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Clinical Report– Characterization of Toe Ulcers Associated with Thin Soles in Dairy Cows

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Abstract

Thin soles have been identified as a major economic problem in large confinement dairy operations, particularly in the United States. These case studies are from two herds, one in the midwest (Herd 1) and the other in the southeast (Herd 2). Herd 1 and Herd 2 had 3,221 and 2,200 lactating cows, respectively, with records of lameness events over a 12-month period. The incidence of thin soles reported in farm records was 30.1% and 12% for Herds 1 and 2, respectively. A diagnosis of thin soles was based on criteria established in a previous study, which include a soft flexible sole on thumb pressure and a short dorsal wall (less than 3 inches; 7.5 cm). Rear feet were more commonly affected. Break or separation of the sole from the white line adjacent to zones 1 and 2 was a consistent finding in severe cases, and was termed a thin sole-induced toe ulcer (TSTU). Thin sole-induced toe ulcer lesions progressed to a subsolar abscess in zone 5, which in the worst cases progressed to septic osteitis of the third phalanx with osseous sequestration.

Thin sole-induced toe ulcer is often reported as white line disease, toe abscess or sole abscess, which leads to inaccurate on-farm lesion recording and misdirected management strategies. The objective of this communication is to distinguish between laminitis-induced toe ulcer, thin sole-induced toe ulcer and white line disease. The treatment approach adopted in the study herds is discussed.

Keywords: bovine, lameness, toe ulcers

Résumé

Les soles amincies ont été identifiées comme étant un problème économique important dans les grandes fermes laitières particulièrement aux États-Unis. Ces deux études de cas proviennent de deux troupeaux l'un dans le Midwest (Troupeau 1) et l'autre dans le sud-est (Troupeau 2). Il y avait 3221 vaches en lactation dans le troupeau 1 et 2200 dans le troupeau 2. Des épisodes de boiterie ont été notés dans les deux troupeaux dans les douze mois précédents. L'incidence de soles amincies notée dans les dossiers de la ferme était de 30.1% dans le troupeau 1 et de 12% dans le troupeau 2. Le diagnostic des soles amincies était basé sur des critères établis dans une étude précédente incluant la présence d'une sole molle et flexible sous la pression du pouce et la présence d'une petite paroi dorsale (moins de 3 pouces: 7.5 cm). Les pieds arrière étaient les plus souvent touchés. Une cassure ou séparation de la sole de la ligne blanche adjacente aux zones 1 et 2 était souvent rapportée dans les cas les plus sévères et était considérée comme un ulcère apical. De tels ulcères associés aux soles amincies progressaient en abcès sous-solaire dans la zone 5 de la région apicale et dans les cas les plus graves progressaient encore plus pour former une ostéite septique de la troisième phalange avec séquestration osseuse.

Des ulcères de l'onglon apical associés aux soles amincies sont souvent considérés comme des maladies de la ligne blanche, ou des abcès de l'onglon apical ou de la sole ce qui entraîne souvent une mauvaise caractérisation de la condition dans les dossiers à la ferme et une gestion inappropriée des cas. L'objectif de cette présentation est de distinguer les cas d'ulcères de l'onglon apical associés à la laminite ou aux soles amincies ou à la maladie de la ligne blanche. L'approche thérapeutique adoptée dans chacun des deux troupeaux est discutée.

