

White Paper on the Use of Suprathel[®] after Enzymatic Debridement with Nexobrid[®]

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INTRODUCTION

Enzymatic debridement (ED) is used for selective eschar removal in deep burns, which preserves the healthy epidermal and dermal parts of the skin. With ED, the extent of the area requiring grafting and the donor area is smaller. After debridement, supporting the undisturbed healing of cutaneous and

WHICH WOUNDS ARE NOT SUITABLE FOR ED:

In burn injuries pretreated with silver sulfadiazine (SSD), other silver products, and iodine, ED have been described to be less successful¹. In general, enzyme-inactivating products such as copper and heavy metals should be avoided³.

The effectiveness of ED in scald injuries might be even lesser⁴. A 100% consensus was reached for this statement among 12 participants in the 2020 consensus⁵. Incomplete debridement can also occur, happened especially during “early” debridement and in old people.

Potential cytotoxicity of ED with respect to keratinocytes and fibroblasts was confirmed but only in vitro⁷. During ED, wound fluid digested the collagen-elastin matrix Matriderm™ for up to 240 minutes. After 240 minutes, the effect was negligible. Since bromelain is generally toxic to skin cells⁷, burn wound fluid dilutes its cytotoxic effects while simultaneously affecting the remaining tissues⁸. In vitro data from animal experiments

epidermal structures is recommended¹. Exsiccation and other factors can deepen the burn. Therefore, a dressing that promotes the healing of epidermal structures and protects dermal structures is necessary; this can be achieved using Suprathel².

There is no evidence for the treatment of **chemical burns** with ED^{1,4}.

ED is not indicated during surgical release for **extended trunk burns in patients with established respiratory compromise, established compartment syndrome** in the extremities, **and high voltage injury**.⁵

ED is highly recommended for deep facial burns and shows excellent results; however, special preparations are needed to protect the sensory organs⁶.

POTENTIAL SIDE EFFECTS OF BROMELAIN:

indicate that bromelain can promote fibrinolysis. Inhibition of cytochrome-P450-2C8 and cytochrome-P450-2C9 results in the enhancement of effects of different drug (amiodarone, amodiaquine, chloroquine, fluvastatin, paclitaxel, pioglitazone, repaglinide, rosiglitazone, sorafenib, torasemid, ibuprofen, tolbutamide, glipizide, losartan, celecoxib, warfarin, and phenytoin). Bromelain can increase the effect of angiotensin-

converting-enzyme inhibitors, fluorouracil, vincristine, benzodiazepines, barbiturates, narcotics, and antidepressant agents⁹.

Wounds should be cleaned by removing blisters and denatured keratin layers by brushing or surgical means, if necessary. Late burns with dry eschars require mechanical removal of the dried superficial levels and prolonged presoaking for up to 12 hours⁵.

TIMING OF ED:

- After an update of the European consensus, the timing was classified as **very early** (within 12 hours of injury), **early** (between 12 and 72 hours), and **delayed** (after 72 hours)⁴.
- It is suggested that ED be performed as early as possible **to prevent compartment syndrome** in patients with circumferential burns of the extremities and extensive trunk burns. However, surgery is suggested when respiratory compromise is established, as in these cases⁴.
- In general, it is suggested that ED be performed within 72 hours of injury by the European consensus.

According to the **regulatory constraints**, 15% of the total body surface area (TBSA) should be considered for ED, and larger areas should be debrided in successive interventions. Spanish experts suggest active treatment against **hypothermia** (when necessary) when presoaking and post-soaking are performed simultaneously in one patient.

PAIN TREATMENT:

For ED, **proper analgesia**, sometimes in the form of general anesthesia, is necessary. This requires monitoring and ventilation facilities, at least on standby.

Regional anesthesia, including anesthesia using catheter techniques, has been suggested for the treatment of extremities¹.

WOUND BED PREPARATION BEFORE ED:

PRESOAKING:

Fresh and moist wounds can be treated immediately. Otherwise, moisturizing for a minimum of 2 hours is recommended. A solution of 0.9% NaCl or another suitable disinfectant solution (e.g., polyhexanide) can be used for this purpose.

Later application is possible in “selected patients” after appropriate preparation (surgical removal of superficial layers followed by treatment or prolonged presoaking). Complete eschar removal should be performed within the first 7 days of injury¹.

