Journal of the American Association for Laboratory Animal Science
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Vol 60, No 3
May 2021
Pages 311–318

Evaluation of Treatment Options for Ulcerative Dermatitis in the P Rat

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Rotational outbred adult rats, phenotypically selected to prefer drinking alcohol ("P" rats) frequently present with self-inflicted wounds and ulcerative dermatitis, similar to that seen in C57BL/6 mice. Historically, veterinary interventions used to address this clinical condition have included triple antibiotic ointment (TABO), Columbia wound powder (CPW), nail trims, or plastic tubes that allow affected animals to hide. More recent studies have suggested that nail trims are the most successful intervention in mice, but this has not been evaluated previously in rats. In this study, we evaluated nail trims in rats and also tested whether placing a pumice stone in the cage would reduce the need for nail trims to reduce self-inflicted wounds. Our hypothesis was that interacting with the pumice stone would dull/trim the rats' nails without causing stress or illness and allow the wounds time to heal. We used 66 P rats that were assigned to 1 of 6 treatment groups (pumice stone, TABO, CWP, huts, nail trims, and an untreated control group) of 11 rats each. Rats were transferred to this study from a colony of experimentally naïve animals that had evidence of dermatitis. The wounds were photographed and measured for 12 wk at 2 wk intervals. At the end of the study, representative skin samples from the site of the wound were collected for histopathologic evaluation of inflammation. Our data showed no significant differences in the inflammation scores. The rats treated with nail trims healed significantly more often than did all of the other treatment groups. This suggests that nail trims are the most effective intervention for treating self-inflicted wounds in P rats.

Abbreviations: CWP, Columbia wound powder; P Rat, rotational outbred adult rats phenotypically selected to prefer drinking alcohol; TABO, triple antibiotic ointment; UD, ulcerative dermatitis

DOI: 10.30802/AALAS-JAALAS-20-000058

Ulcerative dermatitis (UD) is a common disease of mice, with a prevalence rate ranging from 4% to 21%, especially in strains with a C57BL/6 background.[1,2,18] Clinical signs of UD in mice include moderate to severe pruritus-induced self-trauma that progresses from a small, superficial excoriation to deep ulcerations, tissue granulation, and crusts.[2,18] UD can progress to degloved skin sections in severe cases. The exact etiology of this UD is unknown, although multiple factors have been suggested, including sex, genetics (strain), age, diet, season and primary follicular dystrophy.[17,18,34,40] Some studies have indicated that the clinical etiology is behavioral in origin, with the lesions resulting from self-mutilating behavior in response to pruritis and skin inflammation.[6,13]

The alcohol-preferring (P) and alcohol-nonpreferring (NP) lines of rats were developed by phenotypic selection from a Wistar foundation stock.[4,21] They were developed to study ethanol drinking behaviors and the consequences of addiction. Indiana University has one of 2 primary breeding colonies of these rats in the world. Clinically, P rats in our breeding colonies, in which rats are kept for 8 to 12 mo, and are not handled on a daily basis, present with UD, including pruritis-induced self-trauma, with a prevalence of approximately 10%. This prevalence is not inconsistent with the prevalence of dermatitis reported in mice.[2,18] C57BL/6J mice are frequently used in addiction studies, suggesting a possible correlation between addiction and self-mutilation or dermatitis.[12,27,36] This potential relationship suggests that these clinical observations are not unexpected, given links between addiction and compulsive behaviors such as trichotillomania and skin picking.[11,29,30]

Because the etiology of UD is unknown, the identification of appropriate preventive measures is challenging. One suggested preventative measure is the addition of environmental enrichment to the animal's cage, such as tubes or shacks to hide in or chew up, provision of additional nesting material, or food enrichment.[3,24,32] Several topical and injectable therapies have been used to treat UD, including vitamin E,[16,20,22] antioxidants,[8,15] and ibuprofen[9] in drinking water. These therapies rely on antiinflammatory mediated analgesia, alleviating pruritus, antioxidative protection, immune suspension, antisepsis, and local anesthesia. The reported efficacy of these therapies varies widely and these treatments are usually ineffective.[26,34,40]

Nail trimming is another treatment for UD that has shown some degree of success in mice.[1,2] Nail trims may interfere with the maintenance and progression of UD lesions as a mechanical intervention that interrupts the itch-scratch cycle, even though this intervention may not address the underlying pathophysiologic factors contributing to the self-injurious behavior.[38] Studies in the literature have suggested that nail trims can be effective in as many as 90% of UD cases in mice.[1,2,26,37,40] However, this intervention has not previously been investigated in rats.

