

Clinical Impact Upon Wound Healing and Inflammation in Moist, Wet, and Dry Environments

Johan P.E. Junker,* Rami A. Kamel, E.J. Caterson, and Elof Eriksson

Division of Plastic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.



Johan P.E. Junker, PhD

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*Correspondence: Division of Plastic Surgery, Harvard Medical School, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115 (e-mail: jjunker@partners.org).

Abbreviations and Acronyms

EGF = epidermal growth factor

FGF = fibroblast growth factor

HPF = high-power field

IGF-1 = insulin-like growth factor 1

KGF = keratinocyte growth factor

NGF = nerve growth factor

PDGF = platelet-derived growth factor

STSG = split thickness skin graft

TGF = transforming growth factor

Significance: Successful treatment of wounds relies on precise control and continuous monitoring of the wound-healing process. Wet or moist treatment of wounds has been shown to promote re-epithelialization and result in reduced scar formation, as compared to treatment in a dry environment.

Recent Advances: By treating wounds in a controlled wet environment, delivery of antimicrobials, analgesics, other bioactive molecules such as growth factors, as well as cells and micrografts, is allowed. The addition of growth factors or transplantation of cells yields the possibility of creating a regenerative wound microenvironment that favors healing, as opposed to excessive scar formation.

Critical Issues: Although several manufacturers have conceived products implementing the concept of moist wound healing, there remains a lack of commercial translation of wet wound-healing principles into clinically available products. This can only be mitigated by further research on the topic.

Future Directions: The strong evidence pointing to the favorable healing of wounds in a wet or moist environment compared to dry treatment will extend the clinical indications for this treatment. Further advances are required to elucidate by which means this microenvironment can be optimized to improve the healing outcome.

SCOPE AND SIGNIFICANCE

THIS REVIEW HIGHLIGHTS clinical findings regarding treatment of wounds in a moist or wet environment. Moreover, the possible modulation of the microenvironment of the healing wound is discussed, with some examples of current research related to the topic.

TRANSLATIONAL RELEVANCE

Successful treatment of wounds relies on precise control and continuous monitoring of the wound-healing process. This review summarizes the impact and implications of wet or moist treatment of skin wounds. The wet microenvironment, in which the wound surface acts as a highly per-

meable membrane has been suggested to be advantageous for accelerated wound healing in regard to the epithelialization rate and healing outcome. Various treatment solutions can be introduced in the liquid, at known concentrations. This renders the possibility of exact determination of uptake and the rate of elimination, as well as analysis of any byproducts from the wound-healing process.

CLINICAL RELEVANCE

Wet or moist treatment of wounds has been shown to promote re-epithelialization and result in reduced scar formation, as compared to treatment in a dry environment. The

inflammatory reaction is reduced in the wet environment, thereby limiting injury progression. Several studies have compared wet, moist, and dry healing. A wet or moist incubator-like microenvironment provides the fastest healing with fewest aberrations and least scar formation. These clinically relevant observations allow one to resolve translational experiments and relevance to further enhance and define the parameters important to accelerating wound healing.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Definition of the wound microenvironment

The wound microenvironment is defined as the environment exterior to the wound and in direct contact with its surface. It is defined as dry when there is no barrier to contain the extracellular fluid and extracellular matrix in the wound. It is described as moist when a moisture-containing controlled hydration dressing is used to cover the surface of the wound. Finally, it is described as wet when covered with an impermeable membrane that is sealed to the periphery of the wound with adhesives.

Treatment of wounds in a moist environment

There are numerous examples throughout history with exacting efforts to utilize moist wound healing in the earliest of medical writings. The modern concept of employing a moist environment for the treatment of wounds was introduced in the early 1960s by Winter *et al.*¹ Here it was shown in a pig model that the rate of epithelialization after wounding was twice as fast when treated with a moist dressing as compared to dry conditions. This, at the time of a new concept, was in opposition with the generally accepted idea that a dry environment was best for wounds to fight infection. One year later, Hinman and Maibach applied the moist dressing concept in the study of experimental human skin wounds.² Since then, moist dressings have become the standard method for care for chronic wounds.³ A moist environment has been proven to facilitate the healing process of the wound by preventing dehydration and enhancing angiogenesis and collagen synthesis together with increased breakdown of dead tissue and fibrin. This improves the aesthetics of the wound, while decreasing pain. The moist environment has not been shown to increase the risk of infection, as compared to traditional dry therapies.^{4,5}

Improved wound healing in a moist environment under controlled hydration could be attributed to a variety of mechanisms. These include easier mi-

gration of epidermal cells on a moist surface,⁶ faster epithelialization,⁷ but also the prolonged presence of proteinases and growth factors.⁸ Clinical studies suggest that wound fluid from wounds healing under moist conditions stimulates keratinocyte proliferation⁷ and fibroblast growth⁹ with subsequent preservation of growth factors for wound repair¹⁰⁻¹³ (Table 1).