Introduction

Thin soles result from situations where the rate of sole horn wear exceeds the rate of growth. Claw horn characteristics which affect the rate of sole horn wear depend largely on hardness and water content of the claw. Claw horn moisture was found to be higher in cows with thin soles compared to those with normal claws.[18] Claw horn is continually exposed to high moisture conditions, particularly during hot and humid summer months as heat stress management, especially

in the southeastern United States, requires that cows have access to sprinklers and fans, or misting systems. In addition, manure management systems are based on flushing of fresh or recycled water to clean floors in barns, holding areas and travel lanes. As a result, cows are often forced to spend prolonged periods standing in manure slurry. Cows feet are thus wet and soft, and an increased rate of wear is expected.[18] Other factors can also contribute to development of thin soles, such as distance cows must walk between barns and milking areas, particularly when turns are sharp or walkways are sloped. Excessive sole horn wear can also occur in new facilities where freshly cured concrete creates a particularly abrasive surface, often referred to as "new concrete disease".[2,4,12]

Poor cow comfort caused by overcrowding, improper stall design and insufficient bedding may increase the time cows remain standing and moving around, thus extending the time claws are subject to wear.[21] When the number of stalls is equivalent to or less than the total number of cows in the barn, timid animals, such as heifers, may have less opportunity to rest. It is recommended that there be at least 10% more free stalls than cows to permit more choice and encourage lying time. Proper free stall dimensions are important to meet the requirements of cows for normal resting, including 1) freedom for a cow to stretch her front legs forward; 2) freedom for a cow to lie on her side and have sufficient space for her head and neck; 3) freedom for a cow to rest her head on her side; 4) sufficient room for a cow to rest her legs, udder and tail on the free stall platform; and finally 5) have a clean, dry and soft bed. Some US recommendations for Holstein cattle include construction of a free stall 8 ft (2.44 m) long (7 ft 6 in [2.28 m] for two facing rows) and 4 ft (1.22 m) wide, with a brisket board 15 in (38 cm) high and located 5 ft 8 in (1.73 m) from the stall curb. Even longer free stalls, up to 9 ft 8 in (2.95 m), are currently recommended by some.[21]

Since thin soles have become a very common problem, the possibility of over-trimming should always be ruled out in problem herds.[21] Different trimming methods can result in significant differences in sole thickness. For example, one study found that the "Dutch method" of claw trimming resulted in fewer thin soles compared to a method popularized by a veterinarian from the UK.[17] The latter method uses the width of four fingers on one hand to measure dorsal wall length, and reconnection of the white line on the sole at the toe as a guide to estimate sole thickness.[17] The Dutch method is based upon maintenance of a minimum dorsal wall length and sole thickness.[15,17] For the average adult Holstein cow, a dorsal wall length (toe length) of 3 inches (7.5 cm) corresponds to a sole thickness of 0.25 inches (5-7 mm), which under normal circumstances of growth and wear provides enough sole horn to protect the soft structures, such as the corium, on the ventral surface of the third phalanx.[15,17] These authors have observed that foot trimmers who disregard requirements to maintain a minimum toe length are prone to over-trimming the sole.

Clinical Observations

Cows with thin soles were identified in two large dairy herds consisting of 3,221 (Herd 1) and 2,200 (Herd 2) lactating cows, respectively, during examination of animals presented with clinical lameness over a one-year period. Herd 1 was located in the Midwest, and Herd 2 was in the southeastern US. Cows in both herds were kept in free stalls with sand bedding and grooved concrete walk ways. Some cows in Herd 2 had access to dirt lots when weather permitted. The incidence of thin soles in Herd 1 for the period was 30.1% (32.6% for first-lactation cows) and 12% in Herd 2. Criteria established in a previous study served as a basis for the diagnosis, which included a short dorsal wall (less than 3 inches) and a soft, flexible sole on thumb pressure. Back feet were more commonly affected.[18] Lesions other than thin soles observed in this study[18] included 1) hemorrhages in all zones, but primarily at the abaxial sole/white line region in zones 1 and 2 (Figure 1), the heel-sole junction (zones 4 and 6) and