This study aimed to identify a treatment or intervention that was reliably successful for amelioration of dermatitis in the P rat. Although nail trims appear to be the most successful intervention in mice, the larger size of rats makes restraint for nail trims more challenging and potentially stressful for both

Received: 14 May 2020. Revision requested: 23 Jun 2020. Accepted: 20 Oct 2020.
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Figure 1. Description of treatment groups and application frequency. (A) Triple antibiotic ointment was applied using a cotton swab while rat was in cage with minimal restrain on Monday, Wednesday, and Friday. (B) Antiseptic wound powder was applied using a cotton swab while rat was in cage with minimal restraint, on Monday, Wednesday, and Friday. (C) Back nails were trimmed once every 2 wk while under anesthesia so that no restraint was necessary. (D) Shacks were autoclaved and placed in the cage weekly. (E) Lava ledge was autoclaved and placed in the cage and changed weekly.

the rat and research personnel, particularly if the animal is not accustomed to regular restraint. We hypothesized that pumice stones placed in the cage would result in dulling of the nails, providing a similar outcome to that achieved with a nail trim while minimizing any potential stress associated with restraint. We speculated that walking over or manipulating the pumice stone would dull the rats' nails, providing an alternative to nail trims. Based on current suggested treatments in mice, we compared the nail trim and pumice stone interventions with other commonly used interventions such as enrichment (Shepherd Shacks, Shepherd Specialty Papers, Watertown, TN) and topical medication used in mice at our facility (Columbia Antiseptic Wound Powder (SC Sturtevant, Bronxville, NY) and topical antibiotic ointment containing bacitracin zinc (USP 400 units), neomycin sulfate (USP 3.5 mg), and polymixin B sulfate (USP 5000 units) (Phoenix Global Supply Group, White Plains, NY). These treatments and interventions were compared with an untreated control group to assess their effectiveness. We hypothesized that the pumice stone would provide a refinement over nail trims by removing the need to restrain the rat, and that nail trims and the pumice stone would result in better outcomes, such as improved healing, when compared with the other treatments and interventions.

Materials and Methods

Treatment groups. Rats used in this study were singly housed to ensure that cage mates could not interfere with the lesions associated with UD. Rats were transferred from the IACUC approved protocol for the breeding colony once they were identified as having developed clinical UD. These rats had not been used for any other experiments before enrollment in this study. Because clinical enrollment for this study was for 4 y, housing conditions could differ across groups, although these data were not collected. However, this variable was controlled for by enrolling rats according to a strict rotation (for example, first rat = treatment 1, second rat = treatment 2, etc.) before examining the rat. The exception was the group of rats in the nail trim treatment group. Initially these animals were not included as one of the treatment groups due to concerns regarding stress on both the husbandry staff and rats based on the restraint required for nail trims. However, we were advised to include them during the 3-y de novo IACUC review. Because 90% of the rats had already been assigned to treatment when this treatment group was added, enrollment in this group was not effectively randomized. Rats in the nail trim group received hindlimb nail trims while under anesthesia for other assessments described below, so that no additional physical restraint was needed to trim the nails. Topical treatments were administered to rats in their cages using a cotton swab with minimal physical restraint. Each treatment group (Figure 1) had 11 animals (sample size was calculated using an online sample size calculator (www.dssresearch.com/knowledgeCenteer/tookitcalcultors/samplesizecalculations.aspx) with a 5% confidence level and statistical power of 80%. The major experimental read-out was wound size with expected variability of 1. The minimal scientifically meaningful treatment effect for the provision of pumice stones was considered to be 50% smaller wounds as compared with the controls.