Dyson *et al.* compared the effects of moist and dry conditions on dermal repair in a porcine model. An adhesive polyurethane dressing was used as a moist dressing, while gauze dressing exposed to air ensured dry healing conditions. They showed that both the inflammatory and proliferative phases of dermal repair were shorter for wounds under moist conditions when compared with those healing under dry conditions.¹¹ Four years later, the same group performed another comparative study between moist and dry environments, investigating the process of angiogenesis during dermal repair. They concluded that wounds that were allowed to heal in a moist environment were revascularized at a greater rate than those maintained under dry conditions. Angiogenesis also occurred in a more orderly fashion in moist wounds.¹² A study by Vogt *et al.* also used a porcine model to compare the effect of moist, wet and dry environments on wound repair. It found that moist wounds exhibited a higher number of subepidermal neutrophils than wet wounds 5 days postwounding, which may have been caused by the hydrocolloid dressing used (Table 2).¹³ Moist and wet healing environment resulted in less necrosis, faster healing, and better quality of healing than the dry environment.¹³

Table 1. Comparison between different parameters of wound healing under dry versus moist healing conditions

	Dry Environment	Moist Environment	References
Microscopic aspects			
Cellular migration	-	+	6
Keratinocyte proliferation	-	+	7
Fibroblast proliferation	-	+	9
Growth factors activity	-	+	8,10
Angiogenesis	-	+	12
Collagen synthesis	-	+	4
Dead tissue and fibrin	+	-	4,13
Duration of inflammatory and proliferative phases	+	-	11
Clinical aspects			
Incidence of infection	-	-	4,5
Pain	+	-	4,13
Wound aesthetics and quality	-	+	4,13

The pluses and minuses in the table do not reflect quantitative descriptions or absolute values, but rather serve to illustrate healing conditions under dry and moist environments in comparison to each other.

Table 2. Subepithelial infiltrate in moist and wet wounds

Time After Wounding	Wet (Mean ± SEM; n = 8)	Moist (Mean ± SEM; n = 8)	p
Day 5			
All	171 ± 8.90	183.50 ± 17.40	n.s.
Lymphocytes	16.40 ± 4.30	17.10 ± 2.80	n.s.
Fibroblasts	124.00 ± 10.60	132.60 ± 7.90	n.s.
Macrophages	12.60 ± 2.70	12.26 ± 4.80	n.s.
Neutrophils	2.40 ± 0.40	6.20 ± 1.30	0.0156
Others	15.60 ± 2.40	16.90 ± 2.90	n.s.
Day 7			
All	127.00 ± 2.90	149.00 ± 5.60	0.0003
Lymphocytes	5.70 ± 0.70	8.57 ± 2.00	n.s.
Fibroblasts	107.60 ± 2.60	119.30 ± 3.00	0.0031
Macrophages	5.40 ± 37.00	7.59 ± 1.00	n.s.
Neutrophils	1.87 ± 0.29	4.00 ± 1.70	n.s.
Others	7.59 ± 0.50	11.60 ± 1.60	0.0343

Values represent number of cells/10⁻⁶ mm². (Adapted from Vogt et al.¹³) n.s., not significant; SEM, standard error of the mean.