Spanish experts indicate that ED be performed within 24-48 hours of admission. They agree that it should be performed within 7 days of injury. When immediate ED is not possible, the use of Mepilex, with Prontosan® or Vaseline gauze and nitrofurazone as a temporary cover, is suggested¹⁰.

LIMITATION OF THE AREA FOR ED:

Hypothermia, due to soaking, is a contradiction to **hyperthermia, a possible side effect of ED**. Therefore, soaking can be used to reduce the hyperthermic side effect of ED¹⁰.

Areas corresponding to more than 15% of the TBSA could be debrided in one session without adverse effects¹¹, as described by Hofmaenner et al., **who** treated areas corresponding to a median of 18% (interquartile range, 15–19) of the TBSA in one session.

Plexus anesthesia can be used for a prolonged period, covering the post-soaking period and the first dressing change¹².

Further anesthesia is usually not required. Pain levels reported during ED were low in general. Sympathicolysis with regional anesthesia can optimize wound bed perfusion and support healing.

Another option is tumescence anesthesia with long-lasting anesthetics.

TIMING OF APPLICATION OF NEXOBRID:

ED treatment itself should last for 4 hours as per a consensus between all expert groups. Experts do not suggest a repetition

CHOICE OF DRESSINGS AFTER ED:

Expert panels agree on applying a dressing post-ED, protecting the wound from desiccation¹³. Dr. Martinez suggests covering areas with Suprathel, which has regenerative potential for spontaneous healing, and using a hydrocolloid in regions that need grafting¹⁰. Dos Santos followed the same algorithm¹⁴ for burns on the hands.

SOAKING AFTER ED (WET TO DRY PROCEDURE):

The “wet to dry procedure” involves the treatment of the wound with soaked cotton material after ED and leaving it in place until drying is suggested. When the wounds are dry, the pads are gently removed and replaced by other moistened drapes. Changing the dressing also removes adhering debris, further cleaning the wound.

Experts have increased the duration of post-soaking from 2 hours to 4 hours or more.

WOUND ASSESSMENT AFTER ED:

Assessment based on the following factors should be performed within 2 hours of treatment:

Condition of the wound bed and chance of healing, according to the 2017 Consensus	Chance of spontaneous healing
Red or pink	High chance of spontaneous healing
White wound bed with pin-point punctate bleeding	Good chance of healing with acceptable results
Red circles or oval patterns of large diameters	Prolonged healing time; grafting should be considered
Exposed fat	Grafting necessary

GRAFTING AFTER ED:

The **European consensus** suggests traditional grafting, when necessary, after at least 2 days¹. According to Spanish experts, grafting with autologous skin should not be performed before 3–5 days have passed due to increased secretion from the wound. After ED, **wounds often produce large amounts of fluid**

Nevertheless, there have been episodic reports about severe pain during ED despite proper anesthesia for unknown reasons.

of enzyme application on the same wound. Prolonged exposure to enzymes for some more hours does not cause harm¹.

Treatment with a silicone dressing before additional debridement and grafting was linked to prolonged healing time in the Berlin study¹⁵. In such cases, early debridement or the use of Suprathel as a temporary dressing can be considered.

Monclus¹⁰ suggested **prolonging the time of post-soaking** independently from later cover or grafting of three post-soaking procedures, each accounting for a total of 8 hours. Other authors have described a post-soaking period of 4–12 hours (mostly performed overnight)¹².

The European consensus suggests post-soaking with polyhexanide, whereas Spanish experts suggest the use of polyhexanide or soapy chlorhexidine.

and debris. Therefore, tight dressings can cause retention and “swimming off” of the dressing.

This condition is excellently described as a “slimy coat, which consists of exudation from the increased bed swelling and dissolved eschar”¹². The presence of debris in the wound can increase the risk of infection. Exudation and debris can reduce

graft take and increase the risk of dressing dislocation. Increased production of fluid containing debris can occur actively over hours and even for days.

INCOMPLETE REMOVAL OF DECAYED MATERIAL AFTER NEX- OBRID TREATMENT

Rosenberg described that in 75% of cases, a single application of Debrase® was sufficient to remove all necrotic tissue in mixed burns¹⁶. Schulz reported the complete removal of necrotic tissue, not requiring further action, in 90 % of cases¹⁷. In Berlin, a retrospective evaluation of 56 patients with 104 wounds described residual necrosis in 33% of the wounds or 14% of the regions¹⁵.