Animals. Sixty-six adult P rats (42 females and 24 males) were used in this study. The rats ranged from 8 to 80 wk of age (mean age 20.4 wk). This wide range in age was due to the experi-

mental design in which enrollment required presentation with clinical signs. All rats were maintained under 12:12 light-dark cycle housed in standard rat cages (Lab Products individually ventilated caging [approximate dimension 12.13 × 12.13 × 7.37 in], Seaford, DE), although some of the initial enrollees were housed conventionally (Allentown shoebox cages, Allentown Caging, Allentown, NJ [approximate dimension 9.5 × 18.5 × 8.25 in.]) as the institution was in the process of transitioning its rat populations into individually ventilated caging. The change in housing was not tracked during the study. In all housing conditions, the rats were housed with contact bedding (Teklad 7090 Sani Chips, Envigo, Indianapolis, IN) with food (Envigo Rat Chow 2018, Indianapolis, IN) and water provided without restriction. Animals were checked daily by the animal care staff. All health concerns were reported to the veterinary and research team for appropriate interventions. Cages were changed weekly. Temperature and humidity were maintained according to the Guide standards (20° to 26 °C and humidity of 30% to 70%). The health of the colony was screened quarterly using sentinels exposed to dirty bedding from the colony animals. The rat screening program included rat coronavirus, rat parvovirus, Killian rat virus, rat minute virus, rat theliovirus, reovirus 3, pneumonia virus of mouse, *P. carinii*, *C. piliforme*, *M. pulmonis*, *P. pneumotropica*, β-hemolytic *Streptococcus* (Groups A, B, C, G), *Streptococcus pneumoniae, Helicobacter* spp., and endoparasites and ectoparasites. This study was approved by the Indiana University School of Medicine IACUC. The animal care and use program is accredited by AAALAC, International and is compliant with all applicable federal regulations.

Photographing and measuring UD lesions. Once randomly assigned to a treatment group, rats were anesthetized and their UD-associated lesions were photographed and measured (Figure 2). Photographs were necessary to get clear photographs and accurate measurements of the lesions. Anesthesia was provided by using isoflurane (Isoflurane, USP, Patterson Veterinary) administered using a bell jar Three people performed the assessments throughout the study after initial training to ensure consistency in data collection. If concerns developed about consistency in assessment, the photographs were available for additional review. Measurements and evaluations were completed by one of the 3 trained individuals at each time point. All wounds on each rat were measured in centimeters using a ruler. The width and shortest length were measured and then those 2 numbers were multiplied to calculate an approximate surface area of the lesion. The same type of ruler was used for all measurements.

To assess progress and determine if humane endpoints had been met, wounds in all rats, including the controls, were photographed and measured at least every 2 wk by the research team. The rats were also checked daily by the animal care team as part of their daily assessments of all animals in the facilities. Factors assessed included activity level, dehydration greater than 10%, lack of responsiveness of external stimuli, hunched posture and any bleeding that would not stop in response to gentle pressure. Any evidence of reduced feed intake, exaggerated stretching, or pawing at the sides in the rats treated with the pumice stone were considered particularly concerning, as we did not know if rats would ingest the pumice stone and what clinical signs it might cause if ingested. If rats showed any of these signs, then the animal was euthanized for humane reasons. Rats were also euthanized before the study ended if their wounds were considered severe, which was defined as continued enlargement of the wound as compared with previous weeks, evidence of severe infection, or demonstration of excessive pain or distress