Manufacturers have taken the cue from researchers following Winter's postulate and worked to provide today's market with a wide range of moist dressings such as hydrocolloids that absorb the wound fluid under a semiocclusive dressing,^{5,14} foams,^{15,16} alginates,¹⁷ and hydrogels.^{18,19} Dumville *et al.* performed four systematic reviews of the Cochrane database on each of the four dressing families to evaluate its role in the healing of diabetic ulcers.²⁰⁻²³ A systematic review by Wiechula suggests that moist wound-healing products have distinct clinical advantages over nonmoist products in the management of split-thickness skin donor sites.²⁴

Treatment of wounds in a wet environment

The success of wet wound healing was espoused in 1861, where a report published by Hebra described the treatment of burns using "continuous baths."²⁵ Patients with major open burn wounds were treated by submersion in bathtubs. The treatment would continue for extended periods of time, and was found to reduce pain and weight loss. The patients survived until treatment in water was discontinued. During the Second World War, Bunyon, a Medical Officer and Lieutenant in the British Navy, treated wounded soldiers using the "envelope" method.²⁶ This procedure also relied on the employment of fluid surrounding the wounded area. These historical examples represent two of the first described strategies to treat wounds in a wet environment.

When Bunyan added bleach to the fluid surrounding the wounds, he noticed less pain, reduced amount of necrotic tissue, and fewer infections in the patients who received the envelope treatment. Since then, several irrigation systems have been

developed, for instance by Svedman,²⁷ Kinetic Concepts Incorporated,²⁸ and Zamirowski.²⁹ Owens and Wenke suggested that earlier irrigation in a contaminated wound resulted in superior bacterial removal in their goat model.³⁰ The authors, however, found in another study that irrigants other than saline solutions or high-pressure devices may not have the best clinical outcome regarding bacterial removal.³¹ Another article by the same group concludes that pulsed lavage is a more effective and efficient method of irrigation to remove bacteria in a complex musculoskeletal wound.³²

To expand the utility of the treatments, antimicrobial solutions have been used as irrigation fluid. Collectively, these efforts illustrate the difficulties of delivering precise amounts of antimicrobials and antibiotics via an irrigation system. In practice, the concentrations of antimicrobials are kept quite low to avoid the possibility of toxicity. The above examples also illustrate the difficulties in producing a cost-effective device serving as a vehicle for the liquid.

In his study published in 1983, Svedman compared wound healing under saline irrigation with conventional saline dressings and concluded that wound contraction was similar under both conditions, but the wound blood flow, measured by a laser Doppler flowmeter, increased earlier with irrigation.³³

In 1992, Breuing *et al.* published a study comparing the healing of partial-thickness burns and excisional porcine skin wounds in a wet environment to dry control wounds.³⁴ The wet environment was achieved by encapsulating the wounds in a transparent chamber attached to the skin peripheral to the wound. Liquid containing antibiotics were delivered into the chamber through a port and left in place between 1 and 5 days. Outcome parameters studied included the amount of necrosis and exudates produced from the wound, as well as the amount of protein content and electrolytes in the wound fluid. The authors concluded that the depth of necrosis of the dermal wound bed was significantly reduced in wet wounds when using the wound chamber compared to a dry environment. Seven days after wounding, the necrosis in the partial-thickness wounds treated in a dry environment was 866 μm compared to zero in the wet environment. The study continued to attempt to identify markers of healing in the wounds. The wound fluid was collected daily, and the amounts of potassium, calcium, and total protein were assayed. The protein amount in the wound exudate reached zero at the time of complete re-epithelialization of

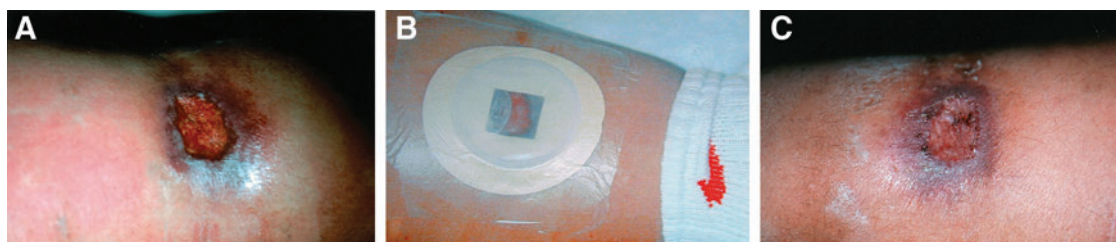


Figure 1. Chronic venous stasis ulcer treated in a wet environment. **(A)** Wound after two failed debridements and split-thickness skin graft. **(B)** The wound chamber with antibiotics covering the wound. **(C)** The healed wound 3 weeks after débridement and split-thickness skin graft. (Reprinted with permission from Vranckx *et al.*³⁵) To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

the wounds. This was observed in the healing of burns as well as excisional wounds. In summary, the wound chamber protected the wound and stopped the injury progression in terms of necrosis. No adverse effects were noted on a normal skin or the wound itself.³⁴