As the microscopic completeness of necrotic tissue removal is challenging to evaluate in a clinical situation, one can assume that a small proportion of necrotic tissue can remain, which is not visible on simple inspection. Self-cleaning over a specific period or actions to clean the wound before definitive closure with grafts or dressings might be necessary. Necrotic tissue can be found at different times, even when no necrotic tissue was visible before.

Necrosis observed immediately after ED:

The European consensus suggests “additional eschar removal by hydrosurgery or standard of care”¹ if non-vital tissue is

The “Zentrum für Schwerbrandverletzte mit Plastischer Chirurgie Berlin” is one of the biggest burn centers in central Europe and has longstanding experience with ED. They investigated 56 patients, of whom 42 were treated with Suprathel®¹⁵; the others with silicone dressings.

Even when no necrotic tissue was detected directly after ED, necrotic tissue or pseudoeschar could be found later. The origin of this necrotic tissue is unclear. It may be derived from thermal injury, toxic or delayed effects of the enzymes used, or burn wound progression. Di Lonardo et al. observed that the lytic action of bromelase spared partially damaged dermis¹⁹

found after ED, to achieve complete eschar removal within 7 days. There are no further suggestions for grafting in this context.

Residual necrosis observed after some days during the first dressing change:

This type of necrotic tissue is generally addressed as **pseudoeschar**. The European consensus defines pseudoeschar as “a specific layer sticking to the wound that may develop several days after treatment”¹. The experts’ therapeutic advice is to leave it in place and “consider” surgical debridement after more than 14 days.

The risk of infection may advocate early surgical removal.

Late necrosis detected after more than 1 week during a dressing change:

Such late pseudoeschar formation was attributed to the use of SSD creams by Palao¹⁸. Nevertheless, the Berlin group described late pseudoeschar development under silicone dressings when no early pseudoeschar had been visible. Grafting after surgical removal of this late necrosis was linked with prolonged healing time.

EXPERIENCE FROM BERLIN:

and stated that it might develop into a neo-eschar by desiccation.

ED complete:

When **ED was completed**, a **dermal layer with regenerative potential** (no visible subcutaneous fat or vessels) with **no necrotic tissue** can be found **during the first dressing change**; the chance for undisturbed healing under Suprathel without the need for further operative procedures is high. The expected total healing time was approximately 27 days, with an estimated percentage of spontaneous healing of 75%. Healing after

grafting (25%) due to different factors occurs within the same time frame¹⁵. In these patients, a reduction in grafting and donor areas can be confirmed.

Pseudoeschar:

In all patients showing **early and late pseudoeschars**, debridement and grafting were performed on day 7. The corresponding healing time was 23 days in the Suprathel® group, which was shorter than that in the silicone group, regardless of grafting.

When a **late pseudoeschar presents after initial complete debridement, grafting** after the removal of all necrotic tissues is suggested

Completely debrided wounds with regenerative potential **without early pseudoeschar can be treated conservatively with**

Suprathel or grafted based on the extent of injury or bacterial growth, most of the **other wounds benefit from early debridement and grafting.**

When a wound shows residual necrosis after ED, debridement and grafting are indicated, even after a short treatment period with Suprathel to avoid a prolonged healing period. The area to be transplanted could not be reduced in patients who underwent later operation. Conservatively treated plants did not undergo transplantations.

Conclusion:

Burn wound treatment after ED with Suprathel results in a shorter healing time as compared to that with silicone membranes, both in spontaneously healed and operated wounds. Necrotic tissues should be removed early.

WHAT CAN BE A STANDARD SCHEDULE FOR AND AFTER ED:

Wound cleaning	1 h
Presoaking	0-4 h
Application of ED	4 h
Removal of debris	0.2 h
Evaluation: wound depth, residual necrosis, staging of wound (1-4) ¹⁸	Residual necrosis Yes/No
1 st wet to dry procedure	4 h
2 nd wet to dry procedure	Till the next morning
Complete removal of residual necrosis (Versajet, Weck)	
First dressing	Jelonet and Polyhexanide
First dressing change on day 3 or 4	
Evaluation: Pseudoeschar (YES or NO)	Early pseudo eschar Y/N
Removal of necrotic tissue + dressing (Suprathel) or grafting	Day 3 or 4
Dressing on day 7 (Infection: YES or NO)	Day 7 or 8 Late Pseudoeschar Y/N
Leaving the dressing in place or debridement and grafting	

Suggested indications for surgery after ED

Based on the wound status:

- **Visible fat** or no dermal remnants indicate grafting after 4 days, as suggested by the European consensus.
- **Visible residual necrosis after ED** must be removed, as this contributes to a prolonged healing period.