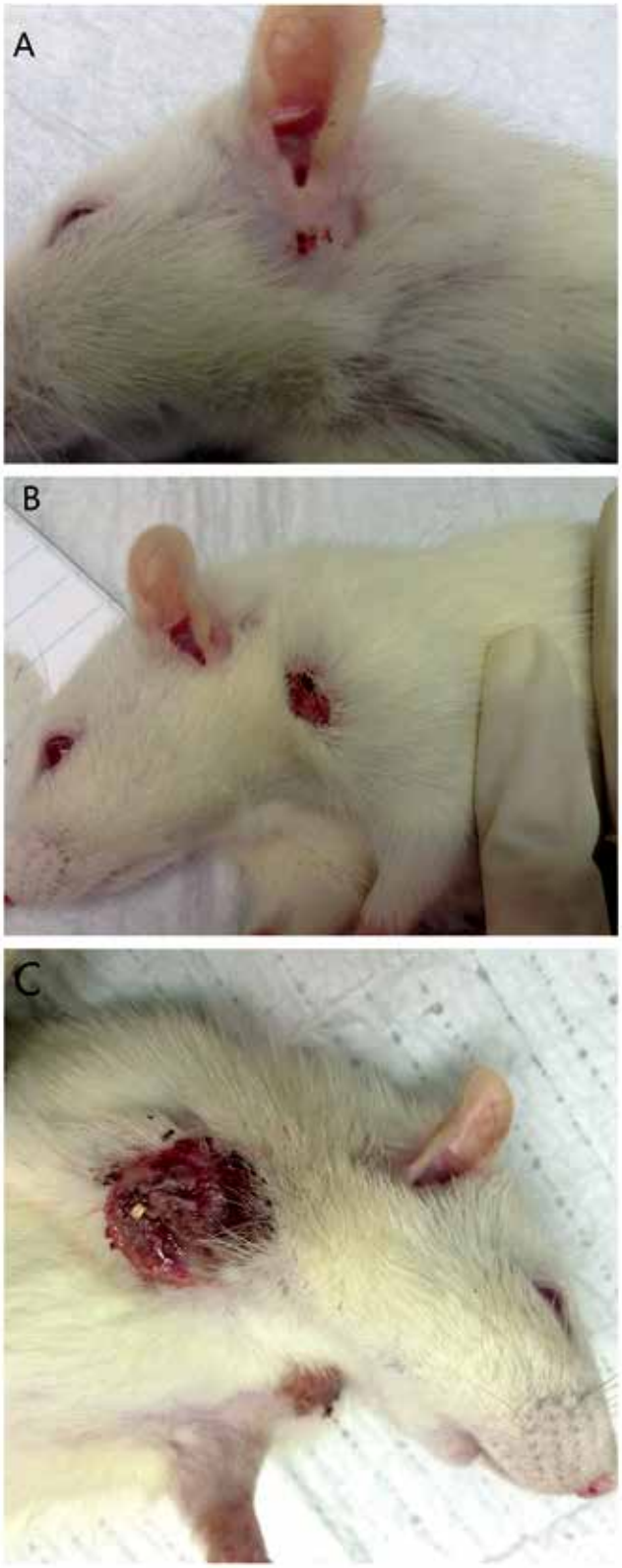

Figure 2. Picture of lesions (A) mild (B) moderate (C) Severe (euthanized early for humane reasons)

(for an example, see Figure 2 C). If daily checks identified rats that required attention, the veterinary staff and research team were notified to perform an assessment. Samples of wounds were obtained from all rats and submitted for histopathologic evaluation of inflammation.

Euthanasia and Histopathologic Evaluation of Inflammation. All rats were euthanized with carbon dioxide (30% VDR/min of 100% carbon dioxide) when wounds had healed, if wounds were too severe and humane endpoints were met, or at the end of the 12 wk experimental period. The area surrounding the wound was shaved, and the skin was submitted for histopathologic evaluation. If the rat was in the pumice stone group, the stomach and intestines were also checked to ensure pumice stone was not ingested.