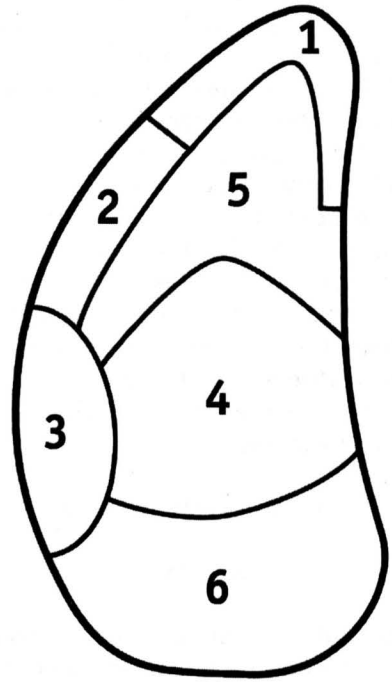

Figure 1. Zones of the claw. 1: White line at the toe. 2: Abaxial white line. 3: Abaxial heel-wall junction. 4: Sole-heel junction. 5: Apex of the sole. 6: Heel

axial area of zone 4; 2) sole ulcers, particularly in zone 4 (typical ulcer) and zone 6 (heel ulcer); and 3) break or separation of the sole from the white line (TSTU), previously described as white line separation, adjacent to zones 1 and 2. This separation of the sole from the white line can clearly be seen at the junction of the sole with the white line in zones 1 and 2 (Figures 3 and 4), and was a consistent finding in severely thin-soled cows. Undermining of the sole follows separation, with abscessation and damage to the exposed corium in the region of the toe (toe abscess).[14]

Observations made in Herd 1 showed that the highest incidence of thin soles occurred in second-lactation cows between 60 and 250 days-in-milk.[20] In both herds, the highest overall incidence of thin soles occurred during summer months.[13,20]

Thin-soled cows that develop lameness generally present with one of the following conditions:

1. Thin soles that are flexible to finger pressure but have no ulceration, thus no exposure of the underlying corium.
2. Thin soles that are flexible to finger pressure and have a break in the epidermis that exposes the underlying corium (toe ulcer).
3. Thin soles that have progressed beyond the stage of ulceration and have formed a subsolar abscess at the toe (toe abscess). At this stage, the white line may also be involved. Infection can cause necrosis of both the laminar corium and laminar horn (white line).
4. Thin soles that have progressed to the point of subsolar abscessation and osteitis of the third phalanx[14,16] (complicated toe abscess – osseus sequestration).

Because of fairly good lameness detection in both herds, most cows presented with lesions described as categories 1 and 2 above, with fewer cases in categories 3 and 4. The exact number in each category was not recorded in the two herds.

Treatment and Management of Thin-soled Cows

Treatment of cows with thin soles requires careful evaluation of the sole of all claws. Generally speaking, thinning and thus flexibility of the sole is greatest on the lateral claw of rear feet and the medial claw of front feet; front claws are less commonly involved since the sole horn is thicker and contains less moisture.[18] The first objective in treatment is to determine if one of the two claws being evaluated on each foot can support the weight on that limb if fitted with a foot block to elevate the thin-soled claw. If the answer is yes, then a block is fitted to the most sound (claw with the healthier and thicker sole) of the two claws. On the other hand, if it is determined that neither claw can support the weight of the respective limb, then neither claw should be fitted with a block and the animal should be moved and housed in an area free of concrete or other hard surface. Special-needs areas close to milking facilities and constructed with soft flooring surfaces are often used when available. An alternative to housing in special-needs areas is a grassy area or dry lot close to the parlor that limits the distance cows must walk on hard or abrasive surfaces during recuperation and horn growth.

In cases where the condition has progressed to ulceration, subsolar abscess formation or osteitis of the third phalanx, additional corrective trimming and debridement procedures are necessary. All loose and undermined claw horn associated with the lesion should be carefully removed without causing damage to adjacent tissues of the corium. Sole horn separation from the corium can become quite extensive in cases where the solar corium has become traumatized, infected and a subsolar abscess has formed. Apart from formation of a subsolar abscess, the infection may spread into the white line, resulting in necrosis of the white line with separation from the wall. The overlying, separated portion of the wall should be removed to the point where reattachment between the wall and healthy corium is evident.