Modulating the wound microenvironment

By treating wounds in a controlled wet environment, delivery of antimicrobials, analgesics, other bioactive molecules such as growth factors, as well as cells and micrografts, is allowed. The objective when applying topical antimicrobial agents is to eradicate contamination, as well as prevent wound colonization. Due to the favorable concentration gradient that is achieved with top-

ical application, the active concentration of antimicrobials at the wound site is increased by orders of magnitude compared to traditionally used IV delivery.³⁵ According to the same principles, local analgesics will make a wound pain free. Before treatment methodologies based on topical administration of high-dose antibiotics are adapted in a clinical setting, thorough studies regarding toxicity and dosing regimens are required. In studies performed by us and others, no negative effects on the healing wound or the healthy surrounding skin have been observed. Clinical studies defining the specific indications and contraindications are the next step in assessing the potential of high-dose topical antibiotics in the treatment of wounds.

Table 3. Limited list of selected growth factors for modulation of wound microenvironment

Growth Factor	In Vitro Effects	Products for Clinical Use
PDGF	Stimulates the production of other growth factors. Assumes a role in remodeling.	Chemicon (Millipore) Becaplermin gel 0.01% (rhPDGF)
TGF- β	Regulates cellular migration and proliferation. Proteinase expression. Fibronectin binding interactions. Terminates cell proliferation. Stimulates collagen production.	None
IGF-1	Assumes a role in fibroblast proliferation and migration. Stimulates matrix production.	None
VEGF	Stimulates angiogenesis.	None
Basic FGF (aka FGF-2)	Stimulates angiogenesis. Regulates cell migration and proliferation.	None
KGF-1 (aka FGF-7) KGF-2 (aka FGF-10)	Enhances proliferation and migration of keratinocytes. Are downregulated in fetal wound repair.	None
NGF	Regulates angiogenesis. Enhances functional properties of various inflammatory cells, including neutrophils, macrophages, and mast cells. Accelerates cutaneous wound-healing rate.	None
EGF	Stimulates keratinocytes to produce hyaluronic acid. Stimulates fibroblast function. Implicated in cellular motility and migration during wound repair. Implicated in formation of granulation tissue.	None

All of the effects mentioned in the table above were studied *in vitro* or in animal models, and have yet to be proven clinically in humans, except for PDGF. PDGF, platelet-derived growth factor; TGF- β , transforming growth factor beta; IGF-1, insulin-like growth factor 1; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; KGF, keratinocyte growth factor; NGF, nerve growth factor; EGF, epidermal growth factor.

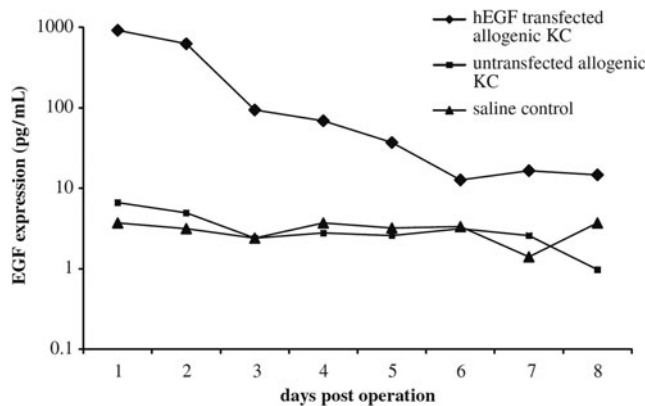


Figure 2. *In vivo* expression of human epidermal growth factor (hEGF) in wound fluid retrieved daily from wound chambers and determined by ELISA. EGF expression: 920 pg/mL hEGF on day 1 and 624.5 pg/mL on day 2. In control wounds, EGF expression reached 6.6 pg/mL on day 1. (Reprinted with permission from Vranckx *et al.*⁵⁹) KC, keratinocytes.

The addition of growth factors or transplantation of cells yields the possibility of creating a regenerative wound microenvironment that favors healing, as opposed to excessive scar formation.

Principally, the liquid in the chamber becomes a reservoir and acts as a sustained release system. The tissue absorption is easily deduced from the remaining concentration of the agent in the chamber after a certain time.