Scoring of Slides Submitted for Histopathologic evaluation of Inflammation. An evaluation of the inflammation of the skin sites was performed to look for evidence of confounding factors (such as concurrent infection) that might have contributed to the development or exacerbation of dermatitis. To provide consistency, the same veterinarian (CB) was blind to treatment group and did all the scoring. Scoring was based on the following items: granulation tissue (1 profound, 2 some, 3 absent), inflammatory infiltrates (1 plenty, 2 moderate, 3 few), and collagen fiber orientation (1 vertical, 2 mixed, 3 horizontal). Scores for each category were summed; low totals represented poor healing, and high totals represented good healing. The total of each of the 3 individual scores was compared between groups. Representative skin samples are shown in Figure 3.

Statistical Analysis. To compare the success rate of each intervention and treatment, a Kaplan–Meier survival estimate was performed. Weibull fit and lognormal fit tests were used to assess fitness of the data. A Cox proportional hazards test was performed to compare each treatment with the unmanipulated control. In addition, a proportional hazard fit analysis was performed to compare all treatments. Each rat was scored as "wound(s) present" or "wound(s)" absent at each 2 wk time point. Data was right censored, eliminating rats lost to follow up (euthanized due to severity of lesion) and those with lesions at 12 wk (considered as nonsurvivors). The histopathology inflammation scores were compared between with an ordinal logistical model and effect likelihood ratio. Statistical analysis was performed with JMP (SAS, Cary, NC).

Results

Gross Necropsy Results. No pumice stones were found in the stomach or gastrointestinal tract of any of the rats in the pumice stone treatment group.

Survival Data. The results of the survivability analysis are displayed in Figure 4. As shown in Table 1, 8% of the rats (8 of 66) were euthanized before the end of the study (at week 10 or earlier) due to severity of the wounds. An additional 5 were lost to follow-up due to unexpected death. The nail trim treatment had significantly improved healing as compared with the other treatment groups ($P = 0.0183$). When compared with the unmanipulated control, no significant improvements were found for the pumice stone ($P = 0.8131$), TABO ($P = 0.7386$;), hut (0.9749), or Columbia wound powder ($P = 0.4344$). The nail trim group showed a significant improvement ($P = 0.0139$) as compared with the unmanipulated control group. When data were analyzed using the proportional hazard fit model, nail trims performed significantly better than all groups, except for Columbia Wound Powder ($P = 0.0576$). Data are presented in Table 2.

Histopathology Inflammation Scoring. No significant differences were found between the total inflammation scores for the control group and the groups treated with Columbia Wound Powder (degrees of freedom = 1, effect likelihood $\chi^2 = 2.46$, $P = 0.1166$), the topical antibiotic ointment (degrees of freedom = 1, effect likelihood $\chi^2 = 0.01$, $P = 0.9182$), hut enrichment (degrees of freedom = 1, effect likelihood $\chi^2 = 0.9726$), nail trims (degrees of freedom = 1; effect likelihood $\chi^2 = 1.90$, $P = 0.1675$), or pumice stone (degrees of freedom = 1, effect likelihood $\chi^2 = 0.00$, $P = 0.9727$). Histopathology scores are presented in Table 3.