Based on the wound progress:

- **Early pseudoeschars** represent necrosis that was not visible in the first evaluation after ED. If they are not visibly superficial, it is recommended to remove them to avoid a prolonged healing period and infection.

- **Late pseudoeschars** represent necrosis that was not visible before or was not removed in the prior evaluations. It has to be treated in the same way as mentioned above.
- **Wounds not healed within 3 weeks without a tendency for repair** should be considered for grafting, although Hoecksema et al. successfully challenged the rule of 21 days²⁰. Although a prolonged healing duration can be expected without grafting, higher rates of hypertrophic scars were not found.

RECOMMENDATIONS FOR SUPRATHEL AFTER ED

The European consensus summarized their experience after treating more than 500 patients but did not recommend any special dressing after the ED procedure. In this consensus, the participants **recommended dressings or templates that provide comfort and reduce pain and the frequency of dressing changes**¹. Suprathel has all of these properties. In other publications, some authors from this consensus explicitly confirmed that Suprathel is an appropriate dressing after ED¹².

In the Spanish consensus, Suprathel is described as the preferred dressing after ED because of its properties. Furthermore, seven experts from the central Spanish burn units who have treated >350 patients with ED recommended Suprathel¹⁰. At the 18th European Burns Association Congress (EBA) in 2019, multiple posters showing positive results with Suprathel after ED were presented.

WHEN NOT TO USE SUPRATHEL:

In cases where pain could not be sufficiently controlled by analgesia during ED, Suprathel should not be expected to reduce pain sufficiently. There is a high possibility that pain cannot be controlled by the pain-reducing effects of Suprathel alone.

WHY USE SUPRATHEL?

Suprathel is a bioactive dressing. Polymers from polyhydroxy acids, mainly based on polylactic acid, have been successfully used in burn treatment for nearly 20 years. There is significant evidence for various clinical benefits of Suprathel such as pain reduction, reduced workload, short healing time, and low complication rates. This provides excellent cosmetic results in superficial, deep partial-thickness, and even small full-thickness burns^{2,21-28}. It has a lower infection rate than Mepitel and Flaminal¹ and reduces burn wound progression²⁹.

It acts as an energy source for cells by providing external lactate and pyruvate, which fuels energy metabolism in the cells^{30,31}. Simulating a hypoxia-like state in wounds without oxygen reduction releases multiple growth factors with effects on fibroblasts, keratinocytes, the

extracellular matrix, and endothelial cells^{32,33}. By supporting wound healing, it reduces burn wound conversion and the need for grafting^{29,34}.

PRECAUTIONS DURING SUPRATHEL TREATMENT:

- We suggest the application of disinfectants over the inner dressing (Suprathel and separation layer) with polyhexanide gel or similar compounds.
- When dressings above the wounds are still wet after 14 days, check for hypergranulation or infection based on the residual necrotic tissue.
 - In the case of developing hypergranulation, consider the use of a topical corticoid ointment.
 - In severe cases, surgical debridement might be necessary.
- When the time of healing is prolonged (> 3 weeks), consider using autografts. Spontaneous healing under Suprathel can only work in areas with enough dermal remnants; otherwise, the wound will heal from the margins over a long time. The longer the healing time due to diminished resources for epithelialization, the worse will be the scar quality.
- Perform compression using elastic bandages over the primary dressing to avoid edema formation and dislocation of Suprathel, especially in strongly exudative wounds. This also works as scar prophylaxis.

HOW LONG CAN SUPRATHEL TREATMENT BE CARRIED ON AFTER ED?

The European consensus suggests checking for the need of autografts after a treatment period of 3 weeks to reduce scarring.

Hoeksema demonstrated that even after extended treatment, the rate of hypertrophic scars was not elevated with the use of topical corticosteroids²⁰. The healing duration observed was 32,7 days on average, ranging from 22 to 57 days.

Nevertheless, a prolonged healing period should be avoided, as it has psychological and social consequences.

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