Because corrective trimming procedures can be very painful, intravenous regional anesthesia should be considered whenever it appears that corrective trimming procedures may be causing discomfort. Local anesthesia is essential for those conditions that require significant debridement of soft tissues and bone. The objective in every case is to remove all necrotic tissue and adjust weight bearing. This is important for management of pain as well as subsequent recovery of the horn-forming tissue of the epidermis.

There are many different opinions among clinicians regarding the best treatment for open lesions involving the corium. Our favored approach for management of small lesions, which result in minimal exposure of the corium, is to leave them untreated. On the other hand, when faced with larger lesions where there is significant exposure of the corium, we prefer to apply a non-irritating topical ointment, such as silver sulfadiazine 1% cream,[a] with a bandage to protect the exposed corium. In our opinion, commonly used topical tetracycline powder, copper sulfate and concentrated forms of iodine have the potential to cause excessive damage to the corium that may restrict or inhibit its ability to support future normal claw horn growth.[6] Exceptions include presence of granulation tissue originating from the corium, such as seen in more chronic open lesions. In such cases, use of compounds that may suppress regrowth of granulation tissue after surgical resection may be desirable. The authors have observed a mixture of oxytetracycline powder and dexamethasone mixed

into a paste, or a commercial product containing a mixture of copper, zinc and sulfur,[b] to be effective. Care should be taken to restrict application of the product to the affected area only. Cases should be examined every seven to 10 days to monitor progress.

Management of individual thin-soled cows not only depends upon severity of the condition, but also lactation, pregnancy status and age. Culling should be considered in cases of non-pregnant older cows with prolonged lactation and low milk yield. Cows with thin soles on all claws with one or more toe ulcers, abscesses in the sole horn and severely lame have a poor prognosis irrespective of age, pregnancy or lactation status. Culling should be considered for these cases based on economic and welfare concerns.

Management of a herd with a thin sole problem is based upon evaluation of the presence of any of the predisposing factors as described above. Cow comfort issues, including use of sand bedding, trimming method, excessive use or pooling of water and abrasiveness of the walking surface should be investigated and corrective action implemented. In both Herds 1 and 2, the highest incidence of thin soles occurred during the summer months. Both herds used sprinklers and fans to cool cows during the summer months, resulting in more exposure of sole horn to moisture. Over-trimming was not a contributing factor, as trimmers from both farms had attended the University of Florida's Master Hoof Care Course and were periodically evaluated by one of the authors (J K Shearer). We postulated that the primary predisposing factors for thin soles in both herds were abrasiveness of the walking surfaces; spilling of sand bedding onto the concrete, which may have further increased the abrasiveness; moisture content of sole horn, particularly during the summer; and periods of heat stress, which may have predisposed cows to laminitis. Installation of rubber belting on concrete walkways in Herd 1 resulted in a reduction of thin-sole cases in first-lactation cows from 32.6% to 4%.[20] The effect of rubber belting was not assessed in Herd 2.

Discussion

The authors have observed that cows with thin soles have a slow, painful gait with or without specific leg lameness. The gait may be described as walking "tender-footed" or "as though walking on egg shells", which may also be a feature of acute laminitis. The difference in thin-soled cows is that sole horn becomes soft, thin and flexible, resulting in painful weight bearing on affected feet and claws. In addition, laminitis usually affects all four feet of cows whereas thin soles manifest lameness more frequently in the back feet,[18] because the sole horn of front feet is thicker and contains less moisture than the back feet.[18] Also, during locomotion cows propel themselves forward with the rear feet, whereas the front feet function to more or less support the front end. The act of propelling the body forward increases friction and wear on the weight bearing surfaces of the rear feet.