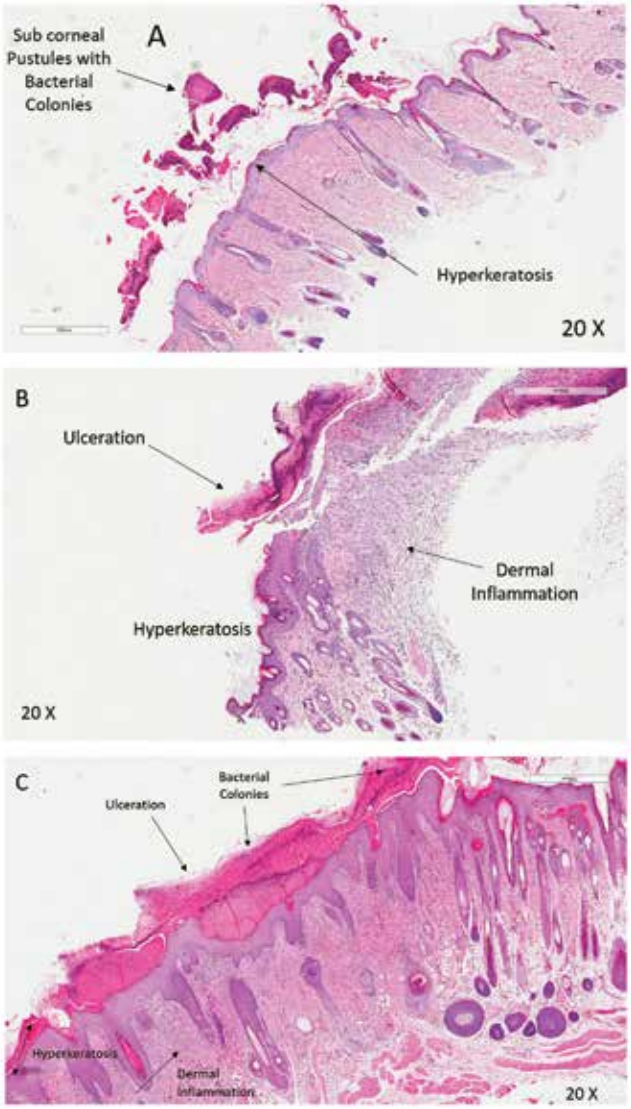

Figure 3. Histopathology pictures (A) healed (B) moderate (C) severe

Discussion

The clinical presentation of the UD in the P rat shares many similarities to clinical disease reported in mice.[1,2,18] Topical interventions are generally unsuccessful in the treatment of dermatitis in mice[2] and in the P rat. This study confirmed that the use of topical treatments such as Columbia wound powder and topical antibiotic ointments (TABO) were no more successful at promoting healing of the ulcerated skin than was no intervention at all.

Similarly, environmental enrichment has been proposed as possible preventative or therapeutic strategy when working with animals (such as mice, cats, and birds) engaging in behaviors that cause alopecia, which can progress to UD.[4,7,10,28,31-33,35,38] In this study, hut enrichment was provided to help decrease the potential stresses experienced by the rats. The intent was to provide rats with a tool whereby they could control their exposure potential stressors such as light variations and human

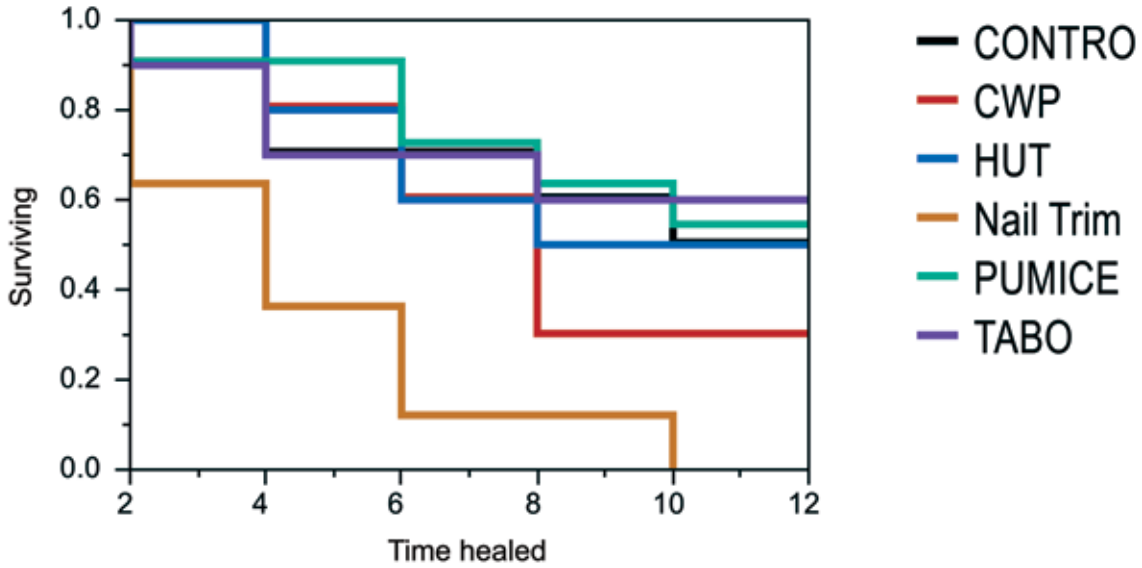

Figure 4. Kaplan Meier survival analysis graph

Table 1. Cumulative status of each animal on study at each 2 wk time point.

