Acellular fish skin grafts for the management of wounds in dogs and cats: 17 cases (2019–2021)

Elise S. Mauer, DVM1; Elizabeth A. Maxwell, DVM, MS2*; Christina J. Cocca, DVM, MS3; Justin Ganjei, DVM4; Daniel Spector, DVM5

1Park West Veterinary Associates, Mount Pleasant, SC
2Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL
3Metropolitan Veterinary Hospital, Copley, OH
4Veterinary Surgical Centers, Vienna, VA
5Animal Medical Center, New York, NY

*Corresponding author: Dr. Maxwell (emaxwell@ufl.edu)

https://doi.org/10.2460/ajvr.21.09.0140

OBJECTIVE
To report the clinical outcomes of the use of acellular fish skin grafts (FSGs) for the management of complex soft tissue wounds of various etiologies in dogs and cats.

ANIMALS
13 dogs and 4 cats with complex wounds treated with FSGs between February 2019 and March 2021.

PROCEDURES
Medical records were reviewed for information regarding cause, location, size of the wound, management techniques, complications, and clinical outcomes.

RESULTS
In dogs, the number of FSG applications ranged from 1 to 4 (median, 2 graft applications). The time between each application ranged from 4 to 21 days (median, 9.5 days). Time to application of the first FSG ranged from 9 to 210 days (median, 19 days). Wounds closed by second-intention healing following the first fish skin application between 26 and 145 days (median, 71 days; n = 12). In cats, 1 or 2 FSGs were used, and the wounds of 3 of 4 cats healed completely by secondary intention. The wounds of 1 dog and 1 cat did not heal. There were no adverse events attributed to the use of the FSGs.

CLINICAL RELEVANCE
For dogs and cats of the present study, complete healing of most wounds occurred with the use of FSGs, the application of which did not require special training, instruments, or bandage materials.

Animals with burns or traumatic wounds from various causes are relatively common in veterinary practice. Early and aggressive treatment of these wounds as well as long-term management are critical for a successful outcome. The current standard of care for wounds in companion animals includes cleaning and debridement, maintaining a moist wound environment, preventing infection, and minimizing dead space. Depending on the location, size, and severity of wounds, primary closure can be difficult or impossible. However, leaving a wound to heal by secondary intention can be a lengthy process and risks the development of resistant infections and large areas of contracture and scarring in affected patients.

Acellular fish skin grafts (FSGs), conventionally used to treat complex or chronic wounds in people, have become available for the management of complicated wounds in animals. The fish skin is obtained from North Atlantic cod and undergoes gentle processing that maintains omega-3 fatty acids, collagen, elastin, laminin, lipids, fibrin, proteoglycans, and glycosaminoglycans. As healing progresses in an FSG-treated wound, the FSG is incorporated into the wound bed within 7 to 10 days, granulation tissue elevates the wound to the height of the wound edges, and accelerated epithelialization closes the wound from the edge. The FSGs are homologous to mammalian skin (ie, having epidermal and dermal components) and have been shown to speed wound healing, serve as an effective antimicrobial barrier, and provide intrinsic anti-inflammatory properties.

The use of FSGs in wound healing has been extensively studied in human medicine; however, to our knowledge, there have been no formal studies evaluating its use in veterinary medicine. The purpose of the study reported here was to report the clinical outcomes following the use of acellular FSGs for the management of complex soft tissue wounds of various etiologies in dogs and cats.
Materials and Methods

Case selection criteria
Through a query to the manufacturer of FSGs (Omega3 Vet; Kerecis Ltd), 31 veterinary hospitals were identified with a history of purchasing FSGs. These hospitals were contacted to contribute cases to this study. Case selection criteria included dogs or cats with complex wounds treated with FSGs between January 1, 2019, and March 31, 2021, per owner consent. There were no exclusion criteria regarding patient signalment or health status.

Medical records review
Medical records of cases were reviewed, and data collected into an electronic spreadsheet (Excel version 2019; Microsoft Corp) included information regarding patient breed, sex, age, and body weight; wound cause, location, size, and initial management; time from presentation to the application of the first FSG; time from application of the first FSG to wound closure; number of FSG applications and time between FSG applications; secondary layers used; number of bandage changes; additional surgical intervention needed; and complications. The primary outcome of the study was the proportion of patients that had complete wound closure by the end of treatment. Additional outcome measures included time to closure, number of FSG applications, and number of product-related adverse events.