In thin-soled cows, specific leg lameness results primarily from what has been previously referred to as "white line disease in the toe region".[13] However, results of studies presented here demonstrate that the lesion has heretofore been described incorrectly. On closer examination, we have observed that the initial lesion is actually a separation of the sole from the white line that occurs commonly in the abaxial region of the toe near the junction of zones 1 and 2 in the early stages of the disease. Since this lesion represents a full thickness break in the epidermis, it is called an ulcer by definition.[10]

The pathogenesis of thin sole lesions, however, is much different than in white line disease or laminitis-induced toe ulcer. These lesions are related to laminitis, whereas TSTU are associated with excessive wear and thinning of the sole, leading to separation of the sole from the inner zone of the white line. One problem in making an accurate diagnosis is that the lesion is often very advanced by the time the veterinary practitioner or trimmer observes it the first time. As a result, many incorrectly define these lesions as laminitis-induced toe ulcers, abscesses or white line disease, and may cause a practitioner to seek correction of a herd laminitis problem rather than evaluate the abrasiveness of the floor or trimming technique.

White line disease is an important clinical entity in dairy herds, and should be distinguished from thin soles because of major differences in predisposing factors, pathogenesis and prevention practices. Thin soles result when the rate of sole horn wear exceeds the rate of growth. White line disease, on the other hand, refers to lesions that affect the junction between the wall and sole, and can be recognized as hemorrhage in the white line, fissure formation with accumulation of environmental debris, or abscessation.

Although laminitis is generally regarded as the primary inciting cause for these changes within the white line, other contributing factors should be considered. One frequent contributing factor is horn overgrowth, particularly the heel of the outer claw of the rear leg.[15] The abaxial white line in the heel is particularly exposed to mechanical injury at the heel/wall/sole junction (zone 3, Figure 1) since most of the weight, or load, is concentrated in that area of the claw at the time of heel strike and also during the initial part of the stride.[8,22] Poor trimming techniques may also predispose to white line lesions, including rounding the outside wall, thus shifting more weight bearing onto the white line, and excessive sloping of

the sole, which may also increase the exposure of the white line during weight bearing.[21] Possible causes of white line disease in the various zones of the claw are shown in Table 1.

White line horn consists of three zones: outer, middle and inner (Figure 2). Horn of the white line is produced by the basal cell layer of the epidermis overlying small papillae (cap papillae) on the laminar corium (sensitive laminae; dermal laminae) and terminal papillae present at the distal ends of the dermal laminae, which undergo a transition into rows of dermal papillae of the sole.[1,3,8] Epidermis overlying the terminal papillae produces horn of the inner layer of the white line and consists of thick horn tubules representing very soft horn, which can easily become separated from sole horn if the sole becomes too thin.

Table 1. Main causes of primary and secondary white line disease per zone.

Axial Zone 1	
	Laminitis induced dyskeratotic horn formation
	Incorrect/cosmetic trimming. Removal of axial weight bearing of wall with exposure of the white line
Apex of the claw (toe) Zone 1	
	Laminitis induced dyskeratotic horn formation
Abaxial Zones 1 and 2	
	Incorrect/cosmetic and over trimming. Removal of abaxial weight bearing of wall with exposure of the white line
	Laminitis induced dyskeratotic horn formation
Zone 3	
	Mechanical break down due to weight bearing
	Laminitis induced dyskeratotic horn formation