	2 wk		4 wk		6 wk		8 wk		10 wk		12 wk	
	Healed	Censored	Healed	Censored	Healed	Censored	Healed	Censored	Healed	Censored	Healed	Censored
Control	1	0	3	0	3	0 (1)	4	0 (1)	5	2 (1)	5	5 (1)
CWP	1	0	2	0	4	0	7	1	7	1	7	4
Hut	0	0 (1)	2	0 (1)	4	0 (1)	5	0 (1)	5	0 (2)	5	4 (2)
Nail trim	5	0	7	0 (1)	9	0 (1)	9	0 (1)	10	0 (1)	10	0 (1)
Pumice	1	0	2	0	3	1	4	1	5	1	5	6
TABO	1	0	3	0	3	0 (1)	4	3 (1)	4	3 (1)	4	6 (1)

"Healed" are animals that were healed and removed from the study. "Censored" animals are generally animals that were lost to follow up because of euthanasia for humane reasons. However, a smaller subset were lost for other reasons (for example, found dead or complications associated with anesthesia or clinical conditions unrelated to the dermatitis study). These animals are indicated parenthetically in the "Censored" columns for completeness.

interaction to help improve the healing of the UD. Likewise, the provision of the pumice stone may have served as a novel item that the rats could interact with in the cage, also providing some novel enrichment that could decrease stress and potentially detract from the scratching behavior associated with UD. However, neither of these interventions were more successful at promoting healing of the ulcerated skin than was no intervention at all. This result is consistent with previous studies showing that enrichment interventions are more successful at preventing underlying conditions that may be correlated with the subsequent development of dermatitis rather than at helping animals recover from an existing lesion.[7,10,14,25,28,31,40] Only a few studies report successful treatment of dermatitis after the clinical dermatitis has already developed.[2,23,34]

Nail trims are now the most commonly used intervention for the treatment of UD in mice.[1,2] Unfortunately, the nail trim group was added to this study when data collection was almost complete for the other therapeutic interventions, which introduces a possible confounding influence on the study results. In addition, sample size was determined using a power analysis that proposed wound size as a major outcome. As we subsequently determined that success or failure of a treatment was of more clinical relevance, the study may not have been sufficiently powered. However, our results are consistent with previous reports that found nail trims to be a possible therapeutic intervention for UD in mice.[1,2,18] Therefore, despite potential confounds in experimental design, our study suggests that nail trims can result in positive outcomes or healing for rats with UD.

The observation that the wound histopathology scores were not significantly different between groups was not unexpected. As healing generally follows a similar profile in the absence of underlying conditions (such as bacterial or parasitic infection), the histopathology scoring primarily served as an additional assessment to identify potential underlying conditions. As the scores did not differ significantly, these data suggest that no underlying factors were potentially confounding the data collected in this study.

In addition to the lack of randomization associated with the nail trim group, other potential confounds were present in this study. One was the transition from conventional housing to individually ventilated caging over the course of the study. As the specific housing situation was not documented at each time point, we could not investigate this potential interaction in this study. Because social isolation of rats can increase stress responses, with concurrent increases in the intake of compounds such as alcohol,[5,19,41] the practice of individually housing rats in IVC may increase the likelihood of self-injurious behaviors. Investigation of the effect of housing conditions on the prevention and treatment of dermatitis in the P rat would be valuable question for future studies, especially given recent analysis of

Table 2. Proportional hazards fit assessment for comparisons between each treatment group.