FSG application
Graft applications were performed on anesthetized or sedated patients, depending on debridement requirements and temperament of the affected animal. The FSGs could have been placed at any stage of wound healing. For acute wounds, sharp debridement removed any necrotic tissues; for older wounds with mature granulation beds, surface debridement stimulated bleeding. After a wound was debrided and lavaged, aseptic technique was used in handling the FSG, including removing it from its packaging, rehydrating it with room-temperature saline (0.09% NaCl) solution for 1 minute, cutting it to fit the size of the wound, fenestrating it with a scalpel for heavily exudative wounds, affixing it (scale pattern up) directly to the wound, and compressing it to the wound until the bleeding stopped. The FSG was then fixed in place (with the use of skin sutures, staples, or sterile medical tape), covered with a nonadherent dressing, bolstered (eg, with negative pressure, calcium alginate, foam dressing, or moist gauze) to ensure contact with the wound bed, covered with a dressing to ensure optimal exudate management, and then wrapped as needed to secure and protect the dressing. Some wounds may have required > 1 FSG sheet for coverage. For dry wounds, a hydrogel may have been used to add moisture. Depending on the size and location of the wound, rate of healing, and rate of graft integration, repeated FSG application may have been indicated. If a wound has not yet epithelialized after full integration of the FSG, then wound debridement and another FSG application could have been performed. Similarly, if an FSG had not fully integrated after 2 weeks of application, then wound debridement and another FSG application could have been performed. Once epithelialization along the wound edges was visible, no further application of FSGs was required. However, if healing stalled, reapplication could have been considered.

Statistical analysis
Numbers, means, medians, and ranges were reported for variables and outcomes of interest for patients overall and grouped by species. An online calculator (Mean, Median, Mode calculator; Edward Furey) was used for calculations.

Results

Animals
Of the 31 hospitals contacted, 10 submitted case details for 13 dogs (6 castrated males, 3 sexually intact males, 3 spayed females, and 1 sexually intact female) and 4 cats (2 spayed females, 1 sexually intact female, and 1 castrated male) that had wounds treated with FSGs between February 2019 and March 2021. For the 13 dogs, 10 breeds were represented, and the median age and body weight were 3 years (range, 5 months to 15 years) and 28 kg (range, 6.8 to 47 kg), respectively. For the 4 cats represented, all were domestic shorthair cats with a mean age and body weight of 3.3 years (range, 8 weeks to 11 years) and 3.6 kg (median, 4.0 kg; range, 1.8 to 4.6 kg), respectively.

Wounds
For both species collectively, causes of wounds were trauma (n = 5), burns (3), dog attacks (3), failed skin flap (2), unknown (2), ulcerated hygroma (1), or incisional dehiscence (1). Location of wounds varied from wounds localized to the distal extremities or affecting multiple body parts (thorax, abdomen, and limbs). The smallest wound was 1 X 2 cm in area, and the largest wound affected > 40% of the patient’s body (Figure 1). All wounds were initially managed with surgical debridement and various primary dressing such as calcium alginate, honey, silver sulfadiazine, or foam, alone or in combination.

Treatment with FSG
Overall, the time from presentation to application of the first FSG ranged from 7 to 300 days (median, 23 days; n = 17). The number of FSG applications ranged from 1 to 4 applications (median, 2 applications; mean, 2.2 applications; n = 17), with 5 of the 17 patients treated with only a single application. For dogs and cats that received > 1 FSG application, the time between each application ranged from 4 to 45 days (median, 10 days; n = 17). For dogs, the time from presentation to application of the first FSG ranged from 9 days to 210 days (median, 19 days; n = 13). The number of FSG applications ranged from 1 to 4 applications (median, 2 applications; mean, 2.5 applications). The time

Unauthenticated | Downloaded 01/02/23 04:20 PM UTC
between each application for patients with > 1 application ranged from 4 days to 21 days (median, 9.5 days; n = 16). For 2 dogs, poor owner and patient compliance resulted in additional bandage changes and the decision to either not repeat FSG application or place additional FSG applications.

The time from presentation to FSG application in cats ranged from 7 to 300 days (median, 106 days; n = 4). Three cats each received 1 FSG application, whereas the remaining cat received 2 applications. This cat had a circumferential wound that spanned from the stifle joint to the tibiotarsal joint of its right hind limb, received its first FSG application 300 days after initial wounding, and received its second FSG application 45 days later.