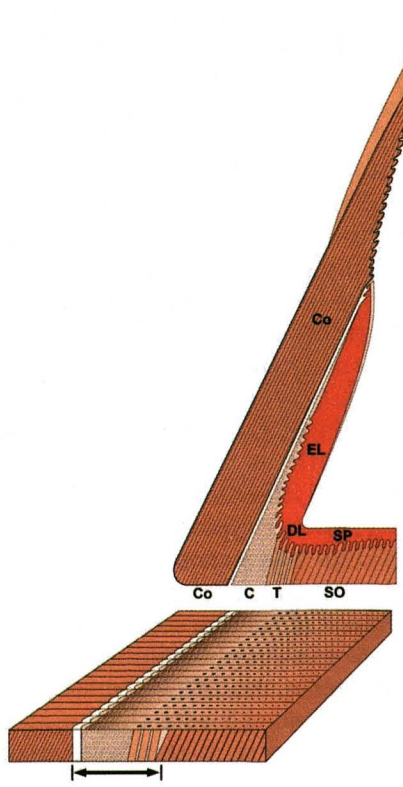

Figure 2. Schematic presentation of normal anatomical structures. P = periople, Co = wall, EL = sensitive laminae, DL = distal part of sensitive laminae, SP = solar corium, C = middle zone of white line, T = inner zone of white line, SO = sole, ↔ = white line (Adapted from Ch Mulling[8])

Figure 3. Bracket indicates break /separation of the sole from the white line. (Adapted from Ch Mulling[8])

Figure 4. Thin sole-induced toe ulcer (TSTU) - note separation of the sole from the white line. Separation of the sole (zone 5) and abaxial white line (zones 1 and 2).

The pathogenesis of white line disease associated with laminitis involves an alteration in the microcirculation of blood to the laminar corium of all four feet during the acute stage of the condition. This usually results in the formation of weak dyskeratotic horn, which may become visible as yellowish horn with varying degrees of hemorrhage several weeks later.[8] Such horn breaks down easily (also referred to as claw horn disruption which is typical of the subclinical stage), allowing penetration of dirt and bacteria which results in abscess formation under the sole or wall, and may eventually form a discharging tract at the coronary band or back of the heel.[1] This may occur in any area of the white line (abaxial zones 1, 2 and 3 or in the axial portion of zone 1). A toe (subsolar) abscess may result when the white line at the apex of the toe is involved.

The pathogenesis of white line disease is also closely related to the biomechanics of normal weight bearing and the physical properties of the walking surface. The outer claw of the hind leg normally bears more weight relative to the inner claw.[15] Since maximum weight bearing occurs at the heel and the heel/wall and sole junction during the heel-strike phase of the stride, overgrowth of the outer claw occurs particularly in this part of the claw.[15,22,23] Since horn of the white line is soft, maximum cell turnover occurs in this region, resulting in immature, incompletely keratinized cells to be in contact with the walking surface, which if abrasive, will predispose to white line separation and disease in zone 3[2,4,12] (Figure 5). Breakdown and separation of the white line may be aggravated by the corrosive effect of manure and keratolytic enzymes produced by anaerobic bacteria.[6,7]

Laminitis-associated toe ulcer starts from the inside and results from downward displacement of the third phalanx.[9] Vascular and inflammatory changes, such as hemorrhage, edema and ischemia in the laminar corium, lead to separation of the tight interdigitation between the dermal folds of the laminar corium and horn leaflets that protrude inward from the wall and suspensory apparatus.[9] The resultant laxity and weight bearing dynamics causes one of two things to happen. One, the apex of the distal phalanx may become displaced ventrally, resulting in pressure necrosis of the solar corium basement membrane and basal layer of the epidermis, or secondly, the distal phalanx may sink with the same end result. Horn cell formation, proliferation and differentiation are impeded, and a sole horn defect results which eventually may manifest as a full-thickness defect in the sole horn at the apex of the toe[9] (Figure 6).

A short dorsal wall is one of the claw characteristics of cows with thin soles.[18] This will shift the weight bearing axis towards the front of the claw, where maximum weight-bearing pressure occurs just prior to the foot being lifted off the walking surface.[5,15,22] This pressure exceeds that of heel strike during locomotion, but is equally divided between the two claws.[22] This increased pressure during weight bearing, and because the sole is normally thinner at the toe (apex of zone 5) as compared to other zones within the weight-bearing surface, may explain why sole/white line separation with toe ulceration is more likely to occur in the toes of thin-soled cows.[23]

