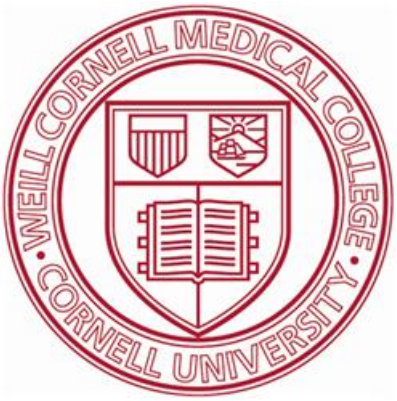
GUIDELINES FOR THE TREATMENT OF ULCERATIVE DERMATITIS IN MICE: A REFERENCE FOR INVESTIGATORS



Memorial Sloan Kettering Cancer Center™

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DESCRIPTION:

Ulcerative dermatitis (UD) is a progressive, debilitating, pruritic (itchy) condition commonly affecting C57BL/6 and related mouse strains. UD initially begins with alopecia (fur loss) and a papular dermatitis over the dorsum of the head and thorax. Ulcerations subsequently develop, may progressively enlarge, and often heal by fibrosis, resulting in skin contracture and possible restriction of limb movement or food prehension (Sundberg, 1994). Secondary bacterial infection may occur and exacerbate the condition and complicate healing. UD must be differentiated from the pruritus and secondary skin trauma (self-inflicted from scratching) associated with other disease processes such as fur mites (such as *Myobia musculi* and *Myocoptes musculinus*).

Initially UD is characterized histologically by profound inflammation of the dermis and epidermis composed of neutrophils, lymphocytes, macrophages, and mast cells. With time and self-trauma, lesions often progress to ulceration of the overlying epidermis with an adhered serocellular crust. The inflammatory response can also involve deeper structures, including muscle, subcutaneous adipose tissue, and nerves. The intact epithelium adjacent to the ulceration is markedly hyperplastic. Chronic lesions have granulation tissue formation progressing to advanced dermal fibrosis (Andrews, 1994). These findings indicate that UD has the potential to confound results in both dermatological and immunological studies.

Despite numerous studies, the exact cause and pathogenesis for UD remain unclear. The current hypothesis is that the condition is multifactorial, including genetic, behavioral, and environmental components. Epidemiologic studies have linked UD to aging, seasonal changes (Kastenmayer, 2006), high vitamin A levels, high fat diets (11%) (Lawson, 2005), diets with increased levels of tryptophan and increased carbohydrate to protein ratios (Dufour, 2010), ad libitum feeding (Blackwell, 1995; Perkins, 1998), and deficiency in inducible nitric oxide synthase (Kastenmayer, 2006).

A study published by Sundberg *et al* (2011) identified a polymorphism in the alcohol dehydrogenase 4 gene (*Adh4*) and differential expression of epithelial retinol dehydrogenase gene (*Dhrs9*) in four C57BL/6 substrains. The study provides preliminary evidence that a polymorphism within *Adh4* combined with elevated *Dhrs9* and a diet high in vitamin A may play a role in B6 dermatitis. In addition, this study found that follicular dystrophy followed by penetration of the hair shaft through the outer root sheath preceded the inflammation characteristic of ulcerative dermatitis.

At MSKCC/WCMC UD lesions are staged according to the table below and are given a higher stage as they increase in size and become more debilitating. Lesions may necessitate euthanasia if they exceed a certain size or depth. They may also necessitate euthanasia if they are located on the head or extremities, which may interfere with food consumption and mobility, respectively.