Antibiotics. In a clinical study by Vranckx *et al.*, wet wound treatment was used in patients who had either not responded to conventional treatment or had wounds that were very difficult to treat with

conventional methods (Fig. 1).³⁵ The wounds were covered by wound chambers and vancomycin and gentamicin were diluted in saline and injected into the wound chamber. Antibiotic concentrations at the wound surface of up to 2,500 times the minimum inhibitory concentration for common bacteria could be achieved, while still limiting the total dose in the wound chamber to one single IV dose of the antibiotic for the particular patient. When the concentration of antibiotics was measured 2 days later, 20% or more of the original concentration remained in the chamber fluid. Since vancomycin and gentamicin are both excreted through glomerular filtration, systemic absorption of the drugs from the chamber fluid is the probable route of elimination. To prevent any systemic toxicity, the infusion of antibiotics in the chamber was limited to one daily i.v. dose per day for a particular patient. In 71% of these 28 wounds, complete healing was achieved during the planned treatment period.³⁵ The wound chamber treatment was not found to cause any injury to the wound itself or to the surrounding intact skin.³⁵

Antifungal agents, such as amphotericin B, can also be introduced in the chamber. Further studies are required to evaluate their utility and possible toxicity.

Analgesics. Pain is a considerable problem in chronic wounds.^{36,37} An ibuprofen foam has been developed to provide both a moist environment for wound healing together with the reduction of temporary and persistent wound pain.³⁸ A study by Cigna *et al.* suggests that the integration of

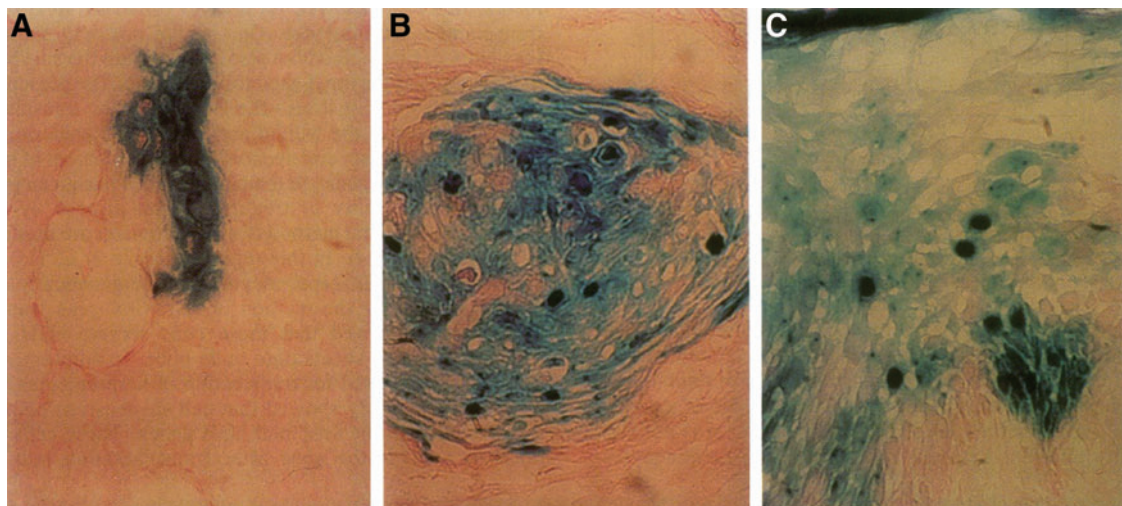


Figure 3. Reconstitution of new epithelium of porcine full-thickness wounds. X-Gal staining to demonstrate lacZ expression. (A) LacZ keratinocytes are first seen in clusters on the bottom of the wounds on day 4, (B) having migrated upward on day 6, and (C) are present in all layers of the epithelium by day 8. (Reprinted with permission from Vogt *et al.*⁶⁰) To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