Differentiation of toe ulcers on the basis of inciting cause (laminitis vs thin soles) can be based on several factors. First is anatomical location. Thin sole-induced toe ulcers occur typically in the sole adjacent to the abaxial white line (transition of zones 1 and 2), whereas laminitis-induced toe ulcers usually occur in the sole at the apex of the toe (zone 5). Secondly, with thin soles there is increased flexibility of the sole, particularly in the area of the TSTU, whereas with laminitis-induced toe ulcer the sole thickness is usually unchanged. Next, claws with thin soles usually have short dorsal walls, and the bearing surface of both the sole and heel is very flat with very little sloping at the interdigital space. Finally, the outer claw of the rear leg is most commonly affected in cows with thin soles caused by excessive wear due to abrasive surfaces, whereas laminitis-induced toe ulcers are more commonly seen in front feet.

Figure 5. White line disease in zone 3.

Figure 6. Laminitis-induced toe ulcer.

Sole lesions caused by over-trimming (iatrogenic sole ulcers/abscesses) may be present in front and/or back feet, and may have a random distribution in zone 5, but are often present in the axial region of zone 5 due to excessive sloping of the sole at the toe.

The outer claw of the hind leg is usually the first to develop a thin sole as a result of normal weight bearing dynamics. Disparity of weight bearing between the two claws of the rear limbs, with the outer claw bearing more weight relative to the inner claw, is progressive. As a result, accelerated wear of the outer claw on hard and abrasive surfaces occurs.[15]

One study found that when the soles of the hind claws were trimmed to the same level to create a flat bearing surface, the sole of the lateral claw was significantly thinner than that of the medial claw.[11] This may relate to a reported difference between the mean soft tissue thickness (corium and subcutis between the inside of the sole and the ventral surface of the distal phalanx) of the medial and lateral claws measured ultrasonographically, with the soft tissue of the outer claw being significantly thicker than that of the inner claw.[19]

Separation and fragmentation of the sole in the abaxial area of zone 5 adjacent to zones 1 and 2 in severely thin-soled cows has been reported previously,[19] and was observed by the authors to be a consistent lesion not only in the two herds described here, but also in other herds (Shearer and van Amstel, personal observations). Based on the nature of the lesion and its anatomical location, the authors feel it is justified to describe the lesion as "thin sole-induced toe ulcer" (TSTU). The term "toe ulcer" has traditionally been used in relation to laminitis, where ventral displacement of the apex of the third phalanx causes pressure necrosis of the corium in the toe region, with toe ulceration as a consequence.[9] The term "toe abscess" is often used loosely, and commonly presented as a primary diagnosis. However, this should be regarded as a secondary problem, and may result in the toe region (zone 5) from thin sole-induced toe ulcer, laminitis-induced toe ulcer, white line disease or foreign body penetration of the sole.

Conclusions

We propose that separation of the abaxial sole (zone 5) from the white line (zones 1 and 2), a common lesion in thin-soled cows, be termed thin sole-induced toe ulcer. This accurately describes the lesion based on its pathogenesis and anatomical location. The thin sole-induced toe ulcer should be distinguished from toe ulcers and white line disease, both of which can be caused by laminitis. Toe abscess is a complicating lesion, and should not be presented as a primary lesion as it is often secondary to thin sole-induced toe ulcer, laminitis-induced toe ulcer, white line disease or foreign body penetration of the sole. Correct lesion identification, cause and recording are important for appropriate lameness prevention strategies in large dairy herds. Toe ulcer in combination with other changes, such as a short dorsal wall (toe) and a flexible sole, strongly suggest that factors predisposing to excessive horn removal/wear should be investigated.

Endnotes

[a]Thermazene, The Kendall Company, Mansfield, MA
[b]Quickhit™ for dairy cattle, SSI Corp, Julesburg, CO

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For subcutaneous injection only in cattle.
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Not for use in calves to be processed for veal.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS

Swine: EXCENEL RTU EZ Sterile Suspension is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis and *Streptococcus suis*.