**Additional wound management**

Overlying applied FSGs, secondary layers included various combinations of petroleum-impregnated cellulose mesh (Adaptic nonadherent dressing; Acelity), superabsorbent polymer foam (Xtralorb; Derma Science), nonadherent gauze pad (Telfa; Covidien), silver-impregnated antimicrobial dressing (AQUACEL Ag; ConvaTec Inc), cotton rolls, or laparotomy pads. One wound was partially closed surgically, while the remaining portion of it was allowed to heal via secondary intention. All remaining wounds were allowed to close via secondary intention.

**Outcomes**

Time to closure following the first FSG in dogs ranged from 26 and 145 days (median, 71 days; n = 12). The remaining dog was lost to follow-up; however, the initial wound was 13 X 26 cm in area and had improved to 2 X 3 cm in area prior to losing contact with the owner. The number of bandage changes ranged from 3 to 51 (median, 12; n = 13). One dog with circumferential degloving injury of the entire left forelimb required punch grafts following 4 applications of FSGs (Figure 2). This dog developed intermittent edema in the paw during treatment, likely owing to compromised vascular supply, lymphatic supply, or both sustained from the original injury. A different dog had an elbow joint hygroma for which 2 FSG applications 21 days apart were used; however, the wound did not heal, and amputation of the limb was elected. No other additional surgical intervention was required for the dogs.

The wounds of 3 of the 4 cats had healed completely by secondary intention in 2 to 12 weeks after 1 FSG application (Figure 3). The remaining cat had a circumferential wound around its right hind limb that never healed; therefore, the limb was amputated.

No adverse events related directly to the application of FSGs were reported. For large complex wounds with minimal potential for contraction, complete epithelialization still occurred; however, regrowth of fur over these areas was inconsistent.

**Discussion**

In this retrospective case series, we evaluated the clinical outcomes following the use of a commercially available acellular FSG in the management of complex wounds in dogs and cats. Our findings indicated that the use of an acellular FSG in treating wounds of various etiologies that cannot be closed via primary closure allowed for healing via secondary intention with no adverse events attributed to the FSGs.

The FSG used in treating the patients of the present report was acellular dermal matrix (ADM) that is very similar to mammalian skin microscopically and FDA approved for use in humans for partial and full-thickness wounds, soft tissue re-
inforcement, traumatic wounds, surgical wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, and draining wounds. Other available ADMs are intestinal submucosal or amniotic tissue from porcine, equine, or bovine donors, and these have also been used in human medicine. A 2015 study of humans compared fish skin ADMs with porcine small intestine submucosa extracellular matrix in the healing of full-thickness wounds and found that wounds treated with fish skin ADMs healed significantly faster. Another benefit found in the use of fish skin ADMs, compared with mammalian ADMs, was that there was no potential risk of autoimmune reactivity, unlike in mammalian grafts. As these are FSGs, there is no risk of communicable diseases. The FSG product is gently processed and retains the structure of dermal tissue and omega-3 polyunsaturated fatty acids, which have antiviral, antibacterial, and anti-inflammatory properties. The natural 3-D microporous structure of the FSG is homologous to the extracellular matrix of the mammalian skin allowing autologous cells, including fibroblasts, to infiltrate and colonize the area and stimulate angiogenesis. This converts the graft into functional living tissue while slowly integrating into the viable wound bed through build-up of new granulation tissue. The FSG is integrated into a wound bed of human tissue between 7 and 10 days and has antimicrobial properties for 24 to 72 hours. In a recent article by Stone et al, the use of FSG resulted in faster vascularization and epithelialization and favorable histologic response, compared with the use of fetal bovine dermis, in treating deep partial-thickness burn wounds in pigs. Fish skin has unique proper-
ties that aid in homeostasis, inflammatory, prolif-
erative, and remodeling stages of wound healing. Debridement resets the wound to the homeostasis stage and activates the coagulation cascade. The 3-D complexity of the fish skin homologous to hu-
man skin and the native porosity allow an ideal en-
vironment for cell recruitment.