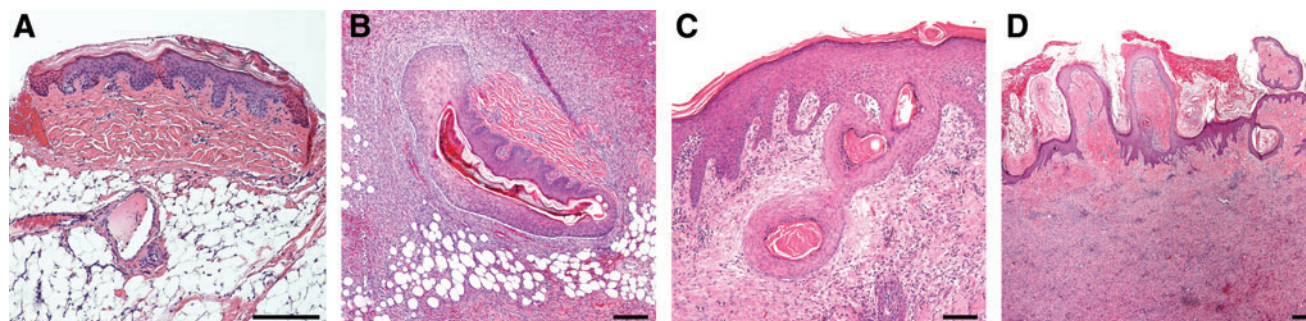


Figure 4. Hematoxylin and eosin–stained section showing porcine wound transplanted with micrografts. **(A)** A micrograft on the wound bed 1 h after transplantation. **(B)** A micrograft in wound 6 days after transplantation showing the micrograft with proliferating keratinocytes. **(C)** Micrografts in wound 10 days after transplantation. The stratum corneum of four different micrografts is surrounded by keratinocytes in different stages of migration. **(D)** Wound 14 days after transplantation showing the dermis and stratum corneum of transplanted micrografts in various stages of transepidermal elimination. Bar equals 200 μm in all panels. (Reprinted with permission from Hackl *et al.*⁶¹) To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

ibuprofen with a polyurethane bio-occlusive dressing in the management of donor sites of split thickness skin grafts (STSG) resulted in faster wound healing compared to gauze dressings and almost eliminated pain and discomfort in all patients treated.³⁹ This has also been investigated in venous leg ulcers in a randomized control double-blind clinical study.⁴⁰ In the wet wound chamber environment analgesics, such as lidocaine, can be introduced to mitigate pain.

Growth factors. A number of growth factors have been showed to promote wound healing in animal models, most noteworthy are the epidermal (EGF), fibroblast (FGF), keratinocyte (KGF), platelet-derived (PDGF), and nerve (NGF) growth factors, as well as transforming growth factors (TGF) alpha and beta (Table 3).^{41–57} The only growth factor reported to have a substantial effect when applied topically to wounds in humans is the PDGF-BB, in promoting healing of refractory

nondiabetic ulcers.⁵⁸ Studies have shown that transplantation of keratinocytes along with *ex vivo* gene delivery of the EGF can increase healing of porcine full-thickness wounds (Fig. 2).⁵⁹ Transplantation of insulin-like growth factor 1 (IGF-1)-expressing keratinocytes improves the healing of porcine full-thickness wounds. In summary, topical administration of growth factors seems to be somewhat effective, although the half-life and biological activity of introduced factors are sometimes difficult to predict.

Transplantation of cells and micrografts in a wet/moist environment. Vogt *et al.* studied the transplantation of cells in a wet wound environment.⁶⁰ It was found that single-cell suspensions of keratinocytes survive, proliferate, migrate to the surface of the wound, forming a new mature epidermis (Fig. 3). The neoepidermis has a basement membrane, basal layer, and undergoes the normal process of differentiation. The formation of these

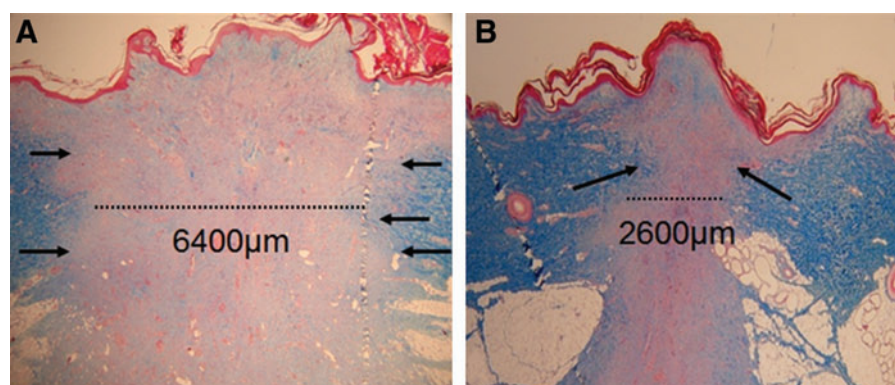


Figure 5. Wet wound healing reduces inflammation and scar formation. Masson's trichrome staining of **(A)** dry and **(B)** wet porcine wounds 28 days postwounding. The dry wound has a significantly greater width of scar tissue compared with the wet wound. Arrows indicate scar tissue borders. (Reprinted with permission from Reish *et al.*⁶⁵) To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

