non-) infectious foot disorders. In the prevention of these disorders, environmental factors, such as the design of the stable and hygiene, should also be taken into account. The development of an adequate treatment and a vaccine are complicated by the multifactorial nature of digital dermatitis.

LITERATURE

A complete reference list can be obtained from the authors on request.

Dieren literair



Buikleg – Eiperitonitis
(S)onnet

Een kip van onverdacht fatsoen
was door een haan van zwakke zeden
arglistig om de tuin geleden,
gelijk dat hanen hennen doen.

De kip heeft toen haar schuld beleden
aan een naburige kalkoen
en onder ’t welverdiend sermoen
zich beide ogen natgeschreden.

Te laat bezield door de begeerte
haar toch niet te redden eer te
bewaren, koos zij zich tot taak

het zondig ei te onderdrukken.
Ze barstte met een knal aan stukken
en stierf voor een verloren zaak.

Kees Stip, alias Trijntje Fop (1913-2001)