A consistently effective therapy has not been identified despite many studies. In one study, the use of a vitamin-E fortified diet (3000 IU/kg) for a period of 8 weeks was shown to be beneficial for lesion healing with 70% of mice (n=71) showing at least a 50% decrease in lesion size (Lawson, 2005). A recent Scandinavian study showed that a vitamin-E fortified diet may accelerate the onset of ulcerative dermatitis when administered to young mice (Mader, 2010). In this study the average age of incidence for ulcerative dermatitis was 41 weeks in mice fed the fortified diet and 89 weeks in mice fed standard diet. However, the study was unable to differentiate the effect of vitamin E from the increased dietary fat content. Even though the vitamin E and high fat diet may be detrimental in young mice, it may still be an effective

treatment for older mice after they develop UD. Another group identified maropitant citrate, a neurokinin (NK1) receptor blocker, as a treatment option that works by preventing substance P from binding and inducing pruritus and scratching behavior (Williams-Fritze, 2011). Non-steroidal anti-inflammatory drugs (NSAIDs) may also be effective in reducing lesion severity. In a recent limited study, mice treated with ibuprofen liquid-gel in the drinking water showed an average reduction of 64.8% in mean lesion size over a nine day period (Ezell, 2012). In addition, nail trimming has also been shown to decrease lesion severity and healing time.

Available treatment options for UD include nail trimming and oral medications. Nail trimming prevents further damage to the wound from scratching. Oral antibiotics may be given to prevent or treat secondary bacterial infections. Feed containing antibiotic (amoxicillin) and/or elevated levels of Vitamin E is available through RARC. Investigators should note that antibiotics may alter tumor growth and may have other biological effects which could impact the animal's experimental use.

STAGING & MANAGING UD LESIONS:

UD lesions are characterized as mild, moderate, or severe and managed accordingly:

Stage	Criteria	Management
Mild	< 10 mm* lesion; No involvement of head or extremities	Treatment Monitor
Moderate	10-20 mm* lesion or involvement of head or extremities (< 3 mm)	Treatment Monitor Consider euthanasia
Severe	> 20 mm* lesion or multiple lesions > 20 mm; > 3 mm lesion on head or extremities; deep ulcerations (ie. muscle exposed); lesions that progress despite treatment	Euthanasia

*largest diameter measurement

TREATMENT OPTIONS:

Nail Trimming:

Trimming should be performed once a week and can be done by the PI following training provided by RARC Veterinary Services (VS) or the trimming can be conducted by VS for a service fee. Please contact MSKCC VS at rarc_VS@mskcc.org or WCMC VS at rarc_VS@med.cornell.edu for current pricing and/or to schedule training.

Diet:

Amoxicillin / Vitamin E Combined Diet replaces the standard rodent chow. Please consider any impact this change of diet may have on your research studies prior to approving this treatment. The average food intake is 4.5 g feed/day/mouse (0.00135 IU/day/mouse) when the food is provided ad lib. This can be added to the cages at the time of cage changing by RARC Husbandry and Operations staff for a supplementary special husbandry fee.

PAIN MANAGEMENT:

If the lesion appears to be painful, at least one dose of one of the following analgesics should be provided and the mouse reassessed to determine the need for further analgesic treatment:

Buprenorphine	0.5 mg/kg SC q4 to 12 hrs
Meloxicam	2 mg/kg PO, SC q24 hrs
Carprofen	5 mg/kg SC q12-24 hrs

Management of Animals with Ulcerative Dermatitis:

When an animal is diagnosed with ulcerative dermatitis, RARC Veterinary Services (VS) will contact the animal user and will provide a treatment recommendation (could be one or all listed above). Treatment is provided only if accepted by the animal user or PI. Other treatments may be requested if the animal user or PI believes the standard treatment recommendations would interfere with their research. If an animal on treatment for UD continues to show progression, then the animal user will be contacted again and additional treatment recommendations or euthanasia may be recommended. When a case of UD is resolved, the animal user and PI are contacted and given the option to discontinue treatment or continue the treatment due to the high probability of recurrence. All cages receiving a medicated diet must have a pink "Special Husbandry" card. If VS recommends the treatment, the VS staff member will arrange for placement of the Special Husbandry card utilizing the EnCCoMPass *Census*.

If a member of the investigative staff observes an animal requiring evaluation by a member of the VS staff, the location of cage, cage #, and a brief description of the problem should be sent to VS via phone (WCMC @ 212-746-1079, MSKCC @ 646- 888-2430) or email (WCMC: rarc_VS@med.cornell.edu; MSKCC: rarc_VS@mskcc.org).

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