structures by the transplanted cells was confirmed by using transfected keratinocytes. In this study setup, low levels of antibiotics were used to reduce the risks of growth of resident opportunistic flora.

Similar results can be achieved when subjecting autologous donor skin to mechanical mincing instead of enzymatic digestion and culture expansion. Skin minced into submillimeter particles and transplanted in a wet environment, will survive and contribute to re-epithelialization, regardless of orientation.⁶¹ Hackl *et al.* demonstrated the possible utility of a 100-fold expansion of a skin graft with complete wound coverage within 14 days in porcine wounds (Fig. 4).⁶¹ Kiwanuka *et al.* compared healing times and outcomes of full-thickness porcine excisional wounds treated with cultured autologous keratinocytes, STSGs, or minced skin micrografts.⁶² Transplantation of micrografts yielded results similar to STSGs in regard to re-epithelialization, scar formation, epidermal maturity, and the Vancouver Scar scale scores.

Moist/wet treatment reduces scarring

Healing of adult human skin wounds is associated with varying degrees of scar formation.⁶³ Scarring can be correlated with the intensity and duration of inflammation during healing.⁶⁴ In 2009, Reish *et al.* published an experimental study performed in porcine wounds in which inflammation, in terms of numbers of inflammatory cells/high-power field 3 days after wounding, was compared in wounds treated either in a wound chamber or with gauze.⁶⁵ Inflammation was greatly reduced in the wounds treated in the wound chamber, and there was a very strong correlation between the number of inflammatory cells on day 3 and the amount of scarring that had developed by day 28 (Fig. 5).⁶⁵ Wet wounds created under sterile conditions, here treated with low concentrations of antibiotics, exhibited a significantly smaller macroscopic scar surface area in all experimental wound groups compared with dry wounds. Wounds with a greater inflammatory cell infiltrate could be predicted to develop more residual scarring.

TAKE HOME MESSAGES

- Wet or moist wound treatment significantly reduces the time required for re-epithelialization, and leads to reduced inflammation, necrosis, and subsequent scar formation, as has been demonstrated in several large animal studies, as well as limited clinical studies
- Wet or moist treatments have no adverse effects on the wound itself, or the surrounding tissue
- A wet environment can allow for precise delivery of antimicrobial agents and analgesics to the healing wound
- Wet environment has been shown to support transplanted cells and micrografts in large animal models and one clinical case, thereby accelerating healing
- Soluble agents, for instance, growth factors or bioactive molecules, can be introduced in a highly controlled manner in a wet wound-healing environment

AUTHOR DISCLOSURE AND GHOSTWRITING

E.E. has filed a number of patents in the fields of negative pressure treatment and transplantation, and is also a member of an LLC that deals with wound healing. J.P.E.J., R.A.K., and E.J.C. have no competing financial interests. No ghostwriters were used to write this article.

ABOUT THE AUTHORS

Dr. Johan Junker is the Director of Wound Healing and Tissue Engineering Research at Brigham and Women's Hospital, and Instructor of Surgery at Harvard Medical School. His background is in tissue engineering, regenerative medicine, and wound healing. **Dr. Rami Kamel** is a research fellow at Brigham and Women's Hospital and Harvard Medical School. **Dr. E.J. Caterson** is a plastic surgeon at Brigham and Women's Hospital and Instructor of Surgery at Harvard Medical School. He is involved in clinical and experimental efforts to modulate wound healing and tissue engineer skin. **Dr. Elof Eriksson** is Chief of the Division of Plastic Surgery at Brigham and Women's Hospital, and Joseph E. Murray professor of Plastic and Reconstructive Surgery at Harvard Medical School. Dr. Eriksson has conducted wound-healing research for more than three decades.

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