Treatment	Treatment	Risk ratio	Prob > Chisq	Lower 95%	Upper 95%
CWP	CONTROL	1.54	0.46	0.49	5.22
HUT	CONTROL	1.00	01.00	0.28	3.60
HUT	CWP	0.65	0.46	0.19	2.04
Nail trim	CONTROL	3.95	0.01*	1.37	12.96
Nail trim	CWP	2.57	0.06	0.97	7.21
Nail trim	HUT	3.95	0.01*	1.38	12.88
PUMICE	CONTROL	0.85	0.80	0.24	3.07
PUMICE	CWP	0.55	0.31	0.16	1.74
PUMICE	HUT	0.85	0.80	0.24	3.06
PUMICE	Nail Trim	0.22	0.00*	0.07	0.62
TABO	CONTROL	0.80	0.74	0.20	3.02
TABO	CWP	0.52	0.29	0.14	1.73
TABO	HUT	0.80	0.74	0.20	3.02
TABO	Nail Trim	0.20	0.00*	0.05	0.62
TABO	PUMICE	0.94	0.92	0.23	3.55
CONTROL	CWP	0.65	0.46	0.19	2.05
CONTROL	HUT	1.00	1.00	0.28	3.60
CWP	HUT	1.54	0.46	0.49	5.20
CONTROL	Nail Trim	0.25	0.01*	0.08	0.73
CWP	Nail Trim	0.39	0.06	0.14	1.03
HUT	Nail Trim	0.25	0.01*	0.08	0.73
CONTROL	PUMICE	1.17	0.80	0.33	4.22
CWP	PUMICE	1.80	0.31	0.57	6.12
HUT	PUMICE	1.17	0.80	0.33	4.23
Nail trim	PUMICE	4.64	0.00*	1.60	15.23
CONTROL	TABO	1.25	0.74	0.33	5.05
CWP	TABO	1.92	0.29	0.58	7.36
HUT	TABO	1.25	0.74	0.33	5.06
Nail trim	TABO	4.94	0.00*	1.62	18.35
PUMICE	TABO	1.07	0.92	0.28	4.31

Significance indicated by asterisk (*) and set at $P < 0.05$.

Table 3. Median histopathology scores for all treatment groups.

	Granulation tissue (1–3)	Inflammation (1–3)	Collagen orientation (1–3)	Total score (3–9)
Control	2	2	2	6
CWP	3	3	3	8
Hut	2	2	2	6
Nail trim	3	3	3	8
Pumice	2	2	2	7
TABO	2	2	2	7

The lower the number, the more severe the median lesion was reported to be; the higher the number, the less severe the median lesion was reported to be.

the potential effect of husbandry on the development of mouse dermatitis.[23] Although the concept that the pumice stone could provide the same outcome as nail trim warrants additional evaluation in both rats and mice, our study suggests that the pumice stone did not improve healing as compared with unmanipulated controls. The pumice stone we used was selected because its size would increase the chances that the rat would walk across it while moving in the cage. However, we did not specifically assess interactions of the rat with the stone. A smaller stone could be picked up and manipulated by the rat; however, manipulation of the pumice stone with the forelimbs would not result in a dulling of the nails on the hindlimbs, which are the limbs primarily used in the scratching behavior that often lead to UD. However, alternative ways to present pumice stones to rats could encourage them to interact with the pumice stone with their hind feet.

In this study, we proposed the pumice stone as a novel alternative to nail trim. The goal of this study was to determine if pumice stones placed in the bottom of their cage would blunt the nails as the rats walked across it, wearing down the nails in a manner that was less stressful than nail trims for both the rat and the handler. However, the data did not support our hypothesis regarding the anticipated benefits associated with the pumice stone. Our study did indicate that every other week nail trims are the most effective intervention for treating self-inflicted wounds in P rats. Future studies could compare the

use of pumice stone to nail trims to prevent dermatitis, or use both of these interventions to determine if the pumice stone can lengthen the time between nail trims. If the rats required nail trims less frequently, then this would reduce the stress on the rat and handler and represent a refinement of husbandry technique.

Acknowledgments

The authors thank Betsy Taylor for her initial suggestion of using pumice stones to decrease the self-injurious behavior of the P rats.

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