The main limitation of the present case series was the small sample size and retrospective nature of the study, with various wound management tech-
niques used. As there was no control group, it was difficult to determine the impact that FSGs had on wound healing. Additionally, there was no set pro-
tocol as to when or how often to apply an FSGs. In human medicine, FSG application for lower extrem-
ity acute and chronic ulcers is performed weekly for 5 to 6 weeks.\textsuperscript{14,15} In a retrospective study\textsuperscript{16} of 51 people with 56 lower extremity wounds, the mean number of acellular FSG applications per patient was 4.9. The mean number of applications in the present study was 2.2, and many animals had an in-
terval > 1 week between applications. Furthermore, 5 of the 17 animals in the present study had only 1 FSG application. It was difficult to extrapolate from our data whether the number of FSG applications were limited to 1 because of a substantial improve-
ment in the wound bed, financial limitations of the owners, patient or owner compliance, or lack of ex-
perience with the use of FSGs. With various wound sizes and times to closure, it was also difficult to predict the effect that multiple FSG applications or the duration of the interval between applications had on wound healing. In the future, a prospective, randomized clinical trial with a more standardized protocol will be needed to further evaluate the clinical effectiveness and determine whether certain characteristics of wounds (eg, healing stage or wound size) influence the number of applications required until complete wound healing occurs.

Our findings suggested that the use of acellular FSGs in companion animals for the management of complex wounds appeared to have been well toler-
ated and easy to apply, with no attributed adverse events reported. The use of acellular FSGs does not require special training, instruments, or bandage materials to apply, making them applicable to wound management in general practice and specialty prac-
tice in veterinary medicine.

Acknowledgments

No external funding was used in this study. The authors declare that there were no conflicts of interest.

References

1. Campbell BG. Moist wound healing in dogs and cats: us-
ing MRDs to improve care. \textit{Today’s Vet Pract.} 2015. Ac-

com/moist-wound-healing-the-new-standard-of-care/

2. Prich CL, Santamaria AC, Simcock JO, Wong HK, Nimmo 
JS, Kuntz CA. Second intention healing after wide local 

omega3 wound matrix for treatment of complicated 
wounds: a multicenter experience report. \textit{Article in Ger-

4. Baldursson BT, Kjartansson H, Konrádsdóttir F, Gudnason 
P, Sigurjonsdottir GF, Lund SH. Healing rate and autoim-
mune safety of full-thickness wounds treated with fish

skin acellular dermal matrix versus porcine small-intestine 
submucosa: a noninferiority study; a noninferiority study. 

5. Kirsner RS, Margolis DJ, Baldursson BT, et al. Fish skin

grafts compared to human amnion/chorion membrane 
allografts: a double-blind, prospective, randomized clini-
tical trial of acute wound healing. \textit{Wound Repair Regen.} 

6. Magnusson S, Baldursson BT, Kjartansson H, Rolfsson O, 
Sigurjonsdottir GF. Regenerative and antibacterial proper-
ties of acellular fish skin grafts and human amnion/chori-

on membrane: implications for tissue preservation in 

7. Magnusson S, Winters C, Baldursson BT, Kjartansson H, 
Rolfsson O, Sigurjonsdottir F. Acceleration of wound heal-
ing through utilization of fish skin containing omega-3 
acceleration-wound-healing-through-utilization-fish-
skin-containing-omega-3-fatty-acids

8. Magnusson S, Baldursson BT, Kjartansson H, et al. Decel-
ularized fish skin: characteristics that support tissue repair. 

9. Magnusson S, Kjartansson H, Baldursson BT, et al. Acel-
ular fish skin grafts and pig urinary bladder matrix assessed 
in the collagen-induced arthritis mouse model. \textit{Int J Low 

10. Bohač M, Danišovič L, Koller J, Draguňová J, Varga I. What happens to an acellular dermal matrix after implan-
tation in the human body? A histological and electron 
doi:10.4081/ejh.2018.2873

11. Bush K, Gertzman AA. Process development and manu-
facturing of human and animal acellular dermal matrices. 
In: Albanna MZ, Holmes JH, eds. \textit{Skin Tissue 
Engineering and Regenerative Medicine}. Elsevier; 2016:103.

tions of acellular dermal matrices in reconstructive sur-
ery. In: Albanna MZ, Holmes JH, eds. \textit{Skin Tissue 
Engineering and Regenerative Medicine}. Elsevier; 2016: 
109–124.

wound closure of deep partial thickness burns with acel-
doi:10.3390/ijms22041590

14. Yang CK, Polanco TO, Lantis JC II. A prospective, post-
market, compassionate clinical evaluation of a novel acel-
elar fish-skin graft which contains omega-3 fatty acids 
for the closure of hard-to-heal lower extremity chronic 

15. Woodrow T, Chant T, Chant H. Treatment of diabetic foot 
wounds with acellular fish skin graft rich in omega-3: a 

use for diabetic lower extremity wound healing: a retro-
spective study of 58 ulcerations and a literature review. 