Cattle: EXCENEL RTU EZ Sterile Suspension is indicated for treatment of the following bacterial diseases:

— Bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

— Acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

— Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

CONTRAINDICATIONS

As with all drugs, the use of EXCENEL RTU EZ Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet (MSDS) please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

RESIDUE WARNINGS:

Swine: When used according to label indications, dosage and route of administration, treated swine must not be slaughtered for 4 days following the last treatment. Use of dosages in excess of those indicated or by unapproved routes of administration may result in illegal residues in edible tissues.

Cattle: When used according to label indications, dosage and route of administration, treated cattle must not be slaughtered for 3 days following the last treatment. When used according to label indications, dosage and route of administration, a milk discard time is not required. Uses of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or milk. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

The effects of ceftiofur on cattle and swine reproductive performance, pregnancy and lactation have not been determined.

Subcutaneous injection in cattle and intramuscular injection in swine can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25° C (68° to 77° F). Protect from freezing. Store upright. **Shake thoroughly prior to use. Visually assure contents are fully resuspended.**

HOW SUPPLIED

EXCENEL RTU EZ Sterile Suspension is available in 100 mL vials.

NADA 141-288, Approved by FDA

U.S. Patent Nos. 4,902,683; 5,736,151

April 2008 820 893 000
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Distributed by:

Pharmacia and Upjohn Company
Division of Pfizer Inc
NY, NY 10017

EXCEDE®

(Ceftiofur Crystalline Free Acid)
Sterile Suspension

For subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle. For subcutaneous injection in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) in beef and non-lactating dairy cattle.

CAUTION

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS

EXCEDE Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in beef, non-lactating dairy, and lactating dairy cattle. EXCEDE Sterile Suspension is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni*.

CONTRAINDICATIONS

As with all drugs, the use of EXCEDE Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing latex gloves.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet (MSDS) please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

Injection of EXCEDE Sterile Suspension into the arteries of the ear is likely to result in sudden death to the animal.

RESIDUE WARNINGS

- **Following label use as a single treatment, a 13-day pre-slaughter withdrawal period is required.**
- **Following label use as a single treatment, no milk discard period is required for this product.**
- **Use of dosages in excess of 6.6 mg CE/kg or administration by unapproved routes (subcutaneous injection in the neck or intramuscular injection) may cause violative residues.**
- **A withdrawal period has not been established for this product in pre-ruminating calves.**
- **Do not use in calves to be processed for veal.**

PRECAUTIONS

Following subcutaneous injection in the middle third of the posterior aspect of the ear, thickening and swelling (characterized by aseptic cellular infiltrate) of the ear may occur. As with other parenteral injections, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

Following injections at the posterior aspect of the ear where it attaches to the head (base of the ear), areas of discoloration and signs of inflammation may persist at least 13 days post administration resulting in trim loss of edible tissue at slaughter. Injection of volumes greater than 20 mL, in the middle third of the ear, may result in open draining lesions in a small percentage of cattle.

The effects of ceftiofur on bovine reproductive performance, pregnancy, and lactation have not been determined.

ADVERSE EFFECTS

Administration of EXCEDE Sterile Suspension into the ear arteries is likely to result in sudden death in cattle. During the conduct of clinical studies, there was a low incidence of acute death (nine out of approximately 6000 animals). Three of these deaths were confirmed to be the result of inadvertent intra-arterial injection. No other adverse systemic effects were noted for either the antibiotic or formulation during any of the clinical and target animal safety studies.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP]. Shake well before using. Contents should be used within 12 weeks after the first dose is removed.

HOW SUPPLIED

EXCEDE Sterile Suspension is available in the following package size: 100 mL vial

U.S. Patent No. 5,721,359 and other patents pending.

NADA #141-209, Approved by FDA

Distributed by:

Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

www.EXCEDE.com or call 1-866-